Age effects of coronary artery bypass graft on cognitive status change among elderly male twins
Neurology 2004;63;2245
DOI 10.1212/01.WNL.0000147291.49404.0A

This information is current as of April 3, 2013

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://www.neurology.org/content/63/12/2245.full.html
Age effects of coronary artery bypass graft on cognitive status change among elderly male twins

G.G. Potter, PhD; B.L. Plassman, PhD; M.J. Helms, BS; D.C. Steffens, MD, MHS; and K.A. Welsh-Bohmer, PhD

Abstract—Background: Research regarding long-term cognitive outcome following coronary artery bypass graft (CABG) is inconsistent, which may be due in part to differential genetic and environmental influences within most study samples. Methods: The authors examined the effect of CABG on cognitive status change scores in members of the National Academy of Sciences–National Research Council Twins Registry of World War II veterans. Subjects were administered the modified Telephone Interview for Cognitive Status (TICS-m) at approximately 3-year intervals between 1990 and 2002 as part of an epidemiologic study of dementia. Results: Based on co-twin control analyses using a repeated-measures analysis of variance matching twins discordant for CABG within the pair (n = 464 individuals) across three age categories (63 to 70, 71 to 73, 74 to 83), the authors found at follow-up that men who had CABG between ages 63 and 70 showed an increase in TICS-m scores and performed better than their co-twin who did not have the procedure. No significant differences were found within twin pairs for the older two age groups following CABG surgery. This age effect was replicated when comparing individuals positive for CABG surgery with nonfamilial, age- and education-matched controls who were negative for CABG. Conclusions: In this study of twin pairs who share many genetic and environmental risks for cerebrovascular problems, the results suggest that timing of the CABG procedure may be important to predicting positive cognitive outcomes.
of time between pre- and post-CABG assessment for the study status scores for the same assessment waves as their twin. Individuals who pre- and post-CABG. Co-twins had to be negative for the CABG assessment waves, thus providing cognitive status scores both reported a CABG procedure during the period between any two pairs included in this study were those in which one member CABG surgery and follow-up administration of the TICS-m was measured. These were repeated-measures analyses. Co-twin control analyses to compare the mean change in TICS-m scores in twin pairs discordant for CABG, both for the entire sample and also using age as a between-group variable. These were repeated-measures analyses of variance blocked by twin pair, with repeated (within-group) measures that included 1) TICS-m scores pre- and post-CABG and 2) CABG history categorized as positive vs negative for this procedure. To analyze age as a between-group variable, we divided the sample into three categories (63 to 70, 71 to 73, 74 to 82) that were empirically derived prior to analysis to produce approximately equal numbers for each group. Interactions of the repeated measures with age group were included as well. In addition to these principle analyses, we conducted an analysis to assess possible effects of pre-existing cerebrovascular risk factors on our results. We also examined the role of education on CABG outcome. Finally, we conducted the main analyses described above pairing individuals positive for CABG surgery with non-familial, CABG-negative controls from the Twins Study database who were matched on age, education, and pre-CABG TICS-m score.

Methods. Participants. The participants in this study were enrolled in the Duke Twins Study of Memory in Aging, and were members of the National Academy of Sciences–National Research Council (NAS-NRC) Registry of World War II veteran male twins. As part of the Duke Twins Study of Memory in Aging, surviving and consenting twin pairs were administered a telephone cognitive status measure every 3 to 4 years beginning in 1990 as part of a screening and assessment protocol for dementia. During the waves of data collection spanning 1996 through 2002, additional information was obtained on medical history, including CABG surgery and year of surgery, if applicable. This information was collected directly from the participant in most cases, and from a proxy informant if the participant was unable to respond due to cognitive, medical, speech, or hearing disorder. Approximately 7% of the participants had at least some information collected by proxy. The telephone screenings were administered by professional organizations using a standardized protocol. Those who administered the interview were trained to identify and minimize distractions and third-person participation during modified Telephone Interview for Cognitive Status (TICS-m) administration. The TICS-m was administered before information was collected about health history, so interviewers were effectively blinded to the participant’s CABG status. Participants completed the telephone screening with different interviewers at each assessment wave.

Participant selection. The study sample included 232 twin pairs (mean age at baseline TICS-m = 69.40, SD = 3.21), 95 of which were monozygotic. Zygosity was determined from NAS-NRC Twins Registry data based on best available information from questionnaire responses, fingerprint analysis, and anthropometric data from military records.9 Methods of establishing zygosity are estimated by cross-validation to be 95% correct.9 Twin pairs included in this study were those in which one member reported a CABG procedure during the period between any two assessment waves, thus providing cognitive status scores both pre- and post-CABG. Co-twins had to be negative for the CABG procedure (i.e., twin-pair discordant for CABG) and have cognitive status scores for the same assessment waves as their twin. Individuals with suspected dementia were excluded. The mean length of time between pre- and post-CABG assessment for the study sample was 3.75 years (SD = 0.83). The mean latency between CABG surgery and follow-up administration of the TICS-m was 1.41 years based on data for the year in which CABG surgery occurred.

Modified Telephone Interview for Cognitive Status. The original TICS instrument10 and its modified form11 provide a brief assessment of cognitive function that can be administered via telephone as part of a cognitive status screening. The TICS-m is modeled after the Mini-Mental State Examination (MMSE), but enhances its content with the inclusion of immediate and delayed recall of a 10-item word list. It produces scores ranging from 0 to 50, and is highly correlated with the MMSE.12 Although participants may have completed the TICS-m during as many as four assessment waves, the only two TICS-m scores included in the current study were those from the waves that occurred directly before and after the proband’s CABG surgery.

Statistical methods. We used co-twin control analyses to compare the mean change in TICS-m scores in twin pairs discordant for CABG, both for the entire sample and also using age as a between-group variable. These were repeated-measures analyses of variance blocked by twin pair, with repeated (within-group) measures that included 1) TICS-m scores pre- and post-CABG and 2) CABG history categorized as positive vs negative for this procedure. To analyze age as a between-group variable, we divided the sample into three categories (63 to 70, 71 to 73, 74 to 82) that were empirically derived prior to analysis to produce approximately equal numbers for each group. Interactions of the repeated measures with age group were included as well. In addition to these principle analyses, we conducted an analysis to assess possible effects of pre-existing cerebrovascular risk factors on our results. We also examined the role of education on CABG outcome. Finally, we conducted the main analyses described above pairing individuals positive for CABG surgery with non-familial, CABG-negative controls from the Twins Study database who were matched on age, education, and pre-CABG TICS-m score.

Results. Mean age at time of TICS-m administration, mean years of education, and mean TICS-m scores are presented in table 1. 

Based on co-twin control analysis of the entire sample, we found that the mean change in TICS-m scores within twin pairs discordant for CABG was not significantly different for individuals who had undergone this procedure relative to their co-twin who had not. Our analysis for age effects, however, tested the interaction of CABG status and age at CABG surgery on TICS-m change and found an interaction effect of age group and CABG history, $F(2,229) = 4.55$, $p = 0.0116$ (figure). In the pairwise comparisons, the youngest group of individuals (age 63 to 70) demonstrated an increase in mean TICS-m score following CABG surgery relative to their co-twin who did not have the procedure ($p = 0.0024$). No difference was found between pairs in the two older age groups (age 71 to 73, $p = 0.6671$; age 74 to 82, $p = 0.3917$). This pattern remained when monozygotic and dizygotic pairs were analyzed separately.

We used an analysis of variance dependent on twin pairing to examine whether differences in follow-up intervals contributed to the observed effects of age group and CABG status. We found no significant interaction between CABG status and age group based on variations in time elapsed between pre- and post-CABG administration of the TICS-m.

Because a number of cerebrovascular risk factors can potentially affect cognitive status and CABG outcome, we examined several self-reported medical conditions to assess possible effects of these conditions on our results. These conditions were 1) stroke, 2) hypertension, 3) elevated cholesterol, 4) heart attack, and 5) congestive heart failure. We compared whether the ratio in which these conditions occurred between CABG and non-CABG individuals varied as a function of age group. Based on Mantel-Haenszel tests for combined effects and for heterogeneity, we found that none of these conditions were associated with differential age-group effects of TICS-m change (table 2). 

Based on the idea that higher levels of education may have a differential effect on cognitive status, we conducted additional education-stratified analyses of TICS-m change following CABG. To maintain twin pairing by approximate education level, probands whose education level differed from their co-twin by more than 2 years were deleted from this analysis, which reduced the sample by approximately one-third ($n = 160$). Twin pairs with education at or above 14 years were compared with twin pairs obtaining less than 14 years on the variables of CABG status, TICS-m change, and age group. To evaluate whether education
level might affect outcome, dichotomized education categories were added to the original model, including all interactions. None of the effects involving education approached statistical significance, suggesting that the pattern of improvement on TICS-m among probands aged 63 to 70 following CABG surgery was consistent across both education groups.

Finally, we sought to assess whether our findings of non-significant change in TICS-m scores in the two older age groups following CABG surgery were due to strong genetic and environmental similarities that masked actual differences between proband and co-twin. To this end we constructed a separate independent control group matched on age, education, and baseline TICS-m score; appropriate matches were not available for 10 probands.

Table 1 Mean values for age, years of education, and pre- and post-TICS-m scores grouped by twin-paired and case-control samples

<table>
<thead>
<tr>
<th>Pairs</th>
<th>63–70</th>
<th>71–73</th>
<th>74–83</th>
</tr>
</thead>
<tbody>
<tr>
<td>Twin pairs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CABG No</td>
<td>82</td>
<td>87</td>
<td>63</td>
</tr>
<tr>
<td>Age, y</td>
<td>66.02 (1.85)</td>
<td>69.93 (1.15)</td>
<td>73.03 (1.96)</td>
</tr>
<tr>
<td>Education, y</td>
<td>13.67 (2.86)</td>
<td>13.80 (3.05)</td>
<td>14.05 (2.93)</td>
</tr>
<tr>
<td>Pre-TICS-m</td>
<td>34.32 (3.33)</td>
<td>33.62 (4.52)</td>
<td>33.93 (4.34)</td>
</tr>
<tr>
<td>Post-TICS-m</td>
<td>33.45 (4.18)</td>
<td>32.24 (5.12)</td>
<td>32.29 (4.93)</td>
</tr>
</tbody>
</table>

Non-familial (control) pairs

| CABG No     | 81    | 84    | 57    |
| Age, y      | 66.05 (1.82) | 69.81 (1.27) | 72.82 (1.89) |
| Education, y| 13.65 (2.98) | 14.13 (2.57) | 14.13 (2.57) |
| Pre-TICS-m  | 34.33 (4.32) | 34.23 (4.14) | 34.34 (4.49) |
| Post-TICS-m | 33.70 (5.24) | 33.01 (4.34) | 32.81 (4.24) |

Age bands are expressed by mean age at time of proband’s CABG surgery (unadjusted SD). Age = age at pre-TICS-m administration. Non-familial controls were matched to probands on age (±1 year), education, and baseline TICS-m score; appropriate matches were not available for 10 probands.

TICS-m = Telephone Interview for Cognitive Status–modified; CABG = coronary artery bypass grafting.

Table 2 Cerebrovascular risk conditions diagnosed prior to CABG surgery

<table>
<thead>
<tr>
<th>Age, y</th>
<th>CABG</th>
<th>CHF</th>
<th>Cholest.</th>
<th>HTN</th>
<th>MI</th>
<th>Stroke</th>
</tr>
</thead>
<tbody>
<tr>
<td>63–70</td>
<td>No</td>
<td>82</td>
<td>42.7</td>
<td>40.2</td>
<td>9.8</td>
<td>7.9</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>82</td>
<td>9.8</td>
<td>48.8</td>
<td>54.9</td>
<td>47.6</td>
</tr>
<tr>
<td>71–73</td>
<td>No</td>
<td>87</td>
<td>5.8</td>
<td>37.9</td>
<td>32.2</td>
<td>14.9</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>87</td>
<td>9.2</td>
<td>44.8</td>
<td>40.2</td>
<td>46.0</td>
</tr>
<tr>
<td>74–83</td>
<td>No</td>
<td>63</td>
<td>4.8</td>
<td>27.0</td>
<td>46.0</td>
<td>14.3</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>63</td>
<td>7.9</td>
<td>47.6</td>
<td>49.2</td>
<td>23.8</td>
</tr>
</tbody>
</table>

Endorsed medical conditions as reported during telephone interview.

CABG = coronary artery bypass grafting; Age = age at CABG in proband; CHF = congestive heart failure (includes pulmonary edema); Cholest. = cholesterolemia (includes elevated triglycerides); HTN = hypertension; MI = myocardial infarction.

Figure. Mean change in modified Telephone Interview for Cognitive Status (TICS-m) scores for coronary artery bypass grafting (CABG) negative co-twins, CABG-positive probands, and CABG-negative non-familial controls presented by age band at time of proband’s CABG surgery. Open bar = CABG negative; shaded bar = CABG positive; filled bar = control. Corresponding standard error lines for the interaction of bypass status and age are derived from repeated-measures analysis of variance. *p = 0.0024 for comparison of proband and co-twin; p = 0.0004 for comparison of proband and control.
TICS-m after CABG surgery and no significant difference in the older two groups (see the figure). This was evidenced in an interaction effect, $F(2,219) = 4.21, p = 0.0161$, and significance in pairwise tests (age 63 to 70, $p = 0.0004$; age 71 to 73, $p = 0.4412$; 74 to 83, $p = 0.5502$).

To estimate the typical test-retest performance on the TICS-m from the general population of the NAS-NRC Twins Registry, we calculated change scores for individuals of approximately equivalent age to the young, middle, and oldest CABG groups. The average TICS-m change was $-0.41$ for the young age group ($n = 10,518$), $-0.87$ for the middle age group ($n = 4,788$), and $-1.71$ for the oldest age group ($n = 3,730$). Although these estimates reveal some deviations from our observed values, the pattern of age-related decline is evident in this heterogeneous sample.

Discussion. CABG surgery was associated with better cognitive outcome for individuals who had this procedure at younger ages. Twins who had CABG surgery between ages 60 and 73 demonstrated improvement in cognitive status on the TICS-m 1 to 2 years post-surgery relative to their co-twins who did not have the procedure, whereas no significant changes in TICS-m scores were found between proband and co-twin in the older groups. This interaction of age and CABG surgery on cognitive change was significant in the context of a co-twin control design in which pairs shared many genetic and environmental risks for cardiovascular problems and cognitive function. Moreover, this result was replicated in an analysis comparing the probands with closely matched non-familial controls. This interaction was not associated with differential age effects for the ratio of cardiovascular and cerebrovascular conditions occurring between CABG and non-CABG individuals, nor was it associated with education. Thus, this appears to be a robust finding.

Although there is research suggesting that increased age is associated with greater risk of cognitive impairment following CABG surgery, our finding of age-related improvement following CABG surgery does not appear to have been reported previously. Our young group (age 63 to 70) that demonstrated improvement is comparable to the age ranges of studies finding both improvement and decline in long-term cognitive status. Education level is similar as well. One difference in the current study is that the sample is all male, but sex has thus far not been found to be a predictor of long-term cognitive change following CABG surgery. Based on the state of current research, no single explanation presents itself as an explanation for our findings. Younger individuals may demonstrate a differential cognitive benefit from CABG surgery because earlier intervention reduces exposure to the multiple sources of potential long-term damage associated with a poorly functioning heart; for example, inadequate supply of oxygenated blood to the brain due to coronary artery blockage. Cognitive improvement, however, may strongly depend on concomitant behavior changes to lower cardiovascular risks. Another possible explanation is that younger individuals may have better physical tolerance for the CABG procedure itself, which may reduce the risk of adverse cognitive outcomes by promoting faster recovery and rehabilitation. These explanations receive some support from the nonsignificant trend toward TICS-m decline in the two older groups following CABG.

One issue to consider in the interpretation of our results is the sensitivity of the TICS-m in detecting cognitive changes associated with CABG surgery. While some researchers have argued that brief measures like the MMSE are insufficiently sensitive to cognitive changes associated with CABG, the TICS-m improves upon the sensitivity of the MMSE with the addition of a longer word-recall task, among other items. The TICS-m was found to be predictive of individuals with diagnosis of mild cognitive impairment, with the recall as the most predictive factor. In addition, the TICS-m has been shown to be sensitive to cognitive changes in dementia and traumatic brain injury. Consistent with these findings, it is notable that we found a significant effect of CABG surgery using such a measure, whereas our literature review highlights that studies employing more extensive neuropsychological testing have not yielded consistent evidence for such an effect. We believe that our ability to replicate our results in both high- and low-education groups, and in both twin-paired and case-control analyses, supports the adequate sensitivity of the TICS-m in the context of the current study. Nonetheless, we acknowledge that some neurocognitive changes may not be detected using a brief assessment instrument like the TICS-m, and that it is possible we may have found significant effects in older age groups using a more sensitive and comprehensive test battery.

Another consideration in the interpretation of our findings involves the merits of global vs domain-specific measures of cognitive function. A possible limitation associated with using a global screening assessment of cognitive function is that it provides less information regarding specific domains of cognitive function that may be most sensitive to the effects of CABG surgery. To examine specific domains of performance on the TICS-m, we undertook an exploratory analysis examining four cognitive scales derived from factor analysis of the TICS-m (recent memory, language/attention, proper name recall, and personal orientation), but found that no single cognitive factor associated with CABG surgery emerged over the others. While this post hoc analysis is not meant to substitute for domain-specific neuropsychological assessment, it does suggest that global screening is a valid assessment approach given that many studies identify the release of microemboli during the CABG procedure as the primary etiology for post-CABG cognitive impairment, and that this is generally associated with global changes in group-based comparisons.

The current results were found in the context of a co-twin control design, and it is informative to dis-
cuss advantages and disadvantages of this design relative to other methodologic approaches. The purpose of using a twin-paired design in this study was to control for genetic and environmental contributions to cognitive outcome that are inherently more heterogeneous in non-biologically related comparison groups; however, table 2 illustrates that there are still varying levels of discordance for cerebrovascular risk factors within twin pairs, as well as for the CABG surgery itself. While some clinical samples have used controls matched on severity of selected cardiovascular conditions, we were unable to implement this analytical approach because there was not a sufficient number of individuals with a given cardiovascular condition who also met our matching criteria. Thus, in a research population where it is not possible to account for all potential differences between cases and controls, a twin-paired design can produce findings that are complementary to those derived from other case-control methodologies.

Several methodologic issues that could not be addressed in this study relate to the constraints of studying cognitive outcomes using large epidemiologic datasets. For instance, we did not have information about the specific techniques and equipment used in each individual’s CABG surgery or about the number of grafts that were performed. Pre-existing medical conditions were largely based on retrospective report from the individuals or a knowledgeable informant, rather than from direct medical data. We also do not have sufficient information about pharmacotherapy or lifestyle changes that might account for improvement following CABG surgery. On the other hand, an advantage of using a population-based sample is that it may limit some of the biases that could be found in a self-selected sample presenting at a tertiary care center. Another advantageous feature of the current methodology is that cognitive status was assessed well before CABG surgery, rather than shortly before treatment for an acute cardiac condition.

Considering all of the factors discussed above, we believe the clinical significance of our findings lies in our identification of a trend suggesting differential cognitive outcome for CABG surgery at younger vs older ages, which is consistent with a larger medical consensus on the importance of early intervention to reduce adverse cardiovascular and cerebrovascular outcomes. It will be important to explore the current population-based findings in the context of controlled clinical studies.

Acknowledgment
The authors acknowledge the technical, administrative, and scientific contributions of Deborah Drosdick, Tiffany Newman, and Drs. John Breitner and James Burke.

References
Age effects of coronary artery bypass graft on cognitive status change among elderly male twins

Neurology 2004;63;2245
DOI 10.1212/01.WNL.0000147291.49404.0A

This information is current as of April 3, 2013

Updated Information & Services
including high resolution figures, can be found at:
http://www.neurology.org/content/63/12/2245.full.html

References
This article cites 13 articles, 5 of which can be accessed free at:
http://www.neurology.org/content/63/12/2245.full.html#ref-list-1

Citations
This article has been cited by 5 HighWire-hosted articles:
http://www.neurology.org/content/63/12/2245.full.html#related-urls

Subspecialty Collections
This article, along with others on similar topics, appears in the following collection(s):
All Genetics
http://www.neurology.org/cgi/collection/all_genetics
All Neuropsychology/Behavior
http://www.neurology.org/cgi/collection/all_neuropsychology_behavior
Vascular dementia
http://www.neurology.org/cgi/collection/vascular_dementia

Permissions & Licensing
Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at:
http://www.neurology.org/misc/about.xhtml#permissions

Reprints
Information about ordering reprints can be found online:
http://www.neurology.org/misc/addir.xhtml#reprintsus