International Journal of Cardiology 216 (2016) 68–77

Contents lists available at ScienceDirect

International Journal of Cardiology

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

Development and validation of cardiovascular risk scores for haemodialysis patients

Stefan D. Anker [a,*,1], Iain A. Gillespie [b,1], Kai-Uwe Eckardt [c,1], Florian Kronenberg [d,1], Sharon Richards [e,1], Tilman B. Drueke [f,1], Peter Stenvinkel [g,1], Ronald L. Pisoni [h,1], Bruce M. Robinson [h,1], Daniele Marcelli [i,1], Marc Froissart [j,1], Jürgen Floege [k,1], On behalf the ARO Steering Committee (collaborators):

[a] Innovative Clinical Trials, Department of Cardiology & Pneumology, University Medical Center Göttingen (UMG), Göttingen, Germany
[b] Center for Observational Research (CfOR), Amgen Ltd., Uxbridge, United Kingdom
[c] Nephrology and Hypertension, University of Erlangen-Nuremberg, Germany
[d] Division of Genetic Epidemiology, Department of Medical Genetics, Molecular and Clinical Pharmacology, Medical University of Innsbruck, Innsbruck, Austria
[e] Global Biostatistics, Amgen Ltd., Uxbridge, United Kingdom
[f] Inserm U 1018, Paul Brousse Hospital, Paris Sud University, Villejuif, France
[g] Department of Renal Medicine, Karolinska University Hospital Huddinge, Stockholm, Sweden
[h] Arbor Research Collaborative for Health, Ann Arbor, MI, United States
[i] EMEALA Medical Board, Fresenius Medical Care, Bad Homburg, Germany and Danube University, Krems, Austria
[j] International Development Nephrology, Amgen Europe GmbH, Zug, Switzerland;
[k] Nephrology, RWTH University of Aachen, Aachen, Germany

ARTICLE INFO

Article history:
Received 13 December 2015
Received in revised form 17 April 2016
Accepted 17 April 2016
Available online 20 April 2016

Keywords:
Cardiovascular disease
Nephrology
Risk prediction
Validation
Framingham

ABSTRACT

Background: A simple clinical tool to predict cardiovascular disease risk does not exist for haemodialysis patients. The long-term coronary risk Framingham Heart Study Risk score (FRS), although used in this population, may be inadequate. Therefore, we developed separate risk-scores for cardiovascular mortality (CVM) and cardiovascular morbidity & mortality (CVMM) in a Fresenius Medical Care-based haemodialysis patient cohort (AROii).
Methods: Applying a modified FRS approach, we derived and internally validated two-year risk-scores in incident European adult patients randomly assigned to a development (N = 4831) or a validation (N = 4796) dataset. External validation was conducted in the third Dialysis Outcomes and Practice Patterns Study (DOPPS III) cohort. Additional discrimination comparing to the FRS was performed.
Results: The overall two-year CVM and CVMM event rates were 5.0 and 22.6 per 100 person-years respectively. Common risk predictors included increasing age, cardiovascular disease history, primary diabetic nephropathy, low blood pressure, and inflammation. The CVM score was more predictive in AROii (c-statistic 0.72) and in DOPPS III (c-statistic 0.73–0.74) than the CVMM score (c-statistic 0.66–0.67 & 0.63 respectively). The FRS was not predictive of either CVM (c-statistic 0.54) or CVMM (c-statistic 0.56) in AROii.
Conclusions: We describe novel, easy-to-apply and interpret CV risk-scores for haemodialysis patients. Our improved cardiovascular prediction performance over traditional (FRS) scores reflected its tailored development and validation in haemodialysis populations, and the integration of non-classical cardiovascular risk factors. The lower expected versus observed CVM and CVMM risk suggests the existence of novel cardiovascular risk factors in this patient population not measured in this study.

1. Introduction

Chronic kidney disease (CKD) represents a major public health problem, affecting 13% of adults in the United States of America [1] and 6–11% in Europe [2]. Poor quality of life, high incidence of morbidity and an increased risk of death [3] all contribute to the substantial disease burden. The premature mortality risk for haemodialysis patients exceeds not only that in the general population but also that of patients with other chronic diseases: a mortality rate of 19.2 per 100 person-years was recently estimated for incident European haemodialysis patients, versus 1.2 per 100 person-years in the general population [4].

Cardiovascular disease (CVD) is the leading cause of morbidity and mortality in CKD patients, and in dialysis patients CVD is responsible for approximately 45% of all-cause mortality [5,6]. Despite this, a simple clinical tool to assess short-term CVD risk in haemodialysis patients does not exist. Use of the Framingham Heart Study score – a tool designed to derive ten-year coronary CVD risk in the general population – to assess CV risk in haemodialysis patients may be

* Corresponding author.
[1] This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

http://dx.doi.org/10.1016/j.ijcard.2016.04.151
0167-5273/

inadequate [7,8] as a number of traditional risk factors for cardiovascular disease in the general population (e.g. elevated serum cholesterol [9] or Body Mass Index (BMI) [10]) are not related to reduced survival in advanced CKD. Furthermore, the CVD risk in CKD patients is also affected by a large number of non-traditional risk factors, such as disturbed mineral-bone homeostasis, uremic toxins, anaemia, oxidative stress and protein energy wasting (PEW). Thus, there is an obvious need to develop a CVD risk score specifically for patients with ESRD. The objective of this study was to derive and validate risk scores for two-year CVD in a European haemodialysis patient population. Specifically we sought to differentiate fatal CV events from any CV events (fatal and non-fatal).

2. Methods

2.1. Study population and baseline recruitment

The Analysing Data, Recognising Excellence and Optimising Outcomes ('ARO') research initiative [11] comprises haemodialysis patients at participating European Fresenius Medical Care (EU-FMC) facilities. Anonymized patient-level medical and drug history data are captured quarterly, as are ICD-10 coded hospitalizations and deaths. The current study used the second ARO cohort ('AROii'), which consists of consecutive incident adult patients with no history of renal transplantation and <6 months on dialysis (median dialysis vintage of 4 days upon admission) recruited from >300 EU-FMC facilities in 14 European countries between 2007 and 2009 [12]. Data were further restricted to patients remaining in the study for ≥3 months. All ethical and regulatory obligations concerning patient data were met locally and informed consent was obtained from all patients [11].

2.2. Follow-up

Follow-up commenced on the date of patients' first EU-FMC haemodialysis session; time at risk accrued from the end of baseline (the first three months of follow-up) until patients experienced the event of interest (Table 1, with a full list of codes in Supplementary Table 1) or were censored for the following reasons: undergoing renal transplantation, being lost to follow-up (LTFU; (arbitrated on >45 days without continuous EU-FMC dialysis treatment) or follow-up end (30 March 2012).

2.3. Descriptive analysis

All analyses, replicated independently by a second data analyst, were performed using SAS (version 9.2; SAS, Cary, N.C., USA). Baseline

Table 1
Summary of first cardiovascular mortality and first cardiovascular morbidity and mortality event in a European incident hemodialysis cohort. Conditions accounting for ten or more events in either group shown.

CV Class	Condition	CVM[a]	CVMM[b]
MACE[c]	Cardiac arrest	230 (31.8)	213 (9.9)
	Acute myocardial infarction	80 (11.1)	159 (7.4)
	Cerebral infarction	56 (7.7)	150 (7)
	Stroke, not specified as haemorrhage or infarction	28 (3.9)	77 (3.6)
	Angina pectoris	2 (0.3)	24 (1.1)
	Occlusion and stenosis of precerebral arteries, not resulting in cerebral infarction	0	13 (0.6)
	Other cerebrovascular diseases	3 (0.4)	12 (0.6)
	Other (<10 events)	2 (0.3)	1 (0.05)
	MACE sub-total	401 (55.5)	649 (30.2)
Other major	Heart failure	134 (18.5)	243 (11.3)
	Chronic ischaemic heart disease	25 (3.5)	208 (9.7)
	Atherosclerosis	5 (0.7)	193 (9)
	Other peripheral vascular diseases	3 (0.4)	62 (2.9)
	Angina pectoris	1 (0.1)	46 (2.1)
	Intracerebral haemorrhage	38 (5.3)	43 (2.0)
	Arterial embolism and thrombosis	2 (0.3)	42 (2.0)
	Other acute ischaemic heart diseases	2 (0.3)	40 (1.9)
	Aortic aneurysm and dissection	11 (1.5)	32 (1.5)
	Pulmonary embolism	17 (2.4)	24 (1.1)
	Other (<10 events)	6 (0.8)	14 (0.7)
	Other major sub-total	244 (33.7)	947 (44.0)
Other misc.[d]	Atrial fibrillation and flutter	3 (0.4)	155 (7.2)
	Other venous embolism and thrombosis	1 (0.1)	49 (2.3)
	Hypotension	0	43 (2)
	Other cardiac arrhythmias	6 (0.8)	36 (1.7)
	Cardiomyopathy	7 (1)	35 (1.6)
	Vascular disorders of intestine	25 (3.5)	34 (1.6)
	Hypertensive heart disease	3 (0.4)	32 (1.5)
	Vascular dementia	6 (0.8)	26 (1.2)
	Other cerebrovascular diseases	3 (0.4)	22 (1)
	Phlebitis and thrombophlebitis	0	22 (1)
	Transient cerebral ischaemic attacks and related syndromes	1 (0.1)	21 (1)
	Other symptoms and signs involving the circulatory and respiratory systems	18 (2.5)	14 (0.7)
	Gangrene, not elsewhere classified	0	13 (0.6)
	Complications of procedures, not elsewhere classified	0	13 (0.6)
	Paroxysmal tachycardia	0	11 (0.5)
	Sequelae of cerebrovascular disease	5 (0.7)	11 (0.5)
	Other (<10 events)	0	17 (0.8)
	Other miscellaneous sub-total	78 (10.8)	554 (25.8)
Total		723	2150

[a] Cardiovascular mortality.
[b] Cardiovascular morbidity & mortality.
[c] Major adverse cardiovascular events.
[d] Miscellaneous.