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Sudden death in adults with repaired coarctation of the aorta: A case for sex-based risk factors

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Abstract

Background: Sudden cardiac death (SCD) is an important risk for adults with repaired coarctation of the aorta (rCoA). We aimed determine if there are clinical risk factors for SCD in adults with rCoA.

Methods and results: SCD events and clinical data from all adults with rCoA at a tertiary care center (2007–2017) were evaluated. In 167 adults with rCoA (39 ± 11 years old, 75 (45%) female)

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*All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

Disclosures related to this work

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CRediT authorship contribution statement

Lauren Lastinger: Writing – review & editing, Methodology, Investigation, Data curation, Conceptualization. **Marc Lee:** Writing – review & editing, Data curation. **Lauren Hassen:** Writing – review & editing, Data curation. **Omer Cavus:** Writing – review & editing, Data curation. **Saurabh Rajpal:** Investigation, Data curation. **Jeremy P. Moore:** Writing – review & editing, Writing – original draft, Investigation, Formal analysis. **May Ling Mah:** Writing – review & editing, Writing – original draft, Supervision, Investigation. **Elisa A. Bradley:** Writing – review & editing, Writing – original draft, Supervision, Resources, Methodology, Investigation, Formal analysis, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcchd.2024.100500.

SCD occurred in 8 (5%) (vs. age-matched adults 0.9%). Those with SCD demonstrated significant QTc prolongation (QTc: 479 ± 16 vs. 434 ± 30 msec, $p < 0.001$). Overall, adults with rCoA and a prolonged sex-normative QTc interval had a 12-fold increased risk of SCD (x^2 (1) = 12.3, $p < 0.001$), with men sustaining SCD at younger ages (42 ± 13 years vs. women 60 ± 10 years, $p < 0.05$). Multiple logistic regression modeling demonstrated that prolonged QTc selectively advanced risk for SCD in men only (x^2 QTc prolongation 8.46, $p < 0.005$ and x^2 age 0.29, $p = 0.587$), whereas in women, age was associated with SCD risk (x^2 QTc prolongation 2.84, $p = 0.092$ and x^2 age 7.81, $p = 0.005$). Non-sustained ventricular tachycardia, ventricular dysfunction, and myocardial fibrosis did not significantly impact SCD risk.

Conclusions: There is an unanticipated high burden of SCD in adults with rCoA, occurring in men at younger age than women, suspicious for primary electrophysiologic dysfunction. Future investigation of sex-specific SCD risk in rCoA is important to better understand this disease and its late phenotype.

Keywords

Coarctation of the aorta; Adult congenital heart Disease; Congenital heart disease; Sudden cardiac death; Late survival; Survival

1. Introduction

Coarctation of the aorta (CoA) is a form of moderately complex congenital heart disease (CHD), occurring in ~2200 U. S. born babies each year [1], and accounting for up to 8% of all forms of CHD [2]. The rate of surgical success is excellent (repaired CoA, rCoA); however long-term mortality is significantly elevated with 10-, 20- and 30-year survival estimated at 91%, 84% and 72% respectively [3]. Adults with rCoA remain one of the highest risk CHD cohorts for premature death, yet the mechanism driving this risk is poorly understood, as surgical repair typically occurs via a lateral thoracotomy *without* requirement for a ventriculotomy or atrial incision–both conditions that may increase late arrhythmia risk. Previous studies have suggested that coronary artery disease [3] or residual left ventricular hypertrophy [4] were likely the source of increased late mortality in rCoA, and that older age at repair may be an important risk factor [3]. However, more recent data refutes these hypotheses [5], and other studies suggest that arrhythmia leading to sudden cardiac death (SCD) may be an important cause of early mortality, occurring commonly before the fourth decade of life [6].

In other forms of adult CHD (ACHD), such as repaired tetralogy of Fallot (ToF), there is a well-established association with late cardiac arrest and SCD. In many cases, a surgical source of arrhythmia is found, for example in ToF where *peri*-ventriculotomy fibrosis acts as a source of arrhythmic substrate, and has been found to correlate with channels of abnormal myocardial conduction [7]. Although ToF is the most well-studied group when it comes to ACHD SCD risk, adults with other types of CHD requiring either ventriculotomy or atrial incision have also demonstrated increased late risk for the development of arrhythmia [8]. However, the high burden of premature death and SCD in adults with rCoA remains perplexing, as primary electrophysiologic abnormalities are not typically demonstrated or expected based upon the approach to childhood repair. Whereas other cohorts of adults

with CHD have benefitted from understanding SCD mechanisms and the changes in care that have resulted from this [9], those with rCoA continue to demonstrate substantial early mortality [10]. To assess risk more accurately, we aimed to evaluate a contemporary cohort of adults with rCoA to determine if there are important clinical characteristics that may be associated with risk for SCD, and perhaps provide clues that may lead us to better understand the mechanism for fatal arrhythmia.

2. Methods

Clinical and imaging data from sequential adults with rCoA presenting between 2007 and 2017 were collected. No exclusions regarding type or timing of repair were applied. We evaluated the cohort for SCD events inclusive of the following: witnessed sudden cardiac arrest (SCA), sustained ventricular tachycardia >30 s (VT) and/or ventricular fibrillation (VF), resuscitated out-of-hospital arrest, appropriate implantable cardioverter-defibrillator (ICD) discharge), or unwitnessed death with autopsy or death certificate consistent with sudden death. The most recent electrocardiogram in controls, and most proximate temporal ECG to the SCD event in affected individuals, was reviewed with special attention to the QRS duration and QTc value using Bazett's formula and leads II and V5 (LL).

To assess myocardial fibrosis, two independent advanced imagers evaluated cardiac magnetic resonance imaging (CMRI) in sequential patients to determine if late gadolinium enhancement (LGE) was present, and if so, whether the location and extent of LGE present correlated with SCD (ML, SR). In the case where there was disagreement between the two reviewers, a third blinded imager assessed and uploaded measurements to arbitrate the final reported data. To determine whether the presence of non-sustained VT (<30 beats of ventricular tachycardia with rate >120 beats per minute; NSVT) was linked with late SCD risk, independent review for NSVT events via Holter, event, or implantable looping monitor was performed, in those patients with clinically available data.

Continuous variables were evaluated with analysis of variance and categorical variables with Chi Square, where appropriate. Multiple logistic regression was carried out using the Wald test. The Kaplan-Meier method was used to estimate survival, and curve comparisons were made using the Wilcoxon log-rank test (censoring in both groups was the same). For all parameters, an α level of <0.05 was considered significant. The data was analyzed using JMP® Pro, Version 16.0.0. SAS Institute Inc., Cary, NC, 2021. This study was approved by the local Institutional Review Board and the study conformed to the ethical guidelines of the Declaration of Helsinki.

3. Results

3.1. Prevalence, events, demographic description

There were 167 adults with rCoA (39 ± 11 years old, 75 (45%) female) included in this study, and 8 (5%) SCD events (45 ± 15 years old) occurred in the cohort during the 10-year timeframe (Fig. 1). The SCD rate in the rCoA population was higher than the age-matched U.S. population (*Centers for Disease Control and Prevention WONDER Database*) over the same time period (4040 SCD events in 451,592,639 persons; SCD event rate: 0.9%

vs 5%; $p < 0.0001$) [11]. In adults with rCoA and SCD, there was no difference in age at presentation or age at initial repair, nor was there difference in sex, body mass index, comorbid coronary disease, hypertension, or hyperlipidemia (Table 1). Between men and women, there were expected differences in QRS duration and QTc, however there was no difference in QT prolongation when considering sex normative QT values (Supplemental Table 1). Left ventricular function was statistically, although likely not clinically different in men and women (LVEF men 57 ± 10 vs. women 61 ± 7%, $p < 0.05$) and expectedly, unindexed coarctation isthmus measurements were smaller in women (1.4 + 0.4 vs. 1.7 + 0.5, $p < 0.0001$). (Supplemental Table 1).

3.2. Electrophysiologic findings: the impact of sex on risk

Patients with SCD displayed significant prolongation of the rate corrected QT interval (QTc: 479 ± 16 vs. 434 ± 30 msec, $p < 0.001$) and 6 (75%) patients with SCD had QTc prolongation in excess of currently accepted sex normative values (>450msec in men and >470msec in women) when compared to the No SCD group (26 (16%)), $p < 0.001$) [12]. Overall, adults with rCoA and a prolonged sex-normative QTc interval had a 12-fold increased risk of SCD (x^2 (1) = 12.3, $p < 0.001$) (Fig. 2, Supplemental Table 2). Given that the average age of SCD in men occurred in the fourth decade (42 ± 13 years vs. women 60 ± 10 years, $p < 0.05$), age, sex, and prolonged sex normative QTc were examined in the multivariate model and demonstrated that prolonged QTc appears to impact risk for SCD most. However, when men and women were analyzed individually, prolonged QTc was selectively important to advanced risk for SCD in men only (x^2 QTc prolongation 8.46, $p < 0.005$ and x^2 age 0.29, $p = 0.587$), whereas in women, age appeared to be most associated with SCD risk (x^2 QTc prolongation 2.84, $p = 0.092$ and x^2 age 7.81, $p = 0.005$) (Table 2).

To determine whether the presence of NSVT was linked with late SCD risk, we evaluated NSVT events via Holter, event or implantable looping monitor in the same cohort. In total there were 15 NSVT events in 70 patients with available data, and there was no relationship between NSVT events in those with and without. Additionally, there was no difference in QRS duration (119 ± 34 vs. 107 ± 23msec, $p = 0.20$), QTc interval (448 ± 30 vs. 435 ± 31, $p = 0.15$), or left ventricular systolic function (56 ± 9 vs. 59 ± 9%, $p = 0.24$) in patients with a documented NSVT event (Supplemental Fig. 1).

3.3. Cardiac function

Finally, we sought to determine if left ventricular systolic function and/or fibrosis, a potential early marker of left ventricular dysfunction and arrhythmic substrate, impacted SCD risk in adults with rCoA. Our analysis demonstrated an insignificant difference, although perhaps clinically meaningful changes, in left ventricular ejection fraction (LVEF) between unaffected and SCD groups (LVEF: 60 ± 7 vs. 49 ± 15%, $p = 0.12$) (Supplemental Figure 1). To assess myocardial fibrosis, two independent advanced imagers evaluated cardiac magnetic resonance imaging (CMRI) in sequential patients. Within the rCoA cohort, 164 (98%) patients had CMRI imaging available. We found no evidence of qualitative or quantitative difference in LGE between those with SCD versus those without (2.6 ± 1.8% vs. 3.4 ± 4.4%, $p = 0.66$). However, similar to prior studies [13], we did find an association

between the presence of LGE and NSVT events (x^2 6.5, p = 0.011), yet there was no association between the presence of LGE and SCD events (x^2 0.73, p = 0.392).

4. Discussion

In this contemporary cohort of adults with rCoA, similar to prior studies, we demonstrate substantially elevated risk for SCD when compared to age-matched population-based controls. For the first time, we demonstrate that risk for SCD in rCoA is associated with prolongation of the QTc interval above sex normative standards. Importantly, this risk appears to be greatest in men, who on average sustained SCD in the fourth decade, compared to their female counterparts, who sustained SCD on average in the sixth decade of life. While sex has been shown to impact risk in acquired cardiovascular disease, for the first time in this study, we uncover sex-specific risk factors for SCD in rCoA.

It has been long recognized that SCD is an important cause of early mortality in adults with rCoA. The earliest clinical data that evaluated long-term follow-up in adult rCoA survivors came from the Mayo Clinic and showed that patients operated on between 1946 and 1981 demonstrated 72% survival at 30 years, with SCD noted as one of the top causes of late death [3]. About 10 years later, Canadian ACHD mortality data (1981–1992) was released and confirmed that SCD was the cause of death in all adult rCoA patients in their cohort [14]. Perhaps with the institution of guideline-based specialized care that occurred in the early 2000s, a recent modest decline in the rate of SCD has been demonstrated, however, overall risk for SCD still remains significantly elevated compared to non-CHD cohorts. For instance, in a recent Spanish cohort report, the third most common ACHD group to suffer sudden cardiac arrest were those with rCoA (behind transposition and single ventricle), occurring at 1.9 events/1000 person years [6]. In line with this, we demonstrated that 5% of adults with rCoA experienced SCD, occurring 5 times more frequently than the general population. Interestingly, the proportion of SCD in rCoA that we found is significantly elevated when compared to other previously held “high-SCD-risk” CHD cohorts, such as Tetralogy of Fallot (ToF), where SCD risk is estimated at ~ 2% per decade [8], perhaps suggesting that advances in care have improved SCD risk in other types of CHD such as ToF, but not in rCoA.

It is well established that when compared to men, women demonstrate delay in the development of acquired cardiovascular diseases such as coronary artery disease and atherosclerosis, which has been attributed to the presence of estrogen [15], and supported by studies that demonstrate risk escalation after menopause [16,17]. However, CHD is fundamentally different than acquired CVD, and it seems counterintuitive that there would be sex-based differences, especially relating to SCD, as we have shown in this cohort with rCoA. One may postulate this is due to the development of underlying acquired CVD such as coronary artery disease, however, recent studies would suggest this is not the case [5]. Left ventricular hypertrophy and heart failure have also been proposed as contributors to the development of acquired CVD in those with rCoA, and therefore SCD risk. Yet more recent studies suggest that chronic mild pressure overload does not lead to heart failure, but rather diastolic dysfunction [18], a less established contributor to electrical dysfunction and SCD. We acknowledge that two men in this cohort sustained SCD with LVEF <35%, which may

be due to the presence of primary cardiomyopathy, and perhaps not directly related to rCoA. Yet, when we examined cardiac MRI and echocardiograms from the overall cohort, systolic function and myocardial fibrosis were not found to be significantly different between adults with rCoA who experienced SCD and those that did not. This would appear to discredit the hypothesis that a primary cardiomyopathic process contributes to late SCD risk in adults with rCoA, and would suggest that a broader investigation of potential etiologies is warranted.

A single study evaluating QTc and JTc dispersion in neonates with rCoA found no significant prolongation [19]. In adults, the PREVENTION-ACHD study demonstrated that QT dispersion ≥70msec is one of several important risk factors for sudden death in adults with CHD, however did not outline specific risk for those with rCoA [20]. In this cohort we show for the first time that prolongation of QTc above sex normative values was present in most patients with SCD, and importantly, this was associated with increased risk for SCD in men. A primary electrophysiologic source for SCD in rCoA seems plausible, given that QT prolongation and dispersion have previously been proposed as risk markers for patients with congenital heart disease and tetralogy of Fallot [21,22], and polymorphisms in genes associated with LQTS have been shown to be overrepresented among SCD victims [23,24]. Similarly, pulmonary valve replacement for RV dilation is associated with reduction in the QT interval, suggesting the repolarization abnormality to be a manifestation of global myopathy [25]. Whether genetic polymorphisms, global myopathic changes, or an as yet undetermined mechanism is responsible for the prolonged QT intervals observed in this cohort remains unknown in the context of this study.

It could be hypothesized that the same patients may demonstrate precursor arrhythmic risk factors, such as NSVT. However, we found that the presence of NSVT did not appear to have an impact on SCD risk. Although NSVT can be considered a marker of SCD risk in some populations, particularly repaired TOF, in most it is deemed clinically insignificant [26], which appears to hold true in adults with rCoA, to the extent that this data remains representative of the global population. These findings taken together, indicate that there is likely uncoupling of structural myocardial dysfunction and electrophysiologic characteristics which impact late SCD risk in rCoA. If we embrace the idea that primary electrical dysfunction may be responsible for SCD in rCoA, we propose that this data should compel research in search of mechanisms that directly lead to electrical dysfunction late after high afterload conditions, likely requiring both animal and cellular models.

4.1. Study limitations

The study of late cardiovascular morbidity and mortality in adult CHD is challenging, limited predominantly by small sample size, as is seen in this case-series. Roughly half of the cohort had electrophysiologic testing (Holter, looping or event monitors) to screen for NSVT, and therefore the data is impacted by incomplete evaluation for NSVT events. As with any retrospective study, the data may have limited, or no applicability, to prospective cohorts. Selection bias is likely present, as the study was completed retrospectively at a single timepoint, before which, those that sustained SCD at younger ages would be excluded from analysis, perhaps missing the most severe forms of disease. Genetic testing

for arrhythmogenic genetic polymorphisms is not routinely done clinically in this condition, and was not available for any included subjects. Despite the recognized limitations of this data, we propose that the findings support the investigation of this disease in the context of sex- and electrophysiologic-based risk factors and mechanisms.

5. Conclusions

In summary, these data provide evidence that SCD risk in adult men with rCoA could be linked to primary electrophysiologic dysfunction marked by QTc prolongation. The data would suggest that women are likely at lower risk for an additional 10–15 years, and that age is a more important risk factor than QTc prolongation. In the absence of fibrotic substrate from congenital heart surgically-mediated myocardial scarring, or impact from systolic dysfunction, the cause for previously unrecognized electrical dysfunction in this cohort requires further study to confirm this association and to determine if there are distinct etiologies for SCD risk in late rCoA survivors, and whether this risk is mediated by sex-specific factors.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

CHD	Congenital heart disease
CoA	Coarctation of the aorta
NSVT	Non-sustained ventricular tachycardia
QTc	QT interval corrected
SCA	Sudden cardiac arrest
SCD	Sudden cardiac death
VF	Ventricular fibrillation
VT	Ventricular tachycardia

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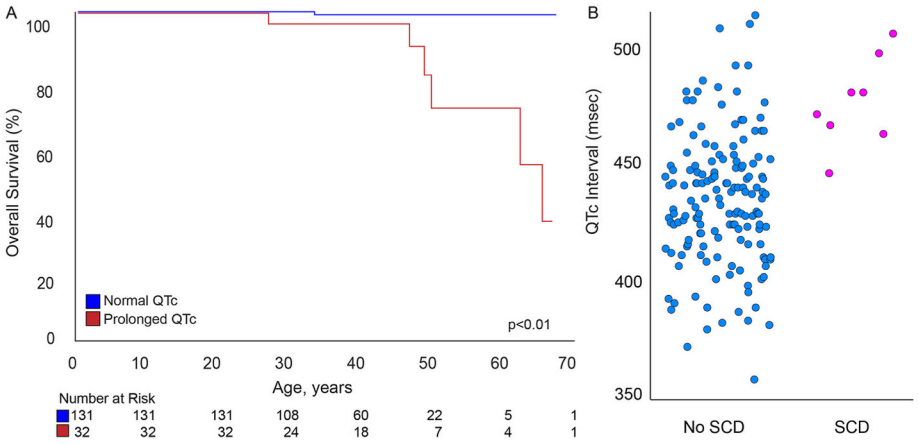

Fig. 1. Survival in Adults with Repaired Coarctation of the Aorta

Overall, adults with repaired coarctation and a prolonged QTc interval demonstrated diminished survival compared to those with normal a QTc interval (A). Sex normative QTc prolongation was present in most patients who sustained sudden cardiac death (SCD) (B).

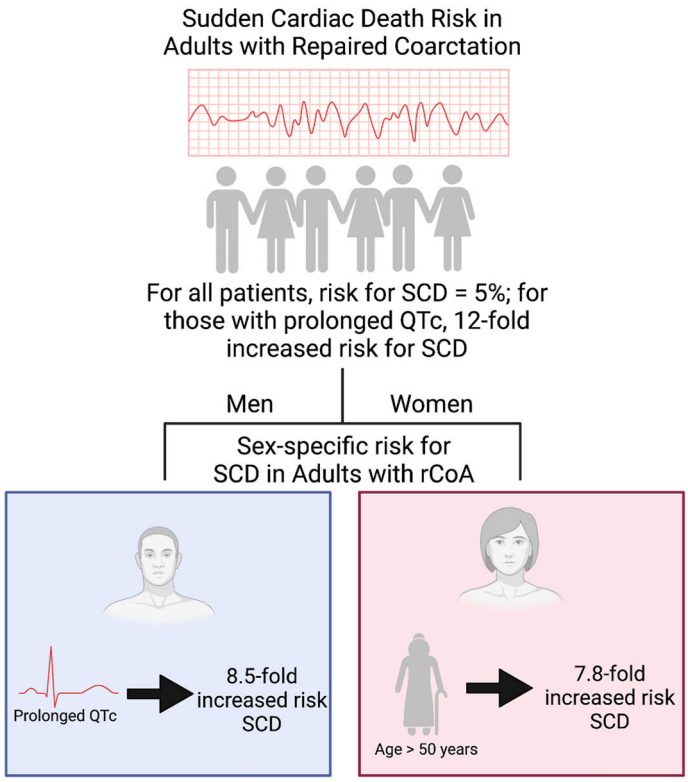

Fig. 2. /Proposed Graphical Abstract SCD Risk in Adults with Repaired Coarctation

In 167 adults with rCoA, SCD was found in 8 (5%) patients (compared to 0.9% in age-matched controls). Overall, adults with rCoA and a prolonged sex-normative QTc interval had a 12-fold increased risk of SCD (x^2 (1) = 12.3, $p < 0.001$). Men that experienced SCD were younger (42 ± 13 years vs. women 60 ± 10 years, $p < 0.05$), and when prolonged QTc was present, it impacted risk selectively in men (x^2 QTc prolongation 8.46, $p < 0.005$ and x^2 age 0.29, $p = 0.587$), whereas in women, advanced age increased SCD risk more than QTc prolongation (x^2 QTc prolongation 2.84, $p = 0.092$ and x^2 age 7.81, $p = 0.005$).

Table 1

Demographic characteristics.

Characteristics Mean ± SD or Frequency (%)	All patients (n = 167)	SCD Event (n = 8)	No SCD Event (n = 159)	P-value
Basic Demographics				
Age (years)	39 ± 11	45 ± 15	39 ± 11	0.105
Age at repair (years)	6 ± 7	5 ± 7	7 ± 8	0.640
Sex (female)	75 (45%)	3 (38%)	72 (44%)	0.664
BMI (kg/m2/mL)	30 ± 7	30 ± 6	30 ± 7	0.809
Hypertension	110 (65%)	6 (75%)	104 (65%)	0.567
Hyperlipidemia	36 (21%)	3 (38%)	33 (21%)	0.292
Electrocardiogram				
QRS Duration (msec)	108 ± 24	133 ± 38	107 ± 22	0.091
QTc Duration (msec)	436 ± 31	479 ± 16	434 ± 30	<0.001
Prolonged Sex-Normative QTc	32 (19%)	6 (75%)	26 (16%)	<0.001
Imaging				
Echocardiogram, LVEF (%)	59 ± 9	49 ± 17	60 ± 7	0.115
Cardiac MRI, LVEF (%)	62 ± 9	50 ± 18	62 ± 8	0.086
Cardiac MRI, Isthmus	1.6 ± 0.4	1.5 ± 0.5	1.6 ± 0.4	0.550
Diameter (cm)				
Cardiac MRI, LGE	40 (24%)	3 (38%)	37 (19%)	0.392

BMI: body mass index, LVEF: left ventricular ejection fraction, MRI: magnetic resonance imaging, QTc: corrected QT interval, SCD: sudden cardiac death, SD: standard deviation.

Table 2

Multiple logistic regression models.

Variable	Chi Square	P value
All Subjects		
Age	3.65	0.056
Sex	0.37	0.543
Prolonged Sex- Normative QTc	9.16	0.003
Entire Model x^2	16.8	<0.001
Men Only	**Chi Square**	**P value**
Age	0.29	0.587
Prolonged Sex- Normative QTc	8.46	0.004
Entire Model x^2	9.2	0.010
Women Only	**Chi Square**	**P value**
Age	7.81	0.005
Prolonged Sex- Normative QTc	2.84	0.092
Entire Model x^2	11.6	0.003

In this model, “age” refers to the dichotomous split of age ≥50 years (and <50 years). While across all subjects, prolonged QTc appears to impact risk for SCD most, when men and women were analyzed individually, prolonged QTc appears selectively important to advance risk in men, whereas age appears to be more important in women.