Peripheral Vascular Disease

High mortality risks after major lower extremity amputation in Medicare patients with peripheral artery disease

W. Schuyler Jones, MD, a,b Manesh R. Patel, MD, a,b David Dai, PhD, a Sreekant Vemulapalli, MD, b Sumeet Subherwal, MD, MBA, a,b Judith Stafford, MS, a and Eric D. Peterson, MD, MPH a,b Durham, NC

Background  Little is known regarding the contemporary outcomes of older patients with peripheral artery disease (PAD) undergoing major lower extremity (LE) amputation in the United States. We sought to characterize clinical outcomes and factors associated with outcomes after LE amputation in patients with PAD.

Methods  Using data from the Centers for Medicare and Medicaid Services from January 1, 2000, to December 31, 2008, we examined the national patterns of mortality after major LE amputation among patients 65 years or older with PAD. Cox proportional hazards models were used to investigate the association between clinical variables, comorbid conditions, year of index amputation, geographic variation, and major LE amputation.

Results  Among 186,338 older patients with identified PAD who underwent major LE amputation, the mortality rate was 13.5% at 30 days, 48.3% at 1 year, and 70.9% at 3 years. Age per 5-year increase (hazard ratio [HR] 1.29, 95% CI 1.29-1.29), history of heart failure (HR 1.71, 95% CI 1.71-1.72), renal disease (HR 1.84, 95% CI 1.83-1.85), cancer (HR 1.71, 95% CI 1.70-1.72), and chronic obstructive pulmonary disease (HR 1.33, 95% CI 1.32-1.33) were all independently associated with death after major LE amputation. Subjects who underwent above knee amputation had a statistically higher hazard of death when compared with subjects who underwent LE amputation at more distal locations (HR with above the knee amputation 1.31, 95% CI 1.25-1.36).

Conclusions  Older patients with PAD undergoing major LE amputation still face a slightly high mortality risk, with almost half of all patients with PAD dying within a year of major LE amputation. (Am Heart J 2013;165:809-815.e1.)
Methods

Data sources

We obtained the 100% inpatient Medicare standard analytic files and corresponding denominator files from the Centers for Medicare and Medicaid Services from January 1, 2000, through December 31, 2008. The inpatient files contain institutional claims for facility costs covered under Medicare Part A. The denominator files contain beneficiary demographic and clinical characteristic data. We restricted the study population to those patients with fee-for-service Medicare Part A and B enrollment at the index admission and censored patients if they switched to managed care and/or dropped Medicare Part A or B.

Identification of patients

We identified beneficiaries for whom an International Classification of Diseases, Ninth Revision (ICD-9-CM) diagnosis code or procedure code for LE PAD was reported during the study period (online Appendix A). After selecting this PAD cohort, we then identified those beneficiaries who underwent a first major LE amputation during the study period as those for whom an ICD-9-CM procedure code (84.13-84.18) for above knee or below knee amputation was reported. In subjects who underwent multiple LE amputations, those that occurred after the index major amputation were not included in the analysis.

Statistical analysis

We present categorical variables as frequencies with percent-ages and continuous variables as means with SDs. To test for differences between groups, we used the Pearson $\chi^2$ test for categorical variables and the Wilcoxon rank sum test for continuous variables. Cox proportional hazards models were created to show the hazard ratios (HRs) associated with LE amputation and clinical variables, comorbid conditions, year of index amputation, and geographic variation.

The Duke University institutional review board reviewed and approved this study design. We used SAS statistical software, version 9.2 (SAS Institute Inc, Cary, NC) for all analyses.

Table I. Demographic and clinical characteristics

<table>
<thead>
<tr>
<th></th>
<th>Overall (n = 2,730,742)</th>
<th>PAD without LE amputation (n = 2,544,404)</th>
<th>PAD with LE amputation (n = 186,338)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y), mean ± SD</td>
<td>77.4 ± 7.6</td>
<td>77.3 ± 7.5</td>
<td>78.5 ± 8.2</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Age (y)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>65-69</td>
<td>490,087 (17.9)</td>
<td>459,538 (18.1)</td>
<td>30,549 (16.4)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>70-74</td>
<td>559,312 (20.5)</td>
<td>524,965 (20.6)</td>
<td>34,347 (18.4)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>75-79</td>
<td>627,886 (23.0)</td>
<td>589,502 (23.2)</td>
<td>38,384 (20.6)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>≥80</td>
<td>1,053,457 (38.6)</td>
<td>970,399 (38.1)</td>
<td>83,058 (44.6)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Male</td>
<td>1,352,662 (49.5)</td>
<td>1,263,035 (49.6)</td>
<td>89,627 (48.1)</td>
<td>.001</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>2,342,742 (85.8)</td>
<td>2,217,917 (87.2)</td>
<td>124,825 (67.0)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Black</td>
<td>293,285 (10.7)</td>
<td>240,874 (9.5)</td>
<td>52,411 (28.1)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Asian</td>
<td>17,483 (0.6)</td>
<td>16,417 (0.6)</td>
<td>1066 (0.6)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Other</td>
<td>77,222 (2.8)</td>
<td>69,196 (2.7)</td>
<td>8036 (4.3)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>US geographic region</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>New England</td>
<td>132,094 (4.8)</td>
<td>124,789 (4.9)</td>
<td>7305 (3.9)</td>
<td>.672</td>
</tr>
<tr>
<td>Middle Atlantic</td>
<td>406,576 (14.9)</td>
<td>381,189 (15.0)</td>
<td>25,387 (13.6)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>South Atlantic</td>
<td>595,493 (21.8)</td>
<td>550,437 (21.6)</td>
<td>45,056 (24.2)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>East North Central</td>
<td>525,337 (19.2)</td>
<td>494,627 (19.4)</td>
<td>30,710 (16.5)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>East South Central</td>
<td>217,045 (7.9)</td>
<td>198,798 (7.8)</td>
<td>18,247 (9.8)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>West North Central</td>
<td>195,749 (7.2)</td>
<td>184,858 (7.3)</td>
<td>10,891 (5.8)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>West South Central</td>
<td>332,659 (12.2)</td>
<td>306,032 (12.0)</td>
<td>27,627 (14.8)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Mountain</td>
<td>104,083 (3.8)</td>
<td>98,350 (3.9)</td>
<td>5733 (3.1)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Pacific</td>
<td>220,706 (8.1)</td>
<td>205,324 (8.1)</td>
<td>15,382 (8.3)</td>
<td>.005</td>
</tr>
<tr>
<td>Comorbidities</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cancer</td>
<td>236,135 (8.6)</td>
<td>223,021 (8.8)</td>
<td>13,114 (7.0)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>436,161 (16.0)</td>
<td>388,865 (15.3)</td>
<td>47,296 (25.4)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>987,779 (36.2)</td>
<td>895,135 (35.2)</td>
<td>92,644 (49.7)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Chronic obstructive pulmonary disease</td>
<td>973,553 (35.7)</td>
<td>907,824 (35.7)</td>
<td>65,729 (35.3)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>CAD</td>
<td>1,674,727 (61.3)</td>
<td>1,571,028 (61.7)</td>
<td>103,699 (55.7)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Dementia</td>
<td>97,360 (3.6)</td>
<td>79,930 (3.1)</td>
<td>17,430 (9.4)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1,021,469 (37.4)</td>
<td>909,131 (35.7)</td>
<td>112,338 (60.3)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Hypertension</td>
<td>2,107,597 (77.2)</td>
<td>1,958,113 (77.0)</td>
<td>149,484 (80.2)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Renal disease</td>
<td>448,747 (16.4)</td>
<td>393,778 (15.5)</td>
<td>54,969 (29.5)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

Patient characteristics

Patient demographic characteristics included age, sex, race, state of residence, and zip code of residence. Medicare beneficiaries report race at the time of enrollment. We used previously validated methods to identify comorbid conditions using ICD-9 billing claims for up to 5 years before the index hospitalization. We used the admission date and discharge date from the index hospitalization to calculate the length of stay (LOS). We used the patient’s state of residence to group beneficiaries into 9 US Census Bureau regions (online Appendix B).
Responsibility
This project was funded, in part, by internal support from the Duke Clinical Research Institute. This project was also supported on infrastructure provided by cooperative agreement number U19HS021092 from the Agency for Healthcare Research and Quality. The content is solely the responsibility of the authors and does not necessarily represent the official views of the Agency for Healthcare Research and Quality.

The authors are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the manuscript, and its final contents.

Results
Patient characteristics
There were nearly 3 million Medicare beneficiaries hospitalized for PAD from 2000 through 2008. A total of 186,338 patients (6.8% of the PAD group) underwent major LE amputation during the study period. Table I shows the demographic and clinical characteristics of all Medicare beneficiaries who were hospitalized for PAD and the characteristics of those with and without major LE amputation during the study period.

Among beneficiaries who underwent major LE amputation, nearly 60% were older than 75 years and nearly half were men. Patients with PAD who underwent major LE amputation were more likely to be black (28.1% vs 9.5%, \( P < .001 \)), have diabetes mellitus (60.3% vs 35.7%, \( P < .001 \)), and have renal disease (29.5% vs 15.5%, \( P < .001 \)), when compared with patients with PAD who did not undergo major LE amputation.

Clinical outcomes
The median (25th, 75th percentile) follow-up for all patients in this study was 681 days (205 days, 1332 days).

<table>
<thead>
<tr>
<th>Event</th>
<th>From index procedure to event</th>
<th>Rate (%)</th>
<th>95% Lower limit (%)</th>
<th>95% Upper limit (%)</th>
<th>Rate (%)</th>
<th>95% Lower limit (%)</th>
<th>95% Upper limit (%)</th>
<th>Rate (%)</th>
<th>95% Lower limit (%)</th>
<th>95% Upper limit (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality</td>
<td>1 mo</td>
<td>7.4</td>
<td>7.4</td>
<td>7.4</td>
<td>6.9</td>
<td>6.9</td>
<td>7.0</td>
<td>13.5</td>
<td>13.3</td>
<td>13.6</td>
</tr>
<tr>
<td></td>
<td>1 y</td>
<td>25.9</td>
<td>25.8</td>
<td>25.9</td>
<td>24.2</td>
<td>24.2</td>
<td>24.3</td>
<td>48.3</td>
<td>48.1</td>
<td>48.6</td>
</tr>
<tr>
<td></td>
<td>2 y</td>
<td>36.2</td>
<td>36.2</td>
<td>36.3</td>
<td>34.4</td>
<td>34.3</td>
<td>34.4</td>
<td>61.4</td>
<td>61.1</td>
<td>61.6</td>
</tr>
<tr>
<td></td>
<td>3 y</td>
<td>45.1</td>
<td>45.0</td>
<td>45.1</td>
<td>43.2</td>
<td>43.1</td>
<td>43.2</td>
<td>70.9</td>
<td>70.6</td>
<td>71.1</td>
</tr>
<tr>
<td>MI</td>
<td>1 mo</td>
<td>1.9</td>
<td>1.9</td>
<td>1.9</td>
<td>1.9</td>
<td>1.9</td>
<td>1.9</td>
<td>1.2</td>
<td>1.1</td>
<td>1.2</td>
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<tr>
<td></td>
<td>1 y</td>
<td>6.0</td>
<td>6.0</td>
<td>6.0</td>
<td>6.0</td>
<td>6.0</td>
<td>6.1</td>
<td>5.0</td>
<td>4.9</td>
<td>5.1</td>
</tr>
<tr>
<td></td>
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<td>8.7</td>
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<td>7.3</td>
<td>7.2</td>
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<tr>
<td></td>
<td>3 y</td>
<td>10.9</td>
<td>10.8</td>
<td>10.9</td>
<td>11.0</td>
<td>11.0</td>
<td>11.1</td>
<td>8.9</td>
<td>8.8</td>
<td>9.1</td>
</tr>
<tr>
<td>Stroke</td>
<td>1 mo</td>
<td>1.7</td>
<td>1.7</td>
<td>1.7</td>
<td>1.8</td>
<td>1.8</td>
<td>1.8</td>
<td>1.0</td>
<td>0.9</td>
<td>1.0</td>
</tr>
<tr>
<td></td>
<td>1 y</td>
<td>6.6</td>
<td>6.6</td>
<td>6.7</td>
<td>6.8</td>
<td>6.8</td>
<td>6.8</td>
<td>4.3</td>
<td>4.2</td>
<td>4.4</td>
</tr>
<tr>
<td></td>
<td>2 y</td>
<td>9.7</td>
<td>9.7</td>
<td>9.7</td>
<td>9.9</td>
<td>9.9</td>
<td>10.0</td>
<td>6.2</td>
<td>6.1</td>
<td>6.3</td>
</tr>
<tr>
<td></td>
<td>3 y</td>
<td>12.1</td>
<td>12.0</td>
<td>12.1</td>
<td>12.4</td>
<td>12.4</td>
<td>12.4</td>
<td>7.5</td>
<td>7.4</td>
<td>7.7</td>
</tr>
</tbody>
</table>

Table II. Rate of death, MI, and stroke after major LE amputation during the study period

Figure 1

The occurrence of death, MI, and stroke in patients hospitalized for PAD with and without major LE amputation: cumulative incidence rates of all-cause mortality (A), MI (B), and stroke (C) after major LE amputation.
From 2000 through 2008, the 30-day, 1-year, and 3-year overall mortality rates after major LE amputation were 13.5%, 48.3%, and 70.9%, respectively. Rates of MI and stroke at 30 days, 1 year, and 3 years are also shown in Table II and Figure 1. When compared with patients with PAD who did not undergo major LE amputation, patients with major LE amputation had significantly higher rates of mortality at 30 days, 1 year, and 3 years (Table II and Figure 1). Rates of MI and stroke were lower in patients with PAD after major LE amputation compared with those without LE amputation. Length of stay during the index hospitalization was substantially longer in patients with PAD who underwent major LE amputation (LOS [days] ± SD 13.2 ± 13.0) when compared with patients with PAD who did not undergo major LE amputation (LOS [days] ± SD 6.0 ± 7.5, \( P < .001 \)).

Clinical factors associated with mortality after major LE amputation

Table III shows the results of Cox models created to show the clinical predictors of death after major LE amputation. Age per 5-year increase, history of heart failure, renal disease, cancer, and chronic obstructive pulmonary disease were independently associated with death after major LE amputation. A history of coronary artery disease (CAD) and hypertension were associated with reduced risk of death after major LE amputation.

Temporal trends in mortality after major LE amputation

The adjusted HR of death after major LE amputation per year after 2000 was 0.958 (95% CI 0.957-0.959, \( P < .001 \)) (Table III). The 30-day and 1-year mortality rates for patients undergoing major LE amputation in 2000 were 13.8% and 47.8%, whereas the 30-day and 1-year mortality rates for patients undergoing the same procedure in 2008 were 12.7% and 47.7%.

Geographic variation in the occurrence of death after major LE amputation: unadjusted cumulative incidence rates of all-cause mortality and mortality/MI/stroke after major LE amputation according to US Census Bureau regions.

The effect of geography on mortality after major LE amputation

Geographic variation was also independently associated with death after major LE amputation after adjusting for clinical variables and temporal trends. Figure 2 shows
the unadjusted rates of all-cause mortality and mortality/MI/stroke according to US Census Bureaus after major LE amputation. Death after major LE amputation occurred more frequently in the Pacific region (adjusted HR 1.048, 95% CI 1.041-1.056, \(P < .001\)) and 1 year (death rate: LE amputation 48.3% vs no LE amputation 24.2%, \(P < .001\)). This difference remained dramatically higher at 3 years (death rate: LE amputation 70.9% vs no LE amputation 43.2%, \(P < .001\)). The factors associated with this higher mortality including advanced age, heart failure, renal disease, and cancer may have all contributed to these extremely high short- and long-term event rates after major LE amputation. The presence of CAD was associated with a lower risk of death after major LE amputation, potentially highlighting a finding from one of our prior observations in a Danish national registry that patients with clinically identified CAD and PAD are treated more aggressively with medical therapy than those patients with PAD alone.9

These data highlight the unacceptably high rates of mortality in patients with PAD with and without major LE amputation and provide focus for areas of further research and improvement. For clinicians, payers, and policy makers, awareness of the risk of mortality after major LE amputation may provide important opportunities for identification of these high-risk patients with PAD. Further study of this high-risk group of patients will be required to determine if (a) physician and patient education programs and/or aggressive revascularization efforts can help decrease or prevent major LE amputation, (b) care pathways can make major LE amputation procedures safer, and (c) evidence-based treatments for atherosclerosis (ie, antiplatelet agents and statins) or novel therapies can reduce mortality after major LE amputation. These comprehensive efforts have been successfully initiated in coordinated MI, heart failure, and stroke programs10–12; however, the recent American College of Cardiology/American Heart Association performance measures document for adults with PAD does not address patients at risk for or undergoing major LE amputation.13 This strikingly high rate of mortality serves as a call to action for clinicians and researchers to both identify the cause of death in these patients and determine whether processes of care or novel treatment options can influence this mortality rate.

Prior studies of major LE amputation have reported a wide variation of mortality rates at 30 days (6.9%-30.0%)
and 1 year (30.3%-54.0%). Although patient-specific factors are critical determinants of mortality after major LE amputation, 2 additional factors noted in this study, geographic variation and level of amputation, may have contributed to these prior, imprecise event rates. In the current study, both factors remain independent predictors of mortality after major LE amputation after statistical adjustment for baseline variables. When considered separately, the geographic variation observed in mortality rates highlights the need to better understand the impact of unmeasured contributors such as socioeconomic status, access to care, revascularization efforts, wound care, medical therapy, and patient education programs. For those regions with higher rates of mortality, it should also signal that lessons can be learned from regions with lower mortality and that improvement is needed. The significantly higher event rates in those patients requiring extensive amputation (ie, AKA) suggest that every opportunity should be taken to avoid AKAs. Furthermore, a uniform treatment algorithm to determine amputation level at the time of major LE amputation is needed, as much of the decision making about the level of amputation is determined by physician expertise and preference. As a whole, the significance of geographic variation and level of amputation emphasize the importance of developing standardized care pathways and quality initiatives before, during, and after major LE amputation.

An important point of encouragement in the midst of these exceedingly high mortality rates after major LE amputation is the decline in mortality over the study period. The 30-day mortality rates for patients undergoing major LE amputation in 2000 was 13.8%, whereas the 30-day mortality rates for patients undergoing the same procedure in 2008 was 12.6%. There are multiple potential explanations for this declining adjusted rate of mortality after major LE amputation during the study period. It is possible that patients with PAD were treated more aggressively for ischemic heart disease, a fact that may be corroborated by lower cumulative rates of stroke and MI in the amputation cohort. Unfortunately, we were unable to measure the intensity of medical therapy or revascularization in this inpatient Medicare data set. In addition, the implementation of perioperative surgical quality improvement programs in some centers may have influenced the 30-day mortality rates observed in our study. Despite the decline in short-term mortality, the 1- and 3-year mortality rates are similar at the beginning and end of the study period and reflect no significant improvement over time.

The current study has multiple limitations. First, Medicare claims data do not include information regarding the duration, burden, or severity of disease that may affect the rate of major LE amputation and long-term outcomes after major LE amputation. Second, although Medicare Part A data capture inpatient hospital claims, it is possible that some patients with major LE amputation were not included in the current analysis. The use of inpatient claims made it impossible to fully investigate the use of diagnostic testing and revascularization, given a shift from inpatient to outpatient care. Finally, this analysis only included those patients enrolled in fee-for-service Medicare, and the generalizability to all US patients, including non-fee-for-service Medicare beneficiaries, those with private insurance, and younger patients, is unclear.

In conclusion, mortality rates after major LE amputation in patients with PAD remain high in the United States. Since 2000, there appears to have been a decline in the short-term mortality rate after major LE amputation in this population. Future registries and clinical trials should aim to identify both quality improvement programs and standard and novel treatments that decrease this unacceptably high mortality rate. Finally, there remains a critical need for education programs in the United States that focus on prevention, early diagnosis, and aggressive treatment for patients with PAD at high risk for major LE amputation and subsequent death.

Disclosures

W.S.J., D.D., S.V., S.S., and J.S. have nothing to disclose. M.R.P. received research grants from Johnson & Johnson, Pluristem, and Astra Zeneca and is a consultant in Baxter, Genzyme, Bayer, and Ortho McNeil Jansen. E.D.P. received research grants from Bristol Myers Squibb-Sanofi, Merck, Eli Lilly, and Johnson & Johnson.

There are no relevant financial disclosures applicable to this study.

References


Appendix A. ICD-9-CM diagnosis code or procedure code used for inclusion of subjects in the current study

Diagnosis codes:
440.0, 440.2, 440.20, 440.21, 440.22, 440.23, 440.24, 440.3, 440.30, 440.31, 440.32
440.4
440.9
443.9
444.0, 444.2, 444.22, 444.8, 444.81
447.1
445.0, 445.02
250.7, 250.70, 250.71, 250.72, 250.73
707.1, 707.10, 707.11, 707.12, 707.13, 707.14, 707.15, 707.19

Procedure codes:
00.4, 00.40, 00.41, 00.42, 00.43, 00.44, 00.45, 00.46, 00.47, 00.48
38.08, 38.18, 38.38, 38.48, 38.68, 38.91
39.25, 39.29, 39.50, 39.90
99.10

Appendix B. US Census Bureau regions

Division 1:
New England
Connecticut
Maine
Massachusetts
New Hampshire
Rhode Island
Vermont

Division 2:
Middle Atlantic
New Jersey
New York
Pennsylvania

Division 3:
East North Central
Indiana
Illinois
Michigan
Ohio
Wisconsin

Division 4:
West North Central
Iowa

Division 5:
South Atlantic
Delaware
District of Columbia
Florida
Georgia
Maryland
North Carolina
South Carolina
Virginia
West Virginia

Division 6:
East South Central
Alabama
Kentucky
Mississippi
Tennessee

Division 7:
West South Central
Arkansas
Louisiana
Oklahoma
Texas

Division 8:
Mountain
Arizona
Colorado
Idaho
New Mexico
Montana
Utah
Nevada
Wyoming

Division 9:
Pacific
Alaska
California
Hawaii
Oregon
Washington