Clinical research

13-year follow-up of the German angioplasty bypass surgery investigation

Jan Kaehler1*, Ralf Koester1, Wibke Billmann1, Christian Schroeder1, Hans-Jürgen Rupprecht2, Thomas Ischinger3, Roland Jahns4, Albrecht Vogt5, Martin Lampen6, Rainer Hoffmann7, Reimer Riessen8, Joachim Berger9, Thomas Meinertz1, and Christian W. Hamm10

1Department of Cardiology, University Hospital Hamburg, Martinistrasse 52, 20246 Hamburg, Germany; 2Department of Cardiology, Klinikum Rüsselsheim, Germany; 3Department of Cardiology, Klinikum Bogenhausen, Munich, Germany; 4Department of Cardiology, University Hospital Würzburg, Germany; 5Department of Cardiology, Burgfeld Hospital, Kassel, Germany; 6Department of Cardiology, German Heart Center Munich, Germany; 7Department of Cardiology, University Hospital Aachen, Germany; 8Department of Cardiology, University Hospital Tübingen, Germany; 9Institute for Medical Biometrics and Epidemiology, University Hospital Hamburg, Germany; and 10Department of Cardiology, Kerckhoff Heart Center, Bad Nauheim, Germany

Received 14 July 2004; revised 30 April 2005; accepted 2 June 2005; online publish-ahead-of-print 23 June 2005

Aims The German Angioplasty Bypass Surgery Investigation was designed to compare symptomatic efficacy and safety of percutaneous coronary balloon angioplasty (PTCA) with coronary artery bypass surgery (CABG) in patients with symptomatic multi-vessel disease. This follow-up study was performed to determine the long-term outcome of patients following these interventions.

Methods and results From 1986 to 1991, 359 patients with angina CCS class II–IV, age below 75 years, and coronary multi-vessel disease requiring revascularization of at least two major coronary vessels were recruited at eight German centres and randomized to PTCA or CABG. From 337 patients undergoing the planned procedure, 324 patients could be followed-up (96%). Baseline parameters were identical in both groups, 2.2 ± 0.6 vessels were treated in CABG patients, whereas 1.9 ± 0.5 vessels were treated in PTCA patients. Thirty-seven per cent of surgical patients received internal mammary artery grafts, while no stents were used in patients undergoing PTCA. At the end of the 13-year follow-up period, the degree of angina, the degree of dyspnea, and the utilization of nitrates were comparable in both groups. With a total number of 76 deaths, Kaplan–Meier analysis revealed a comparable distribution in both groups. Although time to first re-intervention was significantly shorter in the PTCA group, P < 0.001, frequencies of re-intervention (CABG, n = 94; PTCA, n = 136) and crossover rates (CABG to PTCA, n = 49; PTCA to CABG, n = 51) were comparable in both groups.

Conclusion The results of our 13-year follow-up suggest that in patients with symptomatic multi-vessel disease, both PTCA and CABG are associated with a comparable long-term survival and symptomatic efficacy. How far these results may be altered by developments such as drug-eluting stents or off-pump surgery remains to be determined.

KEYWORDS
Coronary artery disease; Percutaneous coronary balloon angioplasty; Coronary artery bypass surgery; Long-term follow-up; Survival; Symptomatic efficacy

Introduction
Between 1992 and 1996, the German angioplasty bypass surgery investigation (GABI) trial and eight other randomized studies comparing percutaneous coronary balloon angioplasty (PTCA) and surgical bypass grafting (CABG) in patients with angina pectoris were published.1–9 Although these trials differed in design and in the type of patients who were included, their findings were remarkably consistent. At almost any point after the initial treatment, both death rate and rate of non-fatal myocardial infarction (MI) were, by intention-to-treat, essentially the same. However, first year re-intervention rates were higher among patients initially treated by PTCA, and for this interval CABG was undoubtedly the better way of relieving angina pectoris. Follow-up studies over up to 8 years suggested that follow-up re-interventions in the CABG group increased.10–12

The GABI study was designed to compare symptomatic efficacy and safety of PTCA and CABG in patients with symptomatic multi-vessel disease. As coronary artery disease lasts lifelong, this follow-up was performed to determine the long-term outcome of patients undergoing these interventions.

Methods
The GABI study was a multi-centre, randomized trial conducted at eight centres in Germany. Patients were recruited between 1986...
and 1991, and its major findings have been published in 1994. In brief, patients under 75 years of age with symptomatic multivessel coronary disease, CCS class II–IV, and coronary artery stenosis ≥70% were eligible. Revascularization of at least two major coronary vessels had to be clinically necessary and technically feasible with both CABG and PTCA. Patients with complete occlusions, left main coronary artery stenosis ≥30%, lesions of ≥20 mm length, MI during 4 weeks prior to randomization, or previous PTCA or CABG were excluded. The primary endpoint of the study was freedom from angina pectoris (≤CCS II) 1 year after intervention. Secondary endpoints included the incidence of major cardiovascular events (death or MI), procedure related complications, and the number of further interventions. The protocol was approved by the ethics committee of the medical board in Hamburg.

Randomized patients entered the routine bypass surgery or angioplasty program at each participating centre; with both methods it was attempted to obtain a complete anatomical revascularization. MI was defined as the development of new Q-waves associated with creatine kinase of ≥2 times upper limit of the normal range. Unstable angina was defined as angina at rest during 24 h preceding intervention. CCS classification was used for grading of angina pectoris and NYHA classification was used for grading of cardiovascular function. Systolic left ventricular function at inclusion was determined by echocardiography.

For the current follow-up, patients were contacted by phone or by mail between 1 June 2002 and 31 January 2003, and interviewed regarding their cardiovascular status, risk factors, concomitant diseases, medication, and subsequent coronary interventions. In addition, patients were asked for consent to verify data and to obtain medical information from their physicians. They were also offered a clinical visit to perform a physical examination, exercise test, echocardiography, and additional exams if necessary. If a patient could not be contacted personally, relatives or local authorities were asked to supply data regarding their whereabouts. When patients had died in the meantime, both their former physicians and authorities were asked for data regarding date and cause of death. From patients presenting for clinical examination, a complete physical examination was obtained, exercise tolerance was determined by treadmill exercise test using a modified Bruce protocol, and left ventricular ejection fraction was determined as described by Simpson. A data-review committee, unaware of treatment assignment, reviewed all available information regarding deaths, MIs, and other relevant medical information before statistical analysis.

**Statistical analysis**

The intention of the GABI study was to show that CABG and PTCA are equally effective in relieving angina. Assuming that freedom from angina could be achieved in 65% of patients after CABG, and that equivalence means differences of <15%, and fixing the type I error at 5% and type II error at 20%, a sample size of 200 patients per group was calculated. As the interim analysis demonstrated that the two groups did not differ regarding the primary endpoint, enrolment was prematurely terminated.

All data of this follow-up were related to the patients undergoing the planned intervention (CABG, n = 161; PTCA, n = 176). In contrast, the description of the symptoms (Figure 1) represents a cross-sectional view of the surviving patients at the time of our 13-year follow-up, potentially biased by missing data of patients who have died. P-values, after stratifying the data for different follow-up intervals into quartiles of follow-up time, were analysed with a logit model (Figure 1A–C) or Wilcoxon–Mann–Whitney test (Figure 1D). Mortality rates and rate ratios were calculated by using the Poisson test.

For the comparison of continuous variables, t-test or Mann–Whitney test were used. Frequencies were compared with Fisher exact test or χ² test as appropriate. Survival was analysed by the Kaplan–Meier method (common closing date 1 June 2002) and log-rank test. A proportional hazard model (Cox regression) was used to estimate the hazard ratio and its 95% confidence interval crude and adjusted for covariables. The dichotome variables assessed were sex, the presence of previous MI, age below or above 65, the presence of diabetes, the disease of two or three
vessels, and a shortening fraction of ~30%. To check the assumption of proportionality of hazards for the variable \( X_1 \), we added a time-dependent covariate \( X_1W = X_1 \log(t) \) to the model. If the proportionality assumptions hold true for \( X_1 \), the regression coefficient for \( X_1W \) should be zero. There was no indication that the proportionality of hazards assumption was violated, the smallest \( P \)-value was 0.54.

Because no a priori hypothesis was specified, the follow-up analysis should be regarded as an exploratory data analysis and the \( P \)-values are descriptive measures. Therefore, no correction of type I error was done. All calculations were carried out by using SPSS version 10.0.8a. Data are presented as mean \( \pm \) SEM.

Results

A total of 8981 patients with multi-vessel coronary disease were screened and 359 patients randomized, 177 to bypass surgery and 182 to angioplasty. With an average interval from randomization to procedure of 53 days, 12 patients assigned to CABG withdrew their consent and four died. In the PTCA group, average interval to procedure was 19 days; five patients of this group withdrew their consent, whereas one died. Therefore, 337 patients finally underwent the planned procedure and were the basis for this study, 161 in the CABG group and 176 in the PTCA group. In-hospital mortality rates were 3 and 1%, respectively. The first year follow-up of these patients revealed a significant reduction of angina in both groups; freedom from angina (CCS <II) was achieved in 74% of patients of the CABG group and in 71% of the PTCA group, \( P = 0.86 \). However, patients in the PTCA group more frequently used anti-anginal medication, 88 vs. 78%, \( P = 0.041 \). Although mortality was comparable in both groups, patients treated by PTCA were more likely to require further interventions, 44 vs. 18%, \( P < 0.001 \).

From the 337 patients undergoing the planned procedure, 324 patients could be followed-up for this study, 160 of the CABG group and 164 of the PTCA group, translating into a follow-up rate of 96% (Figure 2). Population data are depicted in Table 1. In patients undergoing CABG, \( 2.2 \pm 0.6 \) vessels were treated, whereas in patients undergoing PTCA, \( 1.9 \pm 0.5 \) vessels were treated. Thirty-seven per cent of patients undergoing CABG received internal mammary artery grafts, though stents were not yet available for patients undergoing PTCA. Although in CABG patients more left anterior descending arteries were treated, \( P = 0.04 \), left circumflex artery and right coronary arteries were treated in a comparable number in both groups (Table 1).

During follow-up, the current health status could be documented in 244 survivors; an ECG was obtained from 210 patients, an exercise test from 145 patients, and an echocardiography from 144 patients. From all 76 patients who had died in the meantime, the date of death could be determined, whereas the cause of death could be determined in 70 patients revealing no differences between groups (Table 2). Median follow-up interval from procedure to follow-up was 13.0 years; interquartile range was 12.3–15.1 years.

**Figure 2** Flow chart of the GABI study. From 337 patients who underwent the planned procedure, 324 could be followed-up for this study.
With a total number of 76 deaths, Kaplan–Meier analysis revealed a comparable mortality distribution in both groups, $P = 0.55$ (Figure 3).

Overall hazard ratio for mortality PTCA vs. CABG was 1.15 with the 95% confidence interval ranging from 0.69 to 1.70. Hazard ratios for mortality following PTCA or CABG were not different with regard to sex, the presence of previous MI, age around 65, the presence of diabetes, the presence of two- or three-vessel disease, and shortening fractions $\sim 30\%$ (data not shown).

At the time of our 13-year follow-up, both the degree of angina, functional capacity and anti-anginal medication were similar in both groups (Figure 1A–C). In addition, exercise tolerance as determined by treadmill test, as well as systolic LV-function were comparable in both groups, as determined in a subgroup with otherwise representative baseline parameters of patients recruited and followed-up in Hamburg, $n = 69$ and $n = 71$, respectively (Figure 1D). The medication at this point, apart from the use of nitrates, was comparable in both groups (data not shown).

Due to many re-interventions in the PTCA group in the first year, time to first re-intervention was significantly shorter in this group, $P < 0.001$ (Figure 4).

Although the total number of re-interventions was higher in the PTCA group, $n = 136$, than in the CABG group, $n = 94$ (Figure 5), the number of crossovers was comparable, CABG to PTCA = 49 and PTCA to CABG = 51 (data not shown).

### Discussion

Our data suggest that patients with multi-vessel disease, who could undergo either CABG or PTCA, are at relatively low risk for death or MI over the subsequent 13 years. Neither CABG nor PTCA was associated with a major prognostic advantage in our follow-up. However, until further studies, this is limited to patients like those in the GABI study with predominantly two-vessel disease and few concomitant diseases.

Although previous studies have shown similar survival rates for patients with symptomatic multi-vessel disease treated with CABG or PTCA during short- and medium-term intervals,
up to 8 years in the EAST trial,11 our study extends this experience to 13 years. The design of the study and a follow-up rate of 96% ascertain accuracy, and the balance between the groups was retained.

Although it is conceivable, that in this unblinded trial, the decision for re-intervention in the first year could have been biased by awareness of the randomized intervention, after the formal termination of the study, this should not have been relevant to the treatment anymore. Therefore, our study adds valuable information to previous studies comparing CABG with PTCA.17–19

In the BARI trial, survival of patients with treated diabetes mellitus over 5 years was better among those assigned CABG. This benefit was due to lower cardiac mortality in the CABG group, but was confined to patients with diabetes who received at least one internal mammary graft.20 In our study, a comparable trend could be observed as well but was far from statistical significance. In the case, that this trend reflects a true difference, the lack of significance could potentially be attributed to the lower number of CABG patients in the GABI trial receiving arterial grafts (37%), or to the smaller number of patients.

Accordingly, although left ventricular ejection fraction is a recognized determinant of survival in patients with coronary heart disease21 and a covariable of benefit from CABG, we could not document significant differences between the two treatment strategies in this regard.22

Together with larger medium-term studies such as the follow-up of the EAST trial,11 the follow-up of the BARI trial,23 or the Toulouse trial,24 our study demonstrates that the long-term outcome of this kind of patients is comparable with both treatment strategies. According to our data, the selection of a revascularization strategy may therefore be determined by patient and physician preference.25 Although many patients may opt for PTCA, others may prefer the one-stage strategy of CABG.

Limitations
The study initially intended to compare clinical efficacy of both PTCA and CABG within 1 year, but was not powered to detect a difference in survival. Thus, although the mortality analysis of our 13-year follow-up includes 76 deaths, it has only limited power to detect smaller differences in mortality between the two revascularization strategies. However, due to the long follow-up interval, major differences in mortality between the two treatment groups can be ruled out, though the subset analyses should be viewed with caution, as the number of patients in these groups is small.

A potential bias could have been introduced by the fact that more patients of the surgical group died on the waiting list or withdrew their consent and therefore did not have the planned procedure, however, the latter was not for medical reasons and therefore the introduction of a major bias appears unlikely.

Pharmacological aspects have to be taken into account as well. The GABI trial was established before the use of statins became widespread, and the treatment with these drugs could affect long-term outcome differently in patients undergoing CABG or PTCA.26,27 Further, the use of glycoprotein IIb/IIIa receptor antagonists might improve the short-term outcome of patients undergoing PTCA,28,29 but the long-term effects of these drugs are not known. Additionally, off-pump coronary surgery, advances in peri-operative management, and extracorporeal perfusion technology have improved the risk/benefit ratio of CABG in the meantime.

Conclusions
In conclusion, the results of our 13-year follow-up suggest that in patients with symptomatic multi-vessel disease, both PTCA and CABG are associated with a comparable long-term survival and symptomatic efficacy. How far these long-term results may be altered by improved interventional and surgical techniques remains to be determined.

Acknowledgements
The GABI follow-up was sponsored by Jomed, Rangendingen, Germany. However, only the enthusiasm and perseverance of A. Cortes, S. Schneickert, and D. Cunningham made the study possible. The authors also would like to acknowledge the contributions of S. Rossmann and W. Schoebel.
References