Mortality After Primary PCI: A Novel Risk Model Including Vascular Access Site

The ALPHA Score

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Disclosure Statement

I do not have a financial interest / arrangement or affiliation with one or more organizations that could be perceived as a real or apparent conflict of interest in the context of the subject of this presentation.

Background

- Mortality risk of STEMI patients shows high variability.
- In order to assess individual risk, a number of scoring systems have been developed (TIMI, PAMI, Zwolle, CADILLAC, APEX-AMI, GRACE 2.0).
- Most common variables used in existing models: age, Killip class, heart rate and SBP at admission, ECG localization of the MI, ischemia time, GFR, occurrence of triple vessel disease, and final TIMI flow grade.
- Despite this plethora of models, as treatment approaches evolve over time, there is a need to build new risk prediction systems to preserve / improve prognostic accuracy.

Background

- One of the most relevant innovations in this context is transradial primary PCI, since this technique is capable to reduce mortality.
- Previous risk models have not considered access site as a candidate predictor. A model employing access site as a variable would be able to identify patients who may benefit most from transradial primary PCI.
- Furthermore, existing scoring systems may not be accurate for the whole risk spectrum of patients, since many of them were constructed using low risk populations of trials excluding cardiogenic shock.
- For the foregoing reasons, we conducted a single center, prospective cohort study to develop and comparatively validate a registry-based admission risk model including access site as candidate variable for predicting 30-day mortality of STEMI patients.

Methods

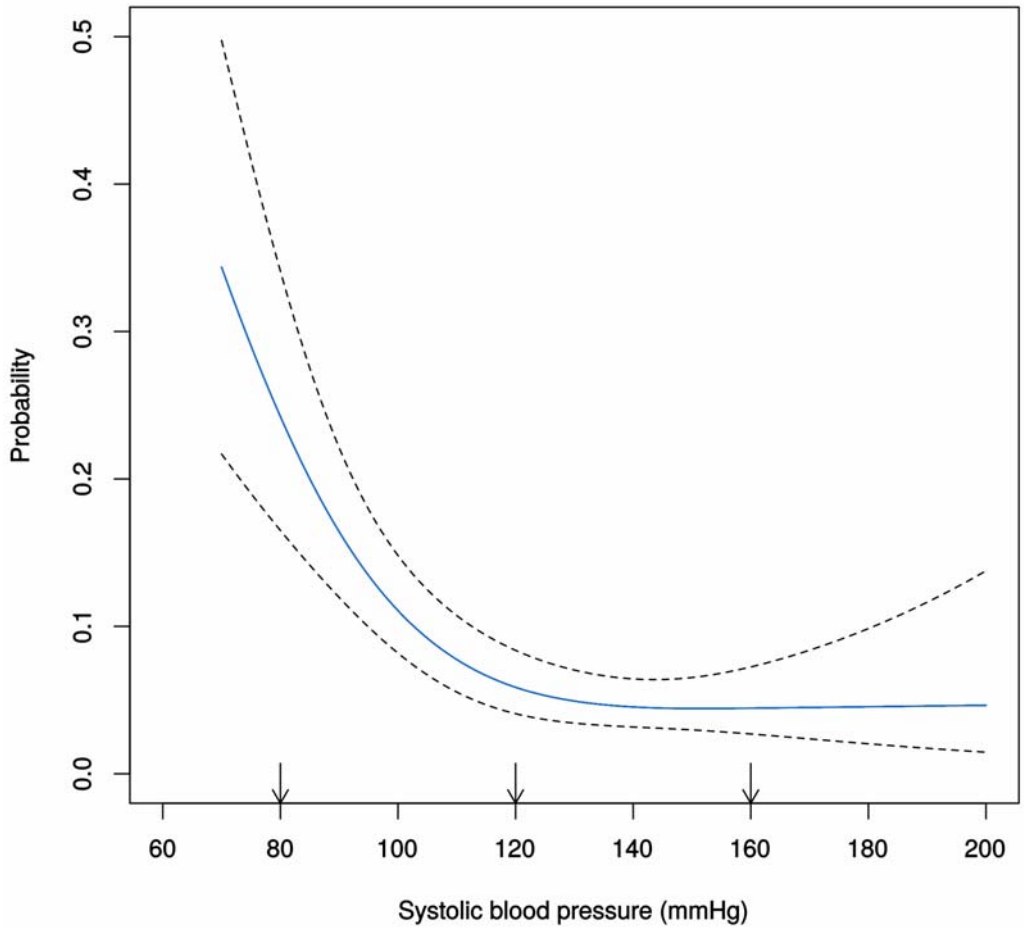
- 1,255 consecutive STEMI patients who were followed-up for a minimum of one year.
- Data were divided by time into development (n=750, ≈60%, 30-day mortality: 7.6%) and validation (n=505, ≈40%, 30-day mortality: 8.1%) sets to allow for non-random variation between the cohorts.
- Eight candidate variables readily available at or soon after presentation:
  - Age, onset-to-door time, heart rate and SBP at admission as continuous parameters,
  - Gender, ECG localization of the infarction, need for life support on or prior to admission (i.e., ALS because of OHCA or cardiac arrest at presentation), and vascular access site were investigated as categorical variables.
- Vascular access site was defined as the artery from which the coronary intervention was actually performed regardless of femoral artery puncture in cases necessitating IABP counterpulsation.

Methods

- To avoid overfitting and determine the most relevant predictors, backward stepwise logistic regression was combined with bootstrap resampling. Variables selected in at least 60% of the 10,000 samples were included in the final model.
- Restricted cubic splines (RCS) were used to explore presence of non-linear relationships of the continuous predictors to log odds of 30-day mortality.
- The model has been validated both internally (using bootstrap resampling) and temporally externally.
- Furthermore, we compared the discriminatory power of the new score with that of previous risk models.

Association of SBP with 30-day Mortality

The relationship was explored using a restricted cubic spline (RCS) with three knots placed at 80, 120, and 160 mmHg (arrows). Dashed lines represent 95% CIs. For the sake of interpretability, instead of log odds, the probability scale is used on the y axis. Wald testing for linearity suggests a non-linear relationship (p=0.0045). Similarly, adjusting for age, heart rate, need for life support, and access site, the association remains non-linear (p=0.0340, curve not shown).



Selection Frequencies of Predictors During Bootstrap Resampling

Variable	Selection rate
Age (years)	10,000 / 10,000; 100.0%
Heart rate (1 / min)	9,995 / 10,000; 100.0%
Systolic blood pressure (as RCS, mmHg)	9,968 / 10,000; 99.7%
Life support on or prior to admission	9,805 / 10,000; 98.1%
Access site (radial / femoral)	6,804 / 10,000; 68.0%
ECG localization (anterior / non-anterior)	3,023 / 10,000; 30.2%
Gender (female / male)	2,322 / 10,000; 23.2%
Onset-to-door time (hours)	1,365 / 10,000; 13.7%

Variables selected in at least 60% of the bootstrap samples were included in the multivariable model.
Addition of the less frequently selected parameters did not improve overall model fit as measured by the likelihood ratio test.

Predictors of 30-day Mortality

Variable	Coefficient	SE	p Value	OR (95% CI)
Intercept	-5.8287	1.7085	0.0006	–
Age (per year)	0.0808	0.0156	<0.0001	1.0842 (1.0516 to 1.1178)
Life support (yes / no)	1.8314	0.4140	<0.0001	6.2427 (2.7731 to 14.0533)
SBP (per mmHg)	-0.0504	0.0126	<0.0001	0.9509 (0.9277 to 0.9746)
SBP' (per mmHg)	0.0298	0.0141	0.0340	1.0303 (1.0022 to 1.0592)
Heart rate (per 1 / min)	0.0430	0.0075	<0.0001	1.0440 (1.0287 to 1.0595)
Access site (radial / femoral)	-0.7253	0.3513	0.0389	0.4842 (0.2432 to 0.9639)

Age, need for life support on or prior to admission, SBP as a non-linear parameter, heart rate, and access site were included in the final model.

For the new risk model the acronym **ALPHA** (**A**ge, **L**ife support, **P**ressure, **H**eart rate, **A**ccess site) has been coined.

Access Site: Effect Size in Context

Study	Population	End Point	Odds Ratio (95% CI)
ALPHA Hizoh et al., 2017	STEMI, registry	30-day all-cause mortality	0.48 (0.24–0.96)
RIVAL (pats. treated with PPCI) Mehta et al., 2012	STEMI, RCT	30-day all-cause mortality	0.46 (0.22–0.97)
RIFLE-STEACS Romagnoli et al., 2012	STEMI, RCT	30-day cardiac mortality	0.54 (0.33–0.89)
Meta-analyis Karrowni et al., 2013	STEMI, RCT	30-day all-cause mortality	0.55 (0.40–0.76)
MATRIX Valgimigli et al., 2015	ACS, RCT	30-day all-cause mortality	0.72 (0.52–0.99)

- **Since our analysis is observational, causal inference may not be justified.**
- **Yet, the effect size in our model is similar to those found in randomized STEMI trials.**

Regression Equation

Individual absolute risk of 30-day mortality may be calculated as follows:

$$\text{Prob}\{\text{mortality} = 1\} = \frac{1}{1+\exp(-X\beta)}, \quad \text{where}$$

$$\begin{aligned} X\hat{\beta} = \; & \\ & -5.83 + 0.08\ \text{Age} \\ & +1.83[\text{LifeSupport} = \text{Yes}] \\ & -0.05\ \text{SBP} + 4.66\times10^{-6}(\text{SBP}-80)_+^3 - 9.33\times10^{-6}(\text{SBP}-120)_+^3 + 4.66\times10^{-6}(\text{SBP}-160)_+^3 \\ & +0.04\ \text{HeartRate} \\ & -0.73[\text{AccessSite} = \text{Radial}] \end{aligned}$$

and $(x)_+ = x$ if $x > 0$, 0 otherwise.

To promote the use of the model in practice, a calculator is available at http://www.alphascore.org

Performance / Validation at 30 Days (Discriminatory Power and Model Fit)

	c-statistic (95% CI)	Calibration intercept† (95% CI)	Calibration slope† (95% CI)	H-L test‡
Internal validation				
Apparent	0.88	0.00	1.00	NA
Optimism*	0.01	0.12	0.07	NA
Optimism-corrected*	0.87	-0.12	0.93	NA
External validation				
Derivation data set	0.88 (0.85–0.92)	0.00 (-0.51–0.51)	1.00 (0.78–1.22)	0.86
Validation data set	0.87 (0.81–0.93)	0.12 (-0.48–0.73)	0.99 (0.74–1.25)	0.56

*Results are based on 10,000 bootstrap samples.
†Ideally, the calibration intercept should be zero while the calibration slope should be equal to one.
‡Hosmer-Lemeshow test: a p value < 0.1 is considered as lack of model fit.

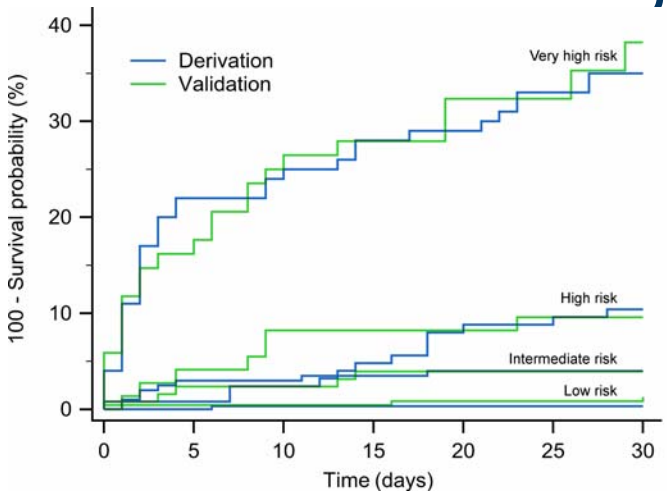
Risk Stratification

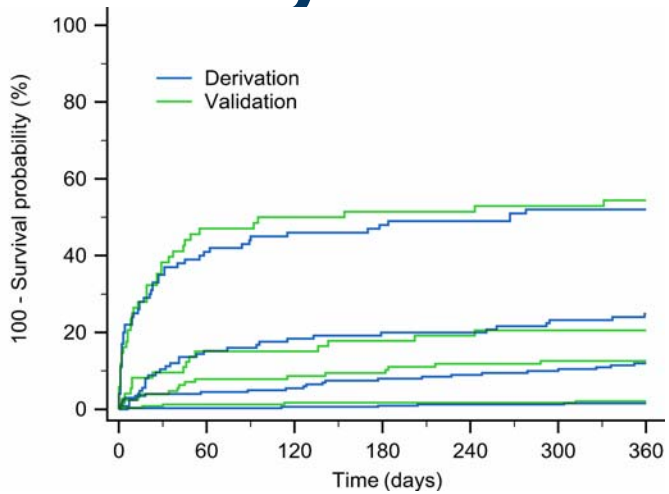
Focusing on clinical applicability, we defined four risk classes based on clinical judgment, sensitivity, specificity, and frequency distribution analyses of the predicted risk.

Risk class (predicted risk of 30-day mortality)	Number/percent at risk	30-day mortality, %	ILR (95% CI)	Sensitivity, % (95% CI)	NPV*, % (95% CI)	Specificity, % (95% CI)	PPV*, % (95% CI)
Derivation (n=750)							
Low (<=0.02)	324/43.2%	0.3	0.0 (0.0-0.3)	98.2 (90.6-100.0)	99.7 (98.3-100.0)	–	–
Intermediate (0.02< to <=0.06)	201/26.8%	4.0	0.5 (0.3-1.0)	–	–	–	–
High (0.06< to <=0.15)	125/16.7%	10.4	1.4 (0.9-2.3)	–	–	–	–
Very high (>0.15)	100/13.3%	35.0	6.5 (4.8-8.9)	–	–	90.6 (88.2-92.7)	35.0 (25.7-45.2)
Validation (n=505)							
Low (<=0.02)	237/46.9%	1.3	0.1 (0.0-0.4)	92.7 (80.1-98.5)	98.7 (96.4-99.7)	–	–
Intermediate (0.02< to <=0.06)	127/25.1%	3.9	0.5 (0.2-1.1)	–	–	–	–
High (0.06< to <=0.15)	73/14.5%	9.6	1.2 (0.6-2.4)	–	–	–	–
Very high (>0.15)	68/13.5 %	38.2	7.0 (4.8-10.1)	–	–	90.9 (88.0-93.4)	38.2 (26.7-50.8)

CI=confidence interval; ILR=interval likelihood ratio; NPV=negative predictive value; PPV=positive predictive value
*30-day mortality in the derivation data set: 7.6%; 30-day mortality in the validation data set: 8.1%.

Risk Stratification, Stability over Time





	Number of cases	Number of controls	c-statistic	Standard error	95% CI	p Value
Derivation data set						
30 days	57	693	0.88	0.02	0.85 to 0.92	<0.0001
180 days	92	658	0.86	0.02	0.83 to 0.90	<0.0001
1 year	112	638	0.85	0.02	0.81 to 0.88	<0.0001
1 year, 30-day survivors	55	638	0.79	0.03	0.74 to 0.84	<0.0001
Validation data set						
30 days	41	464	0.87	0.03	0.81 to 0.93	<0.0001
180 days	64	441	0.85	0.03	0.80 to 0.91	<0.0001
1 year	73	432	0.84	0.03	0.80 to 0.89	<0.0001
1 year, 30-day survivors	32	432	0.79	0.04	0.72 to 0.87	<0.0001

The mortality curves exhibit an increasing trend across the risk strata (logrank test for trend, $p<0.0001$, for both cohorts) in both analyses. Conversely, mortality curves of the two data sets are similar within each risk group.

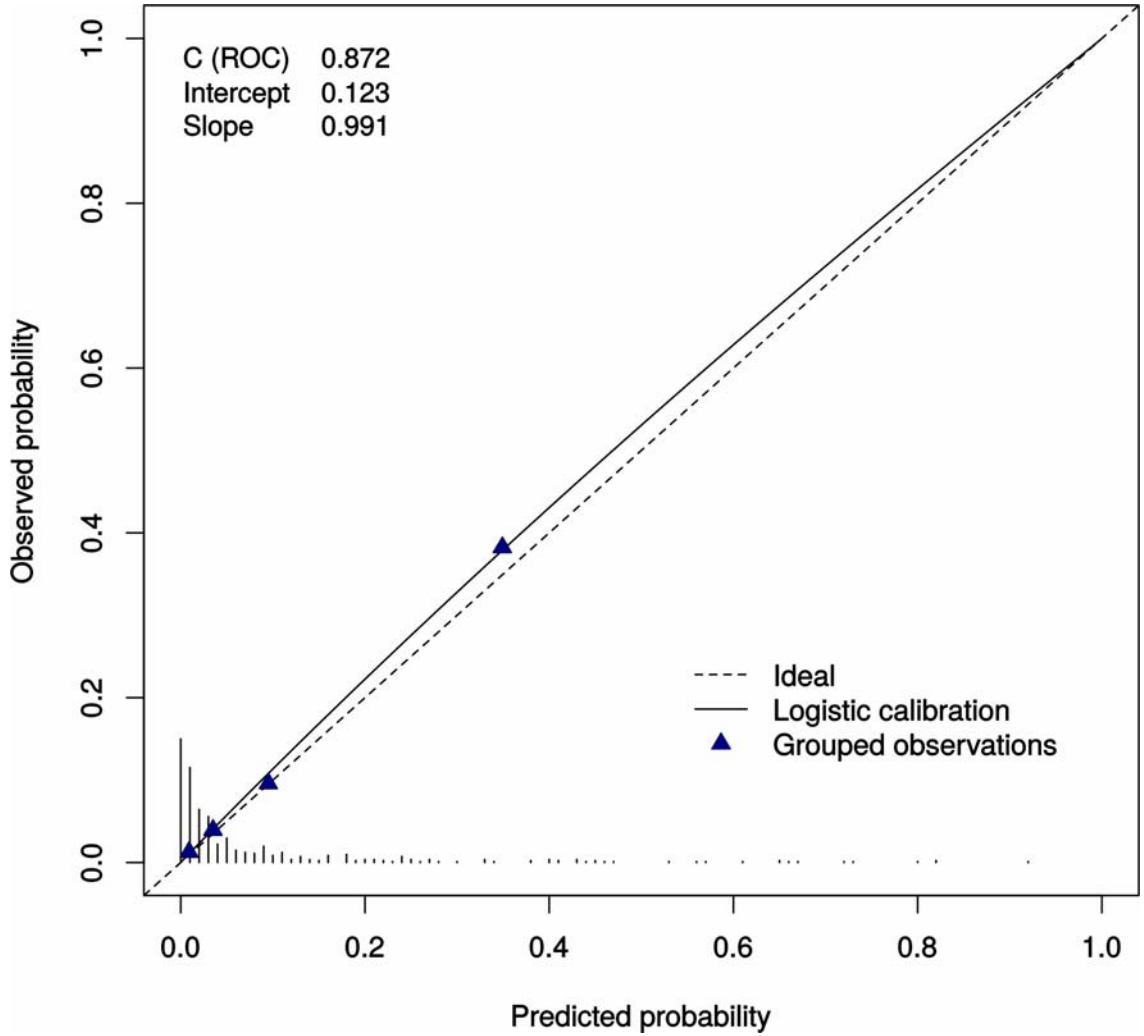
Discriminatory power of the model was stable in both data sets over multiple time points. Moreover, it was adequate even for prediction of one-year mortality among 30-day survivors.

Calibration Plot

Differences between the predicted and observed probabilities of 30-day mortality were small across the whole risk spectrum of the validation cohort.

Blue triangles indicate grouped observations for the four risk classes.

The rug plot across the bottom of the figure shows the distribution of predicted risk.



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Calculator for predicting 30-day mortality risk of STEMI patients treated with primary PCI

Age: Age (years)

Life support: Please Select

Pressure (SBP): SBP (mmHg)

Heart rate: Heart rate (1/min.)

Access site: Please Select

Submit | Reset

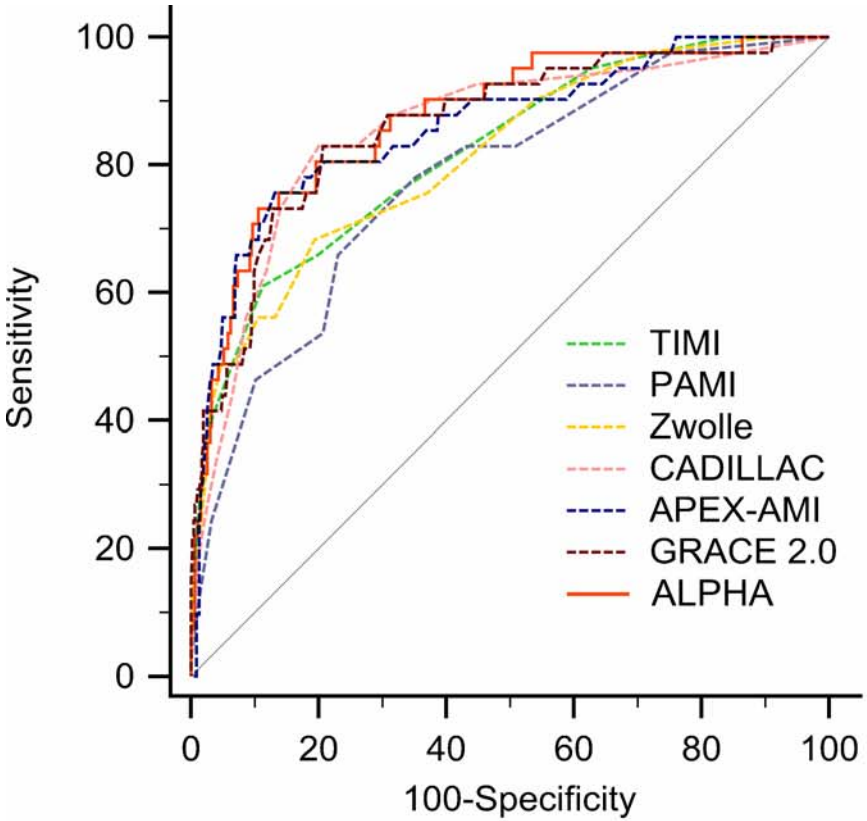
30-day mortality (%):

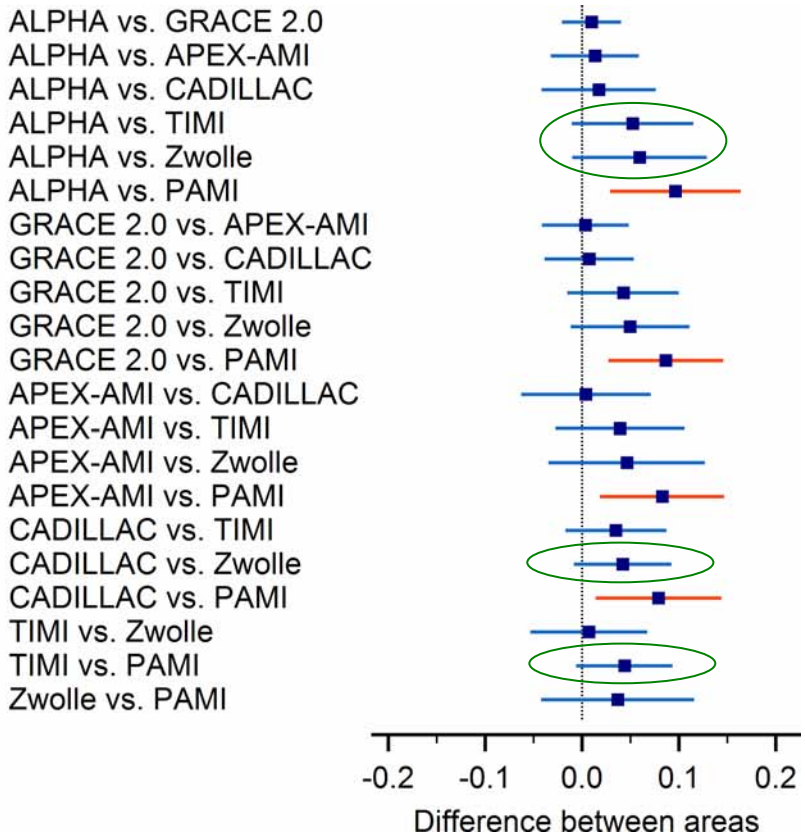
Risk class:

Low risk: 30-day mortality ≤ 2%
Intermediate risk: 2% < 30-day mortality ≤ 6%
High risk: 6% < 30-day mortality ≤ 15%
Very high risk: 30-day mortality > 15%

The calculator is available at http://www.alphascore.org

Comparative Validation





Left panel: ROC curve analysis. The ALPHA score achieved the highest c-statistic (0.87) followed by the GRACE 2.0 (0.86), APEX-AMI (0.86), and CADILLAC (0.85) models, the other risk scoring systems performed less well (0.82, 0.81, and 0.78 for the TIMI, Zwolle, and PAMI scores, respectively).

Right panel: Pairwise comparisons of differences between the areas under the ROC curves. Significant differences are indicated by orange error bars. „Trends" ($0.05 \leq p \leq 0.10$) are marked with green ovals.

Why to Use ALPHA? (Strengths)

- Though in our analysis the ALPHA score does not outperform most of the other models in terms of c-statistic, it has several advantages:
- In contrast to some other models using variables from time-consuming imaging and / or laboratory studies, ALPHA employs only five immediately available and easy-to-measure variables enabling risk assessment at presentation.
- Despite its simplicity, ALPHA achieved the numerically highest c-index for 30-day mortality (validated c-statistic: 0.87) and its discriminatory power was stable over multiple time points.
- Unlike the majority of the studied models, ALPHA is accompanied by an online calculator computing absolute 30-day mortality risk.
  Thus, patients who may benefit most from transradial access may be easily identified at presentation, when the actual vascular access site is still not known, by estimating the absolute risks for the two approaches and subtracting the radial from the femoral one. The difference equals the ARR that is attributable to transradial access.
- Finally, ALPHA is the only model that includes access site as a variable representing contemporary PCI practice.

Limitations

- Our model is based on prospective registry data of a single institution. Our results may not be valid for populations / centers of other geographic regions with different baseline risk, resources, and experience.
- Also, the limited sample size of the validation cohort did not allow the detection of some clinically potentially relevant differences during comparative validation.
- For the above reasons, further validation is warranted to evaluate the discriminatory power of the ALPHA score in these settings.

Conclusions

- We have developed and comparatively validated a simple admission score system for predicting 30-day mortality of STEMI patients treated with primary PCI.
- Using this tool, mortality risk may be precisely assessed and patients who may benefit most from transradial access may be identified at presentation.

References

- J Am Coll Cardiol 2015;66(15_S):B89; doi:10.1016/j.jacc.2015.08.244
- Cardiovasc Revasc Med 2017;18(1):33–39; doi:10.1016/j.carrev.2016.10.002