THE RISK OF MAJOR ADVERSE CARDIAC EVENTS FOR
ADULTS WITH ABOVE KNEE AMPUTATIONS

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Abstract:

Background: It is well known that the risk of cardiac disease is increased for those with lower-limb amputations, likely as a result of the etiology of the amputation. Using a longitudinal population-based dataset we examined the association between above knee amputation status and the risk of experiencing a major adverse cardiac event for those undergoing either dysvascular or traumatic amputations. The association of receiving a prosthesis with the risk of experiencing a major adverse cardiac event was also examined.

Methods/Study Population: All individuals with above knee amputations (N of 162), i.e. knee disarticulation and transfemoral amputation, residing in Olmsted County, MN, between 1987 and 2014.

Data Analysis: A competing risk Cox proportional hazard model was used to estimate the relative likelihood of an individual with an above knee amputation experiencing a major adverse cardiac event in a given time period as compared to a matched control. The cohort was divided by amputation etiology: dysvascular vs. trauma/cancer. Additional analysis was performed on only individuals with an above knee amputation to look at the relationship between prosthesis receipt and major adverse cardiac events.

Results: Individuals with dysvascular above knee amputation had an approximately four-fold increased risk of a cardiac event after undergoing an amputation (HR 3.78, 95% CI: 3.07-4.49). These individuals also had an increased risk for non-cardiac mortality (HR 6.27, 95% CI: 6.11-6.58). The risk of a cardiac event was no higher for those with a trauma/cancer above knee
Conclusion: The high risk of initial mortality stemming from an amputation may preclude many amputees from cardiovascular disease progression. Amputation etiology is also an important factor as cardiac events appear to be more likely amongst patients with dysvascular above knee amputation. Providing a prosthesis does not appear to be associated with a reduced risk of a major adverse cardiac event following amputation.

Keywords: amputation, cardiovascular disease, and survival analysis

Introduction:

Individuals with amputations due to dysvascular causes are at increased risk of cardiovascular disease, which is associated with increased peri- and post-operative mortality [1-3], is one of the leading causes of death [4], and is associated with increased disability [1, 5]. In 2015, there were two million Americans living with limb loss, most commonly due to diabetes and peripheral arterial disease [2]. The age-adjusted above knee amputation (AKA) rate reaches 40 per 100,000 patients with diabetes [6]. Due in part to the aging population and increase in prevalence of those living with diabetes, the number of American amputees is projected to double by the year 2050 [7, 8].

This growing population of dysvascular amputees has a higher prevalence of cardiovascular disease than the general U.S. adult population: up to 75% have coronary artery
disease, 60-80% have hypertension, 15-25% have cerebrovascular disease, and 20-50% have congestive heart failure [4, 9-12]. In comparison, only approximately 37% of U.S. adults have at least one type of cardiovascular disease [13]. Cardiovascular disease remains the leading cause of death and health care expenditure in the U.S., with direct and indirect costs reaching $316.1 billion between 2012 and 2013 [13]. Expenditures are expected to nearly triple by the year 2030, with a large proportion of these growing costs attributable to modifiable risk factors [13-16].

To date studies evaluating major adverse cardiac events (MACE), including cardiac death or non-fatal myocardial infarction, among individuals with AKA have been cross-sectional; there has not been a longitudinal evaluation of MACE risk in a population-based dataset. This study was undertaken to examine the association between AKA status and the long-term risk of experiencing a MACE for those who underwent an amputation due to either dysvascular or traumatic cause. The association between receiving a prosthesis and the risk of experiencing a MACE was also examined.

Methods:

Data Source and Study Population

Individuals with AKA residing in Olmsted County, MN, were identified using the resources available through the Rochester Epidemiology Project (REP). The REP was designed to take advantage of the unique circumstances within Olmsted County: being relatively isolated from other urban areas and having only a few health care providers including Mayo Clinic and Olmsted Medical Center as well as their affiliates [17]. The Olmsted County population is similar to that of the Upper Midwest but is less diverse, wealthier, and more highly educated than
the general U.S. population, yet results have been found to be generalizable to populations outside the Upper Midwest [18].

Using the resources of the REP, AKA (both incident and prevalent AKA patients) were identified using the ICD-9 diagnostic & procedure codes for amputations (84.17 for an AKA procedure or V49.76 indication and individual has an AKA). Each adult with AKA was matched (1:10 ratio) with adults without AKA on age, sex, and duration of residency in Olmsted County. Patients who had denied research authorization for use of their medical records in research were excluded. This study was approved by both the Mayo Clinic and Olmsted Medical Center Institutional Review Boards.

Medical records for AKA individuals were reviewed to confirm their amputation status and level. Additional data obtained included gender, race, amputation etiology, year of amputation (index date), pre and post-amputation comorbidities, and use of prosthesis. Comorbidities were extracted from administrative data and classified using modified Charlson comorbidities via the icd9 package in R [19, 20]. The outcome of interest was whether an individual had a MACE, defined as cardiac death, non-fatal myocardial infarction, or coronary revascularization, while residing in Olmsted County. Events were identified using pre-existing REP scripts for MACE including Berkson, Hospital Adaptation of the International Classification of Diseases (HICDA), ICD-9/-10 diagnostic codes.

**Statistical Analysis**

Due to the relatively high initial rates of mortality among individuals with AKA, a competing risk Cox proportional hazard model was used which accounted for the risk of death due to other cause and the risk of experiencing a MACE in a given time period [21]. The relative
risk (hazard ratio) of individuals with an AKA experiencing a MACE were compared to matched controls. The cohort was divided by amputation etiology: dysvascular vs trauma/cancer. Additional analysis was performed on only AKA to look at the relationship between prosthesis receipt and MACE. Because the prosthesis receipt occurs after the index date for most subjects, prosthesis status was treated as a time-dependent covariate. Differences throughout all of the analysis were considered statistically significant at p<.05. Simulated survival curves for each sub-cohort were performed for a man of average age and Charlson Comorbidity Index value to provide a visualization of model results. All statistical analysis was conducted using R version 3.3.2 [22].

**Results:**

The study population included a total of 162 individuals with AKA; 107 with amputation due to dysvascular etiology and 55 secondary to trauma or cancer. Mean age at amputation was 75.7 ± 11.3 years for those with dysvascular disease and 32.5 ± 20.8 years for those with AKA due to trauma or cancer (p<0.001). Men with dysvascular AKA were significantly younger at time of amputation than females with dysvascular AKA (p= 0.020, Table 1). Those with dysvascular amputations had significantly higher mortality rates at one and five years compared to those with AKA secondary to trauma or cancer (p< 0.001, Table 1).

**Table 1: Demographic Information**

<table>
<thead>
<tr>
<th>Amputation Etiology</th>
<th>Total</th>
<th>Men (number (%))</th>
<th>Mean Age at Amputation Years (SD)</th>
<th>Mortality Rate (%)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Men</td>
<td>Women</td>
<td>1 year</td>
</tr>
<tr>
<td>Dysvascular</td>
<td>107</td>
<td>55 (51.4%)</td>
<td>73.27 (10.7)</td>
<td>78.33 (11.4)</td>
<td>28%</td>
</tr>
<tr>
<td>Trauma/Cancer</td>
<td>55</td>
<td>39 (70.9%)</td>
<td>31.57 (19.3)</td>
<td>34.57 (24.6)</td>
<td>2%</td>
</tr>
<tr>
<td>All</td>
<td>162</td>
<td>94 (58.0%)</td>
<td>55.97 (25.4)</td>
<td>68.04 (24.16)</td>
<td>19%</td>
</tr>
</tbody>
</table>
Patients with a dysvascular AKA were more likely to have a MACE compared to patients with amputations due to trauma or cancer, with the exception of coronary stent placement (Table 2). When compared to a matched control group, the patients with an AKA due to dysvascular etiology had a greater rate of myocardial infarctions. In contrast, patients with an AKA due to either trauma or cancer had a greater rate of MACE due to a myocardial infarction relative to their control group. Overall, patients with dysvascular and trauma or cancer AKA were no more likely to experience a MACE relative to their respective controls.

*Dysvascular AKA, N=107:* The early and later risk of mortality appeared to change around 2.5 years following a dysvascular AKA as observed in the initial Kaplan-Meir curves (Figure 1). Therefore, a time dependent variable was added to account for this change and satisfy the proportional hazard assumption. Having a dysvascular AKA was associated with a four-fold approximate increase in experiencing a cardiac event both prior to and after 2.5 years of undergoing an amputation (Hazard Ratio (HR) 3.78, 95% CI: 3.07-4.49; HR 4.17, 95% CI: 3.46-4.86). There was also an increased risk for non-cardiac mortality both prior to and after 2.5 years (HR 6.27, 95% CI: 6.11-6.58; HR 3.03, 95% CI: 2.60-3.46) (Figure 1).
Table 2. Incidence of Major Adverse Cardiac Events (MACE) following an Above Knee Amputation

<table>
<thead>
<tr>
<th>Amputation Etiology</th>
<th>Cohort</th>
<th>Coronary Artery Bypass Graft (%)</th>
<th>Ischemic Heart Disease (%)</th>
<th>Myocardial Infarction (%)</th>
<th>Percutaneous transluminal coronary angioplasty (%)</th>
<th>Coronary Stent Placement (%)</th>
<th>Cardiac Arrest (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dysvascular</td>
<td>AKA, n=107</td>
<td>3 (4.2)</td>
<td>7 (9.9)</td>
<td>52 (73.2)</td>
<td>2 (2.8)</td>
<td>0 (0)</td>
<td>7 (9.9)</td>
</tr>
<tr>
<td></td>
<td>Controls, n=1070</td>
<td>23 (5.4)</td>
<td>110 (26.0)</td>
<td>235 (55.6)</td>
<td>12 (2.8)</td>
<td>2 (0.5)</td>
<td>41 (9.7)</td>
</tr>
<tr>
<td>Trauma/Cancer</td>
<td>AKA, n=55</td>
<td>1 (9.1)</td>
<td>1 (9.1)</td>
<td>7 (63.6)</td>
<td>1 (9.1)</td>
<td>0 (0)</td>
<td>1 (9.1)</td>
</tr>
<tr>
<td></td>
<td>Controls, n=550</td>
<td>4 (4.5)</td>
<td>17 (19.3)</td>
<td>46 (5.2)</td>
<td>8 (9.1)</td>
<td>0 (0)</td>
<td>13 (14.8)</td>
</tr>
</tbody>
</table>

NB: Events and percentages represent the respective proportion of those individuals experiencing a MACE.

Figure 1. Time dependent probability of a MACE or death for individuals with an AKA due to dysvascular disease compared to matched control subjects without an amputation. Individuals with a dysvascular AKA have a significantly increased risk of MACE or death compared to control subjects.
AKA due to trauma or cancer, N=55: The early and later risk of mortality appeared to change around 10 years following a trauma or cancer related AKA as observed in the initial Kaplan-Meir curves (Figure 2). Therefore, a time dependent variable was added to account for this change and satisfy the proportional hazard assumption. Those with an AKA had no significant increase in experiencing a cardiac event within 10 years or beyond 10 years relative to the controls (HR 1.30, 95% CI: 0.30-5.85; HR 1.60, 95% CI: 0.67-3.80). Adjusted non-cardiac mortality risks did not appear to differ from the controls (HR 1.94, 95% CI: 0.54-6.91; HR 1.45, 95% CI: 0.72-2.93).

Figure 2. Time dependent probability of a major adverse cardiac event (MACE) or death for individuals with an above knee amputation due to trauma or cancer compared to matched control subjects without an amputation. Individuals with an AKA do not differ in risk of MACE or death compared to control subjects.
AKA (dysvascular and trauma/cancer) with prosthesis, N=70: Those receiving a prosthesis had almost a 60% reduction in risk of death (HR 0.40, 95% CI: 0.26-0.64). There was no difference in risk of experiencing a cardiac event for those with or without a prosthesis (HR 1.20, 95% CI: 0.55-2.62) (Figure 3). The only covariates associated with an increased risk of MACE were age at time of amputation (HR 1.02, 95% CI: 1.01-1.03) and a higher Charlson Comorbidity index (HR 1.25, 95% CI: 1.17-1.33).

Figure 3. Time dependent probability of a MACE or death for individuals with an AKA who received a prosthesis compared to those who did not receive a prosthesis. While there was no significant difference in risk of experiencing a MACE, there was a significant reduction in risk of death.

Discussion:
This study determined the longitudinal risk of MACE in patients with an AKA. Unlike previous studies which only evaluated cardiac events throughout the perioperative time period or up to five years post amputation [9, 10, 23], this study uniquely calculated the risk as a function of time over a 30 year time span in a well characterized population-based observational study. This unique, population-based study suggested that the high risk of initial mortality stemming from an amputation event may preclude many amputees from progression of cardiovascular disease. Mortality rate among individuals with dysvascular AKA in our study was 28% at one year and 45% at five years, which is lower than previously reported ranges of 43-54% mortality at one year and 40-90% at five years [12, 24, 25]. Those with dysvascular amputations had a higher mortality rate than those with AKA secondary to trauma or cancer, which is also consistent with the literature [5, 23, 25-27]. Etiology of the amputation is also an important factor, as MACEs were more likely among patients with dysvascular AKA.

Dysvascular disease progression and need for amputation is a significant risk factor for MACE, and studies show that level of amputation is also important. Mohammedi et al. followed 11,140 patients with diabetes over a median time period of 9.9 years and found that, compared to those without peripheral artery disease, those with lower extremity ulceration and/or amputation were at a significantly higher risk of cardiovascular death, myocardial infarction, and all-cause mortality (HR 1.91, 1.50, and 1.39 respectively) [28]. They did not perform separate risk analyses for patients with ulceration and amputation which is likely why reported risk factors were lower compared to those in our study. Perioperative cardiac event rate is reported to be higher among individuals undergoing AKA compared to those undergoing below knee amputation, 6.8% and 3.6% respectively [23].
The risk of mortality due to cardiovascular disease in patients with AKA has been well studied in the military population. Hrubec and Ryder showed that after 15 years, the mortality rate in soldiers with an AKA was significantly higher than in the general population and in veterans with limb preservation [29]. They also showed that soldiers with bilateral AKA have a 3.5 times relative risk of mortality compared to veterans who had limb salvage procedures [29]. Modan et. al evaluated the 24-year mortality rates of male traumatic lower limb amputees (n = 201) of the Israeli army compared with a cohort sample representing the general population (n =1,832), and found that mortality rates were significantly higher (21.9% vs. 12.1%) in military amputees than in controls [30]. Cardiovascular disease mortality was the main cause for this difference. This study differs from the findings reported by Modan, since the adjusted non-cardiac mortality risk in the patients with AKA due to trauma or cancer did not differ from controls [30].

Several studies have revealed that only about one-quarter of individuals with AKAs receive a prosthesis [31-34]. A 10-year increase in age in the civilian population has been shown to result in a 54% decrease in the likelihood of being fit for a prosthesis [31]. Similarly, a study of elderly U.S. veterans revealed that a 10-year age increase reduced the likelihood of receiving a prosthesis by 78% [35]. Relatedly, the odds of receiving a prosthesis were almost 30 times higher in those able to walk independently prior to an amputation relative to those who could not walk independently [31]. Interestingly, time elapsed between surgery and the prosthesis decision was associated with a rise in the probability of receiving a prosthesis for the first 3 months after the amputation [31]. These data as a whole illustrate the lack of consistent, reliable prosthesis prescriptions and treatment and the unnecessary variability of care that patients with limb loss currently receive. While the data in this study appeared to show that receipt of a prosthesis was
correlated with a decreased mortality risk from non-cardiac events, this was likely due to the fact that to receive a prosthesis one had to live for some time following an AKA and not due to a protective effect from the prosthesis. Due to limitations in the data, it was difficult to account for this endogeneity. Notably, receipt of a prosthesis does not appear to be associated with a reduced risk of a MACE following amputation.

Conclusion:

This unique, population-based study suggests that the high risk of initial mortality stemming from an amputation event may preclude many amputees with dysvascular disease from progression of cardiovascular disease. In contrast, patients who have had an amputation due to trauma or cancer have no greater risk of a MACE than individuals without an amputation. Notably, receipt of a prosthesis was not associated with a decreased risk of experiencing a MACE.

Disclosure:

The authors have no conflicts of interest to disclose.

Acknowledgements;

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