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Comparative Application of Multivariate Models Developed in Italy and Europe to Predict Early (28 Days) and Late (1 Year) Postoperative Death after On- or Off-Pump Coronary Artery Bypass Grafting

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ABSTRACT

Objectives. The aim of this study was to compare the risk of death predictive performances of the OP-RISK, EuroSCORE, and Italian coronary artery bypass grafting (CABG) Outcome studies' functions when applied to a southern Italian cardiac surgery center (Sant'Anna hospital in Catanzaro [SAHCZ]), which contributed data to the Italian CABG Outcome study, and to see if this predictive index may be applied to on- and off-pump interventions.

Methods. The OP-RISK study data set was used to derive Weibull and logistic functions to predict early (28 days) and late (1 year) death rates following CABG based on ejection fraction, heart rate, age, and aortic cross-clamping time. Then the data of 385 CABG patients who underwent operations in 2003 in SAHCZ were collected with 1-year follow-up data, which also included data used to obtain EuroSCORE and Italian CABG Outcome study risk indices.

Results. Short- and long-term observed mortality rates after CABG were 2.59% and 5.88% in the SAHCZ series, largely dependent on whether CABG was alone (1.26% and 3.55%) or associated with ventriculoplasty (4.87% and 10.81%) or valve surgery (15.38% and 28.57%). There was a significant increasing trend ($P = .002$) of observed death rates in equinumeric tertiles of either OP-RISK (both Weibull and logistic) or EuroSCORE in the short term, whereas the trend was not significant for the Italian CABG Outcome study index. OP-RISK functions were significantly predictive for the long term ($P < .005$), as well as when only ejection fraction, heart rate, and age were considered ($P < .011$).

Conclusions. It is essential to use clinical data following CABG when outcome prediction is concerned. OP-RISK and EuroSCORE indices are equally predictive in our experience, and a statistically significant ($P = 0.02$) difference was observed with the Italian CABG Outcome study index, whose trend in tertiles of calculated risk was not apparent, which is unexpected and unexplained. OP-RISK functions were adequate for long-term prediction. Since aortic cross-clamping time may be absent from tested predictive functions (for both short and long term), off-pump CABG mortality may also be predicted as similar to on-pump intervention mortality.

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INTRODUCTION

Risk-adjusted short-term (30 days) outcomes following on- or off-pump isolated coronary artery bypass graft (CABG) in 34,310 of a total 48,634 patients (70%) who underwent CABG operations in 82 centers in Italy have recently indicated that, among 64 centers, 23% were outliers in comparison with a reference mortality rate of 2.61% [Seccareccia 2006]. Crude 30-day mortality rates varied from 0.33% to 7.63% among centers, and 95% confidence intervals ranged from as low as 0 to much higher than 11% [Seccareccia 2006]. The project lasted from January 2002 to September 2004 and was launched by the Italian Ministry of Health in conjunction with the National Institute of Health, based on the voluntary participation of most cardiac surgery centers in Italy [Seccareccia 2003]. Although it was noted that Italy now joins USA and UK in the regular monitoring of cardiac surgical outcomes, which by itself may have the well-known result of improving the performance, this unsurprising study on CABG outcome was also questioned since one may see a new 22-factor risk model useless in comparison with the EuroSCORE experience, inasmuch as the European model was not used alongside the new Italian model [Nashef 2006]. On the other hand, results from the study were criticized since the range of the observational period was extremely wide among the participating centers (6-29 months) and the definition of risk parameters was not well detailed with a reported rate of risk factors well out proportion to all recent internationally published experiences. For example, cardiogenic shock ranged from 0.2% to 7.2%, obstructive peripheral arterial disease was as high as 40% in some centers, and emergency case frequency varied from 0.2% to 14% [Nashef 2006]. It was noted that the study produced a ranking of centers which is peculiar, with the best performing centers having a low volume of work (273 procedures per year) while all centers performing more than 500 procedures per year were in the low rank, a situation not distant from the absurdity of refusing surgery to the sickest patients as an optimal means of reducing mortality rate [Nashef 2006].

Among 15 participating cardiac surgery centers in the Italian CABG Outcome study in southern Italy, of the total 23 recognized, there was only one center in Calabria [Seccareccia 2006], a region of 15,000 km^2 with 2 million inhabitants. The S. Anna Hospital in Catanzaro (see http://bpac.iss.it: center number 100) contributed with 641 patients (1.9% of total included) during 27 months of observation and presented a risk-adjusted 30-day mortality rate in isolated CABG (1.98%) not significantly different from the average overall study [Seccareccia 2006]. By concentrating attention on only patients undergoing operation in 2003 to later obtain 1-year follow-up, the S. Anna Hospital series was selected to reapply multivariate predictive functions of mortality, obtained for both the short and long term, using continuous clinical variables [Puddu 1997, 2002], which has been rarely performed in Italy [Agabiti 2003; Seccareccia 2003; Ugolini 2004; Gimelli 2006; Seccareccia 2006]. A further objective was to use with this material the EuroSCORE [Roques 1995, 1999; Nashef 1999], a validated index of risk not only in Europe [Roques 2000; Nashef 2002; Yap 2006], and to compare its performance with different Italian predictive functions [Puddu 1997, 2002; Seccareccia 2006]. Moreover, whether interventions were performed on- or off-pump [Wijeysundera 2005] was considered and adapted functions were purposefully used.

It is important to stress, as elegantly addressed quite recently [Nilsson 2006], that few comparative studies of different risk algorithms exist and that the relative performance of the risk-scoring systems currently used remains unclear; very few were performed in Italy and only logistic functions were in general compared. On the other hand, there is a high pretest probability that is also different from logistic function–based models and performs adequately for predictive purposes in CABG-oriented contexts [Puddu 1988, 2002; Menotti 2000, 2004].

MATERIALS AND METHODS

To effectively pursue these study objectives, the original data set of the OP-RISK study [Puddu 1997, 2002] were purposefully reanalyzed and the data of all patients receiving CABG interventions at S. Anna Hospital in Catanzaro during 2003 were collected along with the coded results of specific telephone interviews performed by a doctor to assess both short- and long-term cardiovascular death incidence according to a previously reported method [Puddu 1997].

Functions Derived from the OP-RISK Experience

The multicenter OP-RISK study, developed from 1994 to 1996 in Italy [Puddu 1997, 2002], was aimed at: (1) investigating early (28 days) death rates following lone CABG among patients recruited from 4 centers, representing nationwide distribution; (2) defining possible risk factors for early mortality, mostly among clinical continuous variables; (3) building risk functions for early mortality after lone CABG in Italy, based on predictive risk factors. Briefly, a total of 1126 patients were operated on in 4 participating centers. Of these, 2 were located in northern (Milan and Bologna), 1 in central (Rome), and 1 in southern (Naples) Italy and 51 in-hospital deaths (4.53%) were reported officially (to the Italian Society of Cardiac Surgery). Data on 984 patients (87%) with complete 28-day follow-up as obtained by telephone interviews and review of hospital and clinical data were included in the study. Among these patients, crude mortality (4.47%) was similar to that reported officially among the overall patients operated on in the participating centers. Nonincluded patients (n = 142, 13% of total) were frequently from other regions and could not be reached by telephone. In a subgroup of 416 patients operated on at the University of Rome "La Sapienza" cardiac surgery center, 1-year survival was also ascertained. Official in-hospital mortality, as reported to the Italian Society of Cardiac Surgery from 1994 to 1996, ranged in Italy from 2.58% to 3.45% in uncomplicated CABG (89% of total patients operated on) and to 10% in complicated CABG [Puddu 1997, 2002].

The final results of the OP-RISK study were published in 2002 [Puddu 2002] when the CABG Outcome Italian study was launched [Seccareccia 2003, 2006], for which Cox and logistic regression models were produced whereby the potent predictive contribution of ejection fraction, heart rate, age, and aortic cross-clamping time were shown. Furthermore, the performance of the predictive subset of covariates on early mortality was shown to also predict adequately (apart from heart rate) late deaths. Finally, a risk chart to predict early mortality based on the abovementioned 4 covariates was constructed as a means to look for clinical applicability of the results obtained by translating complex multivariate modeling into a daily useful tool.

The original OP-RISK data set was used here to rerun multivariate statistics with methods previously reported in detail [Puddu 2002]. Briefly, accelerated failure time and logistic models were obtained by entering ejection fraction, heart rate, age, and aortic cross-clamping time as predictive covariates of both short- and long-term mortality.

Covariate Selection in the Study Population

Patient-, cardiac-, and operation-related factors as defined and scored in EuroSCORE's Table 2 original publication [Nashef 1999] were considered, along with the variables providing significant multivariate logistic regression coefficients as described in Table 2 of the CABG Italian Outcome study [Seccareccia 2006]. The clinical records of all 385 patients undergoing CABG in 2003 at S. Anna Hospital in Catanzaro were reviewed. A data set was constructed with the mostly discrete (coded 0 or 1) variable series used for EuroSCORE or CABG Italian Outcome studies [Nashef 1999; Seccareccia 2006] and the continuous variables ejection fraction, heart rate, age, and aortic cross-clamping time as defined in the OP-RISK study [Puddu 1997; Puddu 2002] were included. EuroSCORE, CABG Italian Outcome study, and OP-RISK study indices were computed for each patient of the S. Anna Hospital series by considering either scores or Weibull or

Table 1. Rerun of Forced 4-Factor (Continuous) Weibull and Logistic Models in OP-RISK Study Original Data Set to Predict Both Short- and Long-Term Survival After Isolated Coronary Artery Bypass Grafting in Italy*

	Coefficients (*t* Values) of Factors								
	Ejection Fraction	Heart Rate	Age	Aortic Cross-Clamping Time	K	Scale	ROC Area	χ^2	*P*
OP-RISK study short-term prediction†									
Weibull models									
With 4 factors‡	0.1931 (4.53)	−0.1160 (−4.14)	−0.2092 (−3.72)	−0.0412 (−3.06)	30.09	1.98		94.44	.0000
With 3 factors	0.1974 (4.64)	−0.1120 (−3.95)	−0.2118 (−3.78)		26.28	2.01		84.61	.0000
Logistic models									
With 4 factors	−0.0996 (−5.01)	0.05985 (3.74)	0.1297 (4.05)	0.0207 (3.30)	−13.32		0.90	156.06	.0000
With 3 factors	−0.1026 (−5.30)	0.0549 (3.59)	0.1241 (4.05)		−10.66		0.86	165.95	.0000
OP-RISK study long-term prediction§									
Weibull models									
With 4 factors	0.2216 (2.51)	−0.0350 (-0.64)	−0.2438 (−2.06)	−0.0560 (−2.93)	24.47	2.79		24.78	.0001
With 3 factors	0.2421 (2.62)	−0.0262 (−0.46)	−0.2438 (−2.01)		22.05	2.96		16.42	.0009
Logistic models									
With 4 factors	−0.0858 (−3.01)	0.0144 (0.71)	0.0991 (2.47)	0.0174 (2.59)	−6.92		0.84	87.65	.0000
With 3 factors	−0.0864 (−3.22)	0.0100 (0.51)	0.0909 (2.39)		−4.73		0.78	94.14	.0000

*t value indicates a coefficient (model specific) divided by its standard error; K, model-specific constant; ln(t), natural logarithm of time with t expressed in hours.

†ln(t) = 6.5102; n = 687; mortality rate in used denominators = 4.51%.

‡This is the only model as yet published [Puddu 2002] and used to construct a chart with 480 cells to calculate the risk of death within 28 days of coronary artery bypass grafting using 4 continuous covariates, according to a color scale ranging from <5% to ≥40%.

§ln(t) = 9.5376; n = 227; mortality rate in used denominators = 6.61%.

logistic function solutions, based on published results [Nashef 1999; Seccareccia 2006] or recalculations (see Table 1) applicable to the relevant factors. To this end, individual patients' variables were used to compute respective studies' formulae using appropriate constants and coefficients to obtain derived risk. On- and off-pump interventions were also coded. Then by review of clinical forms and by telephone interviews, the vital status was ascertained until at least 365 days from the intervention. At 28 days postoperation (postop) information was obtained on all 385 patients; at 1-year there were 45 patients (of 375 alive at 28 days, 12%) who were unavailable for follow-up.

Statistics

Data in tables, figures, and text are expressed as mean ± standard deviation. Analysis of variance (F statistics) was used to test differences among groups of continuous variables, followed by *t* tests (with Bonferroni's correction) if needed. Chi-square analysis was used to test differences of discrete variables.

We have reported previously in detail the methods to obtain accelerated failure time (Weibull) and logistic models [Puddu 2002]. After obtaining either 4- (ejection fraction, heart rate, age, and aortic cross-clamping time, a series which may be used in on-pump CABG interventions) or 3-factor (ejection fraction, heart rate, and age, a series which may be used in off-pump CABG interventions) predictive (Weibull or logistic) models of both short- and long-term prediction of death in the original OP-RISK data set, these models were back applied to the OP-RISK data themselves and to the S. Anna Hospital series to predict mortality rates (±95% confidence intervals calculated with standard formulae).

For comparative purposes among different short-term model performances, patients of the S. Anna Hospital series were used: OP-RISK study (both Weibull and logistic), EuroSCORE, and Italian CABG Outcome study (logistic in both studies) functions were applied to calculate the respective death risks in each of these subjects. For long-term model performances, because of the absence of pertinent functions from EuroSCORE or Italian CABG Outcome study, only OP-RISK study functions (both Weibull and logistic) were used. Equinumeric tertiles of calculated risks were formed and the proportions of observed deaths were assessed in these tertile classes. The Cochran-Armitage test for trend in proportions (as provided by NCSS 2001 software, Kaysville, UT, USA) and chi-square statistics were used to assess the differences inside and among these distributions. Chi-square tables were also used: with 2 degrees of freedom, absolute chi-square differences of >5.99, >7.82, and >9.21 were considered to provide .05, .02, and .01 *P* values, respectively, in the difference of paired trends. Finally, as a means of providing a potentially meaningful clinical method to evaluate the respective performance of EuroSCORE, Italian CABG Outcome, and OP-RISK studies indices, each of the entire calculated range of these indices was split into 3 parts whose numerical values were similarly large but increasing. Then in each

Table 2. Average Values (± SD of Factors) of 4 Continuous Factors in the OP-RISK Study and S. Anna Hospital Series, According to Subgroup Distributions*

	n	Ejection Fraction, %	Heart Rate, b/min	Age, y	Aortic Cross-Clamping Time, min	n
OP-RISK study average values						
Short-term prediction	687	52 (11)	73 (14)	61 (9)	76 (30)	687
Long-term prediction	227	54 (10)	77 (15)	59 (9)	63 (31)	227
S. Anna Hospital series average values						
Short-term prediction	385	49 (11)	69 (13)	66 (9)	57 (30)	274
Long-term prediction	340	49 (11)	69 (12)	66 (9)	57 (31)	238
Alive at 28 days postoperation	375	49 (11)	69 (13)	65 (9)	56 (26)	266
Dead at 28 days postoperation	10	37 (13)†	79 (12)†	73 (5)‡	118 (74)†	8
Alive at 1 year	320	50 (11)	68 (12)	65 (9)	55 (26)	222
Dead 28 days/1 year postoperation	10	47 (19)	69 (13)	69 (9)	60 (30)	8
Unavailable for follow-up	45	48 (12)	73 (19)	66 (11)	58 (24)	36
Off-pump interventions	111	51 (10)	68 (12)	68 (9)	—	—
On-pump interventions	274	48 (12)†	70 (14)	65 (9)‡	57 (30)	274
Elective interventions	311	50 (11)	68 (12)	66 (9)	59 (31)	216
Emergency interventions	74	46 (11)‡	74 (18)‡	65 (10)	53 (26)	58
CABG alone	318	51 (10)	68 (13)	66 (9)	51 (20)	207
CABG + ventriculoplasty	41	38 (10)	72 (12)	64 (10)	53 (25)	41
CABG + valve surgery	26	44 (11)§	78 (14)§	70 (8)†	112 (47)§	26

*For analysis of variance, in case of 3 subgroups, at least $P < .05$ for ejection fraction subgroups 1 to 2 and 1 to 3; heart rate, subgroups 1 to 3; age, subgroups 1 to 3 and 2 to 3; aortic cross-clamping time, subgroups 1 to 3 and 2 to 3; last column refers to patients (n) undergoing on-pump to CABG for whom the variable aortic cross-clamping time was obtained.

†$P < .05$.

‡$P < .01$.

§$P < .001$.

third, short-term deaths were counted and the proportions calculated in each third of dead and alive individuals. Chi-square analysis with 2 degrees of freedom was similarly used to test differences.

BMDP (Statistical Solutions, Saugus, MD, USA) and NCSS statistical software were used [Puddu 1988, 2002; Menotti 2000, 2004]. A *P* value <.05 was considered significant.

RESULTS

The study included 687 patients undergoing isolated CABG operations from the original OP-RISK data set, showing crude mortality rates of 4.51% and 6.61% (the latter figure from 227 patients) in the short- and long-term, respectively [Puddu 2002]. In 2003, there were 659 patients undergoing cardiac surgery at the S. Anna Hospital and overall there were 30 in-hospital deaths (4.55%). After excluding reinterventions (n = 28), dissections, ascending aorta interventions with conservative surgery on the aortic valve (n = 40), mitral valvulopasty (n = 44) or replacements (n = 36), replacements for (n = 73) or conservative surgery on (n = 15) the aortic valve, and miscellaneous interventions without CABG (n=38), there were 385 patients who underwent CABG, with 10 deaths at 28 days postop (2.59%) and 20 cumulative deaths at 1 year (20 of 340, 5.88%). However at 28 days, information was complete for all patients, whereas 45 patients (12%) were unavailable for 1-year follow-up. In the S. Anna Hospital series, crude mortality rates at 28 days postop for CABG alone, CABG + ventriculoplasty, and CABG + valve surgery were 4 of 318 (1.26%), 2 of 41 (4.87%), and 4 of 26 (15.38%), respectively; corresponding figures for crude mortality rates at 1-year postop were 10 of 282 (3.55%), 4 of 37 (10.81%), and 6 of 21 (28.57%), respectively. These distributions were significantly different ($P < .01$). Therefore, concomitant interventions heavily and expectedly influenced crude mortality rates in the S. Anna Hospital series, in both the short and long term.

Selection of Predictive Models and Covariates

Table 1 shows the predictive model parameters of 4 risk factors selected from the OP-RISK study, after cross comparisons of several different set of covariates and models, used to construct a potentially useful clinical chart using the accelerated failure time (Weibull) model that prevents the necessity of demonstrating the proportionality of hazard rates, as with the Cox model [Puddu 2002]. The "traditionally adopted" logistic model [Puddu 2002] parameters are also shown. Coefficients (which are model dependent and, therefore, may not be compared) and *t* values for ejection fraction, heart rate, age, and aortic cross-clamping time are tabulated out of

Weibull and logistic models either from short- or long-term prediction. All models are statistically significant. ROC plot areas in case of logistic models are excellent, well above accepted cut-off values [Puddu 2002].

The OP-RISK study enabled selection of factors forced in either Weibull or logistic models run to obtain (Table 1) coefficients (and *t* values), constants (K), and scales and ROC plot areas, along with statistical significance of the results [Puddu 2002]. The OP-RISK study was a multicenter investigation performed from 1994 to 1996 in Italy to predict multivariate early and late (ln[t] in hours) mortality after CABG alone, with final results published in March 2002 as the largest country experience (N = 1126) before the Italian CABG Outcome study (N = 34,310) was launched [Seccareccia 2003, 2006]. However, since 1999, the EuroSCORE [Nashef 1999; Roques 1999] results (N = 13,302) were fully obtained with a large validation data set (N = 1479). Therefore the parameters derived from the OP-RISK experience with Weibull and logistic models were used for comparison with those obtained from the EuroSCORE and Italian CABG Outcome studies to investigate the respective performances when back applied to a single center's series of patients (N = 385) operated on in 2003, a center which contributed information to the Italian CABG Outcome assessment (Center number 100, see http://bpac.iss.it/).

The average values of the 4 continuous factors entering the models illustrated in Table 1 are shown in Table 2 for both the OP-RISK study and the S. Anna Hospital series. Table 2 indicates that, based on the average values of ejection fraction, heart rate, age, and aortic cross-clamping time, patients included in 1994 in the OP-RISK study were at higher risk of developing adverse outcome (except in reference to ejection fraction) as compared to patients operated on in 2003 at S. Anna Hospital. Moreover, in the latter series, there were significant differences for these 4 factors according to the status at 28 days postop (alive or dead), whether the presence of on- (n = 274) or off-pump (n = 111, 29%) intervention or elective (n = 311) versus emergency (n = 74, 19%) surgery induced less dramatic differences. Finally, patients undergoing CABG alone (n = 318, 83%) presented with average values of these 4 factors in much better conditions than those receiving ventriculoplasty or valve surgery, clearly pointing to a higher risk of adverse outcome for the latter procedures, as shown by the abovementioned crude mortality rates.

Observed and Predicted Mortality Rates

As a logical corollarium of data illustrated in Table 2, overall observed mortality rates (both for the short and long term) were higher in the OP-RISK than in the S. Anna Hospital series. This is shown in Table 3, which also illustrates predicted mortality rates in both OP-RISK and S. Anna Hospital series along with 95% confidence intervals. It is quite clear that in both experiences the back application of both Weibull and logistic models (irrespective of the included factors number) underestimates OP-RISK study observed rates, whereas S. Anna Hospital rates are more adequately predicted in the short term and overestimated in the long term.

Table 3. Back Application of OP-RISK Study–Derived Multivariate Functions of Table 1 to Predict Both Early (28 Days [Short-Term]) and Late (1 Year [Long-Term]) Mortality Rates

	Mortality Rates	
	Short-Term	Long-Term
Observed, %, (N deaths/N total)		
OP-RISK study	4.51 (31/687)	6.61 (15/227)
S. Anna Hospital series	2.59 (10/385)*	5.88 (20/340)†
Predicted, % (lower-upper 95% confidence intervals)		
OP-RISK study		
Weibull models‡		
With 4 factors	1.01 (0.99-1.03)	10.38 (10.35-10.41)
With 3 factors	1.29 (1.27-1.31)	4.60 (4.57-4.63)
Logistic models§		
With 4 factors	1.06 (1.04-1.08)	3.08 (3.05-3.11)
With 3 factors	1.33 (1.31-1.35)	3.87 (3.84-3.90)
S. Anna Hospital series		
Weibull models‡		
With 4 factors	1.08 (1.06-1.10)	19.70 (19.67-19.73)
With 3 factors	2.04 (2.02-2.06)	10.10 (10.07-10.13)
Logistic models§		
With 4 factors	1.25 (1.23-1.27)	6.58 (6.55-6.61)
With 3 factors	2.29 (2.27-2.31)	8.85 (8.82-8.88)

*Crude mortality rates at 28 days postoperation in coronary artery bypass grafting (CABG) alone, CABG + ventriculoplasty, and CABG + valve surgery were 4 of 318 (1.26%), 2 of 41 (4.87%), and 4 of 26 (15.38%), respectively.

†Crude mortality rates at 1 year postoperation in CABG alone, CABG + ventriculoplasty, and CABG + valve surgery were 10 of 282 (3.55%), 4 of 37 (10.81%), and 6 of 21 (28.57%), respectively.

‡Data derived using the formula $y = 1 - \exp\{-\exp[(\ln(t) - m)/s]\}$ where y is the probability of an event within a specific time (t), ln(t) is the natural logarithm of t, m is the linear combination of a constant (c) and the products of estimated coefficients (b_i) multiplied by 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.

§Data derived using the formula $1/1 + \exp - z$, where $z = \alpha + \beta_1 x_1 + \beta_n x_n$.

Whereas the results of Table 3 condense the general difficulties encountered when one tries to reapply multivariate statistics to the real clinical world [Nilsson 2006], it is important to underline that these discrepancies did exist in the presence of clinically relevant factors having the characteristics of continuous measured variables, although in a relatively short series, and therefore a higher pretest predictive probability as compared to functions using discrete variables [Puddu 1988, 1997, 2002; Menotti 2000, 2004; Nilsson 2006].

Comparing the Performance of Predictive Models

Since an especially important issue of multivariate modeling and prediction relates to which model and/or function is best suited to describe a given phenomenon, the S. Anna Hospital series was used to compare for both the short and

Table 4. Early (28 Days [Short-Term]) and Late (1 year [Long-Term]) Mortality of Patients*

	Death Rates (%) in Tertile Classes of Estimated Risk					
	T1	T2	T3	T3/T1	χ^2	*P*†
S. Anna Hospital series short-term prediction (denominator = 385)‡						
OP-RISK study functions						
Weibull models						
With 4 factors	0	1.6	6.3	6.3/0	10.72	.002
With 3 factors	0.8	0	7.0	8.7	15.06	.002
Logistic models						
With 4 factors	0	1.6	6.3	6.3/0	10.72	.002
With 3 factors	0.8	0	7.0	8.7	15.06	.002
EuroSCORE§	0	1.6	6.3	6.3/0	10.72	.002
Italian CABG Outcome study§	0.8	3.1	3.9	4.9	2.66	.116
S. Anna Hospital series long-term prediction (denominator = 340)‡						
OP-RISK study functions						
Weibull models						
With 4 factors	0	7.9	9.7	9.7/0	10.93	.002
With 3 factors	2.6	3.5	11.5	4.4	9.74	.005
Logistic models						
With 4 factors	0	7.9	9.7	9.7/0	10.93	.002
With 3 factors	3.5	2.6	11.5	3.3	9.75	.011

*Data obtained from patients undergoing operation for whom observed death rates were computed at S. Anna Hospital in 2003. Data was calculated according to the functions derived from the OP-RISK, EuroSCORE, and Italian CABG Outcome studies and were applied to individual patients and then distributed in equinumeric tertiles of calculated risk. T indicates tertile. Tertiles T1, T2, and T3 included 128, 129, and 128 patients for short-term prediction and 113, 114, and 113 patients for long-term prediction, respectively.

†Data derived by performing the Cochran-Armitage proportion trend test (calculated by NCSS software released on December 19, 2001 by www.ncss.com), whereby H_0: p1 = p2 = p3 = . . . pk and H_0 may be rejected with the exact tabulated significance level. Another way to look at these proportions and derived relative risk (T3/T1) is by χ^2 statistics, whereby one may also derive significance of difference among paired predictions with different models, since absolute χ^2 differences >5.99 gives $P < .05$, >7.82 gives $P < .02$, and >9.21 gives $P < .01$.

‡There were 10 deaths at 28 days and 20 deaths at 1 year. Whereas at 28 days, information was complete for all patients, there were 45 patients (12%) who were unavailable for 1 year follow-up. See also Table 2. A conservative approach was considered of 20/340 (5.88%) for the long-term death rate.

§Average (± SD) and extreme values of EuroSCORE and Italian CABG Outcome study indices calculated for S. Anna Hospital series were respectively 7.44 ± 3.01 (range, 2-26) and 3.12 ± 3.77 (range, 0.35-28.09). Since crude mortality rates at 28 days postoperation were significantly different among the categories coronary artery bypass grafting (CABG) alone (n = 318), CABG + ventriculoplasty (n = 41), and CABG + valve surgery (n = 26) (see legend to Table 3), it is of interest to assess whether there is a difference in average values of EuroSCORE or Italian CABG Outcome study indices. The respective values were 7.25 ± 2.75, 7.88 ± 4.03, and 9.04 ± 3.83 for EuroSCORE (F = 4.78, $P < .009$; subgroup 1 versus 3, $P < .10$) and 3.05 ± 3.69, 3.34 ± 3.13, and 3.62 ± 5.43 for the Italian CABG Outcome study index (F = 0.36, *P* was not significant).

long term the performance of previously described predictive functions of CABG outcome in Italy and Europe [Nashef 1999; Puddu 2002; Seccareccia 2006]. To this end, Table 4 describes the results obtained with OP-RISK study functions and both EuroSCORE and Italian Outcome study indices for the short term, whereas only the functions from the former study were used for the long term, lacking those from the other studies. It is evident that in the short term the performance of OP-RISK study models and functions is excellent, irrespective of the included factors number, similar to EuroSCORE. The Italian Outcome study index is, on the other hand, not adequate. A statistical difference exists between trends of death rates from OP-RISK and EuroSCORE–derived tertile classes of estimated risk versus the trend obtained using the Italian Outcome study index. Of note is that the OP-RISK study functions and the factors included showed an optimal performance in the long term.

If the more clinically adapted method of analyzing the proportions of patients who died in each third of the entire calculated range of each predictive index is taken into consideration (global results not shown), the general conclusion derived from Table 4 is confirmed. For example, with EuroSCORE the proportion of short-term deaths, of patients presenting numerical values of calculated risk lying in each third of the index range, were 0.7% (2 of 302), 8.5% (7 of 82), and 100% (1 of 1) (chi-square, 53.40; $P < .0001$). Corresponding figures for the OP-RISK study 3-factor logistic model–based index were 1.7% (6 of 360), 12.5% (3 of 24), and 100% (1 of 1) (chi-square, 48.03, $P < .0001$), whereas for the Italian CABG Outcome study index statistical significance was not achieved and the proportions were 2.5% (9 of 358), 4.2% (1 of 24), and 0% (0 of 3) (chi-square, 0.31; *P* was not significant). These differences were reproduced among on- or off-pump interventions.

DISCUSSION

It has nicely been pointed out [De Paulis 2003] that the baseline mortality for isolated CABG was found to decrease from 3.4% to 0.4% in the absence of any risk factors among the great number of risk factors described in the EuroSCORE database on 19,030 patients [Roques 1999], implicating that the absolute risk of the processes and structure of care is almost absent and that, accordingly, the profound impact of a patient's risk profile on the outcome should guide any study aimed at predicting mortality or at assessing quality of care. Strenuous efforts on both sides of the Atlantic have now clearly shown that clinical risk factors defining preoperative and surgical characteristics may profoundly affect outcome, although large differences exist in the list of those specific factors to be considered significantly predictive [Loop 1975; Kennedy 1980; Parsonnet 1989; O'Connor 1992; Nashef 1999, 2002; Roques 1999, 2000; Shroyer 2003]. There is no doubt, however, that clinical predictors influence outcome more than administrative variables [Puddu 2002; Agabiti 2003; De Paulis 2003; Ugolini 2004; Gimelli 2006]. Thus ejection fraction, heart rate, age, and aortic cross-clamping time, as measured in the OP-RISK study after careful selection from a much larger list [Puddu 1997, 2002] may index mostly important information obtained from different factors in other investigations [Loop 1975; Kennedy 1980; Parsonnet 1989; O'Connor 1992]. A critical point, common to all multivariate predictive approaches and their possible reapplication, is finally whether discrete variables, such as those obtained in the EuroSCORE and CABG Italian Outcome studies [Nashef 1999; Seccareccia 2006] are as effective as continuous clinical variables [Puddu 2002] for predictive purposes [Menotti 2004].

When summarizing the outcome data through a survival predictive model one can have several objectives in mind: (A) to identify variables mechanistically important, to be subsequently investigated in depth in other observational or, preferably, experimental studies; (B) to build a model that can be actually transposed as such to situations external from the one under investigation for prognostic studies at an individual level or to provide a baseline for studies of performance of surgical units. While statistical significance of single independent variables or even degree of fit of one model in respect to another are 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 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 incomparable among investigations [Puddu 1997, 2002]. Only studies comparatively assessing model and covariate selections obtained in different settings, such as this one, may enable conclusions on models' stability. However, these studies were few [Nilsson 2006] and only occasionally performed in Italy, always assessing scores derived from logistic functions.

It is crucial to state that to apply risk functions (independent 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, a fact very well known in epidemiology and whose correct application may lower the inappropriateness of cross applications of functions and experiences to different cultural domains [Menotti 2000, 2004]; (B) model-specific (either Cox, logistic, or Weibull) coefficients need to have been previously derived in the same population [Puddu 2002; Menotti 2004]. In discussing the results of the OP-RISK study, we stated [Puddu 2002] that these were "important for further comparative and/or applicative studies on CABG-related risk assessment monitoring and/or control in Italy. . . Furthermore, a peculiar aspect of our investigation was that both continuous and binary variables (without dichotomising continuous ones) were used and that no score or point system was adopted. So doing enabled all informative content to be used when the predictive models were run."

In this investigation, we show that Weibull or logistic models based on 4 clinical factors with coefficients obtained in the original OP-RISK data set collected in Italy from 1994 to 1996 [Puddu 2002] are as performant as EuroSCORE [Nashef 1999] in defining short-term relative risk of death in a single southern Italian cardiac surgery center, whereas the recently reported Italian CABG Outcome study function [Seccareccia 2003] is not. Moreover, specific Weibull and logistic functions derived from the OP-RISK study experience are very performant in the long term, which reinforces the relevance of the 4 clinical covariates selected for short-term prediction. Our results lend support to the criticisms raised [Nashef 2006] about the Italian CABG Outcome study results [Seccareccia 2006], inasmuch as the S. Anna Hospital series of patients that was the basis for the comparative performance of models in the present investigation (Table 4) was included, although as a small participant, in the Italian CABG Outcome study data set with a crude mortality rate not significantly different from the average overall study result [Seccareccia 2006] (http://bpac.iss.it; 1.98% versus 2.61%; $P = .383$). The reasons for the discrepancy are not clear. Rather, it seems that our results may underestimate the phenomenon. In fact, short-term crude mortality rate was 1.26% (4 of 318) among patients from the S. Anna Hospital series undergoing operation in 2003 with CABG alone and 2.59% (10 of 385) among overall patients included in the comparative assessment of functions. On the other hand, the Italian CABG Outcome study eliminated patients with interventions concomitant to CABG who are, as also shown here, at increased risk for death. It is therefore important to point out that when the distribution of interventions other than CABG alone were considered (Table 4) there was a significant difference for EuroSCORE average values among CABG groups, whereas this was not seen for the Italian CABG Outcome study index.

One peculiar extension of this investigation relates to the possibility of applying the results to the prediction of death in patients receiving off-pump CABG, a technique advocated in comparison to on-pump interventions as decreasing the risk, although with results yet not firmly confirmed since randomized controlled trials did not find, aside from atrial fibrillation, statistically significant reductions in short-term mortality (and morbidity) demonstrated by observational studies [Wijeysundera 2005]. Indeed, ejection fraction, heart rate, and age as predictive factors were of extremely good comparative performance in the short term and were of significant performance in the long term (Table 4), thus indicating that death risks in off-pump CABG interventions may as well be predicted. Of note is that the Italian CABG Outcome study did not analyze on- versus off-pump CABG interventions and neither did it compute the contribution of the category, although information was obtained [Seccareccia 2006].

It was importantly underlined that knowledge of risk and comparative outcomes is no longer an "optimal extra" in cardiac surgery and should be as essential to the surgeon as the knowledge of surgical anatomy and techniques [Nashef 2002]. The choice of a risk model must to some extent depend on the unit and the audit resources to which it has access since the ideal future world with an international database of cardiac surgery to which all units will contribute data and from which accurate and individualized risk assessments will be at hand for surgeons and patients [Nashef 2002] is far from being even programmed. Instead, US algorithms remain proprietary and confidential [Nashef 2002; Shroyer 2003], whereas in Europe the simple additive EuroSCORE model has been shown to work well not only in CABG [Nashef 2002] and across many European countries [Roques 2000], but also in comparison with US models [Nashef 2002] and, with some limits, in different continents [Yap 2006]. The full logistic EuroSCORE model, very useful for some very high-risk patients, may be obtained publicly (www.euroscore.org). Therefore, cross comparison of EuroSCORE in the present investigation reinforces criticisms raised about the Italian CABG Outcome study index [Nashef 2006], especially since that study [Seccareccia 2006] did not compare with EuroSCORE itself [Nashef 2006] without a plausible explanation: most if not all of the covariates used to actually obtain EuroSCORE [Nashef 1999] were also measured [Seccareccia 2006]. On the other hand, our results reinforce the conclusions of the OP-RISK study, which produced a very simple chart based on the Weibull model (a series of which are also disclosed in Table 1) and ejection fraction, heart rate, age, and aortic cross-clamping time (as continuous variables) to index early death risk following CABG in clinical practice [Puddu 2002]. Of note, finally, is that the latter 4 factors had a significant attitude to also index long-term death risk in the present study.

Our study has some limits. Both the original OP-RISK data set and the S. Anna Hospital series are limited in comparison with other databases in this field [Nashef 1999, 2002; Shroyer 2003; Seccareccia 2006]. More specifically, the S. Anna Hospital series presented "only" 10 deaths at 28 days following CABG and 20 cumulative deaths at 1 year, which prevented risk-adjusted analyses in subgroups such as isolated CABG versus CABG with other interventions or on- versus off-pump CABG interventions, an approach that is important for further studies. Moreover, only cardiovascular mortality was assessed, whereas morbidity has been shown as critically important to index quality of care [Shroyer 2003]. As complications occur more frequently than death, risk-adjusted morbidity may in fact differentially impact quality of care and enhance a surgical team's ability to assess their quality, as recently shown from 503,478 CABG procedures in the 1997 to 1999 Society of Thoracic Surgeons US database. Only a slight correlation was found between risk-adjusted operative mortality and morbidity, whose crude rates were 3.05% and 13.40%, respectively [Shroyer 2003]. It remains for further investigations to enlarge this experience, to extend it in shape, follow-up duration, and completeness, and to include morbidity data and socioeconomic modeling of improved health care of enrolled patients.

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