Long-term Mortality in Patients with Asymptomatic Carotid Stenosis: Implications for Statin Therapy

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WHAT THIS PAPER ADDS
All-cause mortality and cardiac mortality in patients with asymptomatic carotid stenosis are very high. They appear to remain high despite the reduction in mortality observed in the general population during the last 20 years. Although risk factors have been identified and risk stratification is possible, most patients are classified as high risk.

Objective: Recent studies with asymptomatic carotid patients on best medical management have shown that the annual risk of stroke has decreased to approximately 1%. There is no evidence that a similar decrease in mortality has occurred. In addition, the intensity of statin therapy for these patients has not yet been determined. The aims of this review were to determine (a) the reported long-term all-cause and cardiac-related mortality in patients with asymptomatic carotid stenosis (ACS) >50%, (b) whether there has been a decrease in mortality in recent years, (c) the available methods of mortality risk stratification, and (d) whether the latest ACC/AHA guidelines on the treatment of serum lipids can be applied to this group of patients.

Methods: Systematic review of PubMed, EuroPubMed, and Cochrane Library and meta-analysis using random effects for pooled proportions were performed regarding long-term all-cause and cardiac-related mortality and the associated risk factors in ACS patients. The last day for literature search was October 30, 2014.

Results: Seventeen studies were retrieved reporting 5-year all-cause mortality in 11,391 patients with ACS >50%. The 5-year cumulative all-cause mortality across all 17 studies was 23.6% (95% CI 20.50–26.80). Twelve additional studies, reporting both all-cause and cardiac mortality with a minimum of 2 year follow-up and involving 4,072 patients were identified. Of the 930 deaths reported, 589 (62.9%; 95% CI 58.81–66.89) were cardiac-related. This translates into an average cardiac-related mortality of 2.9% per year.

Conclusions: All-cause and cardiac mortality in ACS patients are very high. Although risk stratification is possible, most patients are classified as high risk. In view of this high risk, aggressive statin therapy is indicated if the new ACC/AHA guidelines on serum lipids are to be adhered to.

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INTRODUCTION
Two randomized controlled trials (RCTs), the Asymptomatic Carotid Atherosclerosis Study (ACAS) in 1995 and the Asymptomatic Carotid Surgery Trial (ACST) in 2004, recruited patients from 1988 to 2003, and reported that
carotid endarterectomy (CEA) reduced the risk of stroke from about 2.0% to 1.0% per year in patients with asymptomatic internal carotid artery (ACS) stenosis >60% in relation to the distal internal carotid (NASCET criteria). In these trials CEA was associated with a 2–3% 30-day peri- operative risk of stroke or death. However, in these studies, medical treatment and modification of arterial disease risk factors was left to the discretion of the local teams and was suboptimal compared with current practice.

New and more effective medications have been introduced since then, with guideline recommendations for predefined LDL-C and blood pressure (BP) targets for symptomatic patients with atherosclerotic disease, but not for patients with asymptomatic carotid stenosis. Recent reviews of cohort studies on the outcome of patients with ACS treated medically (including the medical arms of randomized carotid endarterectomy trials) indicate that the average annual risk of ipsilateral stroke has fallen to approximately 1% or less. This is attributed to better medical management including statin therapy; however, there are no reports that a parallel decrease has occurred in mortality including cardiac mortality.

The latest American College of Cardiology/American Heart Association (ACC/AHA) guidelines on the treatment of serum lipids state that for non-diabetic individuals aged 40–75 years without clinical evidence of atherosclerotic cardiovascular disease (ASCVD) and an LDL-C of 70–189 mg/dL (1.8–4.9 mmol/L), it is reasonable to prescribe moderate intensity statins when the 10-year risk of developing “hard” ASCVD outcomes (first fatal or non-fatal myocardial infarction [MI], coronary artery disease [CAD] death, fatal or non-fatal stroke) is 5–7.5%. In addition, moderate or high intensity statins are recommended when the 10-year risk of developing a first “hard” ASCVD outcome is >7.5%. Clinical ASCVD was defined as acute coronary syndromes, MI, angina, coronary or other revascularization, stroke or TIA, or peripheral arterial disease (PAD) presumed to be of atherosclerotic origin. These new guidelines which rely on the 10-year risk of developing “hard” ASCVD outcomes to determine the intensity of statin therapy have prompted the current review.

The aims of this review were to determine (a) long-term all-cause and cardiac-related mortality in patients with ACS >50%, (b) whether there has been a decrease in mortality in recent years, (c) the available methods of mortality risk stratification, and (d) whether, based on the currently reported cardiac mortality, the latest ACC/AHA guidelines on the treatment of serum lipids can be applied to this group of patients.

METHODS

All-cause long-term mortality

The PubMed, EuroPubMed, and Cochrane databases were searched for studies with late follow-up in patients with medically or surgically treated ACS, independently by two of the authors (AG and ANN). Any discrepancies were resolved by discussion between the two authors. The (MeSH) search terms were: “carotid” OR “CAS” OR “carotid stenting” OR “carotid endarterectomy” OR “CEA” AND “long-term mortality” OR “late results” OR “5 year mortality” OR “10 year mortality”. Identified studies were searched for relevant publications in their reference lists. All clinical studies reporting cumulative survivals at 5 or 10 years in patients with ACS >50% (NASCET criteria) after medical or surgical management were retrieved. Studies reporting outcomes in patients with an asymptomatic carotid stenosis after treatment of a contralateral symptomatic side were excluded. Studies reporting total mortality in both symptomatic and asymptomatic patients were accepted provided the results were reported separately for these two groups so that only the asymptomatic group could be included. Studies identifying risk factors associated with increased late mortality were also included in the analysis.

The results are reported as 5- or 10-year cumulative mortality for each study and weighted cumulative mortality for all studies based on meta-analysis. Average annual mortality rates were calculated by dividing the 5- and 10-year cumulative mortality by 5 or 10, respectively.

Proportion of cardiac deaths

Because cardiac mortality was reported in only six of the papers with 5- or 10-year follow-up using life table analysis, a second search was performed of the same databases to identify papers that reported the proportion of patients that died from cardiovascular causes while reporting overall mortality in patients with ACS >50% with a minimum of 2 years’ follow-up. Because legitimate analysis was not a criterion for selecting such studies, a separate search became necessary. The last day for both searches was October 30, 2014. This article was prepared in accordance with the guidelines set out by the Preferred Reporting Items for Systematic Review and Meta-analyses (PRISMA) statement.

Pooling of data and regression according to date of publication

Pooling of data was performed using meta-analysis using random effects and associated tests for heterogeneity (Q and I²) using Medcalc (version 15.4). A simple regression was performed plotting 5-year cumulative mortality by year of publication using SPSS version 20.

RESULTS

All-cause long-term mortality in patients with asymptomatic carotid stenosis

One-hundred and twelve studies were identified evaluating late mortality in patients with >50% internal carotid artery (ICA) stenosis. Ninety studies were excluded because they reported mortality results for <5 years or the results were based on a mixture of asymptomatic and symptomatic patients. Five studies were rejected because the degree of carotid stenosis was <50% or not reported at all. Finally, 17 studies remained (Fig. 1 and Table 1).
Twelve of the studies listed in Table 1 reported all-cause long-term mortality in asymptomatic patients after CEA,12–14,16,18,20,21,23–27 and five after medical management.15,17,19,22,28 The smallest study included 42 patients,14 and the largest one, 4,114.26 Eleven studies reported 5-year mortality only. Six studies provided both 5- and 10-year mortality. Five studies included patients with a carotid stenosis >50%, two studies included patients with 50–79% stenosis only, three with >60%, and seven with >70%. In four studies25–28 published in 2013 and 2014, most patients were on statins, but there was no information on whether treatment was to a predefined target. It is not mentioned whether patients were treated with statins in the older studies.

The mean baseline age of patients in different studies ranged from 61 to 74.5 years, 51–100% were males, 43–89% hypertensive, 15–38% diabetic, and 18–64% had a history of CAD or MI (epidemiological data reported in 10 out of the 17 above studies). Of the patients, 21–80% were smokers/ex-smokers (data in 9 from the above studies), 37–54.2% were hyperlipidemic (data in 5 from the above studies), and 33–60% were found to have PAD (data derived from 5 out of 17 studies).

The 5-year weighted average cumulative all-cause mortality across all 17 studies involving 11,391 patients was 23.6% (95% CI 20.50–26.80) (Table 1 and Fig. 2) (average annual mortality 4.6%). In the five studies in which patients (n = 944) did not have a CEA, the 5-year weighted average cumulative all-cause mortality was 24.35% (95% CI 21.65–27.21). In the remaining studies in which patients (n = 10,447) had a CEA before follow-up, the 5-year weighted average cumulative all-cause mortality was 22.7% (95% CI 22.96–23.59).

The lowest 5-year cumulative all-cause mortality of 10% was reported in the subgroup of women reported separately from men in the study by Mattos et al. in 2001.21 The highest mortality, 37%, was found in two studies (Cohen et al. in 1993 and Mansour et al. in 1995).16,17

In the seven studies reporting both 5- and 10-year cumulative mortality involving 3,297 patients, the weighted average cumulative all-cause mortalities were 25.8% (95% CI 24.35–27.36) (average annual mortality of 5.2%) and 52.4% (95% CI 50.65–54.08) (average annual mortality of 5.2%), respectively.

The 5-year all-cause cumulative mortality from the studies listed in Table 1 was plotted against the year of publication (Fig. 3). There was no statistically significant reduction in mortality during the last 30 years (1985–2014).

Exclusion of any single study from the meta-analysis did not substantially alter the overall result of the meta-analysis.
Table 1. All-cause mortality in patients with >50% diameter (NASCET) asymptomatic carotid stenosis (ACS).

<table>
<thead>
<tr>
<th>Author</th>
<th>n</th>
<th>% Stenosis</th>
<th>CEA</th>
<th>5-year cumulative mortality</th>
<th>10-year cumulative mortality</th>
<th>Average annual mortality in years 1–5</th>
<th>Average annual mortality in years 1–10</th>
<th>Risk stratification for mortality</th>
<th>Risk factors identified</th>
<th>Statin therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moore et al., 1985</td>
<td>76</td>
<td>&gt;50%</td>
<td>+</td>
<td>35%</td>
<td>7.0%</td>
<td>5.0%</td>
<td>5.4%</td>
<td>Severity of stenosis</td>
<td>Yes</td>
<td>—</td>
</tr>
<tr>
<td>Hertzer and Arison, 1985</td>
<td>126</td>
<td>&gt;50%</td>
<td>+</td>
<td>26%</td>
<td>56%</td>
<td>5.2%</td>
<td>5.4%</td>
<td>Using suspected myoc. ischemia</td>
<td>Yes</td>
<td>—</td>
</tr>
<tr>
<td>Rosenthal et al., 1987</td>
<td>42</td>
<td>&gt;50%</td>
<td>+</td>
<td>24%</td>
<td>53%</td>
<td>4.8%</td>
<td>5.3%</td>
<td>No</td>
<td>No</td>
<td>—</td>
</tr>
<tr>
<td>Bernstein et al., 1992</td>
<td>180</td>
<td>&gt;50%</td>
<td>—</td>
<td>18%</td>
<td>—</td>
<td>3.6%</td>
<td>—</td>
<td>No</td>
<td>Yes</td>
<td>—</td>
</tr>
<tr>
<td>Cohen et al., 1993</td>
<td>211</td>
<td>&gt;50%</td>
<td>+</td>
<td>37%</td>
<td>—</td>
<td>9.4%</td>
<td>—</td>
<td>Using risk factors</td>
<td>Yes</td>
<td>—</td>
</tr>
<tr>
<td>Mansour et al., 1995</td>
<td>142</td>
<td>&gt;50%–79%</td>
<td>—</td>
<td>37%</td>
<td>—</td>
<td>9.4%</td>
<td>—</td>
<td>No</td>
<td>No</td>
<td>—</td>
</tr>
<tr>
<td>Branchereau et al., 1998</td>
<td>357</td>
<td>&gt;70%</td>
<td>+</td>
<td>25%</td>
<td>41%</td>
<td>5.0%</td>
<td>4.1%</td>
<td>Using associated vascular disease</td>
<td>No</td>
<td>—</td>
</tr>
<tr>
<td>Rockman et al., 1997</td>
<td>425</td>
<td>50–79%</td>
<td>—</td>
<td>23%</td>
<td>—</td>
<td>4.6%</td>
<td>—</td>
<td>No</td>
<td>No</td>
<td>—</td>
</tr>
<tr>
<td>Cao et al., 1999 (SBI +)</td>
<td>103</td>
<td>&gt;60%</td>
<td>+</td>
<td>18%</td>
<td>39%</td>
<td>3.6%</td>
<td>3.9%</td>
<td>Using SBI + or —</td>
<td>No</td>
<td>—</td>
</tr>
<tr>
<td>Cao et al., 1999 (SBI −)</td>
<td>198</td>
<td>&gt;60%</td>
<td>+</td>
<td>14%</td>
<td>31%</td>
<td>2.8%</td>
<td>3.1%</td>
<td>Using SBI + or —</td>
<td>No</td>
<td>—</td>
</tr>
<tr>
<td>Mattos et al., 2001 (Men)</td>
<td>247</td>
<td>60–99%</td>
<td>+</td>
<td>15%</td>
<td>—</td>
<td>3.0%</td>
<td>—</td>
<td>Yes</td>
<td>Yes</td>
<td>—</td>
</tr>
<tr>
<td>Mattos et al., 2001 (Women)</td>
<td>154</td>
<td>60–99%</td>
<td>+</td>
<td>10%</td>
<td>—</td>
<td>2.0%</td>
<td>—</td>
<td>Yes</td>
<td>Yes</td>
<td>—</td>
</tr>
<tr>
<td>AbuRahma et al., 2003</td>
<td>82</td>
<td>60–69%</td>
<td>—</td>
<td>17%</td>
<td>33%</td>
<td>3.4%</td>
<td>3.3%</td>
<td>No</td>
<td>No</td>
<td>—</td>
</tr>
<tr>
<td>Reed et al., 2003</td>
<td>639</td>
<td>&gt;70%</td>
<td>+</td>
<td>28%</td>
<td>—</td>
<td>5.6%</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Kragsterman et al., 2006</td>
<td>631</td>
<td>&gt;70%</td>
<td>+</td>
<td>22%</td>
<td>55%</td>
<td>4.4%</td>
<td>5.5%</td>
<td>No</td>
<td>Yes</td>
<td>—</td>
</tr>
<tr>
<td>Conrad et al., 2013</td>
<td>1791</td>
<td>&gt;70%</td>
<td>+</td>
<td>27%</td>
<td>—</td>
<td>5.4%</td>
<td>—</td>
<td>Conventional risk factors</td>
<td>Yes</td>
<td>Some patients</td>
</tr>
<tr>
<td>Wallaert et al., 2013</td>
<td>4114</td>
<td>&gt;70%</td>
<td>+</td>
<td>18%</td>
<td>—</td>
<td>3.6%</td>
<td>—</td>
<td>Conventional risk factors</td>
<td>Yes</td>
<td>Some patients</td>
</tr>
<tr>
<td>Kang et al., 2014</td>
<td>1758</td>
<td>&gt;70%</td>
<td>+</td>
<td>30%</td>
<td>58%</td>
<td>6.0%</td>
<td>5.8%</td>
<td>Conventional risk factors</td>
<td>Yes</td>
<td>Some patients</td>
</tr>
<tr>
<td>Conrad et al., 2014</td>
<td>115</td>
<td>&gt;70%</td>
<td>+</td>
<td>30%</td>
<td>—</td>
<td>6%</td>
<td>—</td>
<td>Using risk factors</td>
<td>Yes</td>
<td>Some patients</td>
</tr>
</tbody>
</table>

SBI = silent brain infarcts.
in terms of proportion and variability. In addition, limiting the meta-analysis to the large studies published after 2002 produced similar results (Total Random effects proportion: 24.5% [95% CI 19.89–29.52]; \(Q = 135.7; \text{DF} = 6; p < .0001; I^2 = 95.58\)).

Proportion of cardiac deaths

Sixty-five studies analyzing the causes of death in patients with ACS irrespective of duration of follow-up were identified. Forty-five studies were excluded because the follow-up was <2 years or the results were based on mixed cohorts of symptomatic and asymptomatic patients. Eight studies were rejected because they did not mention the degree of stenosis or this was <50%. As a result, 12 studies remained with follow-up >2 years in a total of 4,072 patients (Table 2 and Fig. 4).13,14,16,17,20–22,29,33 The sample size ranged from 42 to 1,101 patients. There were 930 deaths, of which 589 were cardiac-related. The percentage of cardiac mortality in those who died in the different studies varied between 42% and 82% with a weighted average of 62.8% (95% CI 58.8–66.9) (Fig. 5). This translates into an average cardiac-related mortality of 2.9% per year.

Risk factors associated with increased all-cause mortality in ACS patients and stratification into different risk groups for death

Among the 112 studies that were initially retrieved, eight reported on risk factors and hazard ratios (HR) associated with increased all-cause late mortality using univariate analyses (Table 3).16,20,24–28,33 Identified risk factors were: age, diabetes, smoking, CAD, abnormal ECG, congestive heart failure (CHF), chronic obstructive pulmonary disease (COPD), impaired renal function, lack of statin therapy, contralateral internal carotid stenosis or occlusion, intermittent claudication, lacunar infarcts, high risk for surgery, and history of previous vascular surgery.

Multivariable regression analysis with all-cause mortality as the dependent variable was performed in only five studies,16,23,26–28 and stratification into different all-cause

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**Table 2.** Prevalence of all-cause and cardiac-related mortality in 930 patients with >50% diameter (NASCET) asymptomatic carotid stenosis (ACS) who died during follow-up.

<table>
<thead>
<tr>
<th>Author et al., 1986</th>
<th>Patients, n</th>
<th>Mean follow-up, months</th>
<th>All deaths, n</th>
<th>Heart-related deaths, n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chambers et al.</td>
<td>113</td>
<td>23</td>
<td>21</td>
<td>12 (57%)</td>
</tr>
<tr>
<td>Hertzer et al.</td>
<td>126</td>
<td>Up to 10 years</td>
<td>72</td>
<td>38 (53%)</td>
</tr>
<tr>
<td>Rosenthal et al.</td>
<td>42</td>
<td>120</td>
<td>16</td>
<td>10 (62%)</td>
</tr>
<tr>
<td>Meissner et al.</td>
<td>292</td>
<td>39</td>
<td>75</td>
<td>48 (64%)</td>
</tr>
<tr>
<td>Moneta et al.</td>
<td>115</td>
<td>Up to 48</td>
<td>19</td>
<td>8 (42%)</td>
</tr>
<tr>
<td>Cohen et al.</td>
<td>444</td>
<td>48</td>
<td>164</td>
<td>100 (61%)</td>
</tr>
<tr>
<td>Mansour et al.</td>
<td>144</td>
<td>60</td>
<td>20</td>
<td>14 (70%)</td>
</tr>
<tr>
<td>Cao et al.</td>
<td>301</td>
<td>67.3</td>
<td>53</td>
<td>32 (60%)</td>
</tr>
<tr>
<td>Mattos et al.</td>
<td>241</td>
<td>50</td>
<td>38</td>
<td>31 (82%)</td>
</tr>
<tr>
<td>AbuRahma et al.</td>
<td>88</td>
<td>59.5</td>
<td>15</td>
<td>10 (67%)</td>
</tr>
<tr>
<td>Kakkos et al.</td>
<td>1,101</td>
<td>38</td>
<td>162</td>
<td>104 (64%)</td>
</tr>
<tr>
<td>Goliasch et al.</td>
<td>1,065</td>
<td>74</td>
<td>275</td>
<td>182 (66%)</td>
</tr>
</tbody>
</table>
mortality risk groups using independent predictors was
made in three of these\textsuperscript{16,23,26} (Table 4).

In the study by Cohen et al.\textsuperscript{16} published in 1993, three
risk factors were independent predictors of death: diabetes,
abnormal ECG results, and intermittent claudication. In the
absence of any of these risk factors, annual mortality was
5.5%. In the presence of one, two, or three factors, it was
7.5, 11.3 and 13.3%, respectively (Table 4).

In the study by Reed et al.\textsuperscript{23} published in 2003, signif-
ificant risk factors consisted of coronary bypass within 6 months,
CHF, COPD, creatinine $\geq 2.0$ mg/dL ($\geq 176.8$ \text{mmol/L}),
contralateral carotid occlusion, and age $>80$ years. In the
absence of any of these risk factors, annual mortality was
5.6%. In the presence of one, two or more factors and
contralateral carotid occlusion, annual mortality was 10.2,
10.6, and 13.2%, respectively (Table 4).

In the study by Wallaert et al.\textsuperscript{26} published in 2013, three
risk groups were established. Each covariate in the predic-
tion model was classiﬁed as either a major or minor risk
factor for mortality based on its relative contribution to the
final regression equation. Four major risk factors were
identiﬁed: age $>80$ years, insulin-dependent diabetes,
dialysis dependence, and contralateral ICA stenosis 80–
99%. Minor risk factors included age 70–80 years,
noninsulin-dependent diabetes, smoking history, CHF, COPD,
estimated glomerular ﬁltration rate $<60$ ml/min, lack of
statin therapy, contralateral ICA stenosis 50–80%, and

\textbf{Figure 4.} PRISMA 2009 flow diagram 2: cardiac-related mortality.

\textbf{Figure 5.} Forest plot of studies listed in Table 2 showing the
proportion of cardiac deaths in those that died. (Test for hetero-
genocity: $Q = 15.3$; DF 11; $P = 0.167$; $I^2 = 28.3$%; 95% CI for $I^2$ 0.00
to 63.7-random effects).

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{forest_plot.png}
\caption{Forest plot of studies listed in Table 2 showing the proportion of cardiac deaths in those that died. (Test for heterogeneity: $Q = 15.3$; DF 11; $P = 0.167$; $I^2 = 28.3$%; 95% CI for $I^2$ 0.00 to 63.7-random effects).}
\end{figure}
contralateral ICA occlusion. The high-risk group included patients with three major or two major plus two or more minor risk factors (Table 4). Patients with one major plus less than three minor risk factors were classified as medium risk, and patients with less than two minor risk factors as low risk. The annual mortality rate was 1.2% in the low-risk group (27% of the patients), 4.0% in the moderate-risk group (65% of the patients), and 9.8% in the high-risk group (5% of the patients) (Table 4). In this study, 80% of the patients were on statin therapy, but there is no indication whether treatment was to a pre-specified target.

In the two most recent studies, published in 2014, a Cox proportional hazards regression model was used to identify the independent predictors of risk. In the Kang et al. study,27 COPD (HR 1.60; 95% CI 1.42–1.82), diabetes (HR 1.60; 95% CI 1.44–1.77), and CAD (HR 1.42; 95% CI 1.29–1.56) were associated with increased mortality. Female gender (HR 0.89; 95% CI 0.81–0.98) and lipid lowering therapy (HR 0.69; 95% CI 0.63–0.76) were protective. In the Conrad et al. study,28 age (per year; HR 1.06; 95% CI 1.03–1.1), COPD (HR 1.92; 95% CI 1.08–3.41), diabetes (HR 5.08; 95% CI 2.86–9.01), and high risk for surgery (HR 2.51; 95% CI 1.44–4.41) were multivariate predictors of death. However, the authors did not report stratification into different risk groups.

DISCUSSION

The results of this systematic review and meta-analysis indicate that in patients with >50% ACS, 5- and 10-year all-cause mortality was 23% and 52.5%, respectively. Nearly two thirds (63%) of the deaths were cardiac-related.

Table 3. Risk factors and hazard ratios associated with all-cause mortality rates in patients with >50% diameter (NASCET) asymptomatic carotid stenosis (ACS) who died during follow-up.

<table>
<thead>
<tr>
<th>Risk factors</th>
<th>Mortality hazard ratio</th>
<th>Studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.5–1.8</td>
<td>Conrad et al., 2013,25 Goliasch et al., 2012,33 Conrad et al., 201428</td>
</tr>
<tr>
<td>Age &gt;70 years</td>
<td>2.2</td>
<td>Cao et al., 199920</td>
</tr>
<tr>
<td>Age 70–79 years</td>
<td>1.8</td>
<td>Wallaert et al., 201326</td>
</tr>
<tr>
<td>Age &gt;80 years</td>
<td>3.94</td>
<td>Wallaert et al., 201326</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1.63–2.3</td>
<td>Cao et al., 199920 Wallaert et al., 201326,26 Kang et al., 201427 Conrad et al., 201428</td>
</tr>
<tr>
<td>Diabetes + oral medication</td>
<td>1.34</td>
<td>Wallaert et al., 201326</td>
</tr>
<tr>
<td>Diabetes + insulin</td>
<td>1.98</td>
<td>Wallaert et al., 201326</td>
</tr>
<tr>
<td>COPD (chronic obstructive pulmonary disease)</td>
<td>1.66–5.08</td>
<td>Conrad et al., 2013,25 Wallaert et al., 201326,26 Kang et al., 201427 Conrad et al., 201428</td>
</tr>
<tr>
<td>Cardiac disease</td>
<td>1.5–1.78</td>
<td>Wallaert et al., 201326</td>
</tr>
<tr>
<td>No use of statin</td>
<td>1.27–2.1</td>
<td>Conrad et al., 2013,25 Wallaert et al., 201326</td>
</tr>
<tr>
<td>Smoking</td>
<td>1.68</td>
<td>Wallaert et al., 201326</td>
</tr>
<tr>
<td>Creatinine &gt;1.5 mg/dL</td>
<td>2.6</td>
<td>Conrad et al., 201325</td>
</tr>
<tr>
<td>eGFR &lt;60 mL/min</td>
<td>1.3</td>
<td>Wallaert et al., 201326</td>
</tr>
<tr>
<td>Dialysis</td>
<td>3.41</td>
<td>Wallaert et al., 201326</td>
</tr>
<tr>
<td>Lacunar infarcts</td>
<td>1.9</td>
<td>Cao et al., 199920</td>
</tr>
<tr>
<td>Contralateral stenosis 50–80%</td>
<td>1.23</td>
<td>Wallaert et al., 201326</td>
</tr>
<tr>
<td>Contralateral stenosis 80–99%</td>
<td>1.9</td>
<td>Wallaert et al., 201326</td>
</tr>
<tr>
<td>Contralateral occlusion</td>
<td>1.69</td>
<td>Wallaert et al., 201326</td>
</tr>
<tr>
<td>Previous vascular surgery</td>
<td>1.8</td>
<td>Kragsterman et al., 200624</td>
</tr>
<tr>
<td>Claudication</td>
<td>1.68</td>
<td>Cohen et al., 199920</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>1.42</td>
<td>Kang et al., 201427</td>
</tr>
<tr>
<td>Female gender</td>
<td>0.89</td>
<td>Kang et al., 201427</td>
</tr>
<tr>
<td>Lipid lowering agents</td>
<td>0.69</td>
<td>Kang et al., 201427</td>
</tr>
<tr>
<td>High risk for surgery</td>
<td>2.51</td>
<td>Conrad et al., 201428</td>
</tr>
</tbody>
</table>

Table 4. Annual all-cause mortality in low-, moderate-, and high-risk groups of ACS patients in studies in which mortality risk stratification was performed.

<table>
<thead>
<tr>
<th>Author and Year</th>
<th>n</th>
<th>Low-risk group % of cohort</th>
<th>Low-risk group annual mortality</th>
<th>Moderate-risk group % of cohort</th>
<th>Moderate-risk group annual mortality</th>
<th>High-risk group % of cohort</th>
<th>High-risk group annual mortality</th>
<th>Very high-risk group % of cohort</th>
<th>Very high-risk group annual mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cohen et al., 199326</td>
<td>211</td>
<td>15%</td>
<td>5.5%</td>
<td>37%</td>
<td>7.5%</td>
<td>36%</td>
<td>11.3%</td>
<td>12%</td>
<td>13.3%</td>
</tr>
<tr>
<td>Reed et al., 200323</td>
<td>1184</td>
<td>45%</td>
<td>5.0%</td>
<td>36%</td>
<td>6.6%</td>
<td>14%</td>
<td>12.2%</td>
<td>6%</td>
<td>13.4%</td>
</tr>
<tr>
<td>Wallaert et al., 201326</td>
<td>4114</td>
<td>27%</td>
<td>1.2%</td>
<td>65%</td>
<td>4.0%</td>
<td>5%</td>
<td>9.8%</td>
<td>--</td>
<td>--</td>
</tr>
</tbody>
</table>

a 80% of patients were on statins.
mainly MI or CHF subsequent to ischemic episodes. This translates to a 10-year risk of cardiac-associated mortality of 33% (average annual cardiac mortality of 3.3%).

The data also show that the 10 year all-cause mortality is double the 5-year all-cause mortality, indicating that the rate of death is the same throughout the 10-year period (average annual mortality of 5.2% for both the first and second 5-year periods).

Epidemiological studies such as Framingham and the Prospective Cardiovascular Munster Study (PROCAM) classify asymptomatic populations into low-, intermediate- and high-risk groups for cardiovascular events (stroke, MI and fatal stroke or MI). These risk groups are defined according to whether the 10-year risk is <10% (<1.0% per year), 10–20% (1.0–2.0% per year), or >20% (>2% per year), respectively. Using this classification as a reference, patients with >50% ACS are at extremely high risk.

For the age group of 65–74, which corresponds to the age group of patients in the studies listed in Table 1, the risk of death at 1 year for male individuals of the general population in England and Wales is one in 60 based on mortality statistics of 2005. This translates into an annual mortality of 1.67%, a 5-year mortality of 8.33% and a 10-year mortality of 16.7%. Thus, the 5-year all-cause mortality of 23% shown by the meta-analysis in patients with ACS is three times higher than the mortality for the general population of the same age.

In the year 2000, CAD accounted for 25% of all deaths for age groups 60–69 and 70–79 in the UK. In the year 2010, CAD accounted for 18% for age group 60–69 and 21% for age group 70–79. These national statistics indicate that the deaths from CAD in patients with ACS found in this meta-analysis are three times higher than the general population of the same age.

In addition, this meta-analysis suggests that the high mortality in patients with ACS has not declined during the last 30 years, despite a decline in annual stroke rates. Fig. 4 shows a trend which is not statistically significant. This is in contrast with the decline in both all-cause mortality by 45% and CAD mortality by 30% observed in the UK general population of the same age during the period of 1990–2010.

Only the four most recently published studies, mentioned that a proportion of patients were on statins, but there is no information about whether these patients were treated to a pre-specified LDL-C target. It is also not clear whether patients were treated with statins in the rest of the publications included in this review and published prior to 2007.

In the present review, only three studies were identified that proposed scoring systems for better risk stratification of patients with ACS. Annual mortality of 1.2% per year was found in the low-risk subgroup consisting of 27% of the patients of one study (Table 4). It included patients without any risk factors and most were taking statins. In all other subgroups, patients had a mortality >4.0% per year. In terms of cardiac mortality this figure translates into 2.7% per year or more.

The 2013 ACC/AHA guidelines recommend that non-diabetic individuals without clinical (i.e. symptomatic) ASCVD and an LDL-C of 70–189 mg/dL (1.8–4.9 mmol/L) should be treated aggressively with statins in addition to other risk factor modifications when the 10-year risk of ASCVD is >7.5% (average annual risk >0.75%). The rationale provided by the ACC/AHA Expert Panel for this approach is as follows. RCTs show that ASCVD events are reduced by using the maximum tolerated statin intensity in those groups shown to derive benefit. For asymptomatic patients (primary prevention) RCTs have shown that for those with LDL-C levels of 70–189 mg/dL (1.8–4.9 mmol/L) and a 10-year risk of ASCVD >7.5% (average annual risk >0.75%), statin therapy produces a substantial reduction not only in non-fatal ASCVD events but also in total mortality. In the Cochrane meta-analysis of 14 RCTs of statin therapy in primary prevention, statins were associated with a 28% reduction in fatal and non-fatal CAD events (RR 0.72; 95% CI 0.65–0.79), a 22% reduction in fatal and non-fatal stroke (RR 0.78; 95% CI 0.65–0.94), and a 17% reduction in overall mortality (RR 0.83; 95% CI 0.73–0.95). In addition, the absolute benefit was found to be higher in those at higher baseline risk.

The 2013 ACC/AHA guidelines define intensity of statin therapy on the basis of the average expected LDL-C reduction. High-intensity statin therapy lowers LDL-C by ≥50%, moderate-intensity by 30–<50%, and low-intensity by <30%. There is high-level evidence from RCTs that high-intensity therapy is achieved with atorvastatin 40–80 mg daily or rosuvastatin of at least 20 mg, and that high-intensity therapy reduces the ASCVD risk more than moderate-intensity therapy achieved with atorvastatin 10 mg, pravastatin 40 mg, or simvastatin 20–40 mg daily.

On the basis of the high cardiac-related mortality and the 2013 ACC/AHA guidelines it seems appropriate that all patients with ACS >50% should receive high-intensity statin therapy, because even the lowest identifiable risk group has an annual risk >0.75%.

Screening for ACS in the past was based on the belief that it was possible to prevent strokes by operating or stenting most moderate to severe stenotic lesions. This practice, a legacy of the ACAS and ACST, is now outdated. With a current annual stroke risk of ≤1%, this practice is likely to produce more strokes than it can prevent, unless it becomes possible to identify the minority of patients at high risk (>2% per year) for ipsilateral stroke despite optimal medical therapy.

Currently, the finding of an ACS >50% (or even atherosclerotic plaques producing ACS <50%) carries a new message. It identifies individuals at high risk for all atherosclerotic arterial disease manifestations, including CAD-related mortality, who may then benefit from high-intensity statin therapy according to current guidelines for high-risk individuals.

A limitation of the present review is that CEA was performed in most studies prior to follow-up, with only five studies on medical therapy alone. However, a separate
meta-analysis performed in these two groups of studies demonstrated similar 5-year mortality rates.

A second limitation of this review is that there is limited information on statin therapy, and many confounding factors such as other medications, smoking, and diabetes were not available in many of the studies retrieved so adjustments could not be made for them. The various confounding factors and selection of patients in the different studies may be responsible for the heterogeneity on the mortality reported. However, despite this heterogeneity, the 5-year all-cause mortality is high in almost all patients (Table 4).

A third limitation on the appropriateness of the available guidelines for patients with ACS >50% is that their conclusions are based on RCTs evaluating the efficacy of statins in asymptomatic individuals at high cardiovascular risk irrespective of the presence or absence of ACS >50%. The only criterion available for applying the new guidelines to patients with ACS is the high cardiac risk.

For absolute values of cardiac events in patients with ACS on “best” medical treatment, the results of future prospective cohort studies are awaited, such as ACSR-S-OMT (Asymptomatic Carotid Stenosis and Risk of Stroke — Optimal Medical Therapy) or medical arms of randomized studies such as CREST (Carotid Revascularization Endarterectomy versus Stenting Trial). These values will depend on just how intensive the medical therapy will be and how well coexisting silent preclinical CAD is investigated and treated.

CONCLUSIONS

All-cause mortality and cardiac mortality in patients with ACS are very high. They appear to remain high despite the reduction observed in the general population during the last 20 years. Although risk factors have been identified and risk stratification is possible, most patients are classified as high risk. In view of this high risk, aggressive statin therapy is indicated if the new ACC/AHA guidelines on serum lipids are to be adhered to.

CONFLICT OF INTEREST

DPM has given talks, attended conferences, and participated in trials and advisory boards sponsored by MSD.

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REFERENCES


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