Risk factors, endothelial function, and clinical outcome after coronary bypass surgery

Voors, Adriaan Alexander

PART 2: EXPERIMENTAL FINDINGS

Chapter 6

Usefulness of Hypertriglyceridemia in Predicting Myocardial Infarction Late after Coronary Artery Bypass Operation

Adriaan A. Voors[1], Ben L. van Brussel[2], Johannes C. Kelder[1], H.W.Thijs Plokker[1].

1. Dept. of Cardiology, St. Antonius Hospital, Nieuwegein, the Netherlands
2. Dept. of Cardiology, Diaconessenhuis, Eindhoven, the Netherlands.

American Journal of Cardiology 1997 (in press)
Circulation 1993;88-4[suppl.2]:I-259 (abstract)

Abstract

We prospectively followed 446 consecutive patients who had coronary bypass operations 15 years earlier. Serum levels of cholesterol and triglycerides were measured pre-operatively and 5 years after bypass, and we established the relation between these lipid levels and the incidence of myocardial infarction (MI) and cardiac mortality during 15 years follow-up. Follow-up was complete in 99.8% of the patients and averaged 15.4 years for the survivors. Multivariate Cox proportional hazard analysis revealed that patients with pre-operative hypertriglyceridemia (≥ 2.0 mmol/l / 176 mg/dl) had a 2.1 times increased risk for MI during follow-up (p = 0.04). Hypertriglyceridemic patients at 5 years after surgery had a 2.2 times increased risk for MI during the subsequent follow-up period, although this difference was not statistically significant (p = 0.09). The only significant risk factor for MI at 5 years after surgery was smoking. Hypercholesterolemia (≥ 6.5 mmol/l / 254 mg/dl) both pre-operatively and at 5 years after surgery was not a risk factor for MI during follow-up. Cardiac mortality was not significantly related to either hypercholesterolemia or hypertriglyceridemia. Independent predictors for cardiac mortality were poor left ventricular function, diabetes mellitus, incomplete revascularization and the use of sequential bypass grafts. These data provide evidence that hypertriglyceridemia, both pre-operatively and at 5 years after surgery, have predictive value for the incidence of MI during long-term follow-up after venous coronary bypass surgery.

Introduction

Progression of atherosclerosis in aortocoronary saphenous vein grafts was significantly higher in patients with higher cholesterol and triglyceride levels[1-4]. Higher pre-operative cholesterol and triglyceride levels have been associated with increased mortality[5,6], return of angina pectoris[7], re-operation[8,9], and a combination of cardiac events[10,11] after coronary bypass surgery. Few studies assessed the influence of pre-operative cholesterol and triglyceride levels on the incidence of myocardial infarction (MI) and cardiovascular mortality during longterm follow-up after coronary bypass surgery, and few data are available about the influence of *post*-operative lipid levels. We aimed to establish the relation between these lipid levels and the incidence of MI during 15 years follow-up after coronary bypass.

Methods

Patients: A consecutive series of 446 patients underwent isolated aortocoronary saphenous-vein bypass surgery with or without resection of a left ventricular aneurysm at the St.Antonius Hospital, formerly in Utrecht and now in Nieuwegein, the Netherlands, between April 1, 1976 and April 1, 1977. Eighteen patients in whom the operation was combined with a valve replacement were excluded from the analysis. Since we aimed to

describe the longterm effects on mortality after coronary bypass surgery, we excluded thirteen patients who died within 30 days after the procedure. The study-group of the 415 remaining patients consisted of 372 men and 43 women with a mean age of 52.5 years (range 20-73). Characteristics of the patient population are presented in table 1.

Table 1. Clinical characteristics at baseline and at 5 years after surgery.

	Baseline (n=415)	5 years after surgery (n=391)
Age (years)		
≤ 50	147 (35%)	141 (36%)
> 50	268 (65%)	250 (64%)
Female gender	43 (10%)	42 (11%)
Hypercholesterolemia*		
≤ 6.5 mmol/l (254 mg/dl)	79 (19%)	131 (34%)
> 6.5 mmol/l (254 mg/dl)	269 (65%)	203 (52%)
unknown	67 (16%)	57 (15%)
Hypertriglyceridemia*		
≤ 2.0 mmol/l (176 mg/dl)	243 (59%)	72 (18%)
> 2.0 mmol/l (176 mg/dl)	96 (23%)	56 (14%)
unknown	76 (18%)	263 (67%)
Previous myocardial infarction	199 (48%)	185 (47%)
Diabetes Mellitus*	8 (2%)	17 (4%)
Obesity*		
body mass index > 25	86 (21%)	170 (44%)
Systemic Hypertension*	122 (29%)	205 (52%)
Cigarette Smoking*	169 (41%)	120 (29%)
Family history of coronary artery disease	31 (8%)	30 (8%)
Angina pectoris		
I	9 (2%)	9 (2%)
II	154 (37%)	142 (36%)
III	155 (37%)	147 (38%)
IV	97 (23%)	93 (24%)
Number of coronary arteries narrowed >50%		
1	66 (16%)	64 (16%)
2	151 (36%)	143 (37%)
3	198 (48%)	184 (47%)
Left ventricular function		
CASS score: 5-7	267 (64%)	257 (66%)
CASS score: 8-10	81 (20%)	77 (20%)
CASS score: >10	67 (16%)	57 (15%)

CCS = Canadian Cardiovascular Society; CASS = coronary artery surgery study. * These variables were determined at surgery and 5 years after surgery.

Follow-up and data collection: Several follow-up methods were used simultaneously in order to receive as complete information as possible. All patients were followed using

the anniversary method at our outpatient clinic and/or the outpatient clinic of the referring cardiologists. All patients except one, who went abroad and was lost to follow-up 7 years after surgery, were traced at the common closing date of April 1, 1992.

Definitions: *Hypertriglyceridemia* was defined as a fasting serum triglyceride level of > 2.0 mmol/l (176 mg/dl) and *hypercholesterolemia* was defined as a fasting serum cholesterol level of > 6.5 mmol/l (254 mg/dl). A *myocardial infarction* was diagnosed in case of a) large Q waves associated with changes in the S-T segments and T-waves in specific and appropriate leads that indicate the location of the infarct *or* b) specific enzyme alterations in combination with localized serial T waves changes. *Obesity* was defined as a body mass index (weight/height^2) $\geq$ 25. *Left ventricular function* was classified according to the left ventricular wall motion score, as described in the Coronary Artery Surgery Study (CASS) registry[12]. An *impaired left ventricular function* was defined as a CASS-score of > 10.

Laboratory assays: Total serum cholesterol and serum triglyceride levels were measured using samples drawn after an overnight fast before surgery and at 5 years after surgery according to standard laboratory procedure.

Statistical Analysis: To establish the influence of cholesterol and triglyceride levels pre-operatively and at 5 years after surgery on the risk of MI after venous bypass surgery, we produced two prognostic models. In the first model triglycerides and cholesterol were measured before surgery and patients were followed up from surgery to 15 years after surgery. In the second model, triglycerides and cholesterol were measured at 5 years after surgery and patients were followed up from 5 to 15 years after surgery. To identify other factors which were related to cardiac mortality and MI, univariate logrank and Wilcoxon survival analysis was performed on Kaplan-Meier survival curves, from the variables described in table 1. All variables with a significance level of $p < 0.1$ in at least one of these univariate tests, were introduced in a multivariate model proposed by Cox[13]. Age and gender were always included. The assumption of proportional hazards was checked for each predictor variable by estimating the plots of the logarithm of the cumulative hazard. Before surgery and at 5 years after surgery, in some patients, we were not able to establish serum lipid levels. Therefore, we adjusted for the possible selection bias of measuring plasma lipids by analyzing the unknown values as a separate group in the multivariate model. Beside this, we also compared clinical characteristics of patients with known levels and unknown levels. Univariate analysis, and therefore selection of variables for the multivariate model, was performed only on patients with known lipid levels. Correlations were performed using the Pearson or Spearman correlation where appropriate. A p-value of less than 0.05 was considered as statistically significant.

Table 2. Multivariate hazard ratios (95% confidence limits) for cardiac mortality and myocardial infarction of serum cholesterol and triglyceride levels, and other statistically significant predictors for either cardiac mortality or myocardial infarction.

	from surgery to 15 years after surgery				from 5 to 15 years after surgery			
	cardiac mortality		myocardial infarction		cardiac mortality		myocardial infarction	
	HR (95% C.I.)	p	HR (95% C.I.)	p	HR (95% C.I.)	p	HR (95% C.I.)	p
Triglycerides (≥2.0mmol/l/176 mg/dl)	1.18(0.73 - 1.92)	0.49	2.07 (1.03-3.34)	0.04	1.54 (0.75-3.19)	0.24	2.20 (0.87-5.56)	0.09
Cholesterol (≥6.5mmol/l/254 mg/dl)	0.99(0.57-1.74)	0.98	0.74 (0.78-1.21)	0.77	0.74 (0.47-1.19)	0.21	0.68 (0.39-1.18)	0.17
Poor LV-function	2.96 (1.71-5.12)	0.0001	1.62(0.84-3.12)	0.15	2.81 (1.61-4.90)	0.0003	1.56(0.82-2.99)	0.18
Diabetes Mellitus	2.03 (0.58-7.11)	0.27			2.87 (1.25-6.56)	0.01		
Incomplete Revascularization	1.44 (0.87-2.40)	0.16			1.68 (1.00-2.83)	0.05		
Use of sequential grafts	1.48(0.74-2.98)	0.27			2.34(1.17-4.68)	0.02		
Smoking			1.15 (0.70-1.88)	0.58			1.92 (1.17-3.13)	0.01

Results

Follow-up was complete in 99.8% and averaged 15.4 years for the survivors. Thirteen patients (3%) died within 30 days after surgery. These patients were not included for analysis. Actuarial survival after 15 years was 63 %. Actuarial freedom from cardiac survival after 15 years was 74.4 %, and actuarial freedom from MI after 15 years was 77.4 %. Clinical characteristics of this patient group are described in table I. Pre-operatively, serum lipid levels were obtained from 336 patients (81%), and both unstable angina pectoris (67% vs. 14%, $p<0.001$), and the abscence of a previous MI (28% vs. 53%, $p<0.001$) were more prevalent in patients with unknown lipid levels. At 5 years after surgery, serum lipid levels were obtained from 127 patients, and no differences were found between the groups.

Cardiac Mortality: Potential predictors for cardiac mortality were univariately analyzed. The following factors reached a p-value < 0.1 in at least on of these tests: diabetes mellitus, history of MI, number of diseased vessels, left ventricular function, main stem or proximal left anterior descending disease, collateral circulation, surgeon, type of graft used, and completeness of revascularization. Together with age, gender, and serum cholesterol and triglycerides, these variables were entered in the multivariate model. Multivariately analyzed, independent predictors of cardiac death are presented in table II. Hypertriglyceridemic patients at 5 years after surgery seemed to be at increased risk for cardiac death during follow-up (fig.1). However, after adjustment for possible confounding factors, neither hypertriglyceridemia nor hypercholesterolemia were independent predictors for cardiac mortality (table 2 and 3).

Table 3. Cardiac mortality and myocardial infarction event rates from life table analysis. Two models were used, the first measuring lipids before surgery and patients were followed for 15 years, and the second model measuring lipids at 5 years after surgery and patients were followed from 5 to 15 years after surgery.

			from 5 to 15 years after surgery	
	cardiac mortality	myocardial infarction	cardiac mortality	myocardial infarction
triglycerides				
>2.0 mmol/l (176 mg/dl)	30.4%	22.5%	33.5%	21.7%
≤2.0 mmol/l (176 mg/dl)	26.2%	14.6%	19.2%	14.3%
cholesterol				
>6.5 mmol/l (254 mg/dl)	28.4%	17.1%	25.0%	17.3%
≤6.5 mmol/l (254mg/dl)	24.0%	19.4%	29.0%	19.2%

Myocardial Infarction: Potential predictors for cardiac mortality were univariately analyzed. The following factors reached a p-value < 0.1 in at least on of these tests: smoking, history of MI, left ventricular function, main stem disease, and completeness of revascularization. Together with age, gender, and serum cholesterol and triglycerides, these variables were entered in the multivariate model. Multivariately analyzed, pre-operative hypertriglyceridemia appeared to be the only independent predictor for MI during 15 years follow-up (table 2, fig.1). Pre-operative hypercholesterolemia was not

associated with an increased risk for MI. Hypertriglyceridemia at 5 years after surgery seemed to be even a stronger predictor for MI from 5-15 years after surgery (table 2, fig. 1). However, the risk was not statistically significant increased. The only risk factor for MI at 5 years after surgery was smoking (table 2).

Discussion

The results of this study suggest that pre-operative hypertriglyceridemia is an independent predictor of MI during 15 years follow-up after coronary bypass surgery. Increased serum triglycerides at 5 years after surgery also seemed to be an independent predictor for MI. However, this difference was not statistically significant, which may have been due to many unknown triglycerides at 5 years after surgery. Serum cholesterol levels, either measured pre-operatively or at 5 years after surgery, did not influence MI or cardiac mortality during follow-up. Patients undergoing coronary bypass surgery already have higher plasma cholesterol and triglyceride levels.[14-16] Also, angiograhpically proven progression of coronary artery disease after coronary bypass surgery was correlated with pre-operative plasma lipid levels.[1,2,17] However, the influence of pre-operative serum lipid levels on clinical outcome after coronary bypass surgery has been less well described, and different clinical end-points were used. Pre-operative cholesterol and triglyceride levels were significant predictors of the risk of recurrent severe angina pectoris[18] and (cardiac) mortality[6-10] after coronary bypass surgery, and elevated pre-operative triglyceride levels were the strongest risk factor associated with re-operation.[8] In contrast with Lindén et al.[6], we did not find triglycerides to be of predictive value for cardiac mortality. Although there seemed to be some difference in cardiac death between hypertriglyceridemic and normal patients, after adjustment for confounders, the difference was not statistically significant. The most important confounder was the presence of diabetes mellitus, which was both strongly correlated with triglycerides, and was an important predictor for cardiac mortality.

Pathophysiologic studies have shown that there are many factors which have a close relationship with the metabolism of triglycerides.[19] The most important factors are: High-Density Lipoproteins, Low-Density Lipoproteins, Intermediate-Density Lipoproteins, Very-Low-Density Lipoproteins and different types of apolipoproteins and lipases. There is now speculation that triglyceride-rich lipoproteins predispose to atherosclerosis[19], and there are several causes for high levels of these particular subclasses of lipoproteins. Unfortunately, we were not able to adjust for all of these factors which nowadays have proved to correlate with triglycerides, because the study was designed in 1975 when the importance of these factors was not yet fully established. Therefore, we cannot conclude a causal relationship between high triglyceride levels and the incidence of MI after coronary bypass surgery.

Comparisons of clinical characteristics between patients with known and unknown triglycerides revealed that pre-operatively, unknown triglycerides were more prevalent in patients with unstable angina pectoris and in patients without a previous MI. This seems natural, since in unstable patients, less time is available to assess lipid status, and

patients with a previous MI are better monitored for their lipid status. At 5 years after surgery, no differences were found between patients with known and unknown levels, indicating that measuring serum triglycerides at 5 years after surgery was done according to the random initiative of the referring cardiologist.

)◇) = triglycerides ≤ 2.0 mmol/l)) = triglycerides > 2.0 mmol/l

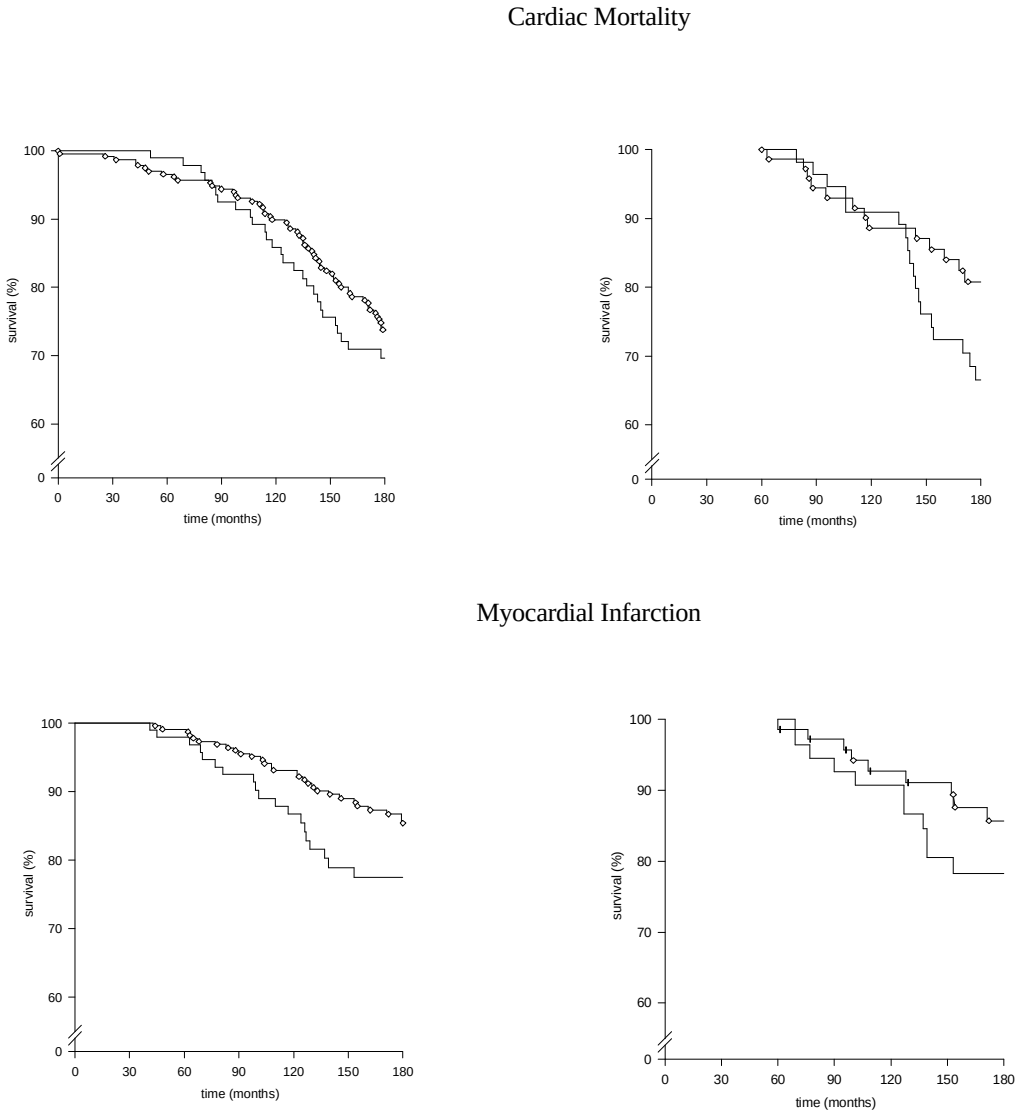

Figure 1. Kaplan-Meier survival curves for cardiac mortality (upper panels) and myocardial infarction (lower panels) after coronary bypass surgery of patients with serum triglycerides ≤ 2.0 mmol/l compared to patients with serum triglycerides > 2.0 mmol/l. Left panels: pre-operative triglycerides and follow-up from surgery to 15 years after surgery. Right panels: triglycerides 5 years after surgery and follow-up from 5-15 years after surgery

Finally, it should be noted that we report on the effects of triglycerides and cholesterol on clinical events after *venous* coronary bypass surgery. At present, it has been shown that arterial grafts have an improved outcome over venous grafts[20-22]. However, for a variety of reasons, venous grafts are continued to be used in the majority of coronary bypass surgery patients, mostly in combination with arterial grafts[23-25] Since it is conceivable that the venous conduits will be the first to cause clinical events, factors that influence the clinical outcome of patients with venous grafts, will remain to be important for the present situation.

References

1. Campeau L, Enjalbert M, Lesperance J, Bourassa MG, Kwiterovich P, Jr., Wacholder S, Sniderman A: The relation of risk factors to the development of atherosclerosis in saphenous-vein bypass grafts and the progression of disease in the native circulation. A study 10 years after aortocoronary bypass surgery. *N Engl J Med* 1984;311:1329-1332

2. Allard C, Goulet C, Grondin CM, Lesperance J, Bourassa MG: Patency of aortocoronary vein grafts and serum triglycerides. Three year follow-up study. *Am J Cardiol* 1974;33:679-680

3. Daida H, Yokoi H, Miyano H, Mokuno H, Satoh H, Kottke TE, Hosoda Y, Yamaguchi H: Relation of saphenous vein graft obstruction to serum cholesterol levels. *J Am Coll Cardiol* 1995;25:193-197

4. Palac RT, Meadows WR, Hwang MH, Loeb HS, Pifarre R, Gunnar RM: Risk factors related to progressive narrowing in aortocoronary vein grafts studied 1 and 5 years after surgery. *Circulation* 1982;66:I40-4

5. Hoffmann RG, Blumlein SL, Anderson AJ, Barboriak JJ, Walker JA, Rimm AA: The probability of surviving coronary bypass surgery. Five-year results from 1,718 patients. *JAMA* 1980;243:1341-1344

6. Linden T, Bondjers G, Karlsson T, Wiklund O: Serum triglycerides and HDL cholesterol--major predictors of long-term survival after coronary surgery. *Eur Heart J* 1994;15:747-752

7. Cataldo G, Braga M, Pirotta N, Lavezzari M, Rovelli F, Marubini E: Factors influencing 1-year patency of coronary artery saphenous vein grafts. Studio Indobufene nel Bypass Aortocoronarico (SINBA). *Circulation* 1993;88:II93-8

8. Fox MH, Gruchow HW, Barboriak JJ, Anderson AJ, Hoffmann RG, Flemma RJ, King JF: Risk factors among patients undergoing repeat aorta-coronary bypass procedures. *J Thorac Cardiovasc Surg* 1987;93:56-61

9. Cosgrove DM, Loop FD, Lytle BW, Gill CC, Golding LA, Gibson C, Stewart RW, Taylor PC, Goormastic M: Predictors of reoperation after myocardial revascularization. *J Thorac Cardiovasc Surg* 1986;92:811-821

10. Stewart JW, Goormastic M, Healy B, Lytle BW, Hoogwerf BJ, Cressman MD, Sheldon WC, Loop FD: Clinical outcome ten years after coronary bypass: effects of cholesterol and triglycerides in 4913 pts. *J Am Coll Cardiol* 1988;11:7A

11. Assmann G, Schulte H, von Eckardstein A: Hypertriglyceridemia and Elevated Lipoportein(a) are Risk Factors for Major Coronary Events in Middle-Aged Men. *Am J Cardiol* 1996;77:1179-1184

12. Myers WO, Schaff HV, Gersh BJ, Fisher LD, Kosinski AS, Mock MB, Holmes DR, Ryan TJ, Kaiser GC: Improved survival of surgically treated patients with triple vessel coronary artery disease and severe angina pectoris. A report from the Coronary Artery Surgery Study (CASS) registry. *J Thorac Cardiovasc Surg* 1989;97:487-495

13. Cox DR: Regression models and life tables. *J R Stat Soc* 1972;34:187-202

14. Averna M, Seip RL, Mankowitz K, Schonfeld G: Postprandial lipemia in subjects with hypobetalipoproteinemia and a single intestinal allele for apoB-48. *J Lipid Res* 1993;34:1957-1967

15. Barboriak JJ, Rimm AA, Anderson AJ, Tristani FE, Walker JA, Flemma RJ: Heart disease indicators in patients with aortocoronary bypass operation. *Cardiology* 1976;61:153-161

16. Billington T, Janus ED, Sinclair HC: Lipids and lipoproteins in patients undergoing coronary-artery surgery. *Med J Aust* 1989;150:302-4,306

17. Blankenhorn DH, Alaupovic P, Wickham E, Chin HP, Azen SP: Prediction of angiographic change in native human coronary arteries and aortocoronary bypass grafts. Lipid and nonlipid factors. *Circulation* 1990;81:470-476

18. Yli Mayry S, Huikuri HV: Clinical and angiographic prediction of myocardial infarction and recurrence of severe angina during a five-year follow-up after coronary artery bypass grafting. *Am J Cardiol* 1993;72:1371-1375

19. Shepherd J, Krauss RM: Pathophysiology of triglyceride-rich particles. A. Metabolism of triglyceride-rich particles. *Am J Cardiol* 1991;68:5A-7A

20. Loop FD, Lytle BW, Cosgrove DM, Golding LA, Taylor PC, Stewart RW: Free (aorta-coronary) internal mammary artery graft. Late results. *J Thorac Cardiovasc Surg* 1986;92:827-831

21. Sergeant P, Lesaffre E, Flameng W, Suy R, Blackstone E: The return of clinically evident ischemia after coronary artery bypass grafting. *Eur J Cardiothorac Surg* 1991;5:447-457

22. Cameron AA, Davis KB, Green GE, Schaff HV: Coronary bypass surgery with internal-thoracic-artery grafts - effects on survival over a 15-year period. *N Engl J Med* 1996;334:216-219

23. van Sterkenburg SM, Ernst SM, Brutel de la Riviere A, Defauw JA, Hamerlynck RP, Knaepen PJ, van Swieten HA, Vermeulen FE: Triple sequential grafts using the internal mammary artery. An angiographic and short-term follow-up study. *J Thorac Cardiovasc Surg* 1992;104:60-65

24. Grondin CM, Campeau L, Thornton JC, Engle JC, Cross FS, Schreiber H: Coronary artery bypass grafting with saphenous vein. *Circulation* 1989;79:I24-9

25. Bourassa MG: Fate of venous grafts: the past, the present and the future. *J Am Coll Cardiol* 1991;17:1081-1083