Original articles

Prediction of early and delayed postoperative deaths after coronary artery bypass surgery alone in Italy

Multivariate predictions based on Cox and logistic models and a chart based on the accelerated failure time model

Paolo Emilio Puddu, Gianluca Brancaccio, Marzia Leacche, Francesco Monti, Mariapaola Lanti*, Alessandro Menotti*, Carlo Gaudio, Ugo Papalia, Benedetto Marino, on behalf of the OP-RISK Study Group (see Appendix 1)

*Department of Cardiac Surgery, "La Sapienza" University of Rome, *Association for Cardiac Research, Rome, Italy*

Key words:
Coronary artery surgery; Mortality; Risk factors.

Background. **The aim of the multicenter OP-RISK (OPerative RISK) study was to investigate the early (28 days) and delayed (365 days) death rates following coronary artery bypass grafting (CABG) among patients representing a nationwide distribution [Centers in Northern (2), Central (1) and Southern (1) Italy] and further to define the multivariate risk factors for the early and delayed mortality after CABG.**

Methods. **Data were collected from 1126 patients undergoing CABG alone. Data were analyzed using Cox and logistic regression models, to accurately assess the major factors influencing survival over time after CABG. Having defined the significant factors, we constructed a chart of the absolute early risk of mortality using the accelerated failure time model.**

Results. **Using the Cox proportional hazards model and logistic regression we have demonstrated that age, preoperative ejection fraction and heart rate, and the duration of aortic cross-clamping are multivariate risk factors in the short and long term. The role of one arterial conduit was also assessed.**

Conclusions. **The OP-RISK study produced relevant information for risk assessment and control in CABG and the results may form the basis for the objective quality assurance and accreditation of cardiac surgical institutions in Italy. Incidentally, Cox model appeared more adequate than logistic model for the assessment of the major factors influencing survival over time after CABG. The risk factors so assessed were used to construct a chart for practical predictive purposes.**

(Ital Heart J 2002; 3 (3): 166-181)

The present study was supported in part by an educational grant from Schering-Plough SpA, Milan, and by the Association for Cardiac Research, Rome, Italy.

Received May 2, 2001; revision received January 21, 2002; accepted February 8, 2002.

Address:

Dr. Paolo Emilio Puddu

Istituto di Chirurgia del Cuore e Grossi Vasi
II Cattedra di Cardiologia
Università degli Studi "La Sapienza"
Policlinico Umberto I
Viale del Policlinico, 155
00161 Roma
E-mail: puddu.pe@iol.it

Risk-adjusted mortality prediction is frequently used to assess the outcome of coronary artery bypass grafting (CABG). By taking into account patient risk factors, this allows more accurate assessment of the quality of care. A detailed understanding of the determinants of morbidity and mortality after CABG would allow clinicians to identify those risk factors that could be modified with the aim of improving the patient outcome, to adjust for baseline differences in outcome studies, and to predict the expected survival for an individual patient. Statistical methods have been applied to this task, ranging from simple univariate analysis to multivariate logistic regression and to more sophisticated methods such as those based on neural networks. However, most regression models require statistical assumptions (linearity, additivity) which may not be justified, and the management of missing data is problematic. Neural networks are a form of artificial intelligence that may obviate some of the problems associated with traditional statistical techniques but which do not, at the present time, offer any greater predictive accuracy than that of Bayesian or logistic regression analysis[1,2]. Unfortunately, these models have been limited to the analysis of the 30-day or in-hospital mortality, but some risk factors appear to influence only the very early mortality, some appear to influence only the late mortality, and others appear to influence both mortality types. On the other hand, the Cox model, largely used in epidemiology, represents a method whereby the major factors influencing survival over time after CABG may be accurately assessed. However, one peculiar disadvantage of Cox model is that of preliminarily demonstrating the proportionality of hazard rates. This may be overcome using the accelerated failure time model.

The multicenter OP-RISK (OPerative RISK) study, developed during 1994-1996 in Italy[3], was aimed at: 1) investigating the early (28 days) death rates following CABG among patients recruited from four centers representing a nationwide distribution; 2) defining the possible risk factors for early mortality and, at the same time, comparing these factors with those reported in previous studies; 3) on the basis of predictive risk factors, building risk functions for early mortality after CABG in Italy; 4) constructing a data bank to enable the long-term follow-up of included individuals considered as a prototype of a nationwide registry for the monitoring of the risk related to CABG in Italy. The present study was aimed to perform a multivariate analysis of the OP-RISK data, using both Cox and logistic regression models. Furthermore, the performance of the selected subset of covariates was assessed to predict the delayed (1 year) deaths in a sub sample of 416 patients operated upon in a single center, also comparing the relative contribution of predictive covariates for early versus late deaths[4] in that center. Finally, a risk chart for the prediction of the early mortality on the basis of a few covariates was constructed as a means of evaluating the clinical applicability of the results obtained, by translating complex multivariate modeling into a daily useful tool.

Methods

Study population. The rationale, development, descriptive statistics of a total of 65 pre-, peri- and postoperative variables collected in the OP-RISK study have been previously described in detail[3]. Briefly, a total of 1126 patients were operated upon in the four participating centers (see Appendix 1). Of these, two are located in Northern (Milan and Bologna), one in Central (Rome) and one in Southern (Naples) Italy and 51 in-hospital deaths (4.53%) were officially reported (to the Italian Society of Cardiac Surgery)[3]. Data on 984 patients (87% of the total) with a complete 28-day follow-up as obtained by telephone interviews and by review of hospital and clinical data were included in the present study. Among these patients, the crude mortality (4.47%) was similar to that officially reported for the overall population of patients operated upon in the participating centers. Non-included patients (n = 142, 13% of total) were frequently residents of other regions and they could not be reached by telephone. An initial univariate analysis on included patients classified as dead (n = 44, 4.47%) or alive (n = 940) at 28 days (155 ± 174 hours, global interval between 12 and 576 hours) of follow-up has been previously reported[3]. In a subgroup of 416 patients operated upon at the "La Sapienza" University of Rome Cardiac Surgical Center, the 365-day survival was also ascertained.

Table I illustrates the mortality as observed in the denominators used to run the multivariate analyses, along with the actual mortality in the whole population of patients. The mortality in the used denominators was similar to the official mortality in the participating centers when the models included 16 variables or less. There was no means of comparing the data between the centers which agreed to participate in the OP-RISK study and those which did not, apart from the official mortality as reported to the Italian Society of Cardiac Surgery which, on average, was similar and ranged from 2.58 to 3.45% in uncomplicated CABG (89% of the total of patients operated upon) and reached 10% in complicated CABG[3]. Neither is it at present possible to compare the OP-RISK data (variables and mortality) with those from other Italian centers mainly due to the lack of a national register or centralized data banks.

Statistical analysis. Data in the tables, figures and text are expressed as mean ± SD or as means ± SE when appropriate. BMDP statistical software was used[5]. A p value < 0.05 was considered statistically significant.

Probabilistic analysis. In order to investigate the correlation between the measured parameters (explanatory

Table I. Multivariate analysis: Cox models* in the OP-RISK study.

	Model 1 (n=984)	Model 2 (n=984)	Model 3 (n=984)	Model 4 (n=984)	Models 5 to 7 (Rome only) (n=416)		
Centers	4	4	4	4	1	1	1
Risk factors (degrees of freedom)	22	16	10	9	9	9	8
Censored at 28 days	470	609	609	609	219		
Deaths at 28 days	18	30	30	30	8		
Censored at 1 year						212	379
Deaths at 1 year						15	27
Missing	496	345	345	345	189	189	10
Mortality (%)							
In used denominator	3.69	4.69	4.69	4.69	3.52	6.61	6.65
In total number	4.47	4.47	4.47	4.47	4.09	6.73	6.73

* = probability of dying at 28 (or 365) days after coronary artery surgery: $1\text{-}Y = S_{(0)}$ expcoeff$_1$ $(x_1 - X_1)$ * expcoeff$_n$ $(x_n - X_n)$.

variables) and the incidence of death, we selected either the Cox model (which takes the time to the event into account) or the logistic model (where the time to the event is not considered)[5,6]. The proportionality of hazard rates was tested before using the Cox model and no deviation preventing the legitimate use of this model was observed. The comparison of the results obtained from the Cox and logistic models represents an important characteristic of this investigation which has rarely been performed in the literature. Both models were run on the same sets of covariates, either continuous (interval) or binary.

Table II describes the variable names, the acronyms, the significance and the type of coding. Among the 65 collected, the variables to be included in the multivariate models were selected on the basis of a parsimony criterion (to enable the highest possible denominators whilst at the same time including a large number of covariates) after careful scrutiny of a previously published univariate analysis[3]. The following situations were compared (Table I):

- the early death prediction in the overall OP-RISK study (n = 984) in model 1 (22 covariates), model 2 (16 covariates), model 3 (10 covariates), and model 4 (9 covariates);
- the early death prediction in one center ("La Sapienza" University of Rome) participating in the OP-RISK study (n = 416) in model 5 (9 covariates);
- the delayed death prediction in the same center (n = 416) in model 6 (9 covariates) and model 7 (8 covariates).

Models 1 to 3 were run to detect the best set of predictive covariates in the overall OP-RISK study. Models 3 and 4 differ in that the former takes into account the role of at least one arterial segment among the grafts used for CABG, whereas the latter does not. Models 5 to 7 were run in the only OP-RISK center where even the 1-year follow-up data were obtained. These latter models compare the early (model 5) and delayed death prediction with (model 6) or without (model 7) the ejection fraction as a covariate.

Chart construction. The accelerated failure time model incorporating the Weibull distribution was used to construct a risk chart for the prediction of the 28-day mortality only, using data from the overall OP-RISK study and the significant covariates of Cox model 4 (age, preoperative ejection fraction and heart rate, and the duration of aortic cross-clamping). In fact, with the accelerated failure time model there is no assumption as to the proportionality of hazard. On the other hand, the chart so derived may be used as a significant practical contribution to the stratification of the patient's risk on the basis of common clinical variables. This may help to simplify most of the possible theoretical considerations in the domain of survival modeling for CABG or different contexts (see Appendix 2).

Table II. Among 65 variables obtained in the OP-RISK study[3], 23 were used to run multivariate statistics, on the basis of both the maximum common denominator principle and of previous univariate analyses: 13 are interval whereas 10 are binary variables.

No.	Acronym	Significance	Interval	Binary
Preoperative factors				
1	Center	Surgical center	1-4	
2	ID	Patient number in each center	1-721	
3	Sex	Male		0-1
166	Age	Year at surgery minus year at birth (years)	25-83	
169	CHF	Congestive heart failure		0-1
170	BMI	Body mass index: weight/(height/100)^2 (kg/m^2)	15.5-57.8	
171	PREAMI	Previous acute myocardial infarction		0-1
17	NYHA	New York Heart Association functional class	1-4	
21	Nbp	Number of bypasses	1-7	
80	Aocountr	Aortic counterpulsation		0-1
81	Urgent	Urgent cardiac surgery		0-1
88	LVEDP	Left ventricular end-diastolic pressure (mmHg)	2-32	
89	MAP	Mean aortic pressure (mmHg)	41-140	
91	EF	Angiographic ejection fraction (%)	18-77	
92	HR	Heart rate (b/min)	42-150	
Perioperative factors				
111	TachIA	Tachycardia (> 130 b/min) at induction of anesthesia		0-1
113	Anestdur	Duration of anesthesia (min)	18-998	
114	Cpbpdur	Duration of cardiopulmonary bypass (min)	11-617	
115	Aocladur	Duration of aortic cross-clamping (min)	11-262	
120	Cptype	Blood cardioplegia*		0-1
178	Art	Bypass with at least 1 arterial segment		0-1
Postoperative factors				
124	Vextra	Ventricular extrasystoles		0-1
131	ASA	Antithrombotic therapy with acetylsalicylic acid**		0-1

For binary variables: 0 = absent; 1 = present, apart from * where 0 = crystalloid cardioplegia alone; ** = antithrombotic therapy 6-12 hours postoperatively to prevent early graft closure due to thrombosis.

Results

Selection of covariates. The significant univariate associations among preoperative factors (age, heart rate and those defining, in general, left ventricular function), perioperative factors [tachycardia (> 130 b/min) at the induction of anesthesia, the total duration of anesthesia, of cardiopulmonary bypass and of aortic cross clamping] and postoperative factors (several arrhythmia types and a lower rate in antithrombotic therapy with acetylsalicylic acid at 6-12 hours postoperatively) with early mortality (either directly or inversely) were disclosed in a previous study[3]. The protective role of CABG performed with at least one arterial segment was also ascertained. Therefore, these univariate predictors of the early mortality following CABG in Italy were not very different from those reported in previous studies performed elsewhere. On the basis of this preliminary experience, the second step, reported in the present investigation, was to run multivariate models aimed at identifying the nationwide coefficients of risk among several pre-, peri- and postoperative variables. After careful scrutiny, using both the parsimony criterion and the clinical relevance of the variables collected, we selected 23 possible covariates. These are described in table II.

Cox models. Tables III and IV provide results and related significance for all Cox models (1 to 7: all global $p < 0.0007$). In these tables, the average values of covariates entered in the respective models are shown, along with the coefficients and t values. $S_{(0)}$, loglikelihood statistics and χ^2 values are also shown. On the basis of loglikelihood statistics and χ^2 values, it is quite clear that among models 1-4 (Table III) the best is model 2 (16 covariates) in which, however, only age, ejection fraction, duration of aortic cross-clamping and postoperative ventricular extrasystoles provided t values $> |1.96|$.

In a more parsimonious model (model 4: 9 covariates, Table I) at an acceptable level of accuracy, the same factors (apart from postoperative ventricular extrasystoles) were included and in all the t values increased, whereas the t value for the preoperative heart rate became significant. Model 4 thus became the basis for the ascertainment of the potency of this smaller series of covariates in predicting both the short- and long-term survivals after CABG in the Rome center. Interestingly, the loglikelihood was larger with the long-term solutions (models 6 and 7).

On the other hand, since the difference between models 3 and 4 relies only on the presence in the former of coding for at least one arterial segment used to perform CABG, as shown in table III, we obtained curves[5] whereby the role of that covariate could be sorted out in a more clinically meaningful way than just by presenting its significant contribution. In order to construct the strata, we considered the sign of each coefficient in the pertinent solution (Tables III and IV) so that when it was positive, to the average value of the respective covariate we added the SD, whereas when it was negative, from the average value of the corresponding covariate we subtracted the SD. We thus compared the stratum including the average values of the factors entering the solution with the respective strata having mean values plus $|1SD|$ or plus $|2SD|$ and so either in the presence (+) or absence (-) of at least one arterial segment used to perform CABG. The results are illustrated in figure 1 (model 3 with and model 4 without the arterial segment). It is quite clear, when evaluating the differences, that the protective role of at least one arterial segment used to perform CABG is evident particularly in the stratum defining those individuals at higher risk (average values of significant covariates plus $|2SD|$). In the latter stratum, the presence of this factor confers a certain degree of protection, which is less evident in the intermediate stratum and practically irrelevant in the stratum with average values.

The survival probability according to strata, but without considering the arterial segment as described above, was also calculated using the same method in the Rome center. It is evident that the short-term survival in this center (model 5, Table IV) was different from the overall OP-RISK study results (model 4, Table III). Table I indicates that the crude mortality in the used denominators was 3.52% (8 of 227) in the Rome center whereas it was 4.69% (30 of 639) in the overall OP-RISK study. These rates were however not statistically different. Figure 2 illustrates that the stratum at the highest risk in the Rome center (average values of significant covariates plus $|2SD|$) had a survival probability similar to the stratum with intermediate risk (average values of significant covariates plus $|1SD|$) in the overall OP-RISK study (compare figure 2, left panel to figure 1, right panel). However, in the Rome center solution, only the contributions of the ejection fraction and of the duration of aortic cross-clamping were significant (although with coefficients similar to those of the overall OP-RISK results). Moreover, in the Rome center, the average ejection fraction was higher (by 2 points) and the average duration of aortic cross-clamping lower (by 12 points), thus justifying these stratified differences and the relatively lower crude mortality rate.

Figure 2 also illustrates the results of the long-term survival probability in the Rome center, constantly based on the strata of the entered covariates (right panel). However, table IV indicates that model 6, which was the basis used to construct these strata with the method described above, included only age and the duration of aortic cross-clamping among significant covariates, whereas the role of the ejection fraction was borderline with a coefficient equal to half the value of that contributing to the short-term prediction. All strata are clearly separated and, interestingly, the stratum with average values of significant covariates does not

Table III. Multivariate analysis: Cox models in the overall OP-RISK study.

Covariates	Model 1 (n=984)			Model 2 (n=984)			Model 3 (n=984)			Model 4 (n=984)		
	x	coeff.	t	x	coeff.	t	x	coeff.	t	x	coeff.	t
1 Center	4.8627	-0.5538	-0.7141	4.8419	0.1727	0.9004	–	–	–	–	–	–
2 ID	367.2090	0.0028	0.8663	306.1815	0.0010	1.0169	306.1815	0.0005	0.5789	306.1815	0.0000	0.0446
3 Sex	0.8258	0.0340	0.0399	0.8263	-0.8772	-1.6814	0.8263	-0.2836	-0.5620	0.8263	0.0103	0.0212
17 NYHA	2.4303	0.3609	0.8417	–	–	–	–	–	–	–	–	–
21 Nbp	2.8770	-0.0191	-0.0475	2.8498	0.1800	0.6483	2.8498	0.1261	0.4993	2.8498	0.0219	0.0879
80 Aocountr	0.0225	1.4671	0.9931	–	–	–	–	–	–	–	–	–
81 Modint	–	–	–	0.0360	0.5581	0.8813	–	–	–	–	–	–
88 LVEDP	12.4365	-0.1016	-1.2012	–	–	–	–	–	–	–	–	–
89 MAP	89.2131	-0.0005	-0.0130	–	–	–	–	–	–	–	–	–
91 EF	52.2398	-0.1378	-2.7675	51.6291	-0.0762	-3.2760	51.6291	-0.0779	-4.0547	51.6291	-0.0831	-4.5641
92 HR	72.7172	0.0224	0.9165	73.1346	0.0234	1.4701	73.1346	0.0461	3.4380	73.1346	0.0484	3.6866
111 TachIA	0.0328	0.2967	0.2310	0.0423	0.0834	0.1335	–	–	–	–	–	–
113 Anestdur	350.9221	0.0038	0.9427	–	–	–	–	–	–	–	–	–
114 Cpbpdur	115.0697	-0.0079	-0.8988	–	–	–	–	–	–	–	–	–
115 AoClamp	73.4406	0.0030	0.2168	74.8247	0.0173	2.4882	74.8247	0.0211	3.5135	74.8247	0.0204	3.4376
120 Cptype	0.4857	-1.5215	-1.3666	–	–	–	–	–	–	–	–	–
124 Vextra	0.1025	2.2272	2.7689	0.1221	2.1870	4.2104	–	–	–	–	–	–
131 ASA	0.4590	-1.1923	-1.0609	0.4867	-1.3279	-1.9835	–	–	–	–	–	–
166 Age	60.9262	0.1681	2.7721	61.1549	0.0743	2.5225	61.1549	0.0902	3.4451	61.1549	0.1019	3.9359
169 CHF	0.0533	0.2359	0.2231	0.0563	-0.3942	-0.7426	0.0563	0.0407	0.0796	0.0563	0.4485	0.9767
170 BMI	26.3741	0.0988	0.8775	26.2944	0.0221	0.3377	26.2944	0.0399	0.6039	26.2944	0.0279	0.4327
171 PREAMI	0.5902	-0.5097	-0.6450	0.5869	-0.3886	-0.9577	–	–	–	–	–	–
178 Art	0.9488	1.9769	1.1242	0.8998	0.1654	0.2775	0.8998	-0.9834	-1.9780	–	–	–
$S_{(0)}$		0.9977			0.9921			0.9878			0.9877	
Loglikelihood		-65.8356			-133.0403			-147.8377			-149.7135	
χ^2		170.45			251.87			120.26			101.58	
DF		22			16			10			9	
p		0.0000			0.0000			0.0000			0.0000	

DF = degrees of freedom. $t > |1.96|$ $p < 0.05$. ID = progressive identification number in each center.

Table IV. Multivariate analysis: Cox models in the Rome center.

Covariates	Model 5 (n=416)			Model 6 (n=416)			Model 7 (n=416)		
	x	coeff.	t	x	coeff.	t	x	coeff.	t
1 Center	–	–	–	–	–	–	–	–	–
2 ID	548.3832	0.0007	0.3135	548.3832	0.0000	0.0271	442.7069	-0.0012	-1.3862
3 Sex	0.8678	0.5815	0.4316	0.8678	1.0440	0.9047	0.8719	0.5461	0.7276
17 NYHA	–	–	–	–	–	–	–	–	–
21 Nbp	3.0485	-0.0594	-0.1135	3.0485	0.1098	0.2885	2.9828	0.1654	0.5989
80 Aocountr	–	–	–	–	–	–	–	–	–
81 Modint	–	–	–	–	–	–	–	–	–
88 LVEDP	–	–	–	–	–	–	–	–	–
89 MAP	–	–	–	–	–	–	–	–	–
91 EF	53.6167	-0.1121	-2.2067	53.6167	-0.0523	-1.5584	–	–	–
92 HR	77.2379	0.0139	0.5192	77.2379	0.0009	0.0461	79.2931	0.0013	0.1045
111 TachIA	–	–	–	–	–	–	–	–	–
113 Anestdur	–	–	–	–	–	–	–	–	–
114 Cpbpdur	–	–	–	–	–	–	–	–	–
115 AoClamp	62.8767	0.0301	3.6325	62.8767	0.0215	3.2627	61.9704	0.0155	3.2166
120 Cptype	–	–	–	–	–	–	–	–	–
124 Vextra	–	–	–	–	–	–	–	–	–
131 ASA	–	–	–	–	–	–	–	–	–
166 Age	59.1586	0.0779	1.4058	59.1586	0.0917	2.3731	59.3498	0.0630	2.3898
169 CHF	0.0881	0.6191	0.5801	0.0881	1.0406	1.3268	0.1256	0.9169	1.9991
170 BMI	26.6648	0.1258	0.9812	26.6648	0.0045	0.0511	26.4563	-0.0294	-0.5027
171 PREAMI	–	–	–	–	–	–	–	–	–
178 Art	–	–	–	–	–	–	–	–	–
$S_{(0)}$		0.9924			0.9742			0.9384	
Loglikelihood		-31.2086			-63.1455			-139.0921	
χ^2		33.24			31.23			27.14	
DF		9			9			8	
p		0.0001			0.0003			0.0007	

DF = degrees of freedom. t > |1.96| $p < 0.05$. ID = progressive identification number in each center.

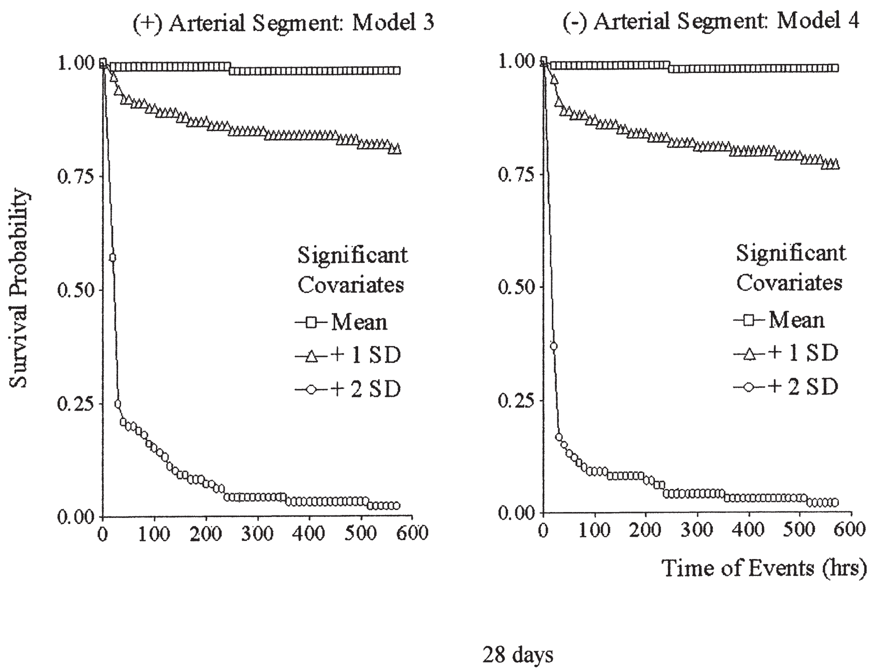

Figure 1. *OP-RISK study (n = 984). Survival based on Cox model with 9 covariates.*

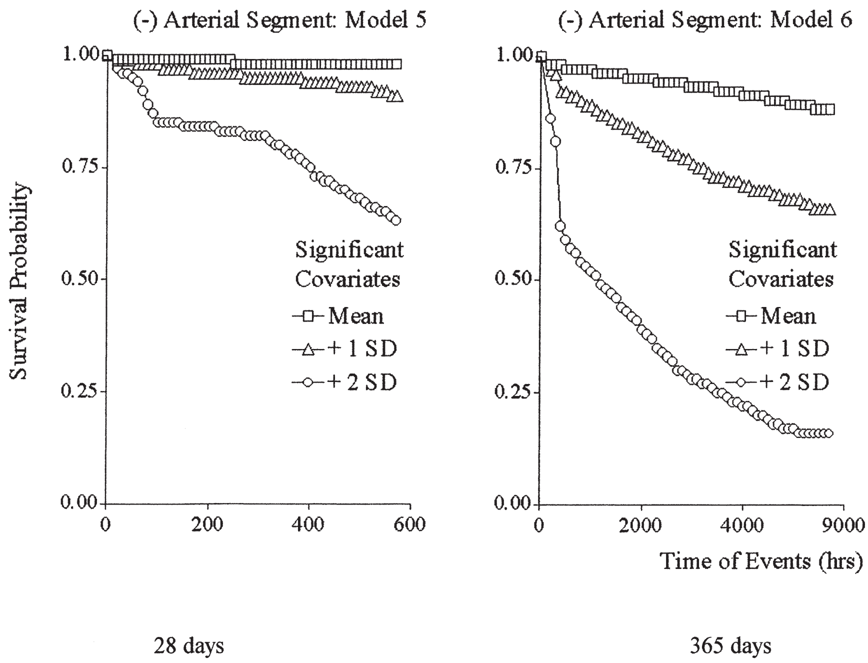

Figure 2. *Rome center (n = 227). Survival based on Cox model with 9 covariates.*

present with a straight line, indicating that also in this group of patients there is space to apply measures aimed at ameliorating the long-term survival.

Logistic models. For direct comparison with the above-mentioned results of the Cox model, after selecting those worthy of further study (thus excluding models 1 and 2 which indeed present with some degree of redundancy) the multivariate assessment was performed by running the corresponding models 3 to 6 using logistic regression, either adopting the forced (Table V) or the stepwise (Table VI) techniques (see Appendix 2). In these tables, the average values of the covariates entered in the respective models are repeated, along with the logistic coefficients and t values. The values of the ROC plot area (as directly calculated using BMDP software) are indicated along with loglikelihood statistics and χ^2 values. All logistic models provided significant results. In general, and quite expectedly[7,8], lower absolute t values of significant covariates were obtained with stepwise than with forced logistic models and with logistic than with Cox models. With forced models the ROC areas were > 0.86 whereas they were > 0.84 with stepwise models. Plots were finally constructed to graphically illustrate these results (Fig. 3).

Accelerated failure time model and the risk chart. As a practical means of transposing to the clinical context the results obtained in our multivariate approach and so as to obtain easily derivable and therefore possible to use information for the forecasting of the short-term probability of survival in individual patients submitted to CABG in Italy, we finally considered that age, preoperative ejection fraction and heart rate, and the duration of aortic cross-clamping were the significant covariates in the above-mentioned models derived from the overall OP-RISK study. To these ends, we then used the accelerated failure time model and the four significant covariates summarized as those having an explanatory role in the overall multivariate approach (as reported above) of the OP-RISK study. The solution of the accelerated failure time model provided the following coefficients among 687 individuals with complete information, of whom 656 were censored at 28 days postoperatively (constant 30.0935, scale 1.9791): -0.2092 (age), 0.1931 (ejection fraction), -0.1160 (heart rate), and -0.0412 (duration of aortic cross-clamping), and all had t values > 3.06. Figure 4 illustrates a 480-cell colored chart, similar in shape to those used to address the probability of the occurrence of coronary, or more in general, of cardiovascular events in population-based investigations[9-11]. The absolute risks of death within 28 days after CABG calculated within categories of the four factors are shown in table VII. Of the 480 chart cells, 254 (53%) indicate a low (< 5%), 134 (28%) an intermediate (5-39%), and 94 (19%) a high (≥ 40%) risk of dying within 28 days of CABG.

The chart enables several clinically important considerations, which are consequent to the spectral interplay of the different categories made for the four significant covariates considered. To elucidate just a few: a low ejection fraction may not always convey an unacceptable risk of dying postoperatively, provided that the operated patient is relatively young and that the duration of aortic cross-clamping is short. On the other hand, even in aged patients a long duration of aortic cross-clamping does not necessarily increase the risk of

Table V. Multivariate analysis: logistic models (forced). Model numbers refer to Cox models.

Covariates	Model 3 (n=984)			Model 4 (n=984)			Model 5 (n=416)			Model 6 (n=416)		
	x	coeff.	t	x	coeff.	t	x	coeff.	t	x	coeff.	t
1 Center	–	–	–	–	–	–	–	–	–	–	–	–
2 ID	306.1815	0.0008	0.74	306.1815	0.0000	0.04	548.3832	0.0018	0.65	548.3832	0.0006	0.35
3 Sex	0.8263	0.1405	0.25	0.8263	-0.0232	-0.04	0.8678	-0.5371	-0.40	0.8678	-1.1660	-0.97
17 NYHA	–	–	–	–	–	–	–	–	–	–	–	–
21 Nbp	2.8498	0.1265	0.44	2.8498	0.0304	0.11	3.0485	-0.1003	-0.18	3.0485	0.0622	0.16
80 Aocountr	–	–	–	–	–	–	–	–	–	–	–	–
81 Modint	–	–	–	–	–	–	–	–	–	–	–	–
88 LVEDP	–	–	–	–	–	–	–	–	–	–	–	–
89 MAP	–	–	–	–	–	–	–	–	–	–	–	–
91 EF	51.6291	-0.0850	-3.85	51.6291	-0.0939	-4.38	53.6167	-0.1182	-2.07	53.6167	-0.0427	-1.16
92 HR	73.1346	0.0517	3.13	73.1346	0.0557	3.47	77.2379	0.0099	0.34	77.2379	0.0078	0.37
111 TachIA	–	–	–	–	–	–	–	–	–	–	–	–
113 Anestdur	–	–	–	–	–	–	–	–	–	–	–	–
114 Cpbpdur	–	–	–	–	–	–	–	–	–	–	–	–
115 AoClamp	74.8247	0.0240	3.72	74.8247	0.0222	3.46	62.8767	0.0278	3.04	62.8767	0.0200	2.86
120 Cptype	–	–	–	–	–	–	–	–	–	–	–	–
124 Vextra	–	–	–	–	–	–	–	–	–	–	–	–
131 ASA	–	–	–	–	–	–	–	–	–	–	–	–
166 Age	61.1549	0.1277	3.72	61.1549	0.1370	4.06	59.1586	0.0953	1.55	59.1586	0.1048	2.44
169 CHF	0.0563	0.7749	1.24	0.0563	0.9410	1.60	0.0881	0.8451	0.74	0.0881	1.8580	2.16
170 BMI	26.2944	0.0761	1.06	26.2944	0.0592	0.84	26.6648	0.1294	1.02	26.6648	0.0200	0.22
171 PREAMI	–	–	–	–	–	–	–	–	–	–	–	–
178 Art	0.8998	-1.2170	-2.10	–	–	–	–	–	–	–	–	–
Constant		-15.27	-4.15		-15.63	-4.38		-10.85	-1.63		-10.41	-2.16
ROC plot area		0.9054			0.9063			0.9033			0.8623	
loglikelihood		-74.360			-88.443			-24.725			-43.385	
χ^2		84.56			93.73			22.83			27.21	
p		< 0.001			< 0.001			< 0.001			< 0.001	

t > |1.96| p < 0.05. ID = progressive identification number in each center.

Table VI. Multivariate analysis: logistic models (stepwise). Model numbers refer to Cox models.

Covariates	Model 3 (n=984)			Model 4 (n=984)			Model 5 (n=416)			Model 6 (n=416)		
	x	coeff.	t	x	coeff.	t	x	coeff.	t	x	coeff.	t
1 Center	–	–	–	–	–	–	–	–	–	–	–	–
2 ID	306.1815		NS	306.1815		NS	548.3832		NS	548.3832		NS
3 Sex	0.8263		NS	0.8263		NS	0.8678		NS	0.8678		NS
17 NYHA	–	–	–	–	–	–	–	–	–	–	–	–
21 nbp	2.8498		NS	2.8498		NS	3.0485		NS	3.0485		NS
80 Aocountr	–	–	–	–	–	–	–	–	–	–	–	–
81 Modint	–	–	–	–	–	–	–	–	–	–	–	–
88 LVEDP	–	–	–	–	–	–	–	–	–	–	–	–
89 MAP	–	–	–	–	–	–	–	–	–	–	–	–
91 EF	51.6291	-0.0863	-4.13	51.6291	-0.0996	-5.01	53.6167	-0.1041	-2.77	53.6167		NS
92 HR	73.1346	0.0575	3.50	73.1346	0.0598	3.74	77.2379		NS	77.2379		NS
111 TachIA	–	–	–	–	–	–	–	–	–	–	–	–
113 Anestdur	–	–	–	–	–	–	–	–	–	–	–	–
114 Cpbpdur	–	–	–	–	–	–	–	–	–	–	–	–
115 AoClamp	74.8247	0.0222	3.52	74.8247	0.0208	3.30	62.8767	0.0238	2.69	62.8767	0.0205	3.04
120 cptype	–	–	–	–	–	–	–	–	–	–	–	–
124 Vextra	–	–	–	–	–	–	–	–	–	–	–	–
131 ASA	–	–	–	–	–	–	–	–	–	–	–	–
166 Age	61.1549	0.1174	3.59	61.1549	0.1297	4.05	59.1586		NS	59.1586	0.0924	2.26
169 CHF	0.0563		NS	0.0563		NS	0.0881		NS	0.0881	2.448	3.75
170 BMI	26.2944		NS	26.2944		NS	26.6648		NS	26.6648		NS
171 PREAMI	–	–	–	–	–	–	–	–	–	–	–	–
178 Art	0.8998	-1.042	-2.06	–	–	–	–	–	–	–	–	–
Constant		-12.23	-4.35		-13.32	-4.92		-0.1772	-0.099		-10.37	-3.68
ROC plot area		0.8805			0.8957			0.8830			0.8486	
Loglikelihood		-76.019			-78.033			-25.587			-42.375	
Improvement χ^2		4.027			9.884			7.954			5.809	
p		0.045			0.002			0.005			0.016	

t > |1.96| p < 0.05. ID = progressive identification number in each center.

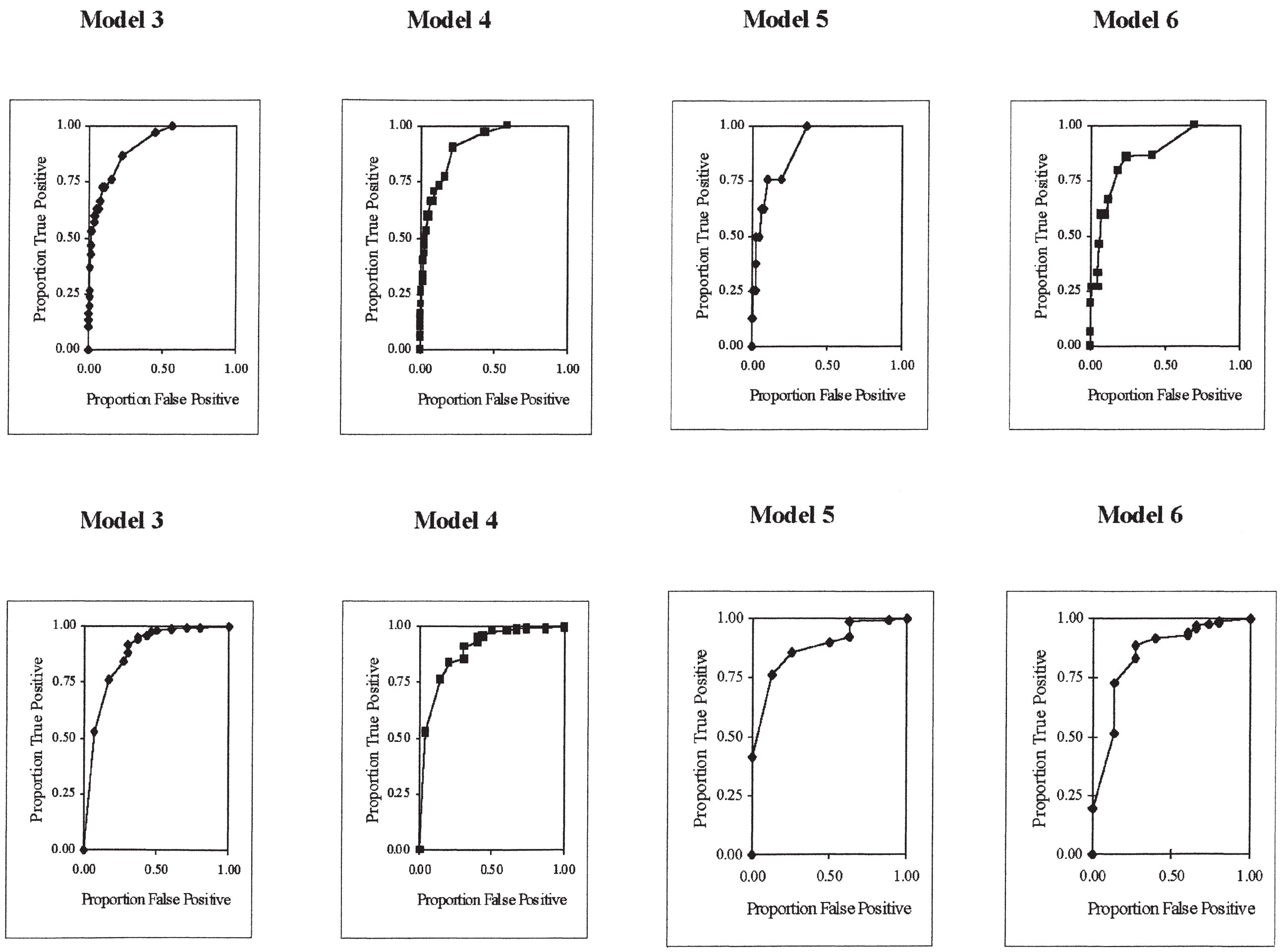

Figure 3. *ROC plot results from the logistic model [either forced* (upper panels) *or stepwise* (lower panels)*]. Model numbers refer to those reported in tables V and VI, which also show ROC plot areas.*

dying, provided that the ejection fraction is preserved. Finally, even in the intermediate categories of ejection fraction, there is a large proportion of patients for whom CABG may be considered as a low-risk procedure provided that either the patients are young or that the duration of aortic cross-clamping is short. In most alluded categories, the preoperative heart rate contributes, indicating that special attention needs to be addressed to this covariate, in particular in relatively older subjects and when ejection fraction is not normal.

Discussion

When summarizing the outcome data through a survival predictive model one can have several objectives in mind: a) to identify variables mechanistically important, for the subsequent in-depth investigation in other observational or, preferably, experimental studies; b) to build a model which can actually be transposed as such to situations external to the one under investigation for prognostic studies at an individual level or to provide a baseline for studies of the performance of surgical units. While the statistical significance of single independent variables or even the degree of fit of one model with respect to another is crucial for purpose a), the overwhelming consideration for purpose b) is the "stability" of the model. The literature on the subject has abundantly shown, on the other hand, that the inclusion or exclusion of an independent variable, which may happen to be significant in one study and not significant in another, may render the results among investigations incomparable.

We have shown that relatively independent of the model used, although expectedly better with Cox than with logistic models, there are four covariates which may explain the early death incidence after CABG. These are the patient's age, the preoperative heart rate and ejection fraction, and the duration of aortic cross-clamping. On the basis of these variables and of their average values it is possible to try to explain crude mortality differences, for example in the overall OP-RISK study vs the Rome center. These variables are easy to obtain and might indeed be used in individual patients to forecast the short-term risk of dying postoperatively. A risk chart may be useful for this purpose and is pre-

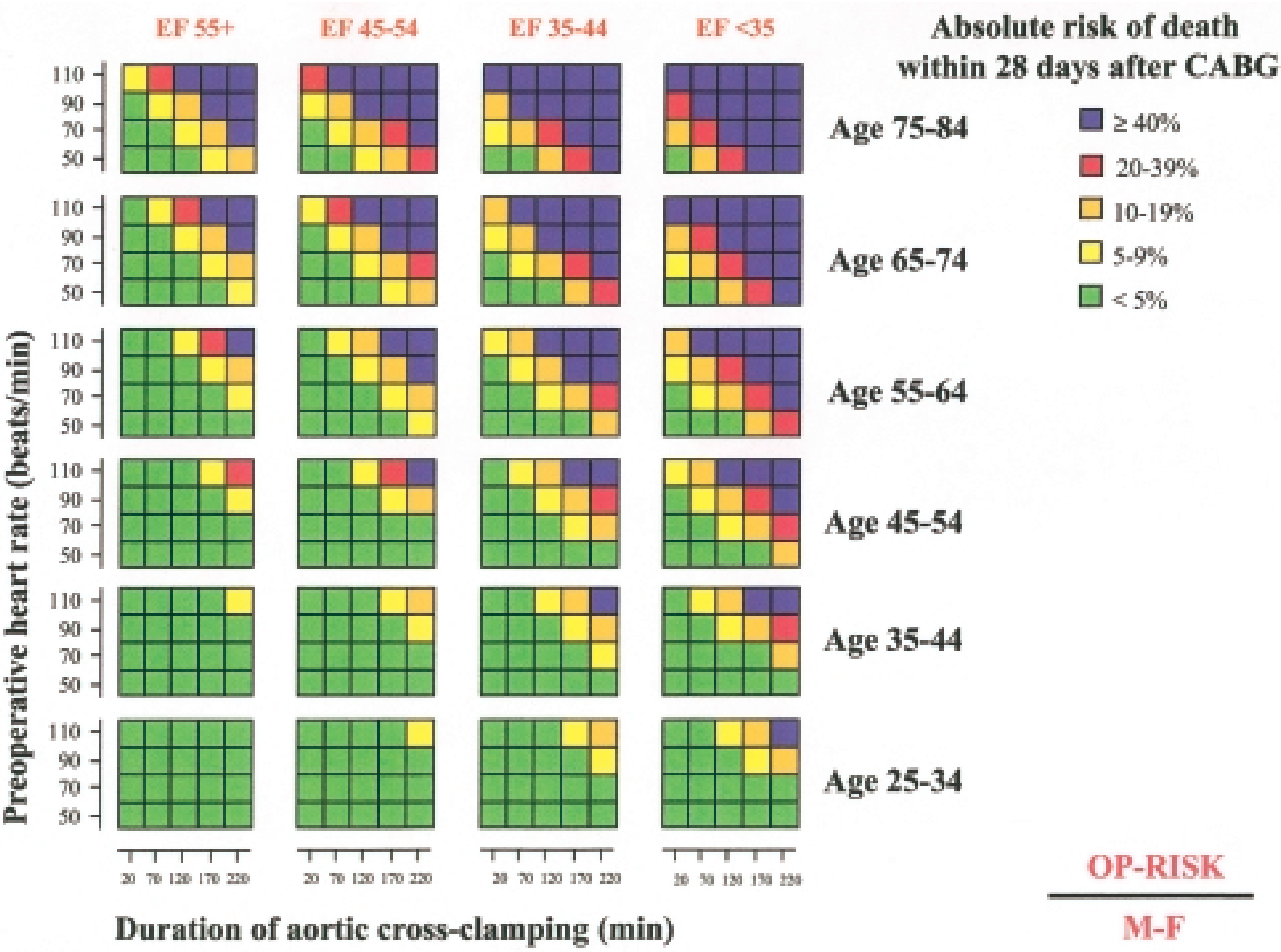

Figure 4. *Chart to calculate the absolute risk of death within 28 days of coronary artery bypass grafting (CABG) using four continuous covariates as derived from the OP-RISK study, according to a color scale ranging from < 5% to ≥ 40%. For the exact figures in each of the 480 cells see table VII. The chart equally applies to males (M) and females (F). Age in years. EF = ejection fraction (%).*

sented here for the first time. Moreover, the same four covariates are useful to construct a long-term multivariate model, which, in the present study, was however possible to obtain with data from only one center. Clearly, further studies in this domain are necessary.

A possible limitation of the present investigation and results is the fact that the number of events is quite small. Besides, the constructed chart contains a large number of cells. However, apart from the very rare investigations where the follow-up is extremely long, these truths also apply for other exercises of this type[9-12]. There is certainly the need to prospectively repeat the recruitment of baseline and follow-up data in larger Italian cohorts of CABG patients, hopefully with complete and more representative information. While the multivariate results of the present study, yet the first in the country, may form a useful basis for comparative purposes, it will be important to also look for other variables especially since the frequency of cardiac surgery without cardioplegia is on the increase.

The results of the OP-RISK study may be used for objective quality control and quality monitoring in cardiac surgery in Italy and their significance may well impinge upon similar studies performed elsewhere since these items are essential aspects of quality assurance and accreditation. In Europe CABG accounted for 184 330 interventions in 1995, two thirds of the overall number of open-heart operations performed with an increase from 1990 of 10% per year per million inhabitants, the steepest growth among cardiac surgical procedures[13]. The situation in Italy is slightly under the average European distribution with a total of 15 692 CABG patients operated upon (55%) out of 28 295 open-heart interventions performed in 1994[14]. As approximately one cardiac surgical center per million inhabitants is active in Europe with an average CABG work load of 390 interventions per center[13] and in Italy this accounts for an estimated expense [integrating monetary values based on the recently introduced Diagnosis Related Groups (DRG) and on a reimbursement policy from public Agencies] of roughly 6 million Euro per center, totaling an overall country expense of 0.3 billion Euro per year (≈2.5% of the 2002 budget deficit), the economic impact of CABG is vast. However, CABG may also represent a critical factor of hospital income, provided the patient's stay is under a giv-

Table VII. Risk (absolute probability) of death within 28 days of coronary artery bypass grafting in men and women aged 25-84 years, as a function of four risk factors.

Heart rate (b/min)	EF 55+					EF 45-54					EF 35-44					EF < 35				
	Aortic cross-clamping time (min)					Aortic cross-clamping time (min)					Aortic cross-clamping time (min)					Aortic cross-clamping time (min)				
	20	70	120	170	220	20	70	120	170	220	20	70	120	170	220	20	70	120	170	220
Age 75-84 years																				
110	8	22	50	86	100	20	48	84	99	100	46	82	99	100	100	80	99	100	100	100
90	3	7	19	45	82	7	18	43	80	99	17	41	78	99	100	39	76	98	100	100
70	1	2	6	17	41	2	6	16	39	76	6	15	37	73	98	14	35	71	97	100
50	0	1	2	6	15	1	2	5	14	35	2	5	13	34	69	5	13	32	66	95
Age 65-74 years																				
110	3	8	21	49	85	8	20	47	84	99	19	45	82	99	100	43	80	99	100	100
90	1	3	7	19	45	2	7	18	43	79	6	17	41	77	99	16	39	75	98	100
70	0	1	2	6	17	1	2	6	16	39	2	6	15	37	73	5	14	35	70	97
50	0	0	1	2	6	0	1	2	5	14	1	2	5	13	33	2	5	12	31	66
Age 55-64 years																				
110	1	3	8	21	49	3	8	20	47	83	7	19	44	81	99	18	42	79	99	100
90	0	1	3	7	19	1	2	7	18	42	2	6	17	40	77	6	16	38	75	98
70	0	0	1	2	6	0	1	2	6	16	1	2	5	15	36	2	5	14	35	70
50	0	0	0	1	2	0	0	1	2	5	0	1	2	5	13	1	2	5	12	31
Age 45-54 years																				
110	0	1	3	8	21	1	3	7	20	46	3	7	18	44	81	7	17	42	78	99
90	0	0	1	3	7	0	1	2	7	17	1	2	6	16	40	2	6	15	38	74
70	0	0	0	1	2	0	0	1	2	6	0	1	2	5	15	1	2	5	14	34
50	0	0	0	0	1	0	0	0	1	2	0	0	1	2	5	0	1	2	4	12
Age 35-44 years																				
110	0	0	1	3	8	0	1	3	7	19	1	2	7	18	43	2	6	17	41	78
90	0	0	0	1	2	0	0	1	2	6	0	1	2	6	16	1	2	6	15	37
70	0	0	0	0	1	0	0	0	1	2	0	0	1	2	5	0	1	2	5	13
50	0	0	0	0	0	0	0	0	0	1	0	0	0	1	2	0	0	1	2	4
Age 25-34 years																				
110	0	0	0	1	3	0	0	1	3	7	0	1	2	7	18	1	2	6	17	41
90	0	0	0	0	1	0	0	0	1	2	0	0	1	2	6	0	1	2	6	15
70	0	0	0	0	0	0	0	0	0	1	0	0	0	1	2	0	0	1	2	5
50	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	1	2

EF = ejection fraction (%).

en DRG-related threshold, which is 29 days in Italy. The cost/benefit ratio may then be switched in favor of the denominator, particularly so if the patient mix includes a large proportion of relatively low-risk individuals. This would enable a rapid bed turnover and concomitantly an increased revenue to the involved surgical center and hospital[15,16]. In this respect, the risk chart presented here may be of critical help.

Both in the United States[6,17-19] and Europe[20,21] there has been awareness that large multi-institutional databases are key ingredients of modern operative risk assessment in CABG and may represent a better and more objective means of quality control when elaborating the basis of the monetary evaluation of care[2,15,16].

However, in spite of the rather complex statistical models, such as Bayesian analysis[22-24] or neural networks[1] proposed so far for risk assessment, most studies made predictions using binary rather or more frequently than continuous variables, thus loosing a lot of information. This was an important obstacle to the implementation of neural networks which may have a theoretical pre-test probability of better performance[1] as compared to simpler models such as logistic regression[6,17,20,23-29], a condition that was not adequately taken into consideration[30]. On the other hand, most logistic regression users did categorize their own variables in order to derive odds ratios whereby the relative risk is obtained. On the other hand, it has not been always clear to what extent the average values of significant risk factors were representative of nationwide distributions[3], especially before the start of the largest databases[2].

A degree of uncertainty does exist with regard to several coefficients of significant covariates in published solutions, the list of risk factors is large enough and there are controversies as to the relevance of some of them if results from initial investigations[22,25,31-33] are compared to more recent ones[1,6,17,18,20,24,26,28,29]. Surprisingly, in this area there is a lack of solutions using the proportional hazards Cox model, a frequently adopted predictive tool for risk assessment in epidemiological studies[34] which has also been previously shown to provide the best possible fit in the presence of a time to event as short as 60 min in experimental studies of coronary artery ligation[7,8].

In the OP-RISK study, significant covariates and representative average values of risk factors such as age, cardiopulmonary bypass time and left ventricular function are not different from those selected elsewhere in similar investigations[16,18,29,35]. The absence of sex, diabetes, hypertension may come as a surprise but this too is supported by other studies[29,36]. Two relatively new risk factors were disclosed: tachycardia at the time of induction of anesthesia and the use of acetylsalicylic acid at 6-12 hours postoperatively. With a Cox proportional hazards model and logistic regression we have also demonstrated that a low ejection fraction, the aortic clamping time, age, heart rate and utilization of one arterial conduit are multivariate risk factors in the short and some of them also in the long term. Smith et al.[4] reported the same conclusions for ejection fraction and age. Otherwise, the severity of angina symptoms and lower weight were associated with an elevated risk of dying only in the early postoperative period, whereas vascular disease, diabetes, and the extent of myocardial damage were associated with an elevated risk of dying only in the long term. These data illustrate the differential influence of risk factors over time.

Assessing the accuracy of a multivariate prediction rule is not a trivial problem[6]. The prediction equation yields a conditional probability for each individual response. This is a number between 0 and 1 that expresses the estimated likelihood of the outcome on the basis of the supplied values for each of the independent variables. However, each patient from our own and similar studies either does or does not experience the outcome in question. Thus, a direct comparison of the predicted and observed outcomes for individual patients is not useful as a performance meter. The use of the ROC technique in assessing the accuracy of diagnostic systems has recently been reviewed[37], also adapting it to the prediction of the coronary artery bypass outcome[6]. It was stressed that the area under the ROC is independent of the relative frequencies of the events and that it allows the comparison of different diagnostic systems by putting them on a common scale[6,37].

In the majority of studies using ROC analysis for the prediction of CABG mortality, the area under the curve has varied from 0.695 to 0.814[6,28,38], with most results clustered between 0.70 and 0.76. Grover et al.[39] expressed the opinion that an area under the curve > 0.80 to 0.85 for CABG mortality prediction may never be achieved. Our results are therefore at variance with this opinion and, in particular, indicate that using both forced and stepwise logistic models ROC areas well over 0.84 may be obtained. It is quite possible that the use of actual ejection fraction values (a covariate that always showed the highest $|t \text{ value}|$ in each model) in the OP-RISK study may have contributed to this result. Thus, the evidence in our study is that the multivariate prediction rules are accurate and accordingly the variables included in the logistic model are reliable descriptors for the outcomes. This result also implies that the quality of data as obtained in our investigation was high enough to enable the optimal ROC result.

When comparing the results obtained by the logistic model with those of the Cox model, it is quite clear that the best fit was provided by the latter model, which reinforces previous experimental observations[7,8] on the one hand, and points to the usefulness of considering the time to event for predictive purposes on the other. Accordingly, Cox model-derived coefficients may be usefully employed for practical purposes in future longitudinal studies aimed at accurately predicting the outcome after CABG. Independently of the limits related to the latter model (see Appendix 2), one may also use the accelerated failure time model, on which the risk chart presented in this manuscript is based.

It is crucial to state that in order to apply risk functions (independently of the selected model) to given individuals, it is essential that: a) the distributions of significant risk factors are known in relation to the population wherefrom those given individuals come; b) model-specific (either Cox, logistic or accelerated failure time model) coefficients need to have been previously derived in the same population. Therefore, the results reported here are important for further comparative and/or applicative studies on CABG-related risk assessment monitoring and/or control in Italy, although the better performance of the Cox versus the logistic model results is of more general interest and certainly needs further consideration and study elsewhere. Furthermore, a peculiar aspect of our investigation was that both continuous and binary variables (without dichotomizing continuous ones) were used and that no score or point system was adopted. So doing, we were able to use all the informative content when the predictive models were run.

It is unclear whether a redundant (say model 2) or a parsimonious (say model 4) model need to be used for predictive purposes and risk stratification, although practical reasons may dictate the use of the latter. Certainly, when the construction of risk charts is the aim as in the present and in other exercises performed to stratify the risk of coronary heart disease in primary prevention[10,11], models containing say 4 to 6 significant covariates may largely be sufficient. It is our hope that the results presented may contribute to the selection of those significant covariates which should always be considered for risk stratification in CABG patients and also possibly contribute to the extent, after further studies, of risk charts in this area specifically elaborated for different surgical techniques.

In conclusion, the OP-RISK study produced relevant information for risk assessment and control in CABG and the results may be later compared, possibly merged (with appropriate statistical methods) and therefore applied to form the basis of objective quality assurance and accreditation of cardiac surgical institutions in Italy. Finally, for more general use, the results from this study indicate that risk assessment is more adequate with the Cox than with logistic models and therefore call for widespread attention to the time to event in CABG patients.

Appendix 1

The OP-RISK Italian Study Group

• Clinical centers
- Department of Cardiac Surgery, II Division of Cardiology "La Sapienza" University of Rome
  Paolo Emilio Puddu, MD, FESC, FACC (Principal Investigator)
  Gianluca Brancaccio, MD
  Marzia Leacche, MD
  Francesco Monti, MD
  Ugo Papalia, MD
  Pietro Paolo Campa, MD
  Benedetto Marino, MD (Study Co-Chairman)
- Division of Cardiothoracic Surgery, Hospital San Raffaele of Milan
  Anna Tramontin
  Giovanni Paolini, MD
  Adalberto Grossi, MD
- Institute of Cardiac Surgery, Second University of Naples
  Luigi Marino, MD
  Cesare Gagliardi, MD
  Nicola Spampinato, MD
- Institute of Cardiac Surgery, University of Bologna
  Carlo Orsi, MD
  Angelo Branzi, MD
  Angelo Pierangeli, MD

• Data coding and analysis
- Association for Cardiac Research of Rome
  Paolo Emilio Puddu, MD, FESC, FACC (Principal Investigator)
  Francesco Monti, MD
  Mariapaola Lanti, MD, PhD
  Alessandro Menotti, MD, PhD (Study Co-Chairman)

Appendix 2

Modeling of survival

The modeling of survival is based on complex mathematics and statistics, which is the common thread to various disciplines aimed at quantifying outcomes. Several models and techniques may be used. We here report a summary for easy referencing and interpreting of the study results.

Cox model. Briefly, the Cox model is an exponential model of survival (Y) prediction whereby it is easy to obtain the probability of an event (for example: the occurrence of early death after CABG alone) function (1-Y) given by:

$$1\text{-}Y = S_{(0)}^{\text{exponent of coefficient } A_1 (x_1 - X_1) \text{ * exponent of coefficient } A_n (x_n - X_n)}$$

which is calculated on the basis of the cumulative proportional hazard [$S_{(0)}$] and of the coefficients of covariates (A_1 to A_n), which enter the final solution of the model. One may run these models (as computed by default BMDP-2L settings as in the present study) with all covariates at step zero (forced method). For a given covariate, a significant association with the event under consideration is disclosed when the respective computed coefficient and its SE show the following relationship: $|(t)$ (that is coefficient/SE)$| > 1.96$, which gives $p < 0.05$. Moreover, it is possible to construct the probability of an event curve once the mean (X) is known for a given covariate, in view of the fact that the Cox model considers the vector or the difference between the value corresponding to the probability under calculation (x) and the mean value as existing in the overall population under study. Finally, it is important to consider the algebraic sign of the coefficient (t) or the value of the exponent of the coefficient (< or > 1) since for a - (t) (or exponent of the coefficient < 1) it follows that the given covariate has protective effects (or an inverse relation with the predicted event) whereas a + (t) (or exponent of coefficient > 1) enables one to define the risk index capabilities (or a direct relation with the predicted event) for another related covariate.

The "traditionally adopted" logistic model. Logistic regression has certainly been the most frequently used model for risk assessment in CABG-oriented investigations[6,17,20,23-29]. The logistic model, which does not handle for the time to event, classifies patients into one of two categories ("alive", equaling 1, or "dead", equaling 0) and applies this to several combinations of discrete and continuous variables[5]. After selecting the best combinations of predictive covariates by the Cox model (models 3 to 7) run in a first step, on the basis of the idea that the time to event was an important contributor to the best fitting[7,8] as compared to models not handling for the time to event, we then used these same sets to run logistic regression. The probability of death may easily be calculated by the logistic function:

$$1 / 1 + \exp - z$$

where $z = \alpha + \beta_1 x_1 + \beta_n x_n$

The logistic function (and the computed values of α, the constant, and β, the logistic coefficient) may be transformed (by using e^{β}, where e is the base of the natural logarithm) to compute the odds, a measure of the association of a binary variable (risk factor) with the occurrence of a given event (here death), which is a commonly used technique for the interpretation of probabilities[40]. To calculate the odds it is therefore necessary to categorize interval variables. This has two inherent disadvantages: first, that of loosing continuity in possible relationships with the index event and second, that of introducing a degree of uncertainty when the reference is defined. Concomitantly, it is hard to find studies where identical reference categories to be fed into the logistic function are constructed. This applies even for common, yet essential variables such as the ejection fraction[3,6,17,18,20,25-28].

ROC curve. Similar to other reports[36,41], in the present investigation the performance of the multivariate logistic model in the prediction of the study responses was evaluated by comparison of the ROC curve[5]. ROC curves are commonly used to evaluate and/or compare the performances of different operators or different diagnostic tests in situations where both the outcome predicted by the operator or test and the true outcome are known. Developed in the field of signal detection theory[37], ROC curves are conveniently used to describe the discrimination abilities of different tests or may be used to explore the trade-offs between the sensitivity and specificity for a test. In the CABG field, ROC curves were proposed as the optimal performance meter for multivariate prediction rules assessing in-hospital mortality[6]. The ROC is a plot of the true-positive rate (sensitivity) versus the false-positive rate (1 minus specificity) evaluated at a number of cut-off points or decision thresholds. The area under the ROC becomes a suitable single number (directly calculated by BMDP software which also depicts the corresponding graph) summary of the diagnostic accuracy of the test (in this investigation, the multivariate logistic model in predicting the study responses). A useless test, such as a coin flip, would yield an area of 0.5 (i.e. a positive test would be equally as likely to be a false-positive as a true-positive). A perfect diagnostic test would have an area under the ROC of 1.0. According to Swets[37], areas "between 0.5 and 0.7 or so represent a rather low accuracy – the true-positive proportion is not much greater than the false-positive proportion. Values of A (area) between 0.7 and 0.9 are useful for some purposes, and higher values represent a rather high accuracy". The area under the ROC curve is independent both of the cut-point criteria chosen and of the prevalence of the outcome of interest. Thus ROC areas may be legitimately compared across study populations (as defined by different sets of covariates)[5,6]. ROC areas were finally used to compare the accuracy of different techniques [forced method versus stepwise (using the maximum partial likelihood ratio test-MPLR)] employed to run the logistic models of this study.

Accelerated failure time model. The log-linear model incorporating the Weibull distribution of hazard is usually designated as an accelerated failure time model[5,40]. The model can be expressed as follows:

$$y = 1 - \exp\{-\exp[(\ln(t) - m)/s]\}$$

where y is the probability that an event occurs within a specific time (t), ln (t) is the natural log of t, m is the linear combination of a constant (c) and the products of estimated coefficients (b_i) times risk factor levels (x_i) (expressed as $c + b_1x_1 + b_2x_2 + b_nx_n$) and s is a scale factor whose reciprocal ($1/s$) is usually called γ, a parameter showing the shape of the hazard. Some relevant characteristics of the model are the following: 1) time represents an explicit covariate of the system and therefore the estimate of the hazard relates to the time between risk factor measurement and events; 2) the coefficients assume a negative algebraic sign when directly related to events (and vice versa a positive algebraic sign when inversely related to events) since their mathematical relationship is with time; 3) γ represents the shape of the hazard as a function of time; 4) a solution can estimate, in a legitimate way, the hazard for any length of follow-up if shorter than the maximum available in the data.

The accelerated failure time model has been repeatedly used in cardiology in disparate situations spanning from the construction of absolute risk charts, including the calculation of risk probabilities in the domain of the population-based prediction of events[10-12] to the prediction of risk factors for the occurrence of spontaneous arrhythmias in *in vitro* models also enabling one to assess the role of pharmacological interventions[42].

References

1. Lippmann RP, Shahian DM. Coronary artery bypass risk prediction using neural networks. Ann Thorac Surg 1997; 63: 1635-43.
2. Grover FL. Cardiothoracic databases: where are we headed? Ann Thorac Surg 1997; 63: 1531-2.
3. Puddu PE, Monti F, Brancaccio GL, et al, for the Gruppo di Studio OP-RISK. Analisi univariata su potenziali fattori di rischio della mortalità precoce (entro 28 giorni) dopo bypass aortocoronarico in Italia. Cardiologia 1997; 42: 957-69.
4. Smith LR, Harrell FE Jr, Rankin JS, et al. Determinants of early versus late cardiac death in patients undergoing coronary artery bypass graft surgery. Circulation 1991; 84 (Suppl III): 245-53.
5. Dixon WJ. BMDP statistical software manual: to accompany the 7.0 software release. Berkeley, CA: University of California Press, 1992.
6. O'Connor GT, Plume SK, Olmstead EM, et al. Multivariate prediction of in-hospital mortality associated with coronary artery bypass graft surgery. Northern New England Cardiovascular Disease Study Group. Circulation 1992; 85: 2110-8.
7. Puddu PE, Jouve R, Langlet F, Guillen JC, Lanti M, Reale A. Prevention of postischemic ventricular fibrillation late after right or left stellate ganglionectomy in dogs. Circulation 1988; 77: 935-46.
8. Puddu PE, Jouve R, Langlet F, Guillen JC, Lanti M, Reale A. Cox's analysis of ventricular fibrillation probability after acute myocardial ischemia in dogs: unilateral (right or left) stellectomy versus beta-blockade. J Appl Cardiol 1989; 4: 89-101.
9. Menotti A, Puddu PE, Lanti M. The use of coronary risk charts. G Ital Cardiol 1999; 29: 1004-6.
10. Menotti A, Puddu PE, Lanti M. Comparison of the Fram-

ingham risk function-based coronary chart with risk function from an Italian population study. Eur Heart J 2000; 21: 365-70.
11. Menotti A, Lanti M, Puddu PE, Kromhout D. Coronary heart disease incidence in northern and southern European populations: a reanalysis of the seven countries study for a European coronary risk chart. Heart 2000; 84: 238-44.
12. Menotti A, Lanti M, Puddu PE. Twenty-five-year cardiovascular disease incidence among middle-aged men. Disease burden, time shape, predictors, risk probabilities. Ital Heart J 2000; 1: 749-57.
13. Unger F. Cardiac interventions in Europe 1995: open heart surgery, PTCA, cardiac catheterisation. Ann Acad Sci Artium Europ 1996; 19: 1-59.
14. Unger F. European survey on cardiac interventions: open heart surgery, PTCA, cardiac catheterisation 1994. Ann Acad Sci Artium Europ 1995; 12: 1-59.
15. Mauldin PD, Weintraub WS, Becker ER. Predicting hospital costs for first-time coronary artery bypass grafting from preoperative and postoperative variables. Am J Cardiol 1994; 74: 772-5.
16. Smith LR, Milano CA, Molter BS, Elbeery JR, Sabiston DC Jr, Smith PK. Preoperative determinants of postoperative costs associated with coronary artery bypass graft surgery. Circulation 1994; 90 (Part 2): 124-8.
17. Higgins TL, Estafanous FG, Loop FD, Beck GJ, Blum JM, Paranandi L. Stratification of morbidity and mortality outcome by preoperative risk factors in coronary artery bypass patients. A clinical severity score. JAMA 1992; 267: 2344-8.
18. Edwards FH, Clark RE, Schwartz M. Coronary artery bypass grafting: the Society of Thoracic Surgeons National Database experience. Ann Thorac Surg 1994; 57: 12-9.
19. Clark RE. The Society of Thoracic Surgeons National Database status report. Ann Thorac Surg 1994; 57: 20-6.
20. Roques F, Gabrielle F, Michel P, De Vincentiis C, David M, Baudet E. Quality of care in adult heart surgery: proposal for a self-assessment approach based on a French multicenter study. Eur J Cardiothorac Surg 1995; 9: 433-40.
21. Salamon R. Report of EuroSCORE study. Info from Département d'Informatique Médicale. Bordeau, 1997: 1-6.
22. Edwards FH, Albus RA, Zajtchuk R, et al. Use of a Bayesian statistical model for risk assessment in coronary artery surgery. Ann Thorac Surg 1988; 45: 437-40.
23. Edwards FH, Clark RE, Schwartz M. Impact of internal mammary artery conduits on operative mortality in coronary revascularization. Ann Thorac Surg 1994; 57: 27-32.
24. Kurki TSO, Kataja M. Preoperative prediction of postoperative morbidity in coronary artery bypass grafting. Ann Thorac Surg 1996; 61: 1740-5.
25. Parsonnet V, Dean D, Bernstein AD, Shankar KG, McDermott JP. A method of uniform stratification of risk for evaluating the results of surgery in acquired adult heart disease. Circulation 1989; 79 (Part 2): 3-12.
26. Hannan EL, Kiburn H, O'Donnell JF, Lukacik G, Shields EP. Adult open heart surgery in New York State. An analysis of risk factors and hospital mortality rates. JAMA 1990; 264: 2768-74.
27. Tuman KJ, McCarthy RJ, March RJ, Najafi H, Ivankovich AD. Morbidity and duration of ICU stay after cardiac surgery. A model for preoperative risk assessment. Chest 1992; 102: 36-44.
28. Tu JV, Jaglal SB, Naylor CD, and the Steering Committee of the Provincial Adult Cardiac Care Network of Ontario. Multicenter validation of a risk index for mortality, intensive care unit stay, and overall hospital length of stay after cardiac surgery. Circulation 1995; 91: 677-84.
29. Higgins TL, Estafanous FG, Loop FD, et al. ICU admission score for predicting morbidity and mortality risk after coronary artery bypass grafting. Ann Thorac Surg 1997; 64: 1050-8.
30. Warner BA. Thoughts and considerations on modeling coronary bypass surgery risk. Ann Thorac Surg 1997; 63: 1529-30.
31. Loop FD, Berrettoni JN, Pichard A, Siegel W, Razavi M, Effler DB. Selection of the candidate for myocardial revascularization: a profile of high risk based on multivariate analysis. J Thorac Cardiovasc Surg 1975; 69: 40-51.
32. Kennedy JW, Kaiser GC, Fisher LD, et al. Multivariate discriminant analysis of the clinical and angiographic predictors of operative mortality from the Collaborative Study in Coronary Artery Surgery (CASS). J Thorac Cardiovasc Surg 1980; 80: 876-87.
33. Edwards FH, Albus RA, Zajtchuk R, Graeber GM, Barry MJ. A quality assurance model of operative mortality in coronary artery surgery. Ann Thorac Surg 1989; 47: 646-9.
34. The Italian Research Group of the Seven Countries Study. Twenty-five year incidence and prediction of coronary heart disease in two Italian rural population samples. Acta Cardiol 1986; 41: 283-99.
35. Sergeant P, Blackstone E, Meyns B. Can the outcome of coronary bypass grafting be predicted reliably? Eur J Cardiothorac Surg 1997; 11: 2-9.
36. Roques F, Nashef SAM, Michel P, et al. Risk factors and outcome in European cardiac surgery: analysis of the Euro SCORE multinational database of 19 030 patients. Eur J Cardiothorac Surg 1999; 15: 816-23.
37. Swets JA. Measuring the accuracy of diagnostic systems. Science 1988; 240: 1285-93.
38. Turner JS, Morgan CJ, Thakrar B, Pepper JR. Difficulties in predicting outcome in cardiac surgery patients. Crit Care Med 1995; 23: 1843-50.
39. Grover FL, Hammermeister KE, Shroyer ALW. Quality initiatives and the power of the database: what they are and how they run. Ann Thorac Surg 1995; 60: 1514-21.
40. Afifi AA, Clark V. Computer-aided multivariate analysis. 2nd edition. New York, NY: Van Nostrand Reinhold Company, 1990.
41. Puddu PE, Sugimoto S, Monti F, et al. Activation or block of adenosine triphosphate-sensitive potassium channel have opposite effects on postcardioplegic myocardial dysfunction, "stunning". A multivariate prediction based on relative operating characteristic curve. Cardiologia 1995; 40: 667-77.
42. Picard S, Rouet R, Monti F, et al. Proarrhythmic effects of DL- and D-sotalol on the "border zone" between normal and ischemic regions of isolated ventricular myocardium and antiarrhythmic effects on reperfusion. J Cardiovasc Pharmacol 1998; 31: 126-39.