Metabolic interventions in heart failure
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Chapter 3

Coronary revascularization in diabetic patients does not reduce their propensity to develop heart failure

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Submitted
Chapter 3

Abstract

Aims
Diabetes predisposes to heart failure (HF), which is often caused by coronary artery disease (CAD). Coronary artery bypass graft surgery (CABG) prevents coronary events in these patients, but whether this also reduces their propensity to develop HF is unknown. We sought to determine whether CABG reduces the propensity to develop HF in diabetic patients with CAD and preserved cardiac function.

Methods
We analysed the IMAGINE trial database, which tested whether treatment with quinapril could reduce cardiovascular events after CABG in 2553 stable low risk patients without left ventricular dysfunction. Cox regression analysis was used to determine whether diabetes was associated with an increased incidence of HF hospitalisations and whether HF in diabetic patients could be explained by the recurrence of coronary ischemia.

Results
Diabetes was present in 253 (10%) patients (average HBA1c 6.8 ± 1.2%). Median follow-up was 2.95 years. The incidence of major adverse coronary events or a composite endpoint of all cause cardiac and cerebrovascular events was comparable between patients with and without diabetes. Diabetes was, however, associated with a 3-fold higher incidence in acute HF (adjusted hazard ratio 3.13; 95% confidence interval 1.36-7.19; p=0.007). Interestingly, acute HF in diabetic patients was never preceded by coronary events. In fact, the recurrence of documented ischemia was lower in patients with diabetes as compared to those without diabetes (adjusted hazard ratio 0.48; 95% confidence interval 0.25-0.95; p=0.034). The incidence of HF was comparable between patients randomised to quinapril or placebo.

Conclusions
Diabetes is associated with an increased incidence of acute HF in patients with preserved cardiac function after CABG. HF developed without the recurrence of epicardial CAD, suggesting that diabetes causes HF through other mechanisms such as a specific diabetic cardiomyopathy.
Coronary revascularization in diabetic patients

Introduction

Diabetes is associated with a two-fold higher lifetime risk of heart failure (HF).\textsuperscript{1-5} Coronary artery disease (CAD) is a major contributor to HF in these patients, because diabetes increases the incidence, complexity and the propensity for recurrence of CAD.\textsuperscript{6} Accordingly, CAD is treated aggressively in diabetic patients and often involves coronary artery bypass graft surgery (CABG). While CABG prevents future coronary events,\textsuperscript{7} it is unknown whether CABG also influences the propensity to develop HF.

To test whether diabetic patients were more prone to develop heart failure after CABG, we used the IMAGINE (Ischemia Management with Accupril post bypass Graft via Inhibition of the coNverting Enzyme) trial database, which evaluated the impact of adding the angiotensin converting enzyme inhibitor (ACEi) quinapril to low risk patients with normal cardiac function after scheduled CABG. Our aim was to investigate whether CABG reduces the propensity to develop HF in patients with diabetes and preserved cardiac function. Due to the known beneficial effects of ACEi therapy in patients with established HF, one might expect that these agents would prevent new HF after CABG as well. The IMAGINE trial allowed us to test this hypothesis as well.

Methods

The design and results of the IMAGINE trial have been described in detail previously.\textsuperscript{8-10} In brief, the IMAGINE study was a double-blind, placebo-controlled, parallel-group, randomized, multicenter international trial, which tested whether early initiation of an ACEi after CABG (initiated within the hospital phase) would reduce the rate of cardiovascular events in patients at relatively low risk. Patients provided written informed consent and were included between November 1999 and September 2004. The ethics committees of all participating institutions approved the research protocol.

Patients

In total, 2553 patients were included and subsequently randomized within 7 days after CABG to the ACEi quinapril or matching placebo. Due to increasing evidence for the benefit of ACEi therapy in patients with diabetes, insulin dependent patients or diabetic patients with significant micro albuminuria were no longer eligible for the study starting November 2001.

Endpoints

We used the same primary endpoint of the IMAGINE trial, as well as an additional composite endpoint of major adverse coronary events (MACE), defined as cardiovascular death or resuscitated cardiac arrest, nonfatal myocardial infarction, coronary revascularization or unstable angina that
required hospitalization, and considered all individual endpoints separately. An episode of documented ischemia was considered valid when typical symptoms were associated with temporary ST deviations on electrocardiogram; a stress test with reversible wall motion abnormalities on echocardiography or reversible nuclear scan defects; coronary angiography demonstrating new compatible lesions. The primary endpoint included the same endpoints as MACE with the addition of documented ischemia that did not require hospitalization, acute HF that required hospitalization and stroke. All individual endpoints were recorded continuously, so each patient could be scored for multiple endpoints. All endpoints, including acute HF hospitalizations were adjudicated by an endpoint committee.

**Statistical analysis**
Data are given as means ± standard deviation when normally distributed, as median and interquartile range in case of skewed distribution and as frequencies and percentages for categorical variables. Differences in variables between groups were compared with student T-test, Mann Whitney-U test, χ2 test or Fishers exact test, where appropriate. Differences between the diabetic and the non-diabetic groups were estimated as a hazard ratio with associated adjusted two-sided 95% confidence interval from a Cox proportional hazards regression model and we investigated whether ACEi therapy prevents new HF in diabetic patients. Cumulative event rates were calculated by the Kaplan–Meier method and displayed graphically. In an exploratory analysis, we investigated the incidence and sequence of coronary events and HF in patients with diabetes. All statistical analysis was performed using SPSS, Chicago version 18.0.

**Results**

**Demographics of the study population**
Of the 2553 patients included in the IMAGINE trial, 253 (10%) had diabetes, of which 96 (38%) were treated with metformin, 104 (41%) with sulphonylurea derivatives and 64 (25%) with insulin. Demographics of the population are given in table 1. Patients with diabetes were significantly older, more often female, less often completely revascularized and had a history of hypertension and higher systolic blood pressures more often than non-diabetic patients. All other demographics were comparable between diabetic and non-diabetic patients.

**Effect of diabetes on the incidence of cardiovascular events after CABG**
The median follow-up duration was 2.95 years. Diabetes was not associated with an increased incidence of the primary IMAGINE endpoint (Hazard ratio 1.06; 95% confidence interval 0.75-1.51; p=0.75) or MACE (Hazard ratio
Table 1. Demographics of the study population according to the presence of diabetes

<table>
<thead>
<tr>
<th>Variable</th>
<th>Non-Diabetic (n=2300)</th>
<th>Diabetic (n=253)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>61 ± 10</td>
<td>62 ± 10</td>
<td>0.037</td>
</tr>
<tr>
<td>Female, n (% of patients)</td>
<td>283 (12)</td>
<td>41 (16)</td>
<td>0.035</td>
</tr>
<tr>
<td>White, n (% of patients)</td>
<td>2214 (96)</td>
<td>239 (95)</td>
<td>0.691</td>
</tr>
<tr>
<td>Quinapril group, n (% of patients)</td>
<td>1159 (50)</td>
<td>121 (48)</td>
<td>0.097</td>
</tr>
</tbody>
</table>

Medical History, n (% of patients)
- Previous MI: 897 (39) vs. 104 (41), p = 0.487
- Previous Stroke: 47 (2) vs. 7 (3), p = 0.632
- Previous CABG: 56 (2) vs. 8 (3.2), p = 0.382
- Previous PCI: 407 (18) vs. 48 (19), p = 0.535
- Hypercholesterolaemia: 110 (9) vs. 102 (11), p = 0.742
- History of hypertension: 1055 (45) vs. 146 (57), p < 0.0001
- Current smoker: 469 (20) vs. 39 (15), p = 0.084

Laboratory values, Mean ± SD
- HBA1C: 5.6 ± 1.2 vs. 6.8 ± 1.2, p = --
- Haemoglobin (mg/dL): 75 ± 42 vs. 74 ± 43, p = 0.802
- LDL cholesterol (mmol/L): 2.8 ± 1 vs. 2.9 ± 1, p = 0.094
- HDL cholesterol (mmol/L): 1.1 ± 0.4 vs. 1.1 ± 0.3, p = 0.191
- Creatinine (µmol/L): 87 ± 18 vs. 88 ± 21, p = 0.496

Hemodynamic measurements, Mean ± SD
- LVEF (%): 60 ± 9.7 vs. 59 ± 9.5, p = 0.211
- Systolic blood pressure (mmHg): 121 ± 14 vs. 124 ± 14, p = 0.002
- Diastolic blood pressure (mmHg): 70 ± 9 vs. 70 ± 9, p = 0.865

Operative characteristics
- Beating heart surgery, n (% of patients): 427 (19) vs. 49 (19), p = 0.723
- Number of distal anastomosis, Mean ± SD: 3.2 ± 1.1 vs. 3.2 ± 1.1, p = 0.719
- Triple vessel disease, n (% of patients): 1470 (64) vs. 170 (67), p = 0.136
- Complete revascularization, n (% of patients): 2044 (99) vs. 211 (88), p = 0.031

Baseline medications, n (% of patients)
- Metformin: - vs. 96 (38)
- Sulphonylurea: - vs. 104 (41)
- Insulin: - vs. 64 (25)
- Beta blocker: 1803 (78) vs. 203 (80), p = 0.057
- Calcium channel inhibitor: 828 (36) vs. 104 (41), p = 0.833
- Angiotensin receptor blocker: 58 (2.5) vs. 14 (3.5), p = 1.000
- ACE inhibitor: 454 (20) vs. 59 (23), p = 0.933
- Platelet inhibitor: 1693 (74) vs. 198 (78), p = 0.104
- Statin: 1490 (65) vs. 160 (63), p = 0.394
- Diuretic: 202 (8.8) vs. 32 (13), p = 0.092

SD, standard deviation; MI, myocardial infarction; CABG, coronary artery bypass graft surgery; PCI, percutaneous coronary intervention; LDL, low density lipoprotein; HDL, High density lipoprotein.
Figure 1 Hazard ratios for the composite endpoints and their components in diabetic compared to non-diabetic patients. MACE, Major Adverse Coronary Event; CV, Cardiovascular.

<table>
<thead>
<tr>
<th></th>
<th>Non-diabetic (n=2300)</th>
<th>Diabetic (n=253)</th>
<th>Unadjusted hazard ratio (95% Confidence Interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary composite endpoint</td>
<td>295 (13)</td>
<td>35 (13)</td>
<td></td>
</tr>
<tr>
<td>MACE</td>
<td>131 (5.7)</td>
<td>18 (7.1)</td>
<td></td>
</tr>
<tr>
<td>All cause mortality or resus. arrest</td>
<td>34 (1.5)</td>
<td>3 (1.2)</td>
<td></td>
</tr>
<tr>
<td>Acute coronary syndromes</td>
<td>100 (4.3)</td>
<td>15 (5.9)</td>
<td></td>
</tr>
<tr>
<td>Coronary revascularization</td>
<td>84 (3.7)</td>
<td>9 (3.6)</td>
<td></td>
</tr>
<tr>
<td>Heart failure hospitalization</td>
<td>20 (0.9)</td>
<td>11 (4.3)</td>
<td></td>
</tr>
<tr>
<td>Documented ischemia</td>
<td>163 (7.1)</td>
<td>9 (3.6)</td>
<td></td>
</tr>
<tr>
<td>Other CV hospitalizations</td>
<td>174 (8)</td>
<td>29 (12)</td>
<td></td>
</tr>
</tbody>
</table>

Figure 2 Survival rate free from heart failure hospitalizations HR, hazard ratio; CI, confidence interval. Adjusted for, age, gender, treatment assignment, days after CABG-surgery, baseline medications, left ventricular ejection fraction, systolic and diastolic blood pressure, creatinine, history of hypertension / percutaneous coronary interventions / myocardial infarction / previous CABG surgery / peripheral vascular disease / stroke, number of distal anastomosis, completeness of revascularization, and beating heart (off pump) surgery.
Coronary revascularization in diabetic patients

1.22; Confidence interval 0.75-2.00; p=0.43 (figure 1). Patients with diabetes displayed a markedly higher incidence of new HF as evidenced by a 3-fold higher frequency of hospitalizations for acute HF (figure 1, 2). In contrast, patients with diabetes had a lower incidence of documented ischemia (figure 1, 2). The other components of the composite endpoints were comparable between patients with or without diabetes (figure 1).

Exploration of heart failure and cardiovascular events in diabetic patients

In patients with diabetes, a hospitalization for acute HF was never preceded by a MACE or documented ischemia and only one patient with diabetes developed a MACE after the initial acute HF hospitalization. In contrast, 25% of the non-diabetic patients that developed acute HF experienced a MACE or documented ischemia during follow up. Randomization to quinapril in patients with diabetes did not affect the incidence of acute HF hospitalizations (Hazard ratio 1.11; Confidence interval 0.45-2.73; p=0.82, test for interaction p=0.778) or other components of the individual endpoints.

Discussion

In the current analysis, diabetes was associated with a markedly higher incidence of acute HF in low risk patients with a normal cardiac function during an average of 2.95 years of follow-up after scheduled CABG. Interestingly, acute HF in these patients was not preceded by evidence of acute or clinically worsening chronic myocardial ischemia, suggesting that mechanisms beyond epicardial CAD were responsible. Finally, quinapril did not influence the propensity for acute HF in these patients.

It is known that diabetes is associated with a worse prognosis, a higher incidence of CAD and an increased risk of developing ischemic HF. Additionally, it has been suggested that diabetes causes a distinct, "diabetic" cardiomyopathy, through increased oxidative stress and activation of detrimental signal transduction pathways by glycosylation. These specific processes underlying diabetic cardiomyopathy are not influenced by revascularization and will therefore continue to exert their detrimental effects on the heart. Accordingly, these pathways could cause HF to develop after adequate revascularization. Our finding that, over a mean 2.95 year follow-up period, revascularization does not prevent HF in diabetic patients with CAD supports the importance of non-ischemic mechanisms as drivers of HF in patients with CAD. However, because of the limited follow-up period, it does not exclude an eventual contribution of worsening CAD to the development of HF in some diabetic patients.

We studied patients with preserved cardiac function, and patients with diabetes had several risk factors for HF with preserved ejection fraction.
(HFpEF), including older age, female sex and a history of hypertension.\(^{18}\) Although ventricular function was not systematically evaluated when HF did develop, it is probable that in many cases HFpEF was the underlying structural abnormality, because no acute coronary event occurred and patients with diabetes had risk factors consistent with HFpEF.

Consistently with the main IMAGINE analysis,\(^9\) we did not find evidence that ACEi therapy prevented HF development in our patients with diabetes. However, our analysis was not powered for this analysis and we can therefore not exclude the possibility that ACEi therapy prevents HF in diabetic patients at low risk, particularly over a long follow-up period. Indeed, several mechanisms, including preservation of renal function, likely contribute over time to reduce the risk of the development of HF in some patients with diabetes.

Despite extensive multivariable adjustments, a retrospective analysis cannot exclude all biases, particularly considering the limited number of events. Although increase in HF in diabetics was impressive, our results may actually reflect an underestimation of the relationship between diabetes and the development of HF because patients with severe diabetes were excluded from the trial. Also, because the IMAGINE study purposely selected low risk patients, should patients with more underlying cardiac disease had been included, the results may have been different.

**Conclusions**

Diabetes is associated with an increased incidence of acute HF in patients with preserved cardiac function after CABG. HF developed without the recurrence of epicardial CAD, suggesting that diabetes can contribute to HF through other mechanisms. Over a mean of 2.95 years, quinapril did not prevent the development of acute HF in patients with diabetes.

**References**
Part 2

**AKIP1 in cardiac stress**