Patient selection for cardiac surgery: Time to consider subgroups within risk categories?

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ABSTRACT

Background: Medical guidelines increasingly use risk stratification and implicitly assume that individuals classified in the same risk category form a homogeneous group, while individuals with similar, or even identical, predicted risks can still be very different. We evaluate a strategy to identify homogeneous subgroups typically comprising predicted risk categories to allow further tailoring of treatment allocation and illustrate this strategy empirically for cardiac surgery patients with high postoperative mortality risk.
Methods: Using a dataset of cardiac surgery patients (n = 6517) we applied cluster analysis to identify homogenous subgroups of patients comprising the high postoperative mortality risk group (EuroSCORE ≥ 15%). Cluster analyses were performed separately within younger (<75 years) and older (≥75 years) patients. Validity measures were calculated to evaluate quality and robustness of the identified subgroups.
Results: Within younger patients two distinct and robust subgroups were identified, differing mainly in preoperative state and indication of recent myocardial infarction or unstable angina. In older patients, two distinct and robust subgroups were identified as well, differing mainly in preoperative state, presence of chronic pulmonary disease, previous cardiac surgery, neurological dysfunction disease and pulmonary hypertension.
Conclusions: We illustrated a feasible method to identify homogeneous subgroups of individuals typically comprising risk categories. This allows a single treatment strategy – optimal only on average, across all individuals in a risk category – to be replaced by subgroup-specific treatment strategies, bringing us another step closer to individualized care. Discussions on allocation of cardiac surgery patients to different interventions may benefit from focusing on such specific subgroups.

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1. Introduction

Over the past decades the importance of tailoring treatment and interventions has frequently been emphasized to balance benefits and harms of treatment and improve effectiveness and cost-effectiveness [1–3]. Ideally, the optimal (preventive) treatment or intervention strategy would be identified and provided for every individual based on their (unique) risk profile, i.e. their combination of risk factors. Currently, risk prediction models are increasingly used to stratify individuals based on their predicted risk and tailor treatment or interventions to *categories* of individuals in which the highest benefit is expected to be achieved (Fig. 1, middle box). For instance, individuals with high predicted EuroSCORE risk may be offered transcatheter aortic valve implementation (TAVI) instead of (surgical) aortic valve replacement (AVR) [4].

Following such risk stratification, guideline simplicity assume that individuals classified into the same risk category form a fairly homogeneous group, as they are all recommended the same treatment or intervention based on average estimates within these risk categories [3,4]. However, individuals with similar, or even *identical*, predicted risk may still be very different. For example, a 61-year old man may have a predicted 30-day mortality risk of 21% due to presence of extracardiac arteriopathy, a recent myocardial infarction (MI), moderate left ventricular ejection fraction (LVEF, 30–50%), an emergency surgery, and critical preoperative state, or alternatively, due to presence of a neurologic dysfunction, poor LVEF (0–30%), pulmonary hypertension, and requiring

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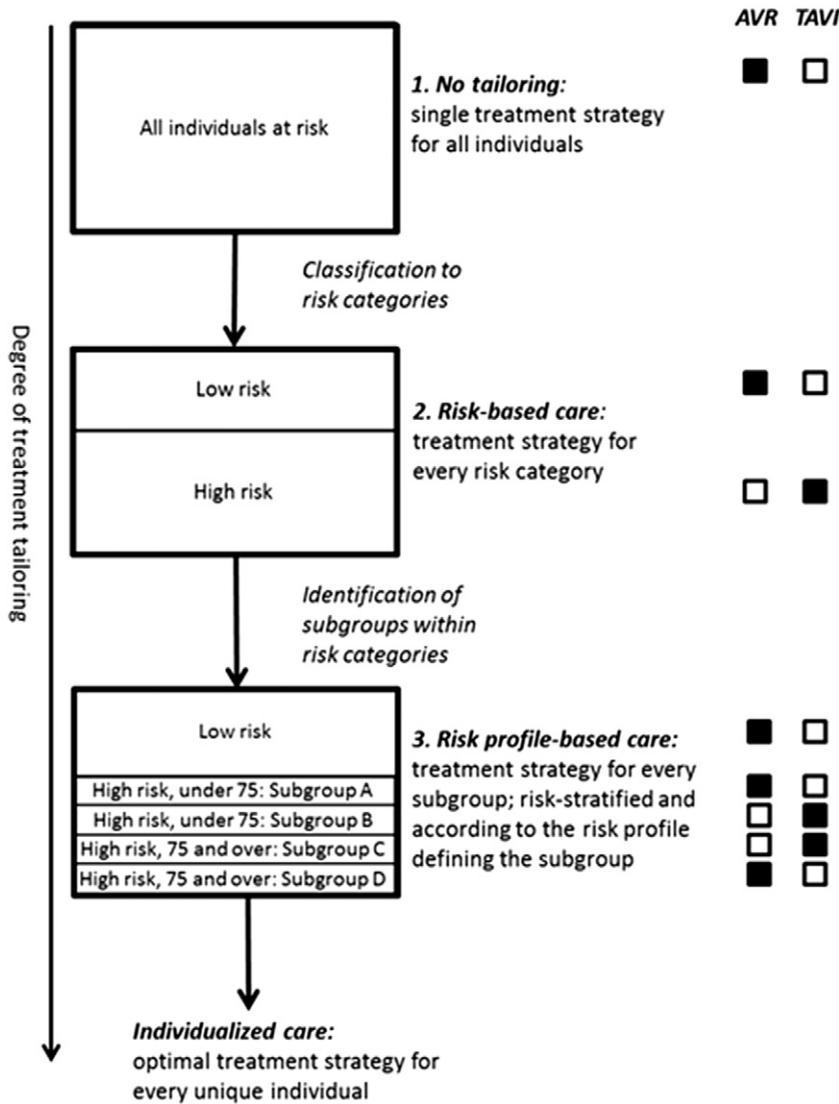E-mail address: a.vangiessen@umcutrecht.nl (A. van Giessen).

Fig. 1. Value of acquiring more evidence on subgroups.
Three levels of evidence are shown for the situation in which groups of individuals can be provided with treatment. In situation 1 (top box) no risk factor information is available and risk prediction is not performed. Hence, a single treatment decision for TAVI or (surgical) AVR needs to be made for all patients, and the (cost-)effectiveness will be the observed average across all these individuals. In situation 2 (middle box), a validated prediction model (e.g. EuroSCORE) is available to classify individuals to risk categories. This allows risk-stratified treatment decisions based on the (cost-)effectiveness of TAVI vs (surgical) AVR in that category, which is the current situation. In situation 3 (bottom box), identification of subgroups within risk categories allows even more tailored care as treatment decisions can now be made separately for each subgroup of individuals, based on corresponding (cost-)effectiveness estimates.

surgery other than isolated CABG [5]. Obviously, the optimal intervention for these two individuals with very different combinations of risk factors may be different even though their estimated mortality risk is equal and they would both be classified as high-risk [4].

Given the effectiveness and costs associated with TAVI, this procedure may not be feasible in all patients (Fig. 1, top box) [6]. While effectiveness and cost-effectiveness could be improved by risk stratification on postoperative mortality risk (Fig. 1, middle box). [7–9], there is an ongoing discussion on whether this is appropriate and sufficient in allocating patients to TAVI instead of (surgical) AVR [10–13]. Patients would ideally be selected for TAVI or SAVR after discussion by a multidisciplinary heart team [14,15]. Measures of frailty that are associated with adverse outcomes, but not incorporated in current risk prediction models, can then also be taken into account. However, such an approach is time consuming, complex, and limited by subjectivity.

It will thus be valuable to discover homogeneous subgroups within risk categories to potentially further differentiate treatment allocation beyond risk stratification, but without requiring a time-consuming or subjective individual assessment [1,2,16]. Identification of such subgroups within risk categories is, however, not commonly performed.

Furthermore, current subgroup analyses typically focus on a single patient characteristic, such as gender or age [17,18], whereas the balance between harms and benefits, even within risk-categories, may depend on the combination of multiple patient characteristics. Therefore, we propose to identify relevant, that is common, subgroups of individuals that typically comprise risk categories, using cluster analysis.

We demonstrate the feasibility of our approach through a clinical illustration for the decision on whether TAVI could be an appropriate alternative to (surgical) AVR (Fig. 1). We identified homogenous subgroups of patients, classified by the logistic EuroSCORE as having a high postoperative mortality risk (≥15%), using previously collected data on cardiac surgery patients [5,19]. Such subgroup identification allows to move from risk-based care (Fig. 1, middle box) to risk profile-based care (Fig. 1, lower box).

2. Methods

Starting point of our approach is the calculation of the predicted risk for every individual concerning the outcome under study. Subsequently, individuals are classified into risk categories, commonly defined by guidelines, as is currently performed. Following risk classification, cluster analysis can be performed on individuals within a risk category to

discover more homogeneous subgroups sharing a common risk profile (a combination of risk factors).

2.1. Identifying subgroups among high-risk cardiac surgery patients

This illustration used data from a cohort of patients (n = 6517) who underwent cardiac surgery between 2006 and 2010 at Isala, Zwolle, a large tertiary center for cardiac surgery in The Netherlands. From this dataset we included all patients for whom the individual postoperative (i.e. 30-days or in-hospital) mortality risk using the logistic EuroSCORE could be calculated (n = 6286, 96.5%). First, we calculated these predicted risks and classified the patients into the low (<15%) and high (≥15%) risk category (Fig. 1, middle box) [19,20]. Next, we performed cluster analysis to identify subgroups among patients within the high-risk category. As age is oftentimes an important factor in both effectiveness and occurrence of complications of treatment [13], we identified subgroups separately among high-risk patients younger than 75 years of age, and patients aged 75 or older.

We applied the TwoStep Cluster method, available in SPSS, using a likelihood similarity measure. As input variables we initially used the predictors of the logistic EuroSCORE [5]. The (SPSS) TwoStep Cluster method can handle this mix of continuous and discrete variables, present in the EuroSCORE as well as many other clinical prediction models [21]. To improve the stability of the identified subgroups, we applied the rule of thumb of including at most k variables if data on at least 2^k individuals was available [22]. Starting with all 18 logistic EuroSCORE predictors, we selected these k variables using backward selection to eliminate those variables with the lowest importance for clustering.

As different clusters may be detected, dependent on features of the data and the type and settings of the cluster analysis, cluster validation is essential in finding the optimal set of subgroups that best fits the underlying data [23]. The quality of the identified subgroups was assessed using the average silhouette width, a measure of how similar individuals in the subgroups are, where a good [0.5–1], fair [0.25–0.5] or poor [≤0.25] value indicates that a strong, weak or no substantial subgroup structure, respectively, is present [24]). Robustness was assessed by replicating the analysis using 1000 datasets bootstrapped from the original [25,26]. To compare the original subgroups to the subgroups identified in the bootstrap samples, the adjusted Rand index was calculated for each sample using the R software environment and the *mclust* package [27,28]. For randomly chosen subgroups this index would have value 0, whereas it would have value 1 if perfectly identical subgroups are identified among the bootstrap samples. Additional information on cluster analysis as well as cluster validation can be found in the Supplementary Methods I.

We performed several cluster analyses with varying outlier handling settings (0%, 5%, 10%, and 25%) and different subgroup numbers; fixed 2–8 clusters or selected by the Bayesian Information Criterion (BIC) (see Supplementary Methods II). We selected outlier settings such that, over the bootstrap samples, on average less than 20% of the individuals were classified as outliers. Using the average silhouette score, the number of subgroups selected by the BIC over the bootstrap samples, and the Rand index, the final number of subgroups was selected.

3. Results

3.1. Operative mortality risk profiles identified in cardiac surgery data

Calculation of the predicted postoperative mortality risk for each patient using the logistic EuroSCORE and subsequent risk classification identified 1064 (16.9%) patients with a risk ≥15%. There was substantial variation in values and presence of risk factors in this group (Table 1). After splitting the high-risk individuals into a younger (<75) and older (≥75 years) group, heterogeneity in risk factors was still present.

3.2. Cluster analysis in patients younger than 75 years of age

Based on the size of this group (n = 562), 9 variables were included (Table 2). The optimal result in this group was obtained when using an outlier handling setting of 5% and 2 clusters. Averaged over all bootstrap samples less than 20% of patients were then classified as outliers, had a fair silhouette score of 0.4, and achieved a Rand index of 0.70. A solution with two clusters was also selected by the BIC in 88% of the bootstrap samples. The cluster analysis results for alternative outlier handling settings and numbers of identified subgroups can be found in Supplementary Results Table 1A.

3.3. Subgroups of patients younger than 75 years of age

Selecting the optimal set of subgroups, 61 (11%) high-risk patients under 75 years were classified as outliers (Table 2A). The largest

subgroup, (subgroup A, n = 282, 50%) consisted of patients who were almost all (90%) in a critical preoperative state *and* had to undergo an emergency operation (86%). About half of these patients had a recent MI (48%), whereas in the second subgroup (subgroup B, n = 219, 39%) this was only 4%. Furthermore, subgroup B contained patients none of whom had unstable angina or an emergency surgery. Also, only 2% of patients in subgroup B were in a critical preoperative state, but almost all patients had surgery other than isolated coronary surgery (92%). Further details on characteristics of these subgroups can be found in Table 2A.

3.4. Cluster analysis in patients older than 75 years of age

Based on the size of this group (n = 502), 8 variables were included (Table 2). The optimal result in this group was obtained when using an outlier handling setting of 5% and 2 clusters. Averaged over all bootstrap samples less than 20% of patients were then classified as outliers, had a fair silhouette score of 0.4 and achieved a Rand index of 0.74. A solution with two clusters was also selected by the BIC in 75% of the bootstrap samples. The cluster analysis results for alternative outlier handling settings and numbers of identified subgroups can be found in Supplementary Results Table 1B.

3.5. Subgroups of patients older than 75 years of age

Selecting the optimal set of subgroups, 85 (17%) high-risk patients aged 75 years and older were classified as outliers (Table 2B). The largest subgroup (subgroup C, n = 287, 57%) consisted of patients none of whom had had a recent MI, were in critical preoperative state, or underwent an emergency operation. A large part (88%) of these patients did have surgery other than isolated cardiac surgery. Conversely, a fair amount of patients in the second subgroup (subgroup D, n = 130, 26%) had had a recent MI (62%). In this subgroup, however, none of the patients had chronic pulmonary disease, previous cardiac surgery, neurological dysfunction disease or pulmonary hypertension. Further details on characteristics of these subgroups can be found in Table 2B.

4. Discussion

Our study demonstrates how cluster analysis can be used beyond risk stratification to identify distinct subgroups of individuals who had been classified within the same risk category, based on their different risk profiles. The illustrated approach allows identification of *relevant* subgroups, i.e. substantial subgroups that make up the majority of the risk category under investigation, based on distinct combinations of characteristics of individuals that lead to the same predicted risk category. Numerous different combinations of patient characteristics may lead to classification into the same predicted risk category particularly when the prediction model includes many predictors, which are difficult to disentangle without a systematic approach such as illustrated here. Identification and characterization of subgroups allows moving from risk-based uniform ('one-size') care (Fig. 1, middle box) to risk profile-based care (Fig. 1, lower box). This takes us another step closer to individualized care by providing the possibility to take into account possible differences in effectiveness and cost-effectiveness of treatment among the identified subgroups instead of the entire risk category [1,2].

For instance, for cardiac surgery patients TAVI could be an appropriate alternative to (surgical) AVR, but given the risks and costs associated with TAVI this procedure may not be feasible in all these patients (Fig. 1, top box) [6]. Effectiveness as well as cost-effectiveness could be improved by selecting eligible patients based on risk stratification using the EuroSCORE (Fig. 1, middle box). Nevertheless, there is an ongoing discussion on whether risk stratification is appropriate and sufficient in allocating patients to TAVI instead of

Table 1
Risk factors of patients within Isala cohort stratified by postoperative mortality risk and age.

Risk factors	Definition	Total (n = 6286)	Low-risk (n = 5022)	High-risk (n = 1064)	High-risk < 75 years (n = 562)	High-risk ≥ 75 years (n = 502)
Patient-related factors						
Age (mean, standard deviation)		66.9 (10.5)	65.9 (10.4)	71.8 (9.6)	65.3 (8.5)	79.2 (3.4)
Sex (%)	Female	30%	29%	38%	33%	44%
Chronic pulmonary disease (%)	Longterm use of bronchodilators or steroids for lung disease	14%	12%	3%	24%	31%
Extracardiac arteriopathy (%)	Any one or more of the following: claudication, carotid occlusion or >50% stenosis, previous or planned intervention on the abdominal aorta, limb arteries or carotids	11%	7%	28%	29%	27%
Neurological dysfunction (%)	Disease severely affecting ambulation or day-to-day functioning	7%	4%	19%	19%	19%
Previous cardiac surgery (%)	Requiring opening of the pericardium	8%	4%	27%	32%	22%
Serum creatinine (%)	>200 μmol/l preoperatively	2%	1%	9%	10%	8%
Active endocarditis (%)	Patient still under antibiotic treatment for endocarditis at the time of surgery	2%	1%	7%	10%	4%
Critical preoperative state (%)	Any one or more of the following: ventricular tachycardia or fibrillation or aborted sudden death, preoperative cardiac massage, preoperative ventilation before arrival in the anaesthetic room, preoperative inotropic support, intraaortic balloon counter pulsation or preoperative acute renal failure (anuria or oliguria, 10 ml/h)	9%	3%	38%	49%	25%
Cardiac-related factors						
Unstable angina (%)	Rest angina requiring i.v. nitrates until arrival in the anaesthetic room	7%	5%	17%	19%	15%
LV dysfunction (%)	Moderate or LVEF 30–50%	33%	30%	47%	43%	50%
	Poor or LVEF <30%	7%	4%	26%	30%	20%
Recent myocardial infarct (%)	(<90 days)	13%	11%	28%	31%	24%
Pulmonary hypertension (%)	Systolic PA pressure > 60 mmHg	3%	1%	11%	12%	11%
Operation-related factors						
Emergency (%)	Carried out on referral before the beginning of the nextworking day	9%	3%	36%	48%	23%
Other than isolated CABG (%)	Major cardiac procedure other than or in addition to CABG	46%	40%	73%	72%	74%
Surgery on thoracic aorta (%)	For disorder of ascending, arch or descending aorta	4%	2%	13%	17%	8%
Postinfarct septal rupture (%)		0%	0%	2%	3%	1%

(surgical) AVR [10–13].The differences in combinations of risk factors present in high-risk patients (Table 1), as well as subgroup analyses of TAVI outcomes and sensitivity analyses in economic evaluations of TAVI age [17,18,29], suggest that benefits and risks, as well as costs, may vary substantially between subgroups within the high-risk category. This indicates that providing either *all* or *none* of the high-risk patients with TAVI is both unlikely to be optimal. Identification of subgroups within risk categories would thus be valuable. Subsequently, the identified subgroups, such as a group of individuals of age 75 and older that have not had a recent MI, were not in critical preoperative state, and did not undergo an emergency operation, but did have surgery other than isolated cardiac surgery (Table 2), can be the starting point for further research. A new study focusing on identifying effectiveness and costs of TAVI in subgroups of patients with the characteristics defined by the subgroups identified by the cluster analysis, allows more optimal allocation of patients to TAVI or (surgical) AVR (Fig. 1, lower box), which may improve both health outcomes and cost-effectiveness [6].

4.1. Limitations and challenges

Performing cluster analysis and cluster validation requires a sufficiently large set of individual patient data [22]. Ensuring a stable set of subgroups that best fits the data [23], cluster validation should be performed and, similar to prediction modeling, subgroup characterizations should ultimately be externally validated [30].

In our illustration we identified subgroups using the risk predictors as cluster variables. This ensures the feasibility of our approach since

evidence on these risk factors, known to be important, are available after risk classification. However, other characteristics that could enhance the distinction between subgroups, preferably those characteristics known or expected to be related to effectiveness and harms of the treatment under investigation, such as B-type natriuretic peptide and comorbidities for TAVI selection [29], can easily be included and may further improve the subgroup identification. Furthermore, we chose to perform the analysis based on risk stratification using the logistic EuroSCORE. More recently, EuroSCORE II and STS-PROM were developed which may improve risk prediction accuracy, although the extent of this improvement varies in literature [7–9].We selected the logistic EuroSCORE because both the EuroSCORE II and STS-PROM require many more variables, some of which were not registered in our data. These newer models, including even more variables, would only increase the likelihood of presence of patients with similar risks, but different risk profiles, enlarging the potential for improvement. Although the subgroup identification strategy shown here is only illustrated based on the logistic EuroSCORE, this generic clustering approach may just as well be applied using any other risk prediction or classification strategy [17].

4.2. Implementation and implications for effectiveness and cost-effectiveness research

Currently, evidence-based medicine is introducing a growing number of guidelines with emphasis on risk stratification [3,4]. As these guidelines regard all individuals within the same risk category to be similar, treatment decisions are based on average effectiveness and

Table 2
Risk profiles of subgroups of patients with high predicted postoperative mortality risk (≥15%).

[A] High-risk patients younger than 75 years of age.

Subgroup	# individuals (% of total)	Critical preoperative state	Emergency	Recent MI	Neurological dysfunction	Extracardiac arteriopathy	Unstable angina	Other surgery	Previous cardiac surgery	Thoracic aortic surgery	Postoperative mortality risk
Total	562 (100%)	49%	48%	31%	19%	29%	19%	72%	31%	17%	31.6%
A	282 (50%)	90%	86%	48%	4%	10%	27%	61%	22%	11%	35.7%
B	219 (39%)	2%	0%	8%	32%	43%	0%	92%	44%	25%	25.0%
Outliers	61 (11%)	33%	41%	38%	43%	64%	52%	51%	28%	21%	31.6%

[B] High-risk patients 75 years and older.

Subgroup	# individuals (% of total)	Recent MI	Critical preoperative state	Emergency	Chronic pulmonary disease	Other surgery	Previous cardiac surgery	Neurological dysfunction disease	Pulmonary hypertension	Postoperative mortality risk
Total	502 (100%)	22%	25%	23%	31%	74%	22%	19%	11%	32.3%
C	287 (57%)	0%	0%	0%	40%	88%	29%	25%	15%	26.1%
D	130 (26%)	62%	59%	56%	0%	52%	0%	0%	0%	34.4%
Outliers	85 (17%)	47%	58%	47%	46%	59%	35%	28%	14%	49.9%

For each identified subgroup risk profiles are horizontally presented by the percentages of individuals in the subgroup for which the corresponding risk factor is present. For instance, reading from left to right; subgroup C consists of 287 individuals (57% of high-risk individuals of age 75 years and older) of whom none have had a recent MI, or are in an emergency of critical preoperative state. In this subgroup 40% had chronic pulmonary disease, 88% received surgery other than isolated CABG, etc. Reading from top to bottom, risk factors can be differentiated between subgroups, e.g. all high-risk individuals of 75 years and older with pulmonary hypertension are either in subgroup C or are outliers. Risk factors are ordered according to their importance in the clustering, where left represents the highest importance. For risk factor definitions, see Table 1 [5,19].

cost-effectiveness estimates across risk categories. There may be substantial value in identification of subgroups within high, as well as low or intermediate, risk categories to further tailor treatment and intervention strategies, but without requiring a time-consuming or subjective individual assessment. Using similarity or distance measures (see Supplementary Methods I) [27], new individuals can be classified to a single specific identified subgroup to ultimately allocate the optimal treatment to every subgroup.

5. Conclusions

Individuals classified into the same risk category can still be very different, causing risk categories to be very heterogeneous. We applied a cluster analysis approach following risk prediction and classification, which allows for identification of relevant, homogeneous subgroups typically present within risk categories. Identification of such subgroups within any risk category, is feasible across all medical domains in which risk stratification is used. Characterization of the identified subgroups allows subsequent subgroup-specific estimation of effectiveness and cost-effectiveness of treatment and thereby contributes to more optimal, tailored treatment strategies.

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Conflict of Interest

None declared.

Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.ijcard.2015.11.034.

References

[1] M. Sculpher, Subgroups and heterogeneity in cost-effectiveness analysis, PharmacoEconomics 26 (9) (2008) 799–806.

[2] J.A. Knottnerus, P. Tugwell, Heterogeneity and clinical reality, J. Clin. Epidemiol. 66 (8) (2013 Aug) 809–811.

[3] T. Yu, D. Vollenweider, R. Varadhan, et al., Support of personalized medicine through risk-stratified treatment recommendations — an environmental scan of clinical practice guidelines, BMC Med. 11 (2013 Jan 9) 7.

[4] S.D. Kristensen, J. Knuuti, A. Saraste, et al., 2014 ESC/ESA guidelines on non-cardiac surgery: cardiovascular assessment and management: the joint task force on non-cardiac surgery: cardiovascular assessment and management of the European Society of Cardiology (ESC) and the European Society of Anaesthesiology (ESA), Eur. Heart J. 35 (35) (2014 Sep 14) 2383–2431.

[5] F. Roques, P. Michel, A.R. Goldstone, S.A. Nashef, The logistic EuroSCORE, Eur. Heart J. 24 (9) (2003 May) 881–882.

[6] M. Neyt, B.H. Van, S. Devriese, S.S. Van De, A cost-utility analysis of transcatheter aortic valve implantation in Belgium: focusing on a well-defined and identifiable population, BMJ Open (2012) 2(3).

[7] I. Ben-Dor, M.A. Gaglia Jr., I.M. Barbash, et al., Comparison between society of thoracic surgeons score and logistic EuroSCORE for predicting mortality in patients referred for transcatheter aortic valve implantation, Cardiovasc. Revasc. Med. 12 (6) (2011 Nov) 345–349.

[8] A.G. Kunt, M.F.A.U. Kurtcephe, M.F.A.U. Hidiroglu, et al., Comparison of original EuroSCORE, EuroSCORE II and STS risk models in a Turkish cardiac surgical cohort, Interact. Cardiovasc. Thorac. Surg. 16 (5) (2013 May) 625–629.

[9] D. Wendt, B.R. Osswald, K. FAU-Kayser, K.F. Kayser, et al., Society of thoracic surgeons score is superior to the EuroSCORE determining mortality in high risk patients undergoing isolated aortic valve replacement, Ann. Thorac. Surg. 88 (2) (2009 Aug) 468–474 (discussion 474-5).

[10] A.W. Leber, M. Kasel, T. Ischinger, et al., Aortic valve calcium score as a predictor for outcome after TAVI using the CoreValve revalving system, Int. J. Cardiol. 166 (3) (2013 Jul 1) 652–657.

[11] J.J. Bax, V. Delgado, V. Bapat, et al., Open issues in transcatheter aortic valve implantation. Part 1: patient selection and treatment strategy for transcatheter aortic valve implantation, Eur. Heart J. 35 (38) (2014 Oct 7) 2627–2638.

[12] M. Ranucci, F. Guarracino, S. Castelvecchio, et al., Surgical and transcatheter aortic valve procedures. The limits of risk scores, Interact. Cardiovasc. Thorac. Surg. 11 (2) (2010 Aug) 138–141.

[13] M. De Feo, M. Vicchio, C.A. Della, et al., Lack of definite indication criteria for choosing between transcatheter implantation and surgical replacement of the aortic valve, J. Cardiovasc. Med. (Hagerstown) 14 (2) (2013 Feb) 158–163.

[14] R. Showkathali, R. Chelliah, B. Brickham, et al., Multi-disciplinary clinic: next step in "Heart team" approach for TAVI, Int. J. Cardiol. 174 (2) (2014 Jun 15) 453–455.

[15] N. Ruparelia, B.D. Prendergast, TAVI in 2015: who, where and how? Heart 101 (17) (2015 Sep 1) 1422–1431.

[16] R. Varadhan, J.B. Segal, C.M. Boyd, A.W. Wu, C.O. Weiss, A framework for the analysis of heterogeneity of treatment effect in patient-centered outcomes research, J. Clin. Epidemiol. 66 (8) (2013 Aug) 818–825.

[17] O. Havakuk, A. Finkelstein, A. Steinvil, et al., Comparison of outcomes in patients ≤85 versus >85 years of age undergoing transcatheter aortic-valve implantation, Am. J. Cardiol. 113 (1) (2014 Jan 1) 138–141.

[18] K. Hayashida, M.C. Morice, B. Chevalier, et al., Sex-related differences in clinical presentation and outcome of transcatheter aortic valve implantation for severe aortic stenosis, J. Am. Coll. Cardiol. 59 (6) (2012 Feb 7) 566–571.

[19] D.R. Holmes Jr., M.J. Mack, S. Kaul, et al., 2012 ACCF/AATS/SCAI/STS expert consensus document on transcatheter aortic valve replacement, J. Am. Coll. Cardiol. 59 (13) (2012 Mar 27) 1200–1254.

[20] C.R. Smith, M.B. Leon, M.J. Mack, et al., Transcatheter versus surgical aortic-valve replacement in high-risk patients, N. Engl. J. Med. 364 (23) (2011 Jun 9) 2187–2198.

[21] J. Bacher, K. Wenzig, M. Vogler, SPSS TwoStep clustering — a first evaluation, Proceedings of the RC33 Sixth International Conference on Social Science. Methodology, 2004.

[22] A.K. Formann, Die Latent-Class-Analyse. Einführung in Theorie und Anwendung, Weinheim, Beltz, 1984.

[23] M. Halkidi, Y. Batistakis, M. Vazigiannis, On clustering validation techniques, J. Intell. Inf. Syst. 17 (2001) 107–145.

[24] L. Kaufman, P.J. Rousseeuw, Finding Groups in Data: An Introduction to Cluster Analysis, John Wiley & Sons, Inc., New York, 1990.

[25] S. Dolnicar, F. Leisch, Evaluation of structure and reproducibility of cluster solutions using bootstrap, Mark. Lett. 21 (1) (2010) 83–101.

[26] A.K. Jain, J.V. Moreau, Bootstrap technique in cluster analysis, Pattern Recogn. 20 (5) (1987) 547–568.

[27] B.S. Everitt, S. Landau, M. Leese, D. Stahl, Cluster Analysis, 5th Edition ed. John Wiley & Sons, Ltd, West Sussex, United Kingdom, 2011.

[28] L. Hubert, P. Arabie, Comparing partitions, J. Classif. 2 (1985) 193–218.

[29] J. Kefer, C. Beauloye, P. Astarci, et al., Usefulness of B-type natriuretic peptide to predict outcome of patients treated by transcatheter aortic valve implantation, Am. J. Cardiol. 106 (12) (2010 Dec 15) 1782–1786.

[30] S.E. Bleeker, H.A. Moll, E.W. Steyerberg, et al., External validation is necessary in prediction research: a clinical example, J. Clin. Epidemiol. 56 (9) (2003 Sep) 826–832.