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Development and validation of a predictive mortality risk score from a European hemodialysis cohort

Jürgen Floege[1], Iain A. Gillespie[2], Florian Kronenberg[3], Stefan D. Anker[4], Ioanna Gioni[5], Sharon Richards[6], Ronald L. Pisoni[7], Bruce M. Robinson[7], Daniele Marcelli[8], Marc Froissart[9], Kai-Uwe Eckardt[10] on behalf of the ARO Steering Committee (collaborators)[11]

[1]Nephrology, RWTH University of Aachen, Aachen, Germany; [2]Center for Observational Research (CfOR), Amgen Ltd, Uxbridge, UK; [3]Division of Genetic Epidemiology, Department of Medical Genetics, Molecular and Clinical Pharmacology, Medical University of Innsbruck, Innsbruck, Austria; [4]Department of Innovative Clinical Trials, University Medical Centre Göttingen, Göttingen, Germany; [5]On behalf of Amgen Ltd, Uxbridge, UK; [6]Global Biostatistics, Amgen Ltd, Uxbridge, UK; [7]Arbor Research Collaborative for Health, Ann Arbor, Michigan, USA; [8]EMEALA Medical Board, Fresenius Medical Care, Bad Homburg, Germany; [9]International Development Nephrology, Amgen Europe GmbH, Zug, Switzerland and [10]Nephrology and Hypertension, University of Erlangen-Nuremberg, Erlangen, Germany

Although mortality risk scores for chronic hemodialysis (HD) patients should have an important role in clinical decision-making, those currently available have limited applicability, robustness, and generalizability. Here we applied a modified Framingham Heart Study approach to derive 1- and 2-year all-cause mortality risk scores using a 11,508 European incident HD patient database (AROii) recruited between 2007 and 2009. This scoring model was validated externally using similar-sized Dialysis Outcomes and Practice Patterns Survey (DOPPS) data. For AROii, the observed 1- and 2-year mortality rates were 13.0 (95% confidence interval (CI; 12.3–13.8)) and 11.2 (10.4–12.1)/100 patient years, respectively. Increasing age, low body mass index, history of cardiovascular disease or cancer, and use of a vascular access catheter during baseline were consistent predictors of mortality. Among baseline laboratory markers, hemoglobin, ferritin, C-reactive protein, serum albumin, and creatinine predicted death within 1 and 2 years. When applied to the DOPPS population, the predictive risk score models were highly discriminatory, and generalizability remained high when restricted by incidence/prevalence and geographic location (C-statistics 0.68–0.79). This new model offers improved predictive power over age/comorbidity-based models and also predicted early mortality (C-statistic 0.71). Our new model delivers a robust and reproducible mortality risk score, based on readily available clinical and laboratory data.

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Correspondence: *Jürgen Floege, Division of Nephrology, RWTH University of Aachen, Pauwelsstrasse 30, 52057 Aachen, Germany.*
E-mail: juergen.floege@rwth-aachen.de

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[11]See Appendix

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Chronic kidney disease (CKD), which has evolved as a global health burden,[1] affects up to 13% of United States (US)[2] and European[3] adults, who suffer a high incidence of comorbidities and an increased mortality risk[4]. Mortality rates in end-stage renal disease patients on chronic HD, relating mainly to cardiovascular complications and infections, remains higher than that of many cancers or heart failure, at up to 19.2 per 100 person-years versus only 1.2 in the general European population.[5]

An improved ability to identify those patients at an increased risk of death appears desirable for several reasons. Thus, identification of high-risk patients may help focus efforts on risk mitigation strategies. In addition, a valid, general, easy-to-use mortality risk score in HD patients could also be used in patient discussions or when scheduling transplants. In health-care economics, such a score may categorize patients in comorbidity-adjusted registries or reimbursement systems, and inform planning. Furthermore, it may also serve as a research tool—homogenizing the case mix entering clinical trials and targeting specific interventions to particular patient subgroups—thus reducing sample sizes without compromising statistical power.

Previously developed risk scores lack applicability, robustness, and generalizability. An early study by Wright,[6] which categorized patients as 'low', 'medium', and 'high' risk on the basis of age and comorbidities, was popularized by Khan[7] who examined the predictive power of this stratification (referred subsequently here as the Wright–Khan mortality index). A scoring system based on prediction model β-coefficients advanced methodologies, allowing objective assessment of contributory factors and their weighted impact.[8] Recent large and complex studies[9–15] used internal validation that contributes little to generalizability. Generalizability may be further limited by restricted patient populations,[9,13] geographic locations,[9,11,15] small sample sizes,[11] or insufficient variables.[9,11–14] The current study therefore aimed to develop, in a large European cohort of incident

HD patients, risk scores for 1- and 2-year all-cause mortality and to validate these scores externally in a similarly sized, predominantly prevalent HD population.

RESULTS

Study population

Between 1 January 2007 and 31 December 2009, 11,508 patients were recruited into the second Analyzing Data, Recognizing Excellence and Optimizing Outcomes (ARO) cohort (AROii; Figure 1). Thirty-seven percent of patients initiated HD within Fresenius Medical Care (FME) facilities; nevertheless, the overall median dialysis vintage was only 4 days upon admission. Nonchronic HD patients, those with no laboratory data, and/or those with a history of transplantation (alone or combined; $N = 773$) were excluded. In addition, 1013 patients left the study during baseline, leaving 9722 patients. During the first and second year of follow-up, 1060 (10.9%) and 654 (9.4%) deaths were reported, respectively, giving 1- and 2-year mortality rates of 13.0 (95% CI 12.3–13.8) and 11.2 (95% CI 10.4–12.1) per 100 person-years, respectively. In the first year, 344 (3.5%) patients left the study owing to a renal transplant, and 1338 (13.8%) patients were lost to follow-up (LTFU); in the second year, 288 patients (4.1%) received renal transplants and 600 (8.6%) patients were LTFU. Patients LTFU did not differ greatly from those who were not (Supplementary Table S1 online). Of the 1938 LTFU patients, 527 (27.2%) patients returned to FME after their follow-up stop date. Patients lost or not lost to transplantation are shown in Supplementary Table S2 online.

Table 1 shows baseline characteristics of the study populations. Although AROii and Dialysis Outcomes Practice Patterns III (DOPPS III) patients were similar in many aspects, we noted some differences. The baseline vascular access differences between AROii and the third Dialysis Outcomes Practice Patterns (DOPPS) cohort patients may be explained by the mix of incident and prevalent patients in DOPPS. Additional differences include geography, dialysis vintage, smoking habits, diabetes, cancer, and cardiovascular disease history. Notably, the proportion of patients dying in each cohort was similar. Within the DOPPS III cohort, mean dialysis vintage differed by 'region' (Europe: 4.1 ± 5.5 years; Japan: 6.9 ± 7.1 years; North America: 3.4 ± 4.1 years; Australasia: 4.5 ± 5.0 years).

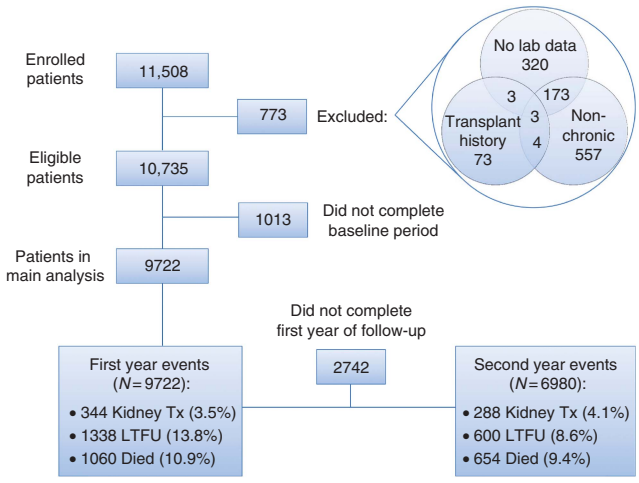

Figure 1 | Derivation of the AROii study population.

Predictors of mortality

In our main AROii analysis (based on a first 3-months on follow-up baseline), increasing age, low body mass index, and a cardiovascular disease or cancer history were independently associated with both 1- and 2-year mortality (Table 2). Former or current smokers were at a greater risk within 2 years but not at 1 year, as were patients with a CKD etiology of diabetic nephropathy or tubulo-interstitial disease. Of the dialysis quality parameters, baseline use of, or change to, vascular access via a catheter was associated with an increased risk for both time periods, as was lower actual blood flow.

Lower hemoglobin concentrations were associated with an increased risk for 1- and 2-year mortality; higher levels were linked with better survival. Baseline inflammation (increased C-reactive protein concentrations and high ferritin levels) was highly predictive of mortality at both 1 and 2 years. Malnutrition and/or inflammation, as evidenced by low concentrations of serum albumin, was also consistently predictive. Predialysis serum creatinine represented an additional risk marker, with lower values associated with higher risk, probably reflecting decreased muscular mass and potentially protein wastage in addition to low serum albumin. Finally, hypercalcemia was associated with a higher 1-year mortality risk.

The results obtained using a 90- to 180-day baseline were remarkably consistent with 0- to 90-day baseline observations, or when LTFU patients were coded as deceased (Supplementary Table S3 online). Of note, the relationship between predialysis serum creatinine and mortality was evident in both analyses, suggesting that any residual renal function at the time of HD initiation in this incident dialysis population could not fully explain this association when a 0- to 90-day baseline was applied.

Risk-score derivation and application

When hazard ratios (HRs) were converted to risk-score points, extreme age had the greatest risk contribution (Table 2). A cancer history was generally more disadvantageous than a cardiovascular disease history. Among laboratory parameters, elevated C-reactive protein concentrations contributed the greatest risk, followed by low albumin and creatinine values. Although lower hemoglobin contributed additive risk, higher hemoglobin values and lower ferritin concentrations contributed most to lowering the risk score.

The risk percentage attributable to risk-score totals differed by follow-up length (Figure 2). The contribution of modifiable risk markers increased as the risk score increased (Supplementary Figure S1 online), but only marginally around 50% of the total risk.