Venous coronary artery bypass surgery: a more than 20-year follow-up study

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Aims Atherosclerosis in venous coronary artery bypass grafts begins early and accelerates from the fifth post-operative year. We studied the influence of 18 variables existing at the time of operation, and of 'classical' risk factors present at 1 and 5 years after operation on the long-term outcome of this type of surgery.

Methods and results Four hundred twenty-eight consecutive patients who underwent isolated venous coronary bypass surgery between April 1, 1976 and April 1, 1977 were followed prospectively. Follow-up was 99.3% complete with a mean duration of 22.8 years for the survivors. Multivariate analysis was performed using the Cox regression model. Actuarial survival after 5, 10, 15 and 20 years is 95, 83, 63 and 47%, respectively. The cumulative probability of event-free survival for cardiac death, acute myocardial infarction and re-intervention at 5, 10, 15 and 20 years, respectively, are 98, 90, 74, 60%; 99, 91, 83, 77%; and 97, 86, 67, 57%. Age and left ventricular function are continuous incremental risk factors for mortality. Left ventricular function and completeness of revascularization, and age and vessel disease are independent predictors of cardiac death and re-intervention, respectively. Hypertension, diabetes mellitus, hypertriglyceridemia, obesity and smoking, present after operation have an independent influence on the occurrence of cardiac events.

Conclusions Risk factors (still) existing 1 and 5 years after operation have a negative influence on the long-term results. This emphasizes the need of treatment of these 'classical' risk factors still present after operation.

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KEYWORDS
Bypass; Follow-up studies; Risk factors

Introduction
Surgical myocardial revascularization is a well-accepted treatment in patients with severe angina pectoris unresponsive to maximal medical treatment. It also prolongs survival in certain subsets of patients with coronary atherosclerosis.1 At the start of coronary artery surgery, in the 1960s, only venous conduits were used. However, the patency of these grafts diminish over time.2–4 Because in the first 5 years after operation the patency of internal mammary artery (IMA) grafts is higher and the attrition rate of these grafts after these years is lower than in venous grafts, exclusive arterial revascularization is preferred.3 However, it
has not been proven beyond doubt that the excellent long-term results of the left IMA graft may be extrapolated to all other arterial conduits.5,6 Even today saphenous vein grafts continue to be used in combination with arterial conduits. As vein grafts are considered 'the weak link' in the long-term follow-up, it remains very important to recognize the pre-operative risk factors as well as the risk factors present after surgery. Treatment of these factors may further improve the long-term outcome of our operated patients. For this reason we once again up-dated the long-term results of a single cohort of consecutive patients who underwent coronary surgery in 1976–1977 and who we have now followed prospectively for more than 20 years.

Methods

Patients

The clinical and angiographic definitions as well as the surgical technique have been described in detail before.7,8 In brief between April 1, 1976 and April 1, 1977, 428 consecutive patients, 383 men and 45 women, with an average age of 52.6 years (range, 20–74 years), underwent isolated venous aortocoronary bypass surgery in our hospital. In 61% of the study-population the severity of pre-operative angina was class III–IV CCS. At coronary angiography three-vessel disease was demonstrated in 48% of the patients, and in 12% significant left main coronary artery disease was present. In 21% of our patients left ventricular function was moderately or severely diminished. Unstable angina pectoris was the indication for surgery in 27% of the patients. A total of 650 single grafts and 328 sequential grafts with two or more distal anastomoses (mean 3.2 distal anastomoses/patient) were placed. A left ventricular aneurysm resection was performed in 25 patients. Complete revascularization was achieved in 78% of the study-group.

Follow-up and data collection

Several follow-up methods were used simultaneously to provide the most complete information possible. All patients were followed using the anniversary method at our outpatient clinic and/or the outpatient clinic of the referring cardiologist. The common closing date was the final quarter of 2001. Exact information about the clinical events studied was obtained in all patients. Follow-up was 99.3% complete. The mean duration of follow-up for the survivors was 22.8 years.

For all patients, the presence of 18 variables was determined at operation. One and 5 years after operation the presence of 'classical' risk factors were ascertained in the patients who were then still alive.

Statistical analysis

The following clinical events were studied: overall mortality, cardiac mortality, acute myocardial infarction and re-intervention. Patients not surviving the operation were excluded from analysis. Likewise, peri-operative myocardial infarction was excluded from statistical analysis of myocardial infarction during follow-up.

To determine the influence of the variables at and after surgery on the long-term results after venous coronary artery bypass surgery we produced three statistical models. The model starting at surgery expresses differences in event rates between times of surgery until the end of follow-up. In the models starting at 1 and 5 years, respectively, after surgery, clinical events which occurred within 1 and 5 years, respectively, after surgery were excluded from analysis and differences in event rates were calculated from 1 and 5 years, respectively, until the end of follow-up. In these models, the data on classical risk factors achieved 1 and 5 years after surgery were used. The other risk factors were assessed at surgery exclusively.

Differences in event rates between the subgroups of variables were estimated in actuarial survival curves following the method described by Kaplan and Meier.9 The log–rank and Wilcoxon tests were used for univariately comparing survival probabilities. Variables with a p value <0.10 were entered in a multivariate 'proportional hazards'
model proposed by Cox. Age was always entered in the multivariate model as a continuous variable. For each variable, the assumption of proportional hazards was checked by estimating plots of the logarithm of the cumulative hazard. The risk of having an event in one sub-group compared to another sub-group is reflected by the hazard ratio.

Fig. 2 Incremental risk factors for death (CASS-WMS, Coronary Artery Surgery Study- Wall Motion Score).
Results

During or within 2 weeks after operation, 13 patients died (peri-operative mortality: 3%). Another five patients died in the first year and 19 patients between 1 and 5 years after operation. So, the variables of 415, 410 and 391 patients were studied in the three different statistical models (Appendix A).

Survival

Actuarial survival after 5, 10, 15 and 20 years was 94.5±1.12, 82.9±1.85, 63.3±2.37 and 47.0±2.46% (mean±SD), respectively. Actuarial survival of the healthy Dutch population matched for age and gender in the corresponding time period was 95.2, 88.4, 79.1 and 67.1% (Fig. 1). In the first 7 years after operation the survival in our patient-population is comparable to the survival for the normal Dutch population, matched for age and gender. After these years the mortality in our patient-population exceeds the mortality of the matched Dutch population. The overall mortality rate is fairly constant in the first 7 years after operation, with a mean of 1.1% yearly. Thereafter mortality increases, especially after the first decade of the operation, to a yearly mean of 3.5%.

Age and left ventricular dysfunction are continuous incremental risk factors for survival. Incomplete revascularization has an influence on overall mortality but loses this in the years after operation. The number of distal anastomoses, as expression of the severity of coronary atherosclerosis, influences overall mortality after the operation. Hypertension and diabetes mellitus present after operation are independent predictors of survival (Fig. 2).

Cardiac survival

Cardiac survival after 5, 10, 15 and 20 years was 97.5±0.77, 89.5±1.52, 74.3±2.26 and 59.9±2.60%, respectively (Fig. 3). In the first 7 years after operation the mean mortality is 0.5% per year. Thereafter it increases to a yearly mean of 2.8%.

The left ventricular function and the completeness of revascularization are continuous incremental risk factors for cardiac mortality. Three-vessel-disease loses its influence on cardiac mortality 5 years after operation. Hypertension and diabetes mellitus are late independent determinants of cardiac survival (Fig. 4).

Acute myocardial infarction

The actuarial freedom from acute myocardial infarction after 5, 10, 15 and 20 years were 98.7±0.56, 90.8±1.48, 82.6±2.02 and 77.1±2.37%, respectively (Fig. 5). The peri-operative myocardial infarction rate was 6%. In the first 3 years after operation none of the patients suffered a myocardial infarction. In the following 2 years 1.3% patients were hospitalised due to a myocardial infarction. After the first 5 years of operation the mean attrition rate for infarction is 1.5% yearly.

There are no continuous incremental risk factors for acute myocardial infarction. Patients with sequential grafts only have an increased risk for suffering a myocardial infarction. Five years after operation this 'risk factor' loses its influence. The same holds true for patients with hypertriglyceridemia. Obesity is an incremental risk factor only in the first years after operation. Patients (still or again) smoking shortly after operation have an increased risk for suffering a myocardial infarction (Fig. 6).

Re-intervention

The actuarial freedom from re-operation 5, 10, 15 and 20 years after operation was 96.5±0.91, 85.5±1.83, 66.7±2.69 and 57.2±3.09%, respectively (Fig. 7). In the first 6 years after operation the need for re-intervention is low with a mean of 0.6% per year. Thereafter this rises to a mean of 2.8% per year.

Age and vessel diseases are continuous incremental risk factors of need for a re-intervention after the initial operation. Left ventricular dysfunction has a late (negative) influence (Fig. 8).

Discussion

Aim of the study

Within the first month after coronary bypass surgery venous grafts may occlude due to
thrombosis and/or technical failure. Between 1 month and 1 year after operation, intima hyperplasia takes place in the still open graft. Thereafter, the development of atherosclerosis in the vein grafts starts which accelerates after the fifth post-operative year.11
Approximately 15% of saphenous vein grafts are occluded within 1 year. In the following 4 years the attrition rate is low (1–2% per year), but thereafter graft closure is 2.5 times more frequent.\textsuperscript{2–4,11,12} So, atherosclerosis has an influence on venous graft function, beginning in the first year and augmenting from the fifth year after operation. This was the specific reason and in fact the aim of the study was to see if the classical risk factors existing at 1 and 5 years after the operation did influence the long-term results after venous coronary bypass surgery. For this purpose the models described in statistical analysis were created.

Survival

The peri-operative mortality and myocardial infarction rate in our patient-group was corresponding for those found in other studies of patients who underwent venous coronary surgery in the same time-period.\textsuperscript{13}

Survival of our study-population did correspond favourably with heterogeneous groups of patients reported in the literature.\textsuperscript{1,14} In this study in the first 7 years after the operation we observe a survival of our patients comparable with that of the normal Dutch population, matched for age and gender. After these first 7 years the mortality in our patients starts to exceed the mortality of the Dutch population. This increasing difference in the following post-operative years is primarily caused by a rise in cardiac mortality. Also, the need for re-intervention does increase distinctly in the seventh post-operative year. This increase in event rates beginning approximately 7 years after operation has also been found in other studies.\textsuperscript{4,11,14} However, it is almost impossible to compare our results with other studies. There are no other prospective long-term follow-up studies with multivariate analysis on a consecutive group of patients who underwent coronary artery surgery with venous grafts only during 1 year in the mid 1970s. In the ACC/AHA guidelines for coronary artery bypass graft surgery (committee to revise the 1991 guidelines for coronary artery bypass graft surgery) it is mentioned that the equations for predicting patient-specific outcomes presented in the former guidelines remain appropriate for use. Amongst others we refer, for the results of our multivariate analysis, to these guidelines.

In this study age and, even more prominent, left ventricular function are incremental risk factors for overall mortality. A distinctly higher risk is found in a severely diminished as compared with a mildly diminished left ventricular function. In the ACC/AHA guidelines for the multivariate risk factor equation for death after the coronary bypass operation is referred to the data from the K.U. Leuven Coronary Surgery Program. Ejection fraction as manifestation of ventricular function is an incremental risk factor in the constant and late hazard phase. In the first analysis age was only a factor in the late phase of follow-up, but a more recent analysis in a bigger patient population revealed younger as well as older age being a risk factor in the constant and late phase.\textsuperscript{15}

As in other studies incomplete coronary revascularization is an independent risk factor for overall mortality, but in our study this factor loses its influence shortly after operation. The number of distal anastomoses is a risk factor, but remarkably, not in the first year after operation.

It has been stated in the guidelines that the predictors of late overall and late cardiac death are identical. In our study this only holds true for left ventricular function and to a lesser extent for older age. We found incomplete coronary revascularization to be a continuous risk factor for cardiac death only. It is unclear why three-vessel disease remains a risk factor for cardiac death. After all, coronary artery bypass grafting neutralizes the incremental risk for premature death from multivessel disease including left main disease.\textsuperscript{16}

Other cardiac events

In this study there is no continuous incremental risk factor for suffering a myocardial infarction. It is remarkable that none of the incremental risk factors for mortality is a risk factor for myocardial infarction. It is known from other multivariate analyses that hypertriglyceridemia is a risk factor
for myocardial infarction, but only in the late hazard phase. In the earlier mentioned studies, sequential grafting was not recognized as an independent predictor of myocardial ischemia after the initial operation.

In other studies incremental risk factors for the need for re-intervention after operation are not mentioned. In our study age is probably a "physician-related" incremental risk factor for re-intervention, i.e. the physician probably decides not to consider re-operation in the very old patients. Presumably this also counts for left ventricular function. Anyway the statement in the guidelines that patients with ischemic left ventricular dysfunction benefit from the operation seems not to hold true in the case of a re-intervention. Notwithstanding the extent of completeness of revascularization, two and three-vessel disease remains an independent risk factor for recurrent myocardial ischemia, which is probably a manifestation of progression of atherosclerosis.

Fig. 6 Incremental risk factors for acute myocardial infarction.
Classical risk factors

Only one 'classical' risk factor present at operation, hypertriglyceridemia, has an independent influence on the long-term result after venous coronary artery surgery. Other classical risk factors present 1 and/or 5 year after the initial operation have an independent influence on the long-term result after coronary surgery with venous grafts. Hypertension and diabetes mellitus present 1 or 5 years after operation are incremental risk factors for overall and cardiac mortality. Hypertriglyceridemia, present 1 year after operation is an independent predictor of the occurrence of myocardial infarction or the need for re-intervention after the initial operation. Obesity and smoking are independent predictors of re-intervention. Together these findings once again underline the importance of the so-called insulin resistance syndrome.

In the Post Coronary Artery Bypass Graft Trial 12 independent prognostic factors for atherosclerosis progression, present at operation, were found: among other high triglyceride level, low high-density lipoprotein-cholesterol, high low-density lipoprotein-cholesterol, high mean arterial pressure, low-ejection fraction, male gender and current smoking. The same investigators did demonstrate that aggressive lowering of low-density lipoprotein (LDL) cholesterol levels reduced the progression in saphenous-vein coronary-artery bypass grafts. They also found a 30% reduction in revascularization procedures and 24% reduction in composite clinical end point (death, myocardial infarction, stroke, bypass surgery, or angioplasty) in patients assigned to aggressive LDL cholesterol level lowering therapy. Of course these results may not be extrapolated to have a similar effect on the treatment of classical risk factors present after operation. Although we did show a beneficiary effect of cessation of smoking after the operation.

Angiography

In the first years after the start of coronary artery surgery, many angiographic studies were performed to objectify the result of surgery as well as to study progression of atherosclerosis in the grafts and in the native coronary circulation. If only new lesions were taken into account atherosclerosis in vein grafts may develop at an accelerated rate as compared with native coronary arteries. On the other hand no big differences were found in the rate of progression of atherosclerosis in vein grafts compared to all native coronary arteries. There is no difference in progression of atherosclerosis between coronary arteries distal to graft insertion and non-grafted arteries. Recent studies have shown that in patients with unstable angina, non Q-wave or Q-wave myocardial infarction after bypass surgery, the culprit lesion in the majority of cases (70–85%) is an atherosclerotic vein graft stenosis. Therefore late vein-graft atherosclerosis and occlusion is called the 'Achilles heel' of venous coronary surgery.

Limitations

Of course the number of patients included limits this study. It also concerns only a single centre experience. Because of the fact that the study was started (prospectively!) as early as in 1976, many of the presently known risk factors were then neither recognized nor treated.

Conclusions

It may be supposed that classical risk factors present at and still present after operation have a great influence on the development and progression of atherosclerosis in venous grafts. Based on our findings, we are convinced that treatment of these factors may improve the long-term results in patients with coronary atherosclerosis in whom one or more venous grafts were implanted during coronary artery bypass surgery.

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Appendix A

Variables at baseline, 1 and 5 years after surgery in 415, 410, and 391 patients, respectively (%).

**Male gender**: 90, 90, and 89. **Age (>50 year)**: 66, 65, and 65. **Myocardial infarction**: 48, 47, and 47. **Heart failure**: 2, 2, and 2. **Preoperative angina pectoris** (Canadian Cardiovascular Society)—Class I: 2, 2, and 2; Class II: 37, 37, and 38; Class III: 37, 37, and 36; and Class IV: 23, 24, and 24. **Number of vessels diseased**—one-vessel: 16, 16, and 16; two-vessel: 36, 37, and 37; three-vessel: 48, 47, and 47. **Left ventricular function**—CASS-WMS > 10 vs. ≤ 8: 64, 65, and 66; CASS-WMS > 5 vs. ≤ 5: 935.

Fig. 8 Incremental risk factors for re-intervention (CASS-WMS=Coronary Artery Surgery Study-Wall Motion Score).

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**0 - 20 year**
- **Older age**: P = 0.0004
- **Two-vessel disease**: P = 0.0169
- **Three-vessel disease**: P = 0.0328

**1 - 20 year**
- **Older age**: P = 0.0008
- **Two-vessel disease**: P = 0.0224
- **Three-vessel disease**: P = 0.0459
- **Hypertriglyceridemia**: P = 0.0285

**5 - 20 year**
- **Older age**: P = 0.0004
- **Two-vessel disease**: P = 0.0036
- **Three-vessel disease**: P = 0.0098
- **Left Ventricular Function CASS-WMS > 10 vs. ≤ 8**: P = 0.0123

References