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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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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 $6.8 \pm 1.2\%$). 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.

Introduction

Diabetes is associated with a two-fold higher lifetime risk of heart failure (HF).[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.[6] Accordingly, CAD is treated aggressively in diabetic patients and often involves coronary artery bypass graft surgery (CABG). While CABG prevents future coronary events,[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.[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

Variable	Non-Diabetic (n=2300)	Diabetic (n=253)	p-value
Age	61 ± 10	62 ± 10	0.037
Female, n (% of patients)	283 (12)	41 (16)	0.035
White, n (% of patients)	2214(96)	239 (95)	0.691
Quinapril group, n (% of patients)	1159 (50)	121 (48)	0.097
Medical History, n (% of patients)			
Previous MI	897 (39)	104 (41)	0.487
Previous Stroke	47 (2)	7 (3)	0.632
Previous CABG	56 (2)	8(3.2)	0.382
Previous PCI	407 (18)	48 (19)	0.535
Hypercholesterolaemia	110 (9)	102 (11)	0.742
History of hypertension	1055 (45)	146 (57)	<0.0001
Current smoker	469 (20)	39 (15)	0.084
Laboratory values, Mean ± SD			
HBA1C	5.6 ± 1.2	6.8 ± 1.2	--
Haemoglobin (mg/dL)	75 ± 42	74 ± 43	0.802
LDL cholesterol (mmol/L)	2.8 ± 1	2.9 ± 1	0.094
HDL cholesterol (mmol/L)	1.1 ± 0.4	1.1 ± 0.3	0.191
Creatinine (μmol/L)	87 ± 18	88 ± 21	0.496
Hemodynamic measurements, Mean ± SD			
LVEF (%)	60 ± 9.7	59 ± 9.5	0.211
Systolic blood pressure (mmHg)	121 ± 14	124± 14	0.002
Diastolic blood pressure (mmHg)	70 ± 9	70 ± 9	0.865
Operative characteristics			
Beating heart surgery, n (% of patients)	427 (19)	49 (19)	0.723
Number of distal anastomosis, Mean ± SD	3.2 ± 1.1	3.2 ± 1.1	0.719
Triple vessel disease, n (% of patients)	1470 (64)	170 (67)	0.136
Complete revascularization, n (% of patients)	2044 (99)	211 (88)	0.031
Baseline medications , n (% of patients)			
Metformin	-	96 (38)	-
Sulphonylurea	-	104 (41)	-
Insulin	-	64 (25)	-
Beta blocker	1803 (78)	203 (80)	0.057
Calcium channel inhibitor	828 (36)	104 (41)	0.833
Angiotensin receptor blocker	58 (2.5)	14 (3.5)	1.000
ACE inhibitor	454 (20)	59 (23)	0.933
Platelet inhibitor	1693 (74)	198(78)	0.104
Statin	1490(65)	160(63)	0.394
Diuretic	202 (8.8)	32 (13)	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.
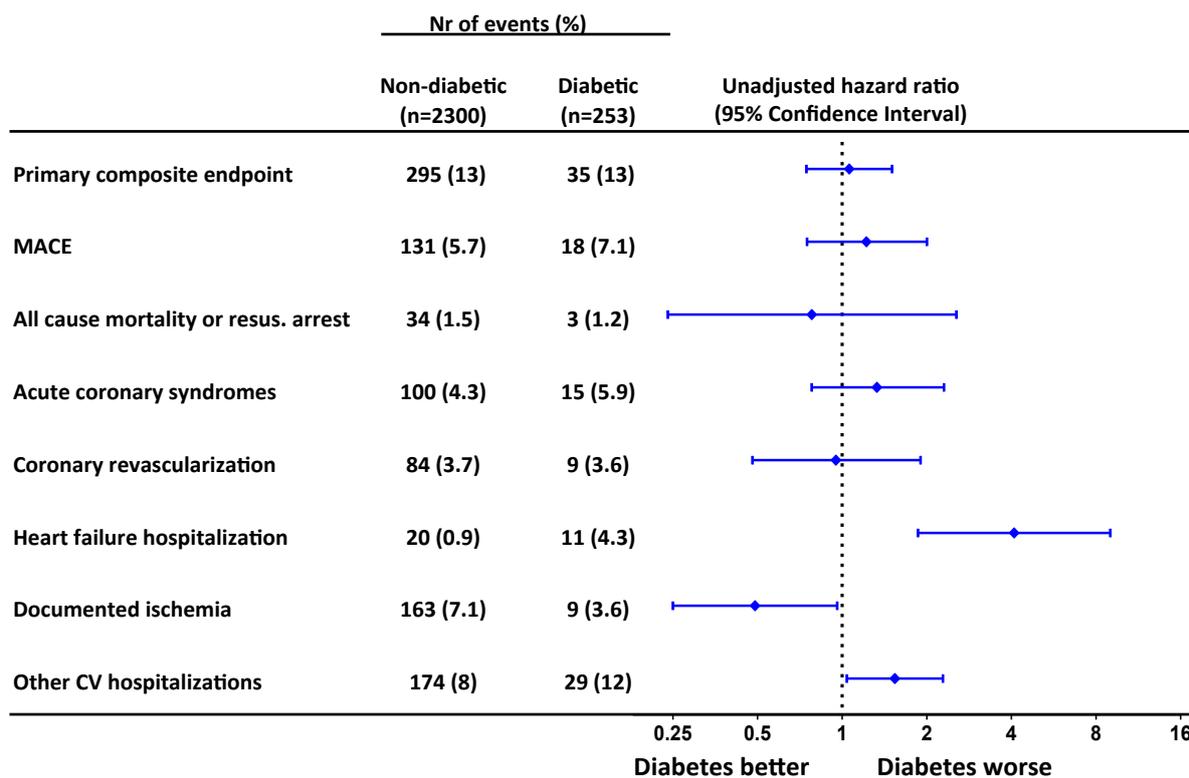
	Nr of events (%)		Unadjusted hazard ratio (95% Confidence Interval)
	Non-diabetic (n=2300)	Diabetic (n=253)	
Primary composite endpoint	295 (13)	35 (13)	
MACE	131 (5.7)	18 (7.1)	
All cause mortality or resus. arrest	34 (1.5)	3 (1.2)	
Acute coronary syndromes	100 (4.3)	15 (5.9)	
Coronary revascularization	84 (3.7)	9 (3.6)	
Heart failure hospitalization	20 (0.9)	11 (4.3)	
Documented ischemia	163 (7.1)	9 (3.6)	
Other CV hospitalizations	174 (8)	29 (12)	

0.25 0.5 1 2 4 8 16

Diabetes better   Diabetes worse

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.
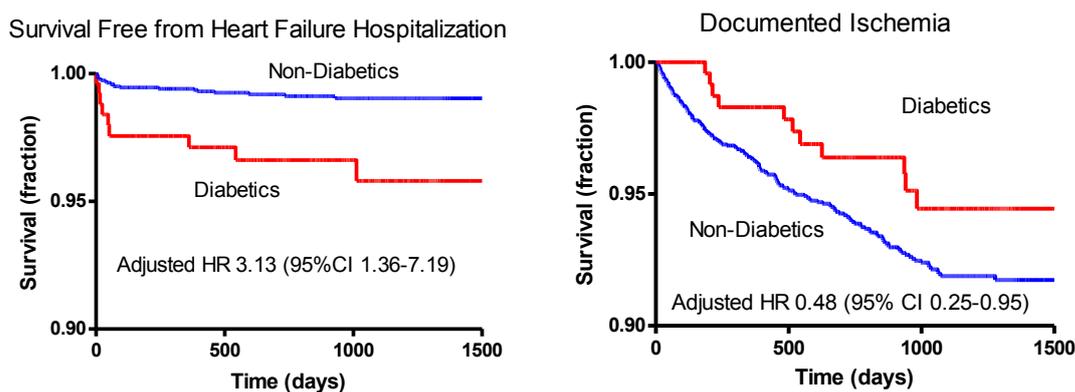
Survival Free from Heart Failure Hospitalization

Non-Diabetics

Diabetics

Adjusted HR 3.13 (95%CI 1.36-7.19)

Documented Ischemia

Diabetics

Non-Diabetics

Adjusted HR 0.48 (95% CI 0.25-0.95)

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.

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.[11-14] 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.[6,15-17] 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
1. Kannel WB, Hjortland M, Castelli WP. Role of diabetes in congestive heart failure: the Framingham study. Am J Cardiol 1974; 34: 29-34.
2. Stratton IM, Adler AI, Neil HA, Matthews DR, Manley SE, Cull CA, Hadden D, Turner RC, Holman RR. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. BMJ 2000; 321: 405-412.
3. Gottdiener JS, Arnold AM, Aurigemma GP, Polak JF, Tracy RP, Kitzman DW, Gardin JM, Rutledge JE, Boineau RC. Predictors of congestive heart failure in the elderly: the Cardiovascular Health Study. J Am Coll Cardiol 2000; 35: 1628-1637.
4. Nieminen MS, Brutsaert D, Dickstein K, Drexler H, Follath F, Harjola VP, Hochadel M, Komaida M, Lassus J, Lopez-Sendon JL, Ponikowski P, Tavazzi L, Euroheart Survey Investigators. EuroHeart Failure Survey II (EHFS II): a survey on hospitalized acute heart failure patients: description of population. Eur Heart J 2006; 27: 2725-2736.
5. Ponikowski P, Anker SD, AlHabib KF, Cowie MR, Force TL, Hu S, Jaarsma T, Krum H, Rastogi V, Rohde LE, Samal UC, Shimokawa H, Budi Siswanto B, Sliwa K, Filippatos G. Heart failure: preventing disease and death worldwide. ESC Heart Failure 2014; 1: 4-25
6. Roy B, Pawar PP, Desai RV, Fonarow GC, Mujib M, Zhang Y, Feller MA, Ovalle F, Aban IB, Love TE, Iskandrian AE, Deedwania P, Ahmed A. A propensity-matched study of the

association of diabetes mellitus with incident heart failure and mortality among community-dwelling older adults. Am J Cardiol 2011; 108: 1747-1753.

7. Habib RH, Dimitrova KR, Badour SA, Yammine MB, El-Hage-Sleiman AK, Hoffman DM, Geller CM, Schwann TA, Tranbaugh RF.CABG Versus PCI: Greater Benefit in Long-Term Outcomes With Multiple Arterial Bypass Grafting. J Am Coll Cardiol 2015; 66: 1417-27.

8. Warnica JW, Gilst WV, Baillot R, Johnstone D, Block P, Myers MG, Chocron S, Ave SD, Martineau P, Rouleau JL. Ischemia Management with Accupril post bypass Graft via Inhibition of angiotensin coNverting enzyme (IMAGINE): a multicentre randomized trial - design and rationale. Can J Cardiol 2002; 18: 1191-1200.

9. Rouleau JL, Warnica WJ, Baillot R, Block PJ, Chocron S, Johnstone D, Myers MG, Calciu CD, Dalle-Ave S, Martineau P, Mormont C, van Gilst WH. Effects of angiotensin-converting enzyme inhibition in low-risk patients early after coronary artery bypass surgery. Circulation 2008; 117: 24-31.

10. Booij HG, Damman K, Warnica JW, Rouleau JL, van Gilst WH, Westenbrink BD. β-blocker Therapy is Not Associated with Reductions in Angina or Cardiovascular Events After Coronary Artery Bypass Graft Surgery: Insights from the IMAGINE Trial. Cardiovasc Drugs Ther 2015; 29: 277-285.

11. Tancredi M, Rosengren A, Svensson AM, Kosiborod M, Pivodic A, Gudbjörnsdottir S, Wedel H, Clements M, Dahlqvist S, Lind M. Excess Mortality among Persons with Type 2 Diabetes. N Engl J Med 2015; 373: 1720-1732.

12. Cavender MA, Steg PG, Smith SC, Eagle K, Ohman EM, Goto S, et al. Impact of Diabetes on Hospitalization for Heart Failure, Cardiovascular Events, and Death: Outcomes at 4 Years from the REACH Registry. Circulation 2015; 132: 923-931

13. Cowie MR, Anker SD, Cleland JGF, Felker GM, Filippatos G, Jaarsma T, Jourdain P, Knight E, Massie B, Ponikowski P, Lopez-Sendon J. Improving care for patients with acute heart failure: before, during and after hospitalization. ESC Heart Failure 2014; 1: 110-145.

14. Kosuga T, Komukai K, Miyanaga S, Kubota T, Nakata K, Suzuki K, et al. Diabetes is a predictor of coronary artery stenosis in patients hospitalized with heart failure. Heart Vessels;doi:10.1007/s00380-015-0669-x. Published online ahead of print 31 March 2015.

15. Authors/Task Force Members, Ryden L, Grant PJ, Anker SD, Berne C, Cosentino F, et al. ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD: the Task Force on diabetes, pre-diabetes, and cardiovascular diseases of the European Society of Cardiology (ESC) and developed in collaboration with the European Association for the Study of Diabetes (EASD). Eur Heart J 2013; 34: 3035-3087.

16. Poornima IG, Parikh P, Shannon RP. Diabetic cardiomyopathy: the search for a unifying hypothesis. Circ Res 2006; 98: 596-605

17. Clark RJ, McDonough PM, Swanson E, Trost SU, Suzuki M, Fukuda M, Dillmann WH. Diabetes and the accompanying hyperglycemia impairs cardiomyocyte calcium cycling through increased nuclear O-GlcNAcylation. J Biol Chem 2003; 278: 44230-44237

18. Brouwers FP, de Boer RA, van der Harst P, Voors AA, Gansevoort RT, Bakker SJ, Hillege HL, van Veldhuisen DJ, van Gilst WH. Incidence and epidemiology of new onset heart failure with preserved vs. reduced ejection fraction in a community-based cohort: 11-year follow-up of PREVEND Eur Heart J 2013; 34: 1424-1431.

Part 2
AKIP1 in cardiac stress