Risk of Stroke After Coronary Artery Bypass Grafting
Effect of Age and Comorbidities

Charlotte Mérie, MD; Lars Køber, MD, DMSc; Peter Skov Olsen, MD, DMSc; Charlotte Andersson, MD; Jan Skov Jensen, MD, PhD, DMSc; Christian Torp-Pedersen, MD, DMSc

Background and Purpose—The risk of stroke after coronary artery bypass grafting (CABG) is known to increase dramatically with age. During recent years, the age of patients operated on has increased and concomitant therapy has changed. Therefore, we have re-evaluated the risk of stroke after CABG.

Methods—Through the Danish National Hospital Register, we identified all 25 159 patients with isolated CABG from 1997 through 2006. Stroke, comorbidities, and medication were further obtained. Risk factors of stroke were determined through regression models.

Results—Overall, 1901 patients (7.6%) suffered a stroke after surgery, 477 patients (2.0%) within 30 days after CABG. Rates of stroke per 100 person-years (95% CI) within 30 days after surgery increased with age: <60 years, 10.1 (7.8–13.0); 60 to 64 years, 18.4 (14.3–23.5); 65 to 69 years, 27.7 (23.0–33.3); 70 to 74 years, 36.0 (30.4–42.6); 75 to 79 years, 36.1 (29.1–44.7); ≥80 years, 38.0 (25.2–57.1). Risks of stroke within 30 days after surgery adjusted for age (reference: age <60 years), sex, relevant comorbidities, and selected medication included: 60 to 64 years: HR, 1.7 (P=0.005; 95% CI, 1.2–2.4), 65 to 69 years: HR, 2.4 (P=0.001; 95% CI, 1.7–3.3), 70 to 74 years: HR, 2.8 (P=0.001; 95% CI, 2.1–3.8), 75 to 79 years: HR, 2.8 (P=0.001; 95% CI, 2.0–4.0), ≥80 years: HR, 3.0 (P=0.001; 95% CI, 1.8–4.9), previous stroke: HR, 4.2 (P=0.001; 95% CI, 3.3–5.4), diabetes: HR, 1.3 (P=0.019; 95% CI, 1.1–1.7), hypertension: HR, 1.4 (P=0.003; 95% CI, 1.1–1.7), peripheral vascular disease: HR, 1.6 (P=0.001; 95% CI, 1.3–2.1), renal failure: HR, 1.7 (P=0.012; 95% CI, 1.1–2.5), statins: HR, 0.8 (P=0.049; 95% CI, 0.7–1.0), clopidogrel: HR, 0.6 (P=0.032; 95% CI, 0.4–1.0).

Conclusions—The increase in stroke with age after CABG is moderate and the relation uncertain in ages older than 70 years. Declining CABG in elderly patients because of risk of stroke purely on the basis of high age is debatable. (Stroke. 2012;43:38-43.)

Key Words: aging ■ atherosclerosis ■ CABG ■ epidemiology ■ risk factors

See related article, page 3.

Since Roach et al published their article on this subject in 1996, the average age of patients referred to cardiac surgery has increased steadily and many aspects of treatment have changed, eg, off-pump surgery and more effective antithrombotic drugs. Because of the risk of stroke and other adverse events, there is reluctance to refer old patients for cardiac surgery, as reflected by the EuroSCORE system,8 a risk stratifying tool, commonly applied by clinicians in selecting suitable candidates for surgery. However, changing therapies may have modified the age-dependent risk of stroke, and the scope of the current study is to assess the significance of increasing age of patients on the risk of developing perioperative stroke after CABG. This study is based on all 25 159 patients who underwent CABG in Denmark during the period from January 1, 1997 to December 31, 2006.
Methods

We used national administrative registries to identify all patients subjected to CABG performed between January 1997 and December 2006, a total of 25 159 patients. Included were only patients who had no previous cardiothoracic procedure performed. A diagnosis of stroke was assumed when recorded in the National Hospital Register (International Classification of Diseases, 10th revision) as codes I61, I62, I63, and I64 types A and B. These diagnoses of stroke have proven to be valid, with positive predictive values of 74% to 97%. Strokes were classified as previous strokes when recorded before the date of the first bypass procedure. Information on comorbidities was identified in a similar way as was the data on stroke, available at http://stroke.ahajournals.org.

Diabetes was considered present when patients used glucose-lowering medication as recorded in the National Prescription Register. Pharmacies in Denmark are obliged to register all prescriptions dispensed as documentation to the Danish Health Care System, which partially reimburses drug expenses for all inhabitants. Medication obtained from other sources was minimal and, therefore, complete registration was ensured. Similarly, concomitant medication within 3 months preoperatively was obtained. The timing of events was known from the date of the diagnostic codes in relation to the date of surgery, and so preoperative and postoperative events could accurately be discriminated.

All analyses were performed using SAS Software (version 9.2, SAS Institute) and STATA (version 10.1, StataCorp). The impact of independent variables on stroke and mortality was assessed using logistic or Cox regression in STATA. The cumulative risk of stroke was calculated, adjusting for competing risk. Statistical significance was defined as \( P < 0.05 \), and all probability values reported were 2-sided. The term relative risk (RR) refers to odds ratios (OR) in logistic models and hazard ratios (HR) in Cox models. Interaction terms are reported when significant. There was no interaction between age and other variables and cardiothoracic center, indicating similar risk in all 5 Danish centers.

The use of personal data in this study was authorized by the Danish Data Protection Agency. There are no requirements for ethical approval for retrospective registry studies in Denmark. All authors have had full access to, and taken full responsibility for, the integrity of the data. All authors have read and agreed to the manuscript as written.

Results

From a baseline population of 4 366 406 individuals in Denmark alive and age \( \geq 18 \) years on January 1, 1997, 25 159 individuals underwent CABG during the next decade, i.e., from 1997 to the end of 2006. Among the patients, 19 933 were men and 5226 were women, with a mean age of 64.7 years (range, 26–96 years). The demographic and clinical characteristics for the patients with and without stroke after surgery are shown in Table 1.

Overall, 1901 of patients (7.6%) suffered a stroke event after the date of surgery; 477 patients had a stroke within 30 days after isolated CABG, representing 2.0% of patients. Within that 30-day postoperative period, 25.1% of all stroke events occurred (Table 1).

The association between stroke and age in absolute, as well as in relative, terms is illustrated in Figure 1 and 2, respectively. Figure 1 shows the estimated age-related rates of stroke within 30 days after CABG per 100 person-years; whereas Figure 2, adjusting for observation time, illustrates the RR with 95% CI in different age groups of having a stroke event within 30 days after CABG. Finally, Figure 3 shows the cumulative incidence of stroke adjusted for competing risk during the year after CABG within different age groups.

During a total study time of 119 215 person-years, 17.1% of patients (4302) died. Of these, 78.8% deaths (3391) were related to cardiovascular disease in general; 8.3% of deaths (356) were stroke-related, whereas 18.5% of deaths (797) were caused by myocardial infarction. Forty-three patients died on the date of surgery, whereas 648 patients died within the next month. Of these deaths, 97% (630) were caused by cardiovascular disease: 35.5% of patients (230) died from myocardial infarction and 8.9% of patients (58) died from stroke. Furthermore, the proportion of fatal strokes seemed to increase with age from 8% (28/345) among patients age \( < 60 \) years to 43% (29/67) among patients age \( > 80 \) years. We found a 2.2-fold increase in mortality among patients with perioperative stroke as compared with patients without stroke. Patients with stroke \( < 30 \) days after surgery had 3.9 times higher risk of death within the next year and 2.3 times higher risk of death overall than did patients without stroke in \( < 30 \) days. Similarly, patients with stroke within 30 days after surgery had 12.7 times higher risk of stroke-related death than did patients without stroke 30 days postoperatively. We tested the association between stroke and/or mortality and age, sex, relevant comorbidities, and selected medication, as well as the relationship between these same covariates and mortality alone (Table 2).

Discussion

We found an incidence of postoperative stroke of 2.0% within 30 days after CABG and 3.0% within 1 year after CABG; this was comparable with incidences for isolated CABG shown by other studies of smaller size, in which incidences of stroke ranged from 0.8% to 6.1%.\(^{3–8}\) Assessing the association between stroke before 30 days after isolated CABG and age (Figure 1), the incidence rate of stroke increased from 10 per 100 person-years from age 55 years to 36 per 100 person-years from 70 years of age and older. Similarly, the risk of stroke (Figure 2) increased by a factor of 1.9 from RR, 1.8; 95% CI, 1.3 to 2.6 (\( P = 0.001 \)) at the age of 60 years, to RR, 3.5; 95% CI, 2.6 to 4.8 (\( P = 0.001 \)) at 70 years of age. In age greater than 70 years, both the incidence rate and the risk of stroke ceased to increase. This finding was contrary to that in other studies,\(^{7,11–13}\) including the study by Roach,\(^3\) who demonstrated an almost exponential increase in the incidence of stroke with age, with an 8-fold increase in the incidence from age 50 to \( > 80 \) years.

A number of studies addressed the outcome of CABG in elderly patients, with special emphasis on octogenarians.\(^{14}\) In general, most studies showed a higher risk of stroke and mortality in this patient group compared with younger patients, with adjusted differences in mortality decreasing over time.\(^{15}\) Authors of these studies recommended consideration of the trade-off between increased early risks in return for improved long-term survival after CABG.\(^{16}\) Discrepancies arose as to which functional impact of surgery is acceptable in patients.\(^{17}\) However, the majority of these studies have been based on low patient numbers, especially regarding elderly patients.

When evaluating the risk of stroke over time, the cumulative incidence of stroke (Figure 3) increased rapidly during the first 30 days postoperatively, representing the impact of
surgery on the risk of stroke. Beyond this time period, it became increasingly unlikely that a novel stroke was triggered by the performed procedure, and the resulting curves most likely imitated the rate of stroke imposed by the continuing progression in the atherosclerotic process. Consistent with other studies,2,5,6,8,18–21 we found previous stroke, diabetes, hypertension, peripheral vascular disease, and renal failure to be significant risk factors for stroke within 30 days after CABG (Table 2), whereas female sex, unstable angina pectoris, previous myocardial infarction, congestive heart failure, peripheral vascular disease, and renal failure increased the risk of overall 30-day mortality.

Previous stroke was found to be a risk factor for stroke within 30 days after surgery, but it was not a predictor of 30-day mortality. Beyond this time period, it became increasingly unlikely that a novel stroke was triggered by the performed procedure, and the resulting curves most likely imitated the rate of stroke imposed by the continuing progression in the atherosclerotic process. Consistent with other studies,2,5,6,8,18–21 we found previous stroke, diabetes, hypertension, peripheral vascular disease, and renal failure to be significant risk factors for stroke within 30 days after CABG (Table 2), whereas female sex, unstable angina pectoris, previous myocardial infarction, congestive heart failure, peripheral vascular disease, and renal failure increased the risk of overall 30-day mortality.

Table 1. Clinical characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Patients With Stroke &lt;30 d After Surgery</th>
<th>Patients Without Stroke &lt;30 d After Surgery</th>
<th>All Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>n</td>
<td>%</td>
<td>n</td>
</tr>
<tr>
<td>Age at surgery</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;70 y</td>
<td>242</td>
<td>50.7</td>
<td>8285</td>
</tr>
<tr>
<td>&lt;60 y</td>
<td>69</td>
<td>14.7</td>
<td>7171</td>
</tr>
<tr>
<td>60 to 64 y</td>
<td>63</td>
<td>13.2</td>
<td>4206</td>
</tr>
<tr>
<td>65 to 69 y</td>
<td>113</td>
<td>27.9</td>
<td>5020</td>
</tr>
<tr>
<td>70 to 74 y</td>
<td>134</td>
<td>28.1</td>
<td>4599</td>
</tr>
<tr>
<td>75 to 79 y</td>
<td>85</td>
<td>17.8</td>
<td>2911</td>
</tr>
<tr>
<td>≥80 y</td>
<td>23</td>
<td>4.8</td>
<td>775</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>355</td>
<td>74.4</td>
<td>19578</td>
</tr>
<tr>
<td>Women</td>
<td>122</td>
<td>25.6</td>
<td>5104</td>
</tr>
<tr>
<td>Comorbidity*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prior stroke</td>
<td>113</td>
<td>23.7</td>
<td>1161</td>
</tr>
<tr>
<td>Diabetes</td>
<td>101</td>
<td>21.2</td>
<td>3613</td>
</tr>
<tr>
<td>Prior myocardial infarction</td>
<td>266</td>
<td>55.8</td>
<td>12746</td>
</tr>
<tr>
<td>Unstable angina pectoris</td>
<td>113</td>
<td>23.7</td>
<td>5511</td>
</tr>
<tr>
<td>History of atrial fibrillation</td>
<td>71</td>
<td>4.9</td>
<td>2515</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>85</td>
<td>17.8</td>
<td>2802</td>
</tr>
<tr>
<td>Hypertension</td>
<td>185</td>
<td>38.8</td>
<td>6401</td>
</tr>
<tr>
<td>COPD</td>
<td>31</td>
<td>6.5</td>
<td>1129</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>68</td>
<td>14.3</td>
<td>1647</td>
</tr>
<tr>
<td>Renal failure</td>
<td>27</td>
<td>5.7</td>
<td>598</td>
</tr>
<tr>
<td>Concomitant medication†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Statins</td>
<td>206</td>
<td>43.2</td>
<td>11998</td>
</tr>
<tr>
<td>Beta blockers</td>
<td>252</td>
<td>52.8</td>
<td>13997</td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td>172</td>
<td>36.1</td>
<td>7609</td>
</tr>
<tr>
<td>Loop diuretics</td>
<td>104</td>
<td>21.8</td>
<td>3864</td>
</tr>
<tr>
<td>Spironolacton</td>
<td>17</td>
<td>3.6</td>
<td>718</td>
</tr>
<tr>
<td>Thiazid diuretics</td>
<td>71</td>
<td>14.9</td>
<td>2383</td>
</tr>
<tr>
<td>Calcium antagonists</td>
<td>204</td>
<td>42.8</td>
<td>8559</td>
</tr>
<tr>
<td>Digoxin</td>
<td>22</td>
<td>4.6</td>
<td>948</td>
</tr>
<tr>
<td>Aspirin</td>
<td>153</td>
<td>32.1</td>
<td>8300</td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>26</td>
<td>5.5</td>
<td>1855</td>
</tr>
<tr>
<td>Warfarin</td>
<td>20</td>
<td>4.2</td>
<td>552</td>
</tr>
<tr>
<td>Phenprocoumon</td>
<td>5</td>
<td>1.1</td>
<td>87</td>
</tr>
<tr>
<td>Dipyridamol + Aspirin combined</td>
<td>8</td>
<td>1.7</td>
<td>61</td>
</tr>
<tr>
<td>Dipyridamol</td>
<td>40</td>
<td>8.4</td>
<td>479</td>
</tr>
</tbody>
</table>

COPD indicates chronic obstructive pulmonary disease; ACE, angiotensin-converting enzyme.

*Comorbidities registered from date of surgery and 18 y preoperatively from the beginning of the National Patient Registry in 1978.
†Medical treatment registered within 3 mo preoperatively.
mortality. This might on the surface contradict EuroSCORE’s use of neurological dysfunction as an indicator of 30-day mortality, but EuroSCORE uses neurological dysfunction to include a condition severely affecting ambulation or day-to-day functioning; this differs substantially from previous stroke, which includes many patients with no or few sequelae. Furthermore, this study cannot be expected to confirm the risk values used in the EuroSCORE system, simply because EuroSCORE was applied in selecting patients for surgery to reduce mortality. Unstable angina pectoris and previous myocardial infarction were not associated with increased risk of stroke. This may be explained by the fact that patients undergoing CABB have had severe coronary atherosclerosis and myocardial infarction, thus blurring such an association. As a contrast, peripheral vascular disease was only present in some of our patients and appeared as a risk factor in this study, indicating the presence of more generalized atherosclerosis than in the average patient in this study.

In contrast to other studies, we found no indication of chronic obstructive pulmonary disease (COPD) being a risk factor for postoperative stroke. This is rather surprising given that hypercapnia associated with COPD is known to induce subsequent changes in cerebral vasoreactivity, which we would expect to have an influence on stroke risk. Furthermore, we did not find COPD to be predictive of postoperative mortality. There may be a selection bias among this patient group given that patients with severe COPD may be rejected as surgical candidates because of concerns about survival; this may explain why COPD is neither a risk factor for postoperative stroke nor for postoperative mortality.

The interpretation of medication data were complex, given that it widely reflected underlying morbidity; for instance, thiazid and calcium antagonists were more likely markers of underlying hypertension, rather than risk factors of stroke per se (Table 2). Nevertheless, we found a possible protective effect of statins (HR, 0.8; \( P = 0.049; 95\% \) CI, 0.7–1.0) on the risk of stroke within 30 days after CABB. Previously, statins have been shown to attenuate thrombotic potential through decreased vascular smooth muscle proliferation, stabilization of atherosclerotic plaques, and inhibition of platelet aggregation, among other ways. Given that stroke in relation to bypass surgery has been suggested to occur as a result of mechanical manipulation of the aorta, we would expect the protective effect of statins on stroke to be more predominant as the adverse effect of surgery ceased. Accordingly, we found a significant protective effect of statins on stroke within 1 year after surgery (HR, 0.8; \( P = 0.031; 95\% \) CI, 0.7–1.0), comparable to findings in other studies. Nevertheless, a large-scale randomized clinical trial has yet to determine the protective effect of statins on stroke. In general, patients with postoperative stroke had significantly higher mortality rates compared with patients without this complication. We found a 3.9-fold increase in 1-year mortality among patients with perioperative stroke as compared with patients without stroke, whereas similar
studies 1–2,26 reported 3- to 10-fold increases in mortality in the presence of perioperative stroke. Studies on long-term mortality reported a greater risk of death within the first year of surgery, whereas survival after 1 year approximated that of patients who did not suffer a stroke.1

Limitations
Because of a lack of information, we were not able to retrieve data on the location or the type of stroke in question. Similarly, we did not have data on the presence or the degree of aortic atherosclerosis. Imaging studies of the aorta were not routinely performed preoperatively in Denmark. The EuroSCORE system9 was widely used as a risk-stratifying tool among cardiothoracic surgeons in selecting patients suitable for surgery. The system acknowledged age to be a risk factor, assigning the score of 1 for every 5 years above 60, which implied a distortion of patients’ preprocedural risk profiles within age groups. We had no information on the number of patients who were rejected for CABG on the basis of age criteria, and we did not have any knowledge on patients’ preoperative EuroSCORE. Furthermore, we were not able to assess possible differences between neurological outcome after on-pump versus off-pump CABG because of inconsistent registration among surgeons; this reflects that the use of extracorporal circulation is administered by the perfusionist, but the coding is left to the surgeon, which is why
registering procedure codes concerning the use of extracorporeal circulation may be overlooked. As opposed to extracorporeal circulation coding, the coding of surgical procedures is carefully described, reflecting that the surgeon is keen on registering his/her procedure properly, given that it reflects his/her work and acts as documentation of his/her experience.

Conclusions

The studies by Roach et al and others have increased the awareness of careful selection of elderly people for CABG to reduce the risk of stroke. This study shows that by applying EuroSCORE criteria in selecting suitable candidates for CABG, the risk of stroke among patients age >70 years has been reduced to a constant rate, rather than representing an exponential increase as previously demonstrated by Roach and other authors. This applies to the age groups of 70 to 74 years, 75 to 79 years, and ≥80 years. Furthermore, our data suggest that the risk of stroke after CABG in patients age >70 years is not caused by age per se, but rather is a consequence of the burden of atherosclerosis; in our study this was expressed by comorbidities such as previous stroke, diabetes, hypertension, peripheral vascular disease, and renal failure.

Disclosures

None.

References

Risk of Stroke After Coronary Artery Bypass Grafting: Effect of Age and Comorbidities
Charlotte Mérie, Lars Køber, Peter Skov Olsen, Charlotte Andersson, Jan Skov Jensen and Christian Torp-Pedersen

Stroke. 2012;43:38-43; originally published online October 27, 2011;
doi: 10.1161/STROKEAHA.111.620880

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/43/1/38

Data Supplement (unedited) at:
http://stroke.ahajournals.org/content/suppl/2011/11/01/STROKEAHA.111.620880.DC1
http://stroke.ahajournals.org/content/suppl/2012/08/14/STROKEAHA.111.620880.DC2

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Stroke can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Stroke is online at:
http://stroke.ahajournals.org//subscriptions/
Supplemental Table S1. Diagnosis codes used for retrieving data on comorbidities.

**Myocardial infarction:** ‘I21’, ‘I22’, ‘410’.

**Unstable angina pectoris (UAP):** ‘I20.0’.

**Previous atrial fibrillation:** ‘I48’, ‘4274’.


Risk of Stroke After Coronary Artery Bypass Grafting
Effect of Age and Comorbidities

Charlotte Mérie, MD; Lars Køber, MD, DMSc; Peter Skov Olsen, MD, DMSc;
Charlotte Andersson, MD; Jan Skov Jensen, MD, PhD, DMSc; Christian Torp-Pedersen, MD, DMSc
(Stroke. 2012;43:38-43.)

Key Words: aging ■ atherosclerosis ■ CABG ■ epidemiology ■ risk factors

Risk of Stroke After Coronary Artery Bypass Grafting (CABG). Baseline group: patients <60 years of age.

Cumulative risk of stroke after coronary artery bypass grafting (CABG).