International Journal of Cardiology 203 (2016) 1103–1108

Contents lists available at ScienceDirect

International Journal of Cardiology

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

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

A. van Giessen [a,*], G.A. de Wit [a,b], H.A. Smit [a], H.M. den Ruijter [c], A.P. Nierich [d], W.W. Jansen Klomp [e], K.G.M. Moons [a], H. Koffijberg [a,f]

[a] Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, the Netherlands
[b] National Institute for Public Health and the Environment, Bilthoven, the Netherlands
[c] Laboratory of Experimental Cardiology, University Medical Center Utrecht, Utrecht, the Netherlands
[d] Department of Anesthesiology and Intensive Care, Isala, Zwolle, the Netherlands
[e] Department of Cardiology, Isala, Zwolle, the Netherlands
[f] Department of Health Technology & Services Research, MIRA Institute for Biomedical Technology and Technical Medicine, University of Twente, Enschede, the Netherlands

ARTICLE INFO

Article history:
Received 1 October 2015
Accepted 4 November 2015
Available online 6 November 2015

Keywords:
Cardiac surgery
Tailored treatment
Subgroups
Risk prediction
Cluster analysis

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.

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 simplicitly 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

* Corresponding author at: Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Mailstop STRAT 6.131, 85500, 3508 GA Utrecht, the Netherlands.
E-mail address: a.vangiessen@umcutrecht.nl (A. van Giessen).

http://dx.doi.org/10.1016/j.ijcard.2015.11.034
0167-5273/

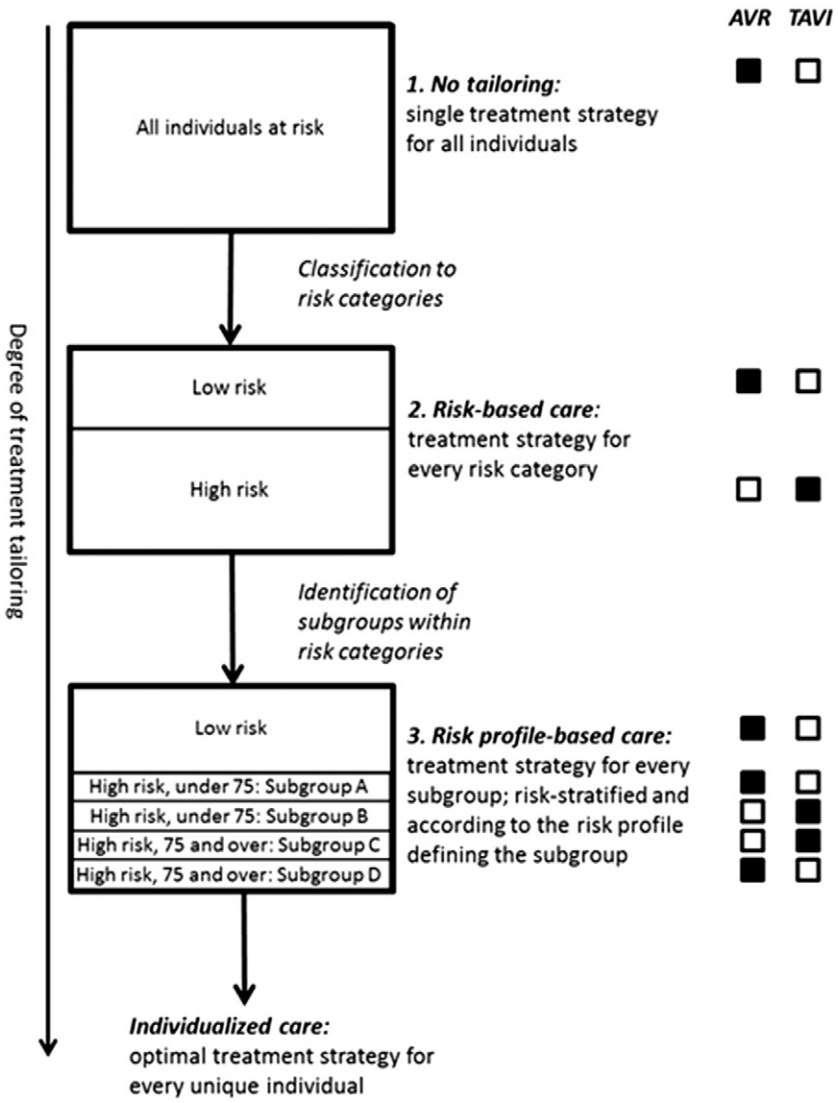

Fig. 1. Value of acquiring more evidence on subgroups.
Three levels of evidence are shown for the situation in which groups of individuals can be provided with treatment. In situation 1 (top box) no risk factor information is available and risk prediction is not performed. Hence, a single treatment decision 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