## Title

Association of Age to Mortality and Repeat Revascularization in End-Stage Renal Disease Patients: Implications for Clinicians and Future Health Policies



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# Association of Age to Mortality and Repeat Revascularization in End-Stage Renal Disease Patients: Implications for Clinicians and Future Health Policies

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## ABSTRACT

**Background:** The clinical effects of age occur over an age continuum, yet age as a primary predictor is often analyzed using arbitrary age cut-points.

**Objective:** To assess whether transformation of a continuous variable such as age using a spline function can uncover nonlinear associations between age and cardiovascular outcomes.

**Design:** Observational retrospective cohort study in 1015 Kaiser Permanente Northern California patients with end-stage renal disease after index coronary revascularization. Age, the primary predictor, was modeled by 5 different techniques: 1) dichotomized at 65 years or older; 2) at 80 years or older (as a sensitivity analysis); 3) categorized as younger than 55 years (reference), 55 to 64, 65 to 74, and 75 years or older; 4) linear (every 5 years) variable; and 5) nonlinear by transformation into a cubic spline. Age categories were changed in a sensitivity analysis.

**Main Outcome Measures:** Primary and secondary outcomes were all-cause mortality and repeat revascularization, respectively.

**Results:** Graphical assessment demonstrated that age dichotomized at either 65 years and older or 80 years and older led to loss of information. Categorized age underestimated or overestimated risk at the extremes of age. A sensitivity analysis demonstrated that an arbitrary change in the age category led to a different conclusion. Age modeled linearly adequately represented mortality risk but was suboptimal with repeat revascularization. Only the cubic spline demonstrated the nonlinear association between age and repeat revascularization.

**Conclusion:** Employing the continuous variable age as a case study, we have demonstrated that the use of flexible transformations, such as spline functions, can unearth clinically meaningful associations that would not have been possible otherwise. Future research should determine whether incorporation of these methods can improve decision making at a population level.

## INTRODUCTION

The association of advancing age with cardiovascular diseases and outcomes is often presented on the basis of an arbitrary age cutoff or as age categories. A possible corollary to this is the lack of consensus of what constitutes "old" or "elderly." There is a growing need to recognize age as a spectrum and to change the current paradigm.[1] The World Health Organization uses the age of 60 years as a cutoff to define "elderly."[2] In the US, most classifications have subjectively raised this cutoff to age 65 years and have arbitrarily categorized age to define individuals as "young old" (60-74 years), "old old" (75-84 years), and "very old" (≥ 85 years).[3] Unfortunately, these age cutoffs have become standard nomenclature[3-6] despite the statistical literature clearly noting that cutoffs and categorization of continuous variables such as age is a "bad idea,"[7] "dangerous,"[8] or even "highly problematic,"[9,10] with total avoidance of such cutoffs suggested. Although the publications of model-based estimates of the relative risk of age dichotomized or categorized continue in the clinical cardiovascular literature,[11-17] the effect of this practice is unknown.

The importance of avoiding breaking up a continous variable (by dichotomization or categorization) is demonstrated by the fact that the functional form of continuous variables (age in the current study) has been selected as one of the most important topics to be handled in the STRengthening Analytical Thinking for Observational Studies: the STRATOS initiative.[18] Using a retrospective observational study design in a cohort of patients with end-stage renal disease (ESRD), we have used the continuous variable age as a meaningful case study example to highlight how arbitrary changes in age categories can dramatically change the perception of the association of age with an outcome. We expand on this and address whether transformation of the variable age, by spline functions, can improve our understanding of the age continuum. This appreciation should lead to changes in our future perspective of cardiovascular care and health policies toward the older adult.

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## METHODS

### Source Population

Our source population consisted of adult members of Kaiser Permanente Northern California (KPNC), a large integrated health care delivery system. The study population was a cohort of patients with ESRD receiving long-term renal dialysis, who were identified from the Health Plan's comprehensive ESRD treatment registry. All subjects had undergone an index coronary revascularization procedure by either percutaneous coronary intervention or coronary artery bypass grafting without another concomitant cardiac surgical procedure between January 1, 1996, and December 31, 2008. We identified a coronary revascularization procedure using International Classification of Diseases, Ninth Revision, or Current Procedural Terminology codes for percutaneous coronary intervention or coronary artery bypass grafting (provided on request).

Patients were followed until their death or were censored when they met any of the following criteria: end of the study as of December 31, 2008; renal transplantation; or disenrollment from the Health Plan.

### Outcomes, Primary Predictor, and Covariates

The primary outcome for the study was five-year all-cause mortality. The secondary outcome, repeat revascularization, was identified by Current Procedural Terminology codes for revascularization after the index revascularization (provided on request). These were ascertained using standard Health Plan databases as well as state death certificates and Social Security Administration files through December 2008. The KPNC institutional review board approved this study, and informed consent was not obtained because of the observational nature of this study.

The primary predictor was age at the index revascularization and was identified through standard Health Plan databases. Age was modeled in 5 different methods: 1) dichotomized at an arbitrary cutoff of 65 years or older; 2) at 80 years or older (as a sensitivity analysis); 3) categorized into 4 age groups (< 55 [reference], 55-64, 65-74, and ≥ 75 years); 4) as a continuous linear variable with a clinically relevant scale (every 5 years); and 5) after transformation to a restricted cubic spline with 4 knots. The knots for the cubic spline were at 44, 59, 67, and 79 years (5th, 35th, 65th, and 95th percentiles). Cubic splines were used to assess nonlinearity. They are known to have flexible functions and are well suited for this type of analysis.[7-10,18-20] We obtained information on baseline patient demographic and clinical characteristics from the Health Plan's clinical and administrative databases.

### Statistical Analysis

Patient characteristics were initially compared by age categories (< 55, 55-64, 65-74, ≥ 75 years) with $\chi^2$ analysis for categorical variables and Kruskal-Wallis or analysis of variance for continuous variables. To assess the hazard of mortality or repeat revascularization at 5 years by different modeling techniques of the

**Table 1. Comparison of baseline clinical variables across age categories**

| Variable | < 55 years (n = 179) | 55-64 years (n = 351) | 65-74 years (n = 335) | ≥ 75 years (n = 150) | p value |
|---|---|---|---|---|---|
| Dialysis duration (mean years ± SD) | 2.27 ± 2.8 | 2.16 ± 2.3 | 2.08 ± 2.14 | 2.10 ± 1.92 | 0.0001 |
| Women (%) | 33.0 | 34.8 | 39.4 | 35.3 | 0.45 |
| Baseline comorbidities (%) | | | | | |
| Atrial fibrillation/flutter | 3.4 | 12.8 | 17.3 | 26.7 | < 0.0001 |
| Diabetes mellitus | 79.3 | 82.6 | 71.9 | 48.7 | < 0.0001 |
| Hyperlipidemia | 78.8 | 86.9 | 82.7 | 82.7 | 0.1 |
| Hypertension | 89.9 | 93.7 | 92.8 | 91.3 | 0.42 |
| Heart failure | 29.6 | 39.3 | 38.5 | 48.0 | 0.01 |
| Liver disease | 5.0 | 6.0 | 2.7 | 1.3 | 0.04 |
| Lung disease | 24.0 | 23.1 | 25.1 | 20.0 | 0.68 |
| Myocardial infarction | 34.1 | 41.6 | 43.0 | 51.3 | 0.02 |
| Stroke/transient ischemic attack | 4.5 | 6.8 | 8.1 | 8.7 | 0.38 |
| Tobacco use | 39.7 | 49.0 | 43.3 | 41.3 | 0.15 |
| Baseline medications (%) | | | | | |
| Angiotensin-converting enzyme inhibitor | 34.1 | 36.5 | 28.9 | 26.0 | 0.06 |
| Angiotensin receptor blocker | 11.7 | 13.4 | 17.6 | 12.0 | 0.2 |
| Calcium channel blocker | 63.7 | 58.9 | 58.5 | 58.0 | 0.66 |
| Beta-blocker | 62.6 | 67.2 | 63.3 | 59.3 | 0.35 |
| Diabetes medication | 62.6 | 58.1 | 53.4 | 28.0 | < 0.0001 |
| Statin | 55.9 | 53.9 | 52.8 | 51.3 | 0.86 |
| Coronary revascularization (%) | | | | | |
| CABG | 41.9 | 48.1 | 47.5 | 28.7 | < 0.0001 |
| PCI | 58.1 | 51.9 | 52.5 | 71.3 | |

CABG = coronary artery bypass grafting; PCI = percutaneous coronary intervention; SD = standard deviation.

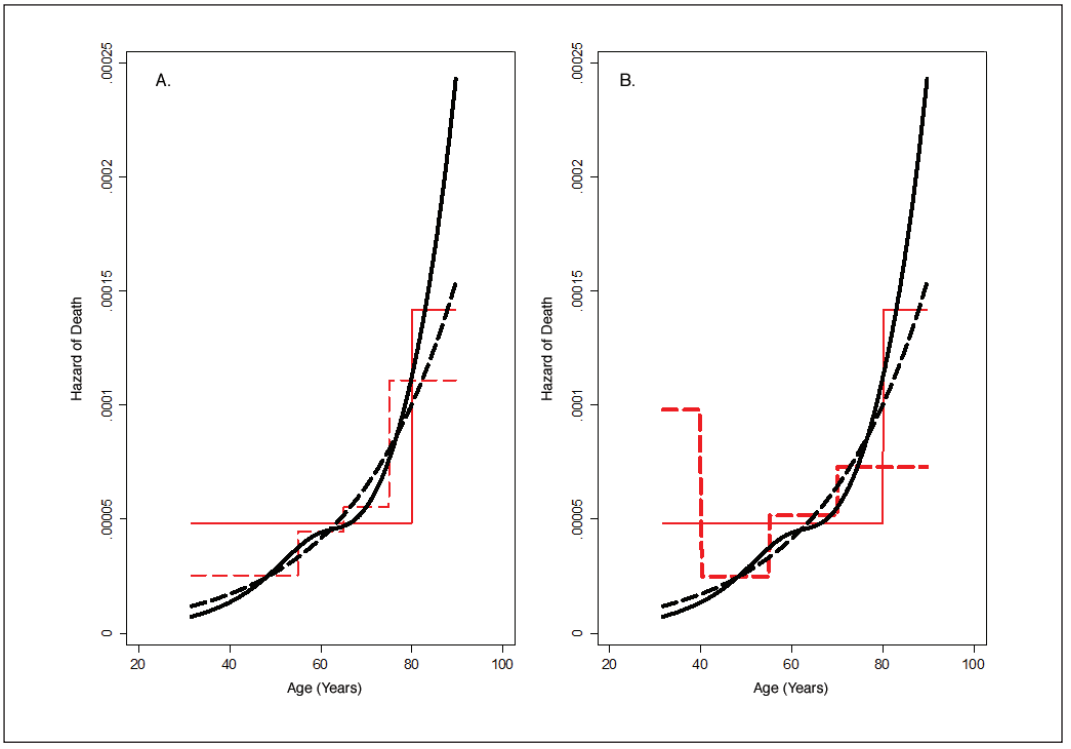


Figure 1. Four standard modeling strategies for the continuous variable age as a function of mortality in the fit of an unadjusted parametric survival regression.

A. Red solid line = age dichotomized ≥ 80 years; red dashed line = age categorized (< 55, 55-64, 65-74, & ≥ 75 years); black dashed line = age as a linear variable; black solid line = age fit as a cubic spline on the log hazard scale.

B. The sensitivity analysis graphically depicts the changes in the red dashed line when there is a change in the age category (< 40, 40-54, 55-69, & ≥ 70 years).

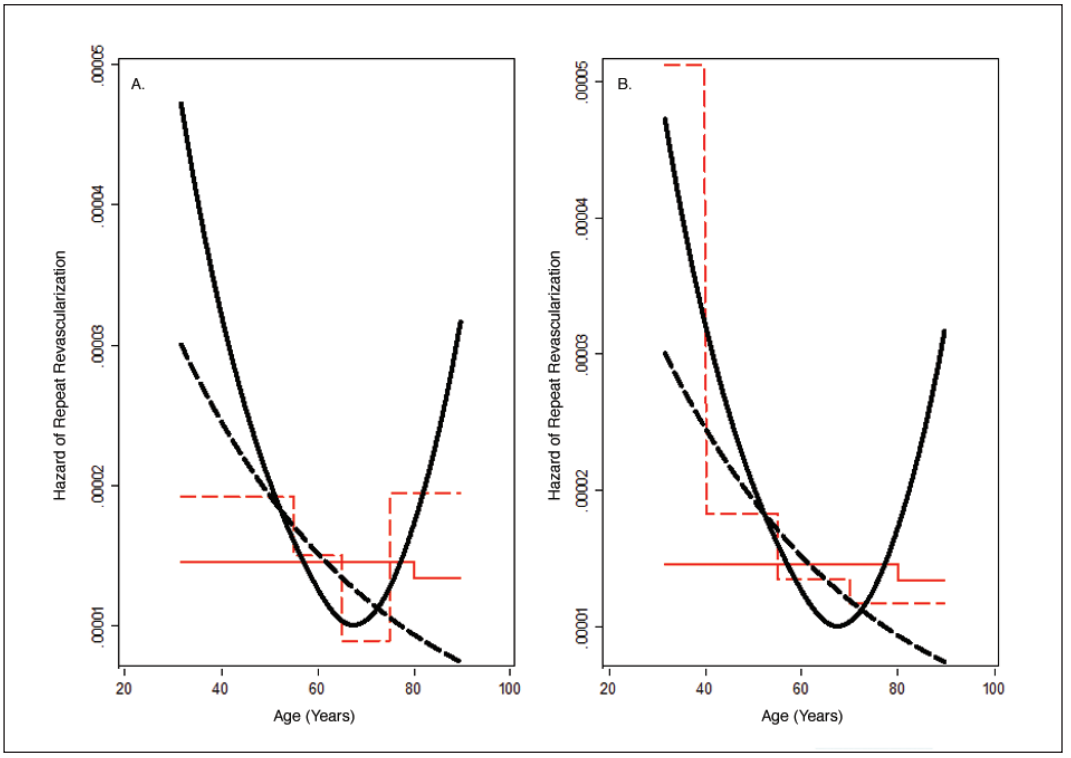


Figure 2. Four standard modeling strategies for the continuous variable age as a function of repeat revascularization in the fit of an unadjusted parametric survival regression.

A. Red solid line = age dichotomized ≥ 80 years; red dashed line = age categorized (< 55, 55-64, 65-74, & ≥ 75 years); black dashed line = age as a linear variable; black solid line = age fit as a cubic spline on the log hazard scale.

B. The sensitivity analysis graphically depicts the changes in the red dashed line when there is a change in the age category (< 40, 40-54, 55-69, & ≥ 70 years).

primary predictor, age, we fit a parametric Weibull survival model (because it enables all models to be graphed on a uniform scale). We then extracted the model-predicted hazard at 5 years with a robust variance estimate that adjusts for within-cluster (facility) correlation. We presented the hazard ratio (HR) both in a tabular format and graphically as a function of age exponentially in the hazard scale. A p value of 0.05 or less was used as the statistical threshold for significance. All statistical analyses were performed using Stata Version 13 software (StataCorp, College Station, TX).

## RESULTS

A total of 1015 patients with ESRD underwent an index revascularization at KPNC by either percutaneous coronary intervention or coronary artery bypass grafting between 1996 and 2008. Of the 1015 patients, 17.6% were younger than age 55 years, 34.6% were between age 55 and 64 years, 33.0% were between age 65 and 74 years, and 14.8% were age 75 years or older. The proportion of patients with a history of myocardial infarction, heart failure, and atrial fibrillation increased, whereas the presence of diabetes mellitus and liver disease decreased with age (Table 1). Table 2 shows the unadjusted and risk-adjusted HR and 95% confidence intervals for the 2 outcomes using the different modeling strategies and the sensitivity analysis. Of note, the point estimates for the unadjusted and adjusted HRs were materially similar.

### Mortality

Table 2 demonstrates that age dichotomized at 65 years old was associated with a risk-adjusted 5-year HR for mortality of 1.77 ($p < 0.0001$), whereas age dichotomized at 80 years was associated with an HR of 2.61 ($p = 0.001$). Compared with the reference age group, all adjusted age categories were significantly associated with mortality: 55 to 64 years (HR = 1.60, $p = 0.01$), 65 to 74 years (HR = 2.09, $p < 0.0001$), and 75 years or older (HR = 3.98, $p < 0.0001$). The trend test for categorized age was statistically significant ($p < 0.0001$). Age as a continuous variable indicated that for every 5-year increase in age the associated HR for death was 1.25 ($p < 0.0001$).

Figure 1A demonstrates that age dichotomized at 80 years overestimated the risk compared with categorized age, linear age, and the cubic spline at the lower end of the age spectrum. However, above age 85 years, risk was overestimated compared with the categorized and linearized age but underestimated compared with the cubic spline. This can be considered information loss or bias. Categorized age was able to capture the data relatively well during the "middle" years, but compared with the cubic spline, it underestimated risk above 80 years. Age linearized tracked well with the cubic spline method but underestimated the risk compared with the cubic spline above 80 years.

### Repeat Revascularization

Table 2 demonstrates that ages dichotomized at 65 and at 85 years were not significantly associated with repeat revascularization. Compared with the reference group, the age category 55 to 64 years was associated with an HR of 0.84 and the age category 65 to 74 years was associated with an HR of 0.63. The age 75 years or older category was associated with an HR of 1.39. Only the unadjusted category 65 to 74 years was statistically significant. The trend test was not significant ($p = 0.07$). Finally, every 5-year increase in age was associated with a nonsignificant HR of 0.93 ($p = 0.3$).

Figure 2A graphically demonstrates that dichotomized age equal to or older than 80 years overestimated the risk of repeat revascularization compared with the linearized method but underestimated

**Table 2. Comparison of effect of three different modeling strategies for the primary predictor, age, on mortality and repeat revascularization[a]**

| | 5-year mortality, hazard ratio (95% CI) | | Repeat revascularization, hazard ratio (95% CI) | |
|---|---|---|---|---|
| **Variable** | **Unadjusted** | **Risk-adjusted** | **Unadjusted** | **Risk-adjusted** |
| Age dichotomized | | | | |
| ≥ 65 years | **1.78 (1.47-2.16)** | **1.77 (1.47-2.15)** | 0.67 (0.45-1.01) | 0.86 (0.58-1.28) |
| ≥ 80 years | **2.79 (1.85-4.21)** | **2.61 (1.49-4.56)** | 0.92 (0.45-1.90) | 0.89 (0.41-1.98) |
| Age categorized | | | | |
| < 55 years | Reference | Reference | Reference | Reference |
| 55-64 years | **1.60 (1.10-2.32)** | **1.60 (1.12-2.31)** | 0.78 (0.51-1.20) | 0.84 (0.62-1.15) |
| 65-74 years | **2.02 (1.51-2.71)** | **2.09 (1.60-2.73)** | **0.46 (0.25-0.87)** | 0.63 (0.38-1.03) |
| ≥ 75 years | **3.92 (2.67-5.77)** | **3.98 (2.74-5.79)** | 1.02 (0.46-2.26) | 1.39 (0.57-3.42) |
| Age linearized | | | | |
| Age (every 5 years) | **1.24 (1.17-1.31)** | **1.25 (1.18-1.32)** | 0.89 (0.77-1.02) | 0.93 (0.81-1.06) |
| Sensitivity analysis[b] | | | | |
| < 40 years | Reference | Reference | Reference | Reference |
| 40-54 years | 0.30 (0.08-1.17) | 0.27 (0.07-1.09) | 0.36 (0.04-3.59) | 0.29 (0.04-2.29) |
| 55-69 years | 0.57 (0.17-1.95) | 0.51 (0.14-1.89) | 0.26 (0.03-2.42) | 0.24 (0.03-1.65) |
| ≥ 70 years | 0.86 (0.24-2.98) | 0.80 (0.22-2.94) | 0.23 (0.02-2.14) | 0.26 (0.04-1.78) |

[a] Risk-adjusted model includes sex, year of index revascularization, type of revascularization, duration of dialysis, number of vessels revascularized, and baseline comorbidities.
[b] For sensitivity analysis, age categories were changed as shown.
Boldface hazard ratios indicate statistical significance; see the text for p values.
CI = confidence interval.

the risk compared with the categorized and the cubic spline method. Categorized age at the aforementioned age categories captured the nadir and the rise of repeat revascularization. However, it underestimated the risk of repeat revascularization compared with the linearized age and the cubic spline in the younger years and just the cubic spline in the older years. Linearized age did not address the nadir around the age of 65 years or the increase in revascularization at either end of the age spectrum. Age transformed to a spline was visually very easy to interpret. This was the only method that overtly noted the "reverse" J or U curve; that is, the decrease in the risk of repeat revascularization with advancing age until around the age of 65, after which there was an increase in the risk of revascularization.

### Sensitivity Analysis

Last, we performed a sensitivity analysis after arbitrarily changing the cutoff to younger than 40 years, 40 to 54 years, 55 to 69 years, and above 70 years for both outcomes. With a change in the categories, the summary estimates of each category were materially different and in the case of mortality demonstrated an opposite result. In the case of repeat revascularization, a continued downward trend was noted and the rise was not seen (Table 2 and Figures 1B and 2B).

**The study findings bring to the forefont the need to complement linear modeling by searching for nonlinear associations.**

## DISCUSSION

The findings from this study demonstrate that dichotomizing age at either of the set ages of 65 or 80 years led to a substantial loss of information, distorted the conclusions, and limited the ability to address outcomes across the age spectrum. A simple change in the age category, as noted by our sensitivity analysis, would have resulted in a different and opposite interpretation. The reliance of a p value would have even further exacerbated the inappropriate interpretation because of residual confounding by known or unknown confounders at each category. We and many other authors recommend avoidance of these methods.[7-10,18] When age was treated as a linear variable, it adequately represented mortality risk but was suboptimal with repeat revascularization. Of the 5 methods, only the spline showed the nonlinear association between age and repeat revascularization.

The current study substantiates the premise that age-related results should be presented as a continuous variable rather than grouped into categories.[7-10,21] The study findings also bring to the forefont the need to complement linear modeling by searching for nonlinear associations.[7,9,22] Although the various specific methods and critiques of assessing nonlinearity are beyond the scope of the current study, application of this method will be very useful for clinicians, accountable care organizations responsible for population management, and clinician researchers interested in studying the effects of age.

The avoidance of cutoffs for continuous variables such as age is well established in the methodologic literature; however, the practice continues in the general cardiovascular literature. It has been clear that this practice overly simplifies or may even distort the relationship of age to an outcome. In fact, dichotomization has been shown to "effectively lose 33% of the data resulting in a serious loss of power in detecting true [associations]" while increasing the Type I error rate.[7] Grouping of age into categories brings up issues of multiple hypothesis testing, assumption of equal risk across categories, and difficulty comparing varying cut-points between studies.[9] The practice of reporting only significant p values is known to be associated with residual confounding that is not often taken into consideration. More importantly, it fails to address linear and nonlinear associations.

Albeit infrequently, cubic splines have been used in the cardiovascular literature to detect nonlinearity without being the primary focus.[23-25] The current work hopes to translate the robust methodologic literature of avoiding cutoffs to a wider audience by having the primary focus aimed toward incorporating nonlinear modeling primarily when age is modeled as the primary predictor. Our unexpected finding of a "reverse" J- or U-shaped curve for repeat revascularization would not have been detected if it were not for using a nonlinear method. However, we do not have a clear understanding of the reason for this finding because the focus of this study was to highlight the use of modeling and did not focus on an attempt to uncover the mechanisms involved. Some have referred to this finding in recurrence risk research as an "index event bias."[26] Further work will need to confirm this finding and assess the possibility of it being an index event bias.

Using our study as an example,[1] if one were to ask "What is the risk of repeat revascularization in patients over the age of 80 years?," the answer varies depending on the model used. Only when graphically representing the 4 methods do we appreciate the increase in repeat revascularization after age of 65-70 years using the cubic spline. Although the quantitative extent of this increase as well as specific nuances of modeling splines can and should be debated, this finding would have been completely missed if the focus was the statistical significance of the data from Table 2. Furthermore, if we were to take a health policy stance, one could assume from findings shown in Table 2 that older adults were not being offered repeat revascularization, perhaps because of their advancing age. However, an assessment of nonlinearity shows that this is not the case and avoids potential costly or dangerous policy decisions.

A strength of our study is that the cohort is from a well-defined primary study base of Kaiser Permanente members during the study period. The study has several limitations, however. The methods presented are generalizable, but the cohort-specific findings may be limited to facilities that provide integrated health care similar to KPNC. We specifically did not evaluate how age as a continuous variable modifies the effect or interacts with baseline comorbidities, either individually or by the number of comorbidities[27] as well as with indices of frailty.[28] We also did not assess how changes in the placement of knots for the cubic spline affected results.

Last, it is important to mention that other methods of nonlinear modeling can be used, such as fractional polynomials, although the focus in the current study was the use of cubic splines.[19,20,29] We chose to use cubic splines for the purposes of this study because it has

been well validated and has been used, albeit sporadically, in the cardiovascular literature. These important topics must be addressed in future work as we expand our knowledge in this area and attempt to define a new clinical paradigm for the cardiovascular care of older adults.[1]

## CONCLUSION

It is acceptable to initially present unadjusted outcomes on the basis of age categories. However, subsequent evaluation of risk adjusted, model-based associations between age and cardiovascular outcomes should be graphically shown by both linear and nonlinear methods to complement standard quantitative presentations. Handling age in this manner, rather than by dichotomization or categorization, will most certainly be unnerving to many clinicians and those who are responsible for health policies. However, further research in this area may lead to fundamental changes in our perspective of cardiovascular care and health policies toward the older adult. ❖

**Disclosure Statement**

*The author(s) have no conflicts of interest to disclose.*

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