International Journal of Cardiology 286 (2019) 43–50

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Predictive ability of ACEF and ACEF II score in patients undergoing percutaneous coronary intervention in the GLOBAL LEADERS study

Ply Chichareon [a,b], Rodrigo Modolo [a,c], David van Klaveren [d], Kuniaki Takahashi [a], Norihiro Kogame [a], Chun-Chin Chang [e], Yuki Katagiri [a], Mariusz Tomaniak [f,g], Taku Asano [a], Ernest Spitzer [e,h], Pawel Buszman [i,j], Janusz Prokopczuk [k], Farzin Fath-Ordoubadi [l], Ian Buysschaert [m], Richard Anderson [n], Keith G. Oldroyd [o], Bela Merkely [p], Scot Garg [q], Joanna J. Wykrzykowska [a], Jan J. Piek [a], Peter Jüni [r], Christian Hamm [s], Philippe Gabriel Steg [t,u], Marco Valgimigli [v], Pascal Vranckx [w], Stephan Windecker [v], Yoshinobu Onuma [e], Patrick W. Serruys [x,*]

[a] Amsterdam UMC, University of Amsterdam, Cardiology, Meibergdreef 9, Amsterdam, the Netherlands
[b] Division of Cardiology, Department of Internal Medicine, Faculty of Medicine, Prince of Songkla University, Songkhla, Thailand
[c] Department of Internal Medicine, Cardiology Division, University of Campinas (UNICAMP), Campinas, Brazil
[d] Department of Biomedical Data Sciences, Leiden University Medical Center, the Netherlands
[e] Erasmus Medical Center, Erasmus University, Rotterdam, the Netherlands
[f] Department of Cardiology, Erasmus Medical Centre, Thorax Centre, Rotterdam, the Netherlands
[g] First Department of Cardiology, Medical University of Warsaw, Warsaw, Poland
[h] Cardialysis Clinical Trials Management and Core Laboratories, Westblaak 98, Rotterdam, the Netherlands
[i] Medical University of Silesia, Katowice, Poland
[j] American Heart of Poland, Ustron, Poland
[k] IV Department of Cardiology, American Heart of Poland, Kędzierzyn Koźle, Poland
[l] Manchester Heart Centre, Manchester Royal Infirmary, Manchester University Foundation Trusts, Oxford Rd, Manchester M13 9WL, United Kingdom
[m] Department of Cardiology, ASZ Hospital Aalst, Merestraat 80, 9300 Aalst, Belgium
[n] Cardiff and Vale University Health Board Heath Park, Cardiff, Wales, United Kingdom
[o] West of Scotland Heart and Lung Center, Golden Jubilee National Hospital, Clydebank, United Kingdom
[p] Heart and Vascular Center, Semmelweis University, Budapest, Hungary
[q] East Lancashire Hospitals NHS Trust, Blackburn, Lancashire, United Kingdom
[r] Applied Health Research Centre, Li Ka Shing Knowledge Institute, St Michael's Hospital, University of Toronto, Toronto, Canada
[s] Kerckhoff Heart Center, Campus University of Giessen, Bad Nauheim, Germany
[t] FACT, French Alliance for Cardiovascular Trials, Hôpital Bichat, AP-HP, Université Paris-Diderot, INSERM U-1148, Paris, France
[u] Royal Brompton Hospital, Imperial College, London, United Kingdom
[v] Department of Cardiology, Bern University Hospital, Bern, Switzerland
[w] Department of Cardiology and Critical Care Medicine, Hartcentrum Hasselt, Jessa Ziekenhuis, Hasselt, Belgium
[x] NHLI, Imperial College London, London, United Kingdom

ARTICLE INFO

Article history:
Received 31 October 2018
Received in revised form 5 February 2019
Accepted 18 February 2019
Available online 20 February 2019

Keywords:
ACEF
ACEF II
Mortality
Percutaneous coronary intervention
GLOBAL LEADERS

ABSTRACT

Background: ACEF score has been shown to have predictive ability in the patients undergoing percutaneous coronary intervention (PCI). The ACEF II score has recently been developed to predict short-term mortality after cardiac surgery. We compared the predictive ability of the ACEF and ACEF II scores to predict mortality after PCI in the all-comers population.

Methods: The ACEF and ACEF II scores were calculated in 15,968 patients enrolled in the GLOBAL LEADERS study. Discrimination and calibration were assessed for outcomes after PCI. Recalibration of the regression model by updating the intercept and slope were performed to adjust the original ACEF model to the PCI setting. In a stratified approach, patients were divided into quintiles according to the score. Outcomes were compared between quintiles.

Results: The ACEF and ACEF II score were available in 14,941 and 14,355 patients respectively. Discrimination for 30-day all-cause mortality was acceptable for both scores (C-statistic ACEF 0.75 and ACEF II 0.77). For

Abbreviations: ACEF, age, creatinine and ejection fraction; ACS, acute coronary syndrome; BARC, bleeding academic research consortium; CABG, coronary artery bypass graft surgery; LVEF, left ventricular ejection fraction; NACE, net adverse clinical events; NSTEMI, non-ST-segment elevation myocardial infarction; PCI, percutaneous coronary intervention; POCE, patient oriented composite endpoints; STEMI, ST-segment elevation myocardial infarction.

* Corresponding author at: P.O. Box 2125, 3000 CC Rotterdam, the Netherlands.
E-mail address: patrick.w.j.c.serruys@gmail.com (P.W. Serruys).

https://doi.org/10.1016/j.ijcard.2019.02.043
0167-5273/

2-year all-cause mortality, the discrimination of ACEF score was acceptable (C-statistic 0.72) while the discrimination of ACEF II score was moderate (C-statistic 0.69). Both scores identified patients at high risk of mortality but overestimated all-cause mortality at 30 days in all quintiles. After recalibration, agreement between predicted and observed 30-day all-cause mortality in both scores are close to the identity line.
Conclusions: The ACEF II model did not improve the predictive ability of the ACEF score. Recalibrated ACEF model can be used to estimated all-cause mortality rate at 30 days after PCI.

1. Introduction

The age, creatinine and ejection fraction (ACEF) score was introduced in 2009 by Ranucci et al. as a simple "parsimonious" tool for predicting in-hospital mortality in patients undergoing elective cardiac surgery [1]. Despite the use of only three variables, this score has an impressive prognostic performance compared with other more complex scores [1,2]. Its simplicity makes it an attractive score to stratify risk in patients undergoing percutaneous coronary intervention (PCI), as confirmed in an all-comer PCI trial showing its good discriminative ability even for long-term outcomes [3,4]. Subsequently, the anatomical SYNTAX score has been added to the ACEF score and has further enhanced the prognostic value of each score [5–7]. Furthermore, the three basic variables of the ACEF score constituted the clinical part of the SYNTAX score II resulting in a better treatment decision making in multivessel coronary artery disease than the anatomic SYNTAX score alone [8]. The ACEF score was included in the 2014 European Society of Cardiology Guidelines on Myocardial Revascularization as a risk model for short-term outcome [9].

Recently, the ACEF score has been amended into the ACEF II score by adding the variables emergency surgery and preoperative anemia [10]. This updated but still "parsimonious model" has been externally validated in a broader spectrum of adult cardiac surgery patients showing good calibration and better discrimination than the original model. Since anemia has an impact on outcomes in patients undergoing PCI and surgery [11] and ST elevation myocardial infarction (STEMI) patients have the worst short-term prognosis among the spectrum of coronary artery disease, the ACEF II model may be a promising risk score to better stratify and predict outcomes in PCI patients provided primary PCI is considered as a surrogate for emergency surgery. Therefore, this study aims to compare the predictive ability of the ACEF and ACEF II score in the all-comers PCI population.

2. Methodology

2.1. Study population

GLOBAL LEADERS study (NCT01813435) was an investigator-initiated, prospective randomized, multi-center, multinational, multicontinental, open-label trial designed to evaluate two strategies of antiplatelet therapy after PCI using uniformly bivalirudin and Biolimus A9 eluting stents (Biomatrix) [12]. In the experimental treatment strategy, patients received aspirin 75–100 mg once daily in combination with ticagrelor 90 mg twice daily for one month; followed by ticagrelor 90 mg twice daily alone for 23 months (irrespective of the clinical presentation). In the reference treatment strategy, patients received aspirin 75–100 mg daily in combination with either clopidogrel 75 mg once daily in patients with stable coronary artery disease or ticagrelor 90 mg twice daily in patients with acute coronary syndrome for 1 year; followed by aspirin 75–100 mg once daily alone for the following 12 months (from 12 to 24 months after PCI). The outcomes were investigator-reported with the assessment of safety by a central safety board. An independent data and safety monitoring committee oversaw the safety of all patients. The main study enrolled 15,991 patients between July 2013 to November 2015 in an "all-comers" design: no restriction regarding clinical presentation, complexity of the lesions or number of stents used. Since 23 patients withdrew consent and requested data deletion from the database, a total of 15,968 patients remained in the study. The primary endpoint of the GLOBAL LEADERS study was the composite of all-cause mortality and new Q wave myocardial infarction within 2 years. The survival status of the patients lost to follow up or those who withdrew their consent was obtained through public civil registry in which >99.95% of the vital status at 2 years were available in the study [12]. All patients provided informed consent. The study complied with the Declaration of Helsinki and Good Clinical Practices.

2.2. ACEF score and modified ACEF II score

The ACEF score was calculated using the formula originally introduced by Ranucci et al. [1]; ACEF score = age/left ventricular ejection fraction +1 (if serum creatinine was ≥2.0 mg/dL). Probability of mortality within 30 days after PCI was obtained from the equation [13]; Mortality risk = $e^{ACEFscore\times 1.24-5.41} / (1 + e^{ACEFscore\times 1.24-5.41})$.

The modified ACEF II score was calculated using the formula adapted from the ACEF II score [10]. Primary PCI was used as a variable instead of emergency surgery in the following formula; modified ACEF II score = age/left ventricular ejection fraction +2.0 (if serum creatinine >2.0 mg/dL) + 3.0 (if primary PCI) + 0.2× hematocrit points below 36%. Probability of mortality within 30 days was obtained from the equation [10]; Mortality risk = $e^{(-4.86+0.75ACEF\ II)} / (1 + e^{(-4.86+0.75ACEF\ II)})$.

Pre-procedural left ventricular ejection fraction (LVEF) was used in the calculation of ACEF score and modified ACEF II score. In case of unavailable pre-procedural value (e.g. STEMI patients), post-procedural LVEF was used instead. Serum creatinine used in the calculation was the value measured closest to pre-PCI, within last two weeks. In this study, patients were excluded if one of the variables required for the ACEF score or modified ACEF II score calculation was not available.

2.3. Objectives and study endpoints

The primary objective is to assess the ability of the ACEF and modified ACEF II score to predict short and long-term outcomes in patients with coronary artery disease undergoing PCI. Primary endpoint was all-cause mortality within 30 days and 2 years after PCI. Secondary endpoints were the patient oriented composite endpoints (POCE) and net adverse clinical events (NACE). POCE was defined as all-cause mortality, any stroke (ischemic and hemorrhagic), any myocardial infarction including periprocedural or spontaneous with STEMI or non-ST-segment elevation myocardial infarction (NSTEMI), and any revascularization (re-PCI or coronary artery bypass graft surgery (CABG) in target or non-target vessel) [14]. NACE was defined as POCE plus bleeding academic research consortium (BARC) type 3 or 5. Individual component of the composite endpoints and definite stent thrombosis according to academic research consortium definition were reported [15]. Composite endpoints were analyzed according to the time to first event.

2.4. Statistical analysis

Patients were classified into quintiles based on ACEF score and modified ACEF II score for the stratified approach. Analyses of the baseline characteristics were performed according to the quintiles of patients. Testing for linear trend between quintiles was performed by generalized linear models using ACEF or modified ACEF II quintiles as a covariable for continuous variables and the Cochran-Armitage test for trend in categorical variables. Kaplan-Meier method was used to estimate the cumulative rates of clinical events and Log-rank test was performed to examine the differences between groups.

Concordance statistics (C-statistic), equivalent to the area under the receiver operating characteristic curve, were calculated for the outcomes at 30 days and 2 years [16]. The discrimination is considered outstanding if C-statistic ≥0.9, excellent if C-statistic ≥0.8 and <0.9, acceptable if C-statistic ≥0.7 and <0.8, poor discrimination if C-statistic >0.5 and <0.7, and no discrimination if C-statistic = 0.5 [17].

Calibration was assessed using calibration plots by quintiles of the ACEF and modified ACEF II score for all-cause mortality at 30 days after PCI [16]. Calibration-in-the-large (model intercept) and calibration slope were obtained for each score by fitting the calculated linear predictor in all patients with 30-day mortality as the outcome in the logistic regression model [16]. The model with the intercept of 0 and calibration slope of 1 represent the perfect predictive model. Negative and positive intercept indicate overestimation and underestimation respectively. Recalibration of the regression model by updating the intercept and slope were performed to adjust the original ACEF model to the PCI setting [16].

Analyses were performed in IBM SPSS Statistics, version 25 (IBM Corp., Armonk, N.Y., USA), R version 3.4.2 using pROC package [18] and Calibration Curves package for the calibration analysis [19]. A two-sided P value <0.05 was considered as statistical significance.

3. Results

3.1. Patients and baseline characteristics

The ACEF score and modified ACEF II score were available in 14,941 patients and 14,355 patients respectively. The main reasons for being unable to calculate the scores were missing values for LVEF and hematocrit (Supplementary Table A). The ACEF score ranged from 0.49 to 9.60 (mean ± SD of 1.25 ± 0.43). Modified ACEF II score ranged from 0.49 to 10.84 (mean ± SD of 1.72 ± 1.19).

Baseline characteristics of the patients enrolled in the GLOBAL LEADERS study and patients according to the ACEF and modified ACEF II score quintiles are shown in Table 1 and Supplementary Tables B and C respectively. The prevalence of diabetes, hypertension, previous stroke, previous myocardial infarction, previous PCI, previous CABG, established peripheral vascular disease, known chronic obstructive pulmonary disease were the highest in the very high risk ACEF score quintile and the high risk modified ACEF II score quintile.

In the very high risk ACEF score quintile, age and serum creatinine was the highest while the LVEF and body mass index were the lowest compared with other quintiles. Similar observations were seen with the modified ACEF II score.

For both scores, the frequency of myocardial infarction including NSTEMI and STEMI were highest in the high or very high risk score quintile, while the frequency of stable angina was higher in the non-high risk quintiles (very low, low or intermediate risk).

3.2. Discrimination and calibration

The discrimination of the ACEF and modified ACEF II score for 30-day all-cause mortality are acceptable with C-statistic of 0.75 and 0.77 respectively (Fig. 1). Although the C-statistics of the ACEF score for 2-year all-cause mortality (C-statistic 0.72) is lower than at 30 days, the discrimination is still acceptable. The discrimination of the modified ACEF II score is poor for 2-year all-cause mortality (C-statistic 0.69). Discrimination of both scores is limited for other outcomes at 30 days and 2 years with the C-statistics in the range of poor to acceptable (Supplementary Table D). Both scores overestimated 30-day all-cause mortality after PCI (Fig. 1). After recalibration, agreement between predicted and observed 30-day mortality in both scores are close to the identity line.

Table 1
Clinical characteristics of the patients in the GLOBAL LEADERS study.

	GLOBAL LEADERS study (n = 15,968)
Age (years), mean ± SD	64.5 ± 10.3
Serum creatinine (mg/dL), mean ± SD	1.0 ± 1.3
Left ventricular ejection fraction (%), mean ± SD	54.9 ± 10.6
Female	23.3 (3714)
Body mass index (kg/m^2) , mean ± SD	28.2 ± 4.6
Diabetes mellitus	25.3 (4038)
Insulin dependent diabetes mellitus	7.7 (1223)
Hypertension	73.6 (11715)
Hypercholesterolemia	69.6 (10768)
Previous stroke	2.6 (421)
Previous myocardial infarction	23.3 (3710)
Previous percutaneous coronary intervention	32.7 (5221)
Previous coronary artery bypass grafting	5.9 (943)
Established peripheral vascular disease	6.4 (1005)
Known chronic obstructive pulmonary disease	5.2 (821)
History of Major bleeding or previous predisposition to bleeding	0.6 (98)
Currently smoking	26.1 (4169)
Cardiac arrest at presentation	0.6 (95)
Clinical presentation	
Stable angina	53.1 (8325)
Unstable angina	12.7 (2022)
Non-ST-segment elevation myocardial infarction	21.1 (3373)
ST-segment elevation myocardial infarction	13.1 (2092)

Data are % (n), unless otherwise specified.

3.3. Outcomes according to ACEF and modified ACEF II score quintiles

For 30-day all-cause mortality, the ACEF score discriminates patients in the high and very high risk quintiles from the other risk groups better than the modified ACEF II score (Fig. 2). The cumulative curves of the very low, low and intermediate quintiles for all-cause mortality at 30 days are non-discriminated in both scores. For POCE and NACE at 30 days, both scores can discriminate the high and very high risk quintiles from other quintiles (Supplementary Figs. A and B) but fail to discriminate patients in very low, low and intermediate risk.

At 30 days, there is a significant difference in the rate of stroke and BARC 3 or 5 bleeding across quintiles in both ACEF and modified ACEF II score. The rate of any myocardial infarction is significantly different across quintiles of the ACEF, but not the modified ACEF II score, whereas the opposite is seen for rates of repeat revascularization and definite stent thrombosis.

The ACEF score discriminates the 2-year all-cause mortality, POCE, and NACE between the high and very high quintiles better than the modified ACEF II score (Fig. 2 and Supplementary Figs. A and B). In the very low, low and intermediate risk quintiles, the cumulative curves for POCE and NACE are non-discriminant for both scores.

At 2 years, there were significant differences in the event rates among the quintiles for both scores in relation to all outcomes except repeat revascularization and definite stent thrombosis (Table 2). The event rate of any stroke, any myocardial infarction, and BARC 3 or 5 bleeding are highest in the very high risk quintile of the ACEF score. However, in the modified ACEF II quintiles, the highest event rates of any stroke occurred in the high risk score quintile.

4. Discussion

The main findings of this study are: 1) the ACEF score predicts short (30 days) and long-term (2 years) all-cause mortality in all-comers patients undergoing PCI. The modified ACEF II score does not improve on the performance of the ACEF score when applied to PCI population. 2) The discrimination of the modified ACEF II score is comparable to the ACEF score for short-term mortality, and lower for 2-year mortality. 3) The ACEF score can identify patients at very high risk of long-term adverse events including all-cause mortality, POCE, NACE, stroke, myocardial infarction, stent thrombosis and BARC3 or 5 bleeding whereas the modified ACEF II score cannot separate outcomes between the high and very high risk groups. 4) Both scores overestimated the probabilities of all-cause mortality at 30 days after PCI. Calibration was improved after updating the model. Agreement between predicted and observed 30-day all-cause mortality in recalibrated model of both scores was close to the identity line.

The modified ACEF II score includes two additional simple and objectively measured variables (hematocrit and primary PCI) which have the potential to improve its predictive ability. However, our study showed that the modified ACEF II score did not improve the predictive performance of the classic ACEF score in patients undergoing PCI. A possible explanation is a substantial difference in short-term mortality between patients undergoing primary PCI and emergency cardiac surgery. Patients undergoing emergency surgery represent a highly selective group with an in-hospital mortality as high as 17.6% [20]. In contrast, the in-hospital mortality rate for primary PCI patients was 2.6% in the US. National Cardiovascular Data Registry [21]. Notably, the 30-day all-cause mortality in STEMI patients in our study (1.3%) was much lower than the aforementioned studies, a finding which confirms that primary PCI is not comparable to emergency surgery as a predictor of mortality.

Anemia adversely affected clinical outcomes in patients undergoing PCI but its impact in this population is less detrimental than in surgical patients. In the present study, hematocrit level is one of the

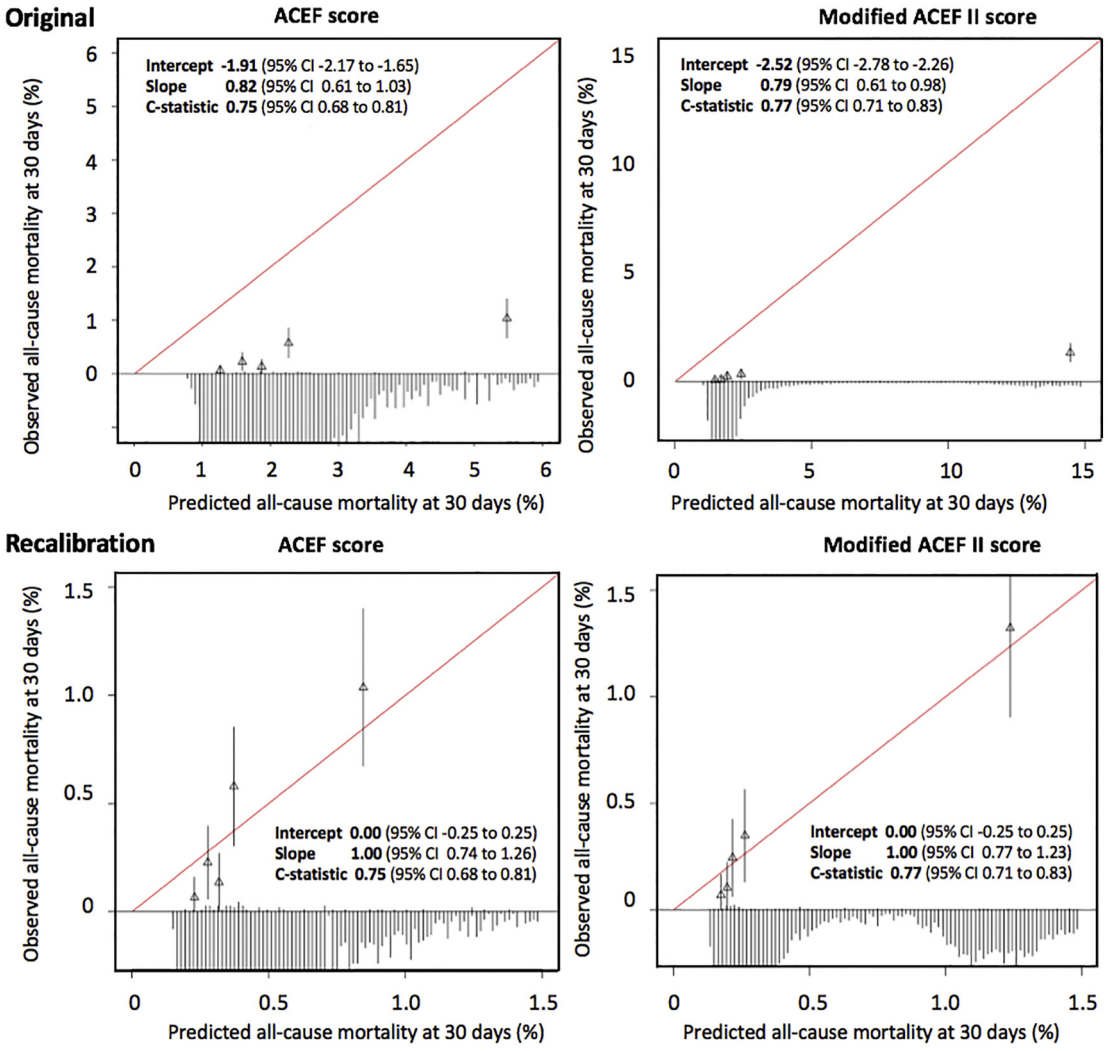

Fig. 1. Calibration plot of ACEF score and modified ACEF II score for all-cause mortality at 30 days after PCI. Original models are displayed in the upper panel and recalibrated models are displayed in the lower panel. Triangles in calibration plot represent 5 groups of patients with mean predicted probability and mean observed all-cause mortality with 95% confidence interval. The distribution of the patients is displayed by the histogram at the bottom of the graph in calibration plot.

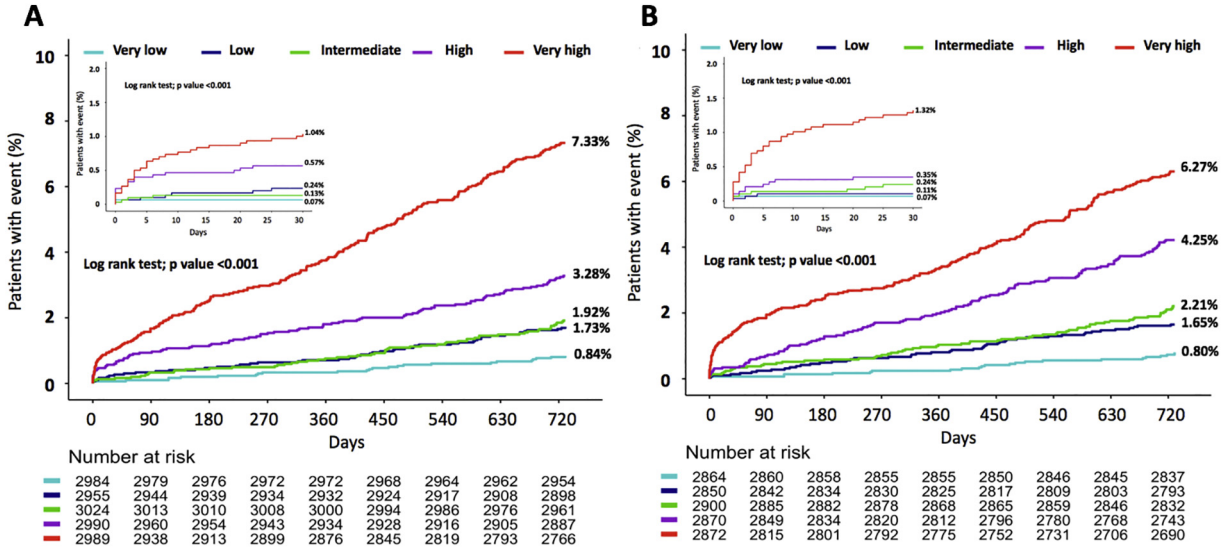

Fig. 2. Kaplan-Meier curves for all-cause mortality at 2 years after index PCI according to the ACEF score quintiles (panel A) and modified ACEF II score quintiles (panel B). The insets show the curves and the outcomes at 30 days after PCI.

independent predictors for all-cause mortality at 30 days after PCI (adjusted hazard ratio 0.94, 0.90–1.00, P 0.032) (Supplementary Table E). However, in the developmental cohort of the ACEF II score, the odd ratio of pre-operative hematocrit for 30-day all-cause mortality was lower (odd ratio 0.86, 95% CI 0.84–0.88) [10]. The hematocrit of surgical patients could be diluted by cardio-pulmonary bypass and strong link between excessive hemodilution and adverse outcomes after surgery is well established [22,23]. The more substantial impact of anemia on short-term mortality in patients undergoing cardiac surgery compared with PCI and the hemodilution with cardio-pulmonary bypass pump during cardiac surgery could provide reasons why the ACEF II model was less predictive in the PCI population.

Both ACEF and modified ACEF II score overestimate 30-day all-cause mortality after PCI. This finding is not unexpected since the risk score developed in the surgical population is applied to the patients treated with percutaneous intervention [24]. In the developmental cohort of the ACEF II score, all-cause mortality within 30 days was 3.7% [10] while 30-day mortality after PCI in the GLOBAL LEADERS study was 0.4%. The almost 10-times higher mortality in the surgical cohort than in the PCI cohort is responsible for the poor calibration of the ACEF score. When a risk score is applied in a new population, the score can be updated to adjust for the substantial differences in clinical characteristics and outcomes between the developmental and the new population [16]. In the present study, the agreement between predicted and observed 30-day mortality after PCI in both scores are improved and close to the identity line after recalibration. Thus, the all-cause mortality at 30 days after PCI can be estimated from the recalibrated ACEF score which still respects the parsimoniousness of the model.

The predictive ability of the ACEF model may relate to clinical presentation of the patients undergoing PCI and additional analysis shows that the discrimination and calibration of both ACEF scores are better in patients presenting with acute coronary syndrome than stable angina (Supplementary Table F and Supplementary Figs. C and D). Majority of the patients enrolled in the GLOBAL LEADERS study was treated for the clinical presentation of stable angina and the proportion of this group is relatively higher when compared with other all-comers trials (Supplementary Table G). However, a substantial number of patients with stable angina in the GLOBAL LEADERS study had elevated cardiac biomarkers prior to PCI. The pre-procedural elevation of the cardiac biomarker in stable coronary artery disease patient has been established as an independent predictor of all-cause mortality after PCI [25]. When the clinical presentations of patients are reclassified according to the presence or absence of cardiac biomarkers, the risk profile of the patients enrolled in the GLOBAL LEADERS study increased substantially with one third of the patients being considered as acute coronary syndrome, according to the NSTEMI definition of the European Society of Cardiology guidelines and the universal definition [26]. Furthermore, when the all-cause mortality of stable and unstable patients without elevated cardiac biomarkers prior to PCI are compared with the patients with the same clinical presentation in whom cardiac biomarkers have been detected, a significant difference in all-cause mortality is observed. However, this post hoc observation is not formally reported in the present analysis, in order to respect the clinical presentation entered in the case record form by the investigators and reported in the main report [12].

4.1. Current role of SYNTAX score in clinical practice as compared with ACEF scores

The SYNTAX score in its more recent version stemming from the SYNTAX II and III trials has undergone major iterations over the last decade. First, the pure anatomical SYNTAX score predicts major adverse cardiac event rate specifically in the SYNTAX trial comparing bypass surgery and PCI in three vessel disease with or without left main disease [27]. Secondly, the clinical SYNTAX score and its logistic expression derived from all-comers trials with PCI, combining the anatomical SYNTAX score with clinical characteristics, predict all-cause mortality at 1, 2, and 3 years [7,28]. Thirdly, the SYNTAX II score, derived from Cox regression model predicts all-cause mortality at 4 years in a population of three-vessel disease with or without left main disease [8]. Fourthly, the SYNTAX score III, that includes the physiological significance of the stenosis and thus ultimately combines anatomy, comorbidities and functionality, predicts all-cause mortality at 4 years in patients with three-vessel disease with or without left main diseases. The major limitation of the anatomical SYNTAX score is that its assessment is time consuming and its substantial inter-observer variability.

The original parsimonious ACEF score does not need the meticulous assessment of the complexity of the anatomy and is readily obtainable. However, the SYNTAX II and III score, because of its detailed description of the anatomy, may serve not only for mortality prediction but for planning and execution of surgery or PCI [29,30].

5. Limitations

Although the main study was designed as an all-comers trial, selection of a relatively low risk population has been documented and the proportion of stable coronary artery disease as categorized by the investigators in the GLOBAL LEADERS study is higher than other all-comers trials. The modified ACEF II score could not be calculated in 10.1% of the patients due to the unavailability of LVEF or baseline hematocrit values. However, there was no difference in short-term and long-term mortality between patients with or without missing variables for ACEF score calculation (Supplementary Table H). Finally, the recalibrated model of the ACEF score require validation in other PCI populations.

6. Conclusion

In this contemporary PCI trial, the predictive ability of the modified ACEF II score was not superior to the original ACEF score. Recalibrated ACEF model can be used to estimated all-cause mortality rate at 30 days after PCI.

Disclosures

Dr. Chichareon reports research grant from Biosensors.

Dr. Modolo reports research grant from Biosensors.

Dr. Spitzer reports institutional grants from the European Cardiovascular Research Institute, during the conduct of the study.

Dr. Buysschaert reports research grant from the European Cardiovascular Research Institute.

Dr. Piek reports non-financial support from Abbott Vascular, and personal fees and non-financial support from Philips/Volcano, outside the submitted work.

Dr. Jüni is a Tier 1 Canada Research Chair in Clinical Epidemiology of Chronic Diseases, this research was completed, in part, with funding from the Canada Research Chairs Programme. Dr. Jüni has received research grants to the institution from Astra Zeneca, Biotronik, Biosensors International, Eli Lilly and The Medicines Company, and serves as unpaid member of the steering group of trials funded by Astra Zeneca, Biotronik, Biosensors, St. Jude Medical and The Medicines Company.

Dr. Hamm reports support from an advisory Board and speakers fee from Medtronic.

Dr. Steg reports grants and personal fees from Servier, during the conduct of the study; grants and personal fees from Bayer/Janssen, grants and personal fees from Merck, grants and personal fees from Sanofi, grants and personal fees from Amarin, personal fees from Amgen, personal fees from Bristol Myers Squibb, personal fees from Boehringer-Ingelheim, personal fees from Pfizer, personal fees from Novartis, personal fees from Regeneron, personal fees from Lilly, personal fees from AstraZeneca, outside the submitted work.

Dr. Valgimigli reports grants and personal fees from Abbott, personal fees from Chiesi, personal fees from Bayer, personal fees from Daiichi

Table 2
Clinical outcomes at 30 days and 2 years after index PCI according to ACEF score and modified ACEF II score quintiles.

	ACEF score quintiles (score)					P value	Modified ACEF II score quintiles (score)					P value
	Very low (0.4915–0.9565)	Low (0.9571–1.0986)	Intermediate (1.1000–1.2361)	High (1.2364–1.4375)	Very high (1.4390–9.6000)		Very low (0.4915–0.9839)	Low (0.9841–1.1452)	Intermediate (1.1455–1.3291)	High (1.3309–2.0303)	Very high (2.0303–10.8400)	
	N = 2984	*N* = 2955	*N* = 3024	*N* = 2989	*N* = 2989		*N* = 2864	*N* = 2850	*N* = 2899	*N* = 2871	*N* = 2871	
Outcomes at 30 days												
Observed all-cause death % (n)	0.07 (2)	0.24 (7)	0.13 (4)	0.57 (17)	1.04 (31)	<0.0001	0.07 (2)	0.11 (3)	0.24 (7)	0.35 (10)	1.32 (38)	<0.0001
Expected all-cause death (%)	1.26	1.58	1.86	2.26	5.48	NA	1.46	1.70	1.92	2.43	14.46	NA
Observed/expected mortality ratio	0.06	0.15	0.07	0.25	0.19	NA	0.05	0.06	0.13	0.14	0.09	NA
Observed all-cause death in experimental arm % (n)	0.14 (2)	0.13 (2)	0 (0)	0.61 (9)	1.06 (16)	<0.0001	0.14 (2)	0.07 (1)	0.14 (2)	0.35 (5)	1.29 (19)	<0.0001
Observed all-cause death in reference arm % (n)	0 (0)	0.34 (5)	0.26 (4)	0.53 (8)	1.01 (15)	0.0005	0 (0)	0.14 (2)	0.34 (5)	0.35 (5)	1.36 (19)	<0.0001
Any stroke % (n)	0.10 (3)	0.10 (3)	0.13 (4)	0.44 (13)	0.30 (9)	0.015	0.03 (1)	0.07 (2)	0.31 (9)	0.42 (12)	0.25 (7)	0.0075
Any myocardial infarction % (n)	0.84 (25)	0.81 (24)	0.73 (22)	0.81 (24)	1.68 (50)	0.0006	0.84 (24)	0.74 (21)	0.83 (24)	1.22 (35)	1.12 (32)	0.26
Any repeat revascularization % (n)	1.81 (54)	1.39 (41)	1.19 (36)	1.71 (51)	2.02 (60)	0.084	1.57 (45)	1.37 (39)	1.18 (34)	1.57 (45)	2.35 (67)	0.0059
Definite stent thrombosis % (n)	0.27 (8)	0.44 (13)	0.23 (7)	0.4 (12)	0.64 (19)	0.097	0.21 (6)	0.25 (7)	0.28 (8)	0.28 (8)	0.98 (28)	<0.0001
BARC3 or 5 bleeding % (n)	0.30 (9)	0.44 (13)	0.40 (12)	0.84 (25)	1.11 (33)	0.0001	0.31 (9)	0.28 (8)	0.66 (19)	0.59 (17)	1.30 (37)	<0.0001
In experimental arm % (n)	0.14 (2)	0.40 (6)	0.27 (4)	1.09 (16)	1.27 (19)	0.0001	0.28 (4)	0.21 (3)	0.64 (9)	0.84 (12)	1.23 (18)	0.0033
In reference arm % (n)	0.46 (7)	0.48 (7)	0.53 (8)	0.60 (9)	0.95 (14)	0.41	0.35 (5)	0.35 (5)	0.68 (10)	0.35 (5)	1.36 (19)	0.0013
Patient oriented composite endpoints % (n)	2.28 (68)	2.00 (59)	1.89 (57)	2.68 (80)	4.12 (123)	<0.0001	2.06 (59)	1.9 (54)	2.01 (58)	2.90 (83)	3.98 (114)	<0.0001
In experimental arm % (n)	2.18 (32)	1.40 (21)	1.33 (20)	2.72 (40)	4.45 (67)	<0.0001	1.98 (28)	1.68 (24)	1.78 (25)	2.80 (40)	3.89 (57)	0.0003
In reference arm % (n)	2.38 (36)	2.61 (38)	2.44 (37)	2.64 (40)	3.79 (56)	0.12	2.15 (31)	2.11 (30)	2.22 (33)	2.99 (43)	4.07 (57)	0.0038
Net adverse clinical events % (n)	2.48 (74)	2.41 (71)	2.22 (67)	3.15 (94)	5.06 (151)	<0.0001	2.31 (66)	2.11 (60)	2.49 (72)	3.42 (98)	4.92 (141)	<0.0001

In experimental arm % (n)	2.25 (33)	1.74 (26)	1.60 (24)	3.20 (47)	5.65 (85)	<0.0001	2.19 (31)	1.82 (26)	2.13 (30)	3.58 (51)	4.77 (70)	<0.0001
In reference arm % (n)	2.70 (41)	3.09 (45)	2.84 (43)	3.10 (47)	4.47 (66)	0.051	2.42 (35)	2.40 (34)	2.82 (42)	3.27 (47)	5.07 (71)	<0.0001
Outcomes at 730 days												
Observed all-cause death % (n)	0.84 (25)	1.73 (51)	1.92 (58)	3.28 (98)	7.33 (219)	<0.0001	0.80 (23)	1.65 (47)	2.21 (64)	4.25 (122)	6.27 (180)	<0.0001
Observed all-cause death in experimental arm % (n)	0.82 (12)	1.74 (26)	1.66 (25)	3.33 (49)	6.57 (99)	<0.0001	0.92 (13)	1.47 (21)	2.06 (29)	4.41 (63)	5.38 (79)	<0.0001
Observed all-cause death in reference arm % (n)	0.86 (13)	1.72 (25)	2.18 (33)	3.23 (49)	8.10 (120)	<0.0001	0.69 (10)	1.83 (26)	2.35 (35)	4.09 (59)	7.21 (101)	<0.0001
Any stroke % (n)	0.41 (12)	0.65 (19)	0.94 (28)	1.40 (41)	1.85 (53)	<0.0001	0.35 (10)	0.78 (22)	1.19 (34)	1.83 (51)	1.12 (31)	<0.0001
Any myocardial infarction % (n)	2.81 (83)	2.91 (85)	2.35 (70)	2.90 (85)	5.24 (151)	<0.0001	2.71 (77)	2.53 (71)	2.66 (76)	3.35 (94)	4.62 (128)	<0.0001
Any repeat revascularization % (n)	10.15 (300)	9.53 (278)	8.95 (266)	10.16 (297)	10.76 (309)	0.16	9.97 (283)	9.62 (270)	8.93 (254)	10.08 (282)	10.42 (289)	0.35
Definite stent thrombosis % (n)	0.64 (19)	0.92 (27)	0.67 (20)	0.85 (25)	1.17 (34)	0.17	0.56 (16)	0.75 (21)	0.63 (18)	0.78 (22)	1.60 (45)	<0.0001
BARC3 or 5 bleeding % (n)	1.15 (34)	1.26 (37)	1.95 (58)	2.83 (83)	3.59 (104)	<0.0001	0.99 (28)	1.31 (37)	2.63 (75)	2.71 (76)	3.39 (95)	<0.0001
In experimental arm % (n)	1.04 (15)	1.08 (16)	1.97 (29)	2.83 (41)	3.83 (56)	<0.0001	1.00 (14)	1.28 (18)	2.39 (33)	2.94 (41)	3.50 (50)	<0.0001
In reference arm % (n)	1.26 (19)	1.45 (21)	1.94 (29)	2.82 (42)	3.34 (48)	0.0002	0.97 (14)	1.35 (19)	2.87 (42)	2.48 (35)	3.28 (45)	<0.0001
Patient oriented composite endpoints % (n)	11.81 (350)	12.14 (356)	11.81 (353)	14.54 (430)	19.47 (576)	<0.0001	11.59 (330)	12.29 (347)	12.11 (347)	16.20 (460)	16.97 (483)	<0.0001
In experimental arm % (n)	11.76 (171)	11.60 (172)	10.91 (162)	14.72 (214)	18.85 (281)	<0.0001	11.66 (164)	12.08 (171)	12.11 (168)	15.83 (223)	16.16 (235)	<0.0001
In reference arm % (n)	11.85 (179)	12.70 (184)	12.70 (191)	14.36 (216)	20.10 (295)	<0.0001	11.52 (166)	12.50 (176)	12.12 (179)	16.57 (237)	17.83 (248)	<0.0001
Net adverse clinical events % (n)	12.44 (369)	12.96 (380)	13.22 (395)	16.16 (478)	21.37 (632)	<0.0001	12.18 (347)	13.11 (370)	14.03 (402)	17.74 (504)	18.63 (530)	<0.0001
In experimental arm % (n)	12.24 (178)	12.14 (180)	12.48 (185)	16.23 (236)	20.87 (311)	<0.0001	12.15 (171)	12.80 (181)	13.77 (191)	17.59 (248)	17.81 (259)	<0.0001
In reference arm % (n)	12.64 (191)	13.81 (200)	13.96 (210)	16.09 (242)	21.87 (321)	<0.0001	12.21 (176)	13.42 (189)	14.28 (211)	17.89 (256)	19.48 (271)	<0.0001

Sankyo, personal fees from Amgen, grants and personal fees from Terumo, personal fees from Alvimedica, grants from Medicure, grants and personal fees from Astrazeneca, personal fees from Biosensors, outside the submitted work.

Dr. Vranckx has received personal fees from AstraZeneca and the Medicines Company during the conduct of the study and personal fees from Bayer Health Care, Terumo, and Daiichi-Sankyo outside the submitted work.

Dr. Windecker's institution has research contracts with Abbott, Amgen, Bayer, Biotronik, Boston Scientific, Edwards Lifesciences, Medtronic, St Jude Medical, Symetis SA, and Terumo outside the submitted work. All other authors declare no competing interests.

Dr. Serruys reports personal fees from Abbott Laboratories, personal fees from Biosensors, personal fees from Cardialysis, personal fees from Medtronic, personal fees from Micel Technologies, personal fees from Sinomedical Sciences Technology, personal fees from St. Jude Medical, personal fees from Stentys, personal fees from Svelte Medical Systems, personal fees from Philips/Volcano, personal fees from Xeltis, personal fees from StentIt and personal fees from HeartFlow outside the submitted work.

All other authors declare no competing interests.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2019.02.043.

References

[1] M. Ranucci, S. Castelvecchio, L. Menicanti, A. Frigiola, G. Pelissero, Risk of assessing mortality risk in elective cardiac operations: age, creatinine, ejection fraction, and the law of parsimony, Circulation 119 (2009) 3053–3061.

[2] M. Ranucci, S. Castelvecchio, M. Conte, G. Megliola, G. Speziale, F. Fiore, et al., The easier, the better: age, creatinine, ejection fraction score for operative mortality risk stratification in a series of 29,659 patients undergoing elective cardiac surgery, J. Thorac. Cardiovasc. Surg. 142 (2011) 581–586.

[3] J.J. Wykrzykowska, S. Garg, Y. Onuma, T. de Vries, D. Goedhart, M.A. Morel, et al., Value of age, creatinine, and ejection fraction (ACEF score) in assessing risk in patients undergoing percutaneous coronary interventions in the 'All-Comers' LEADERS trial, Circ. Cardiovasc. Interv. 4 (2011) 47–56.

[4] B.E. Stahli, M.B. Wischnewsky, P. Jakob, R. Klingenberg, S. Obeid, D. Heg, et al., Predictive value of the age, creatinine, and ejection fraction (ACEF) score in patients with acute coronary syndromes, Int. J. Cardiol. 270 (2018) 7–13.

[5] P.W. Serruys, V. Farooq, P. Vranckx, C. Girasis, S. Brugaletta, H.M. Garcia-Garcia, et al., A global risk approach to identify patients with left main or 3-vessel disease who could safely and efficaciously be treated with percutaneous coronary intervention: the SYNTAX Trial at 3 years, JACC Cardiovasc. Interv. 5 (2012) 606–617.

[6] S. Garg, G. Sarno, H.M. Garcia-Garcia, C. Girasis, J. Wykrzykowska, K.D. Dawkins, et al., A new tool for the risk stratification of patients with complex coronary artery disease: the Clinical SYNTAX Score, Circ. Cardiovasc. Interv. 3 (2010) 317–326.

[7] J. Iqbal, Y. Vergouwe, C.V. Bourantas, D. van Klaveren, Y.J. Zhang, C.M. Campos, et al., Predicting 3-year mortality after percutaneous coronary intervention: updated logistic clinical SYNTAX score based on patient-level data from 7 contemporary stent trials, JACC Cardiovasc. Interv. 7 (2014) 464–470.

[8] V. Farooq, D. van Klaveren, E.W. Steyerberg, E. Meliga, Y. Vergouwe, A. Chieffo, et al., Anatomical and clinical characteristics to guide decision making between coronary artery bypass surgery and percutaneous coronary intervention for individual patients: development and validation of SYNTAX score II, Lancet 381 (2013) 639–650.

[9] S. Windecker, P. Kolh, F. Alfonso, J.P. Collet, J. Cremer, V. Falk, et al., 2014 ESC/EACTS guidelines on myocardial revascularization: the task force on myocardial revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS) developed with the special contribution of the European Association of Percutaneous Cardiovascular Interventions (EAPCI), Eur. Heart J. 35 (2014) 2541–2619.

[10] M. Ranucci, V. Pistuddi, S. Scolletta, C. de Vincentiis, L. Menicanti, The ACEF II Risk Score for cardiac surgery: updated but still parsimonious, Eur. Heart J. 39 (2018) 2183–2189.

[11] T. Pilgrim, F. Vetterli, B. Kalesan, G.G. Stefanini, L. Raber, S. Stortecky, et al., The impact of anemia on long-term clinical outcome in patients undergoing revascularization with the unrestricted use of drug-eluting stents, Circ. Cardiovasc. Interv. 5 (2012) 202–210.

[12] Vranckx P, Valgimigli M, Juni P, Hamm C, Steg PG, Heg D, et al. Ticagrelor plus aspirin for 1 month, followed by ticagrelor monotherapy for 23 months vs aspirin plus clopidogrel or ticagrelor for 12 months, followed by aspirin monotherapy for 12 months after implantation of a drug-eluting stent: a multicentre, open-label, randomised superiority trial. Lancet (London, England). 2018.

[13] M. Ranucci, S. Castelvecchio, The ACEF score one year after: a skeleton waiting for muscles, skin, and internal organs, EuroIntervention 6 (2010) 549–553.

[14] H.M. Garcia-Garcia, E.P. McFadden, A. Farb, R. Mehran, G.W. Stone, J. Spertus, et al., Standardized end point definitions for coronary intervention trials: the academic research consortium-2 consensus document, Eur. Heart J. 39 (2018) 2192–2207.

[15] D.E. Cutlip, S. Windecker, R. Mehran, A. Boam, D.J. Cohen, G.A. van Es, et al., Clinical end points in coronary stent trials: a case for standardized definitions, Circulation 115 (2007) 2344–2351.

[16] E. Steyerberg, Clinical Prediction Models: A Practical Approach to Development, Validation, and Updating, Springer, New York, 2009.

[17] D.W. Hosmer, S. Lemeshow, R.X. Sturdivant, Applied Logistic Regression, Third ed. Wiley, Hoboken, New Jersey, 2013.

[18] X. Robin, N. Turck, A. Hainard, N. Tiberti, F. Lisacek, J.C. Sanchez, et al., pROC: an open-source package for R and S+ to analyze and compare ROC curves, BMC Bioinf. 12 (2011) 77.

[19] B. Van Calster, D. Nieboer, Y. Vergouwe, B. De Cock, M.J. Pencina, E.W. Steyerberg, A calibration hierarchy for risk models was defined: from utopia to empirical data, J. Clin. Epidemiol. 74 (2016) 167–176.

[20] S.W. Grant, G.L. Hickey, I. Dimarakis, G. Cooper, D.P. Jenkins, R. Uppal, et al., Performance of the EuroSCORE models in emergency cardiac surgery, Circ. Cardiovasc. Qual. Outcomes 6 (2013) 178–185.

[21] I.S. Jovin, R.M. Shah, D.B. Patel, S.V. Rao, D.V. Baklanov, I. Moussa, et al., Outcomes in patients undergoing primary percutaneous coronary intervention for ST-segment elevation myocardial infarction via radial access anticoagulated with bivalirudin versus heparin, A Report From the National Cardiovascular Data Registry 10 (2017) 1102–1111.

[22] M. Ranucci, D. Conti, S. Castelvecchio, L. Menicanti, A. Frigiola, A. Ballotta, et al., Hematocrit on cardiopulmonary bypass and outcome after coronary surgery in nontransfused patients, Ann. Thorac. Surg. 89 (2010) 11–17.

[23] Fang WC, Helm RE, Krieger KH, Rosengart TK, DuBois WJ, Sason C, et al. Impact of minimum hematocrit during cardiopulmonary bypass on mortality in patients undergoing coronary artery surgery. Circulation. 1997;96:Ii-194-9.

[24] P.W. Serruys, R. Modolo, M. Reardon, Y. Miyazaki, S. Windecker, J. Popma, et al., One-year outcomes of patients with severe aortic stenosis and an STS PROM of less than three percent in the SURTAVI trial, EuroIntervention 14 (2018) 877–883.

[25] T. Zanchin, L. Räber, K.C. Koskinas, R. Piccolo, P. Jüni, T. Pilgrim, et al., Preprocedural high-sensitivity cardiac troponin T and clinical outcomes in patients with stable coronary artery disease undergoing elective percutaneous coronary intervention, Circ. Cardiovasc. Interv. 9 (2016), e003202.

[26] M. Roffi, C. Patrono, J.P. Collet, C. Mueller, M. Valgimigli, F. Andreotti, et al., 2015 ESC guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: task force for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation of the European Society of Cardiology (ESC), Eur. Heart J. 37 (2016) 267–315.

[27] P.W. Serruys, Y. Onuma, S. Garg, G. Sarno, M. van den Brand, A.P. Kappetein, et al., Assessment of the SYNTAX score in the Syntax study, EuroIntervention 5 (2009) 50–56.

[28] V. Farooq, Y. Vergouwe, L. Raber, P. Vranckx, H. Garcia-Garcia, R. Diletti, et al., Combined anatomical and clinical factors for the long-term risk stratification of patients undergoing percutaneous coronary intervention: the logistic clinical SYNTAX score, Eur. Heart J. 33 (2012) 3098–3104.

[29] R. Modolo, C. Collet, Y. Onuma, P.W. Serruys, SYNTAX II and SYNTAX III trials: what is the take home message for surgeons? Ann. Cardiothorac. Surg. 7 (2018) 470–482.

[30] C. Collet, Y. Onuma, D. Andreini, J. Sonck, G. Pompilio, S. Mushtaq, et al., Coronary computed tomography angiography for heart team decision-making in multivessel coronary artery disease, Eur. Heart J. 39 (2018) 3689–3698.