Cognitive and Cardiac Outcomes 5 Years After Off-Pump vs On-Pump Coronary Artery Bypass Graft Surgery

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Context Conventional coronary artery bypass graft surgery with use of cardiopulmonary bypass (on-pump CABG) is associated with excellent long-term cardiac outcomes but also with a high incidence of cognitive decline. The effect of avoiding cardiopulmonary bypass (off-pump CABG) on long-term cognitive and cardiac outcomes is unknown.

Objective To compare the effect of off-pump CABG and on-pump CABG surgery on long-term cognitive and cardiac outcomes.

Design, Setting, and Participants The Octopus Study, a multicenter randomized controlled trial conducted in the Netherlands, which enrolled 281 low-risk CABG patients between 1998 and 2000. Five years after their surgery, surviving patients were invited for a follow-up assessment.

Intervention Patients were randomly assigned to receive either off-pump (n=142) or on-pump (n=139) CABG surgery.

Main Outcome Measure The primary measure was cognitive status 5 years after surgery, which was determined by a psychologist blinded to treatment allocation who administered 10 standardized validated neuropsychological tests. Secondary measures were occurrence of cardiovascular events (all-cause mortality, stroke, myocardial infarction, and coronary reintervention), anginal status, and quality of life.

Results After 5 years, 130 patients were alive in each group. Cognitive outcomes could be determined in 123 and 117 patients in the off-pump and on-pump groups, respectively. When using a standard definition of cognitive decline (20% decline in performance in 20% of the neuropsychological test variables), 62 (50.4%) of 123 in the off-pump group and 59 (50.4%) of 117 in the on-pump group had cognitive decline (absolute difference, 0%; 95% confidence interval [CI], −12.7% to 12.6%; P=.99). When a more conservative definition of cognitive decline was used, 41 (33.3%) in the off-pump group and 41 (35.0%) in the on-pump group had cognitive decline (absolute difference, −1.7%; 95% CI, −13.7% to 10.3%; P=.79). Thirty off-pump patients (21.1%) and 25 on-pump patients (18.0%) experienced a cardiovascular event (absolute difference, 3.1%; 95% CI, −6.1% to 12.4%; P=.55). No differences were observed in anginal status or quality of life.

Conclusion In low-risk patients undergoing CABG surgery, avoiding the use of cardiopulmonary bypass had no effect on 5-year cognitive or cardiac outcomes.

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tion of coronary anastomoses without a global cardiac arrest. The off-pump procedure, however, is technically more demanding, and it is unknown whether off-pump surgery can match the long-term cardiac benefits of on-pump surgery.

Between 1998 and 2000, we enrolled 281 patients undergoing CABG surgery in the randomized Octopus Study, which compared off-pump to on-pump techniques. Avoiding cardiopulmonary bypass resulted in a trend toward better cognitive outcomes 3 months after the procedure (21% decline after off-pump surgery vs 29% decline after on-pump surgery; \( P = .15 \)), but the effect became negligible at 12 months (31% vs 34%, respectively; \( P = .69 \)). Also, the rate of cardiovascular events (mortality, stroke, myocardial infarction, or coronary reintervention) at 12 months was similar in both groups (12% after off-pump surgery vs 9% after on-pump surgery; \( P = .48 \)).

In 2001, Newman et al reported that the incidence of cognitive decline was 42% 5 years after on-pump CABG surgery. This high percentage of patients with decline suggested that cardiopulmonary bypass may accelerate cerebral aging and that the harmful effects of cardiopulmonary bypass may become more apparent in the long term. Concurrently, angiographic follow-up studies indicated that bypass surgery on the beating heart is associated with slightly more graft failure. It is therefore conceivable that in the long term, patients who undergo an off-pump procedure have better cognitive outcomes but worse cardiac outcomes.

The aim of the present study was to assess the 5-year cognitive and cardiac outcomes of the 281 patients who were included in the Octopus Study and were randomized to off-pump or on-pump CABG surgery.

**METHODS**

**Design and Patients**

The randomized, controlled, multicenter Octopus Study enrolled 281 patients in whom the Octopus card stabilizer device (Medtronic Inc, Minneapolis, Minn) was used and who underwent surgery between 1998 and 2000. These patients were referred for first-time isolated CABG surgery, and an off-pump procedure was deemed technically feasible. Patients were excluded in cases of emergency or concomitant major surgery, Q-wave myocardial infarction in the last 6 weeks, or inability to provide informed consent or undergo neuropsychological testing. After informed consent, patients were randomly assigned to receive off-pump or on-pump CABG surgery.

Patients were recruited in 3 centers in the Netherlands, and the number of participating surgeons was 16. The primary end point of the present follow-up study was cognitive outcomes 5 years after surgery. The study was approved by the ethics committees of the participating centers. All patients gave written informed consent.

**Neuropsychological Assessment**

Patients underwent a battery of 10 standardized and validated neuropsychological tests 1 day before and 3 months, 12 months, and 5 years after their operation. The cognitive results at 3 months and 12 months after surgery have been reported elsewhere. The tests were administered by a trained psychologist blinded to treatment allocation. Each individual’s performance on the neuropsychological tests was compared with his or her performance on the same tests 5 years earlier, on the day before surgery. In accordance with the Statement of Consensus on Assessment of Neurobehavioral Outcomes After Cardiac Surgery, the test battery included tests for motor skills, verbal memory capacity, and attention. In addition, tests were included to assess speed and capacity of working memory, visuospatial capacity, selective and sustained attention, and information processing. Each test yielded 1 or more variables, with different ranges per variable. Eleven main variables were chosen a priori to be used in the analyses. The tests and the cognitive domains that were covered are described in the Box.

**Definitions of Cognitive Decline**

We applied 2 definitions. A “standard” definition was used in the initial Octopus Study and defined cognitive decline as a decrease in a patient’s performance of at least 20% from baseline in at least 20% (ie, 3) of the 11 main variables. Since this definition later appeared to also identify healthy controls as having cognitive decline, an alternative, more conservative definition was used that corrects for the natural variation in performance during repeated testing. Cognitive decline is defined herein as deterioration beyond the normal variation in cognitive performance observed within a short interval (3 months) in a control population of healthy volunteers. The scores of 8 main variables were standardized using the formula of reliable change (RC) as proposed by Jacobson and Truax. In this formula, RC = ([performance at 5 years − performance at baseline] − practice effect)/SD_{diff}.

The practice effect is the controls’ mean improvement from baseline to 3 months after baseline. SD_{diff} is the standard deviation of the controls’ mean 3-month performance minus baseline performance. Patients were considered to have cognitive decline at 5-year follow-up if they had either a mean RC score equal to or less than −1.96 or an RC score equal to or less than −1.96 in 2 or more of 8 main variables.

In both definitions, participants who had a stroke and those unable to undergo testing because of Alzheimer disease were considered to have cognitive decline.

In addition to the 2 analyses based on a dichotomous cognitive outcome measure, we performed a direct comparison of the continuous test scores. To estimate the change in performance from baseline to 5 years after surgery, a standardized change score was calculated for each main variable in each patient by subtracting the preoperative score from the score at 5 years and dividing the difference by the preop-
operative standard deviation of that variable. If improved performance was reflected by a lower score (e.g., in timed tasks), the directional data were reversed so that all improvements gave rise to positive change scores. Per participant, the mean of the 11 standardized change scores was used as a quantitative measure of the overall postoperative change in performance.

Cardiac Outcome Measures
The principal cardiac outcome measure was the occurrence of a cardiovascular event (i.e., death, stroke, myocardial infarction, or coronary reintervention). When either the patient or the general practitioner had suggested that a cardiovascular event had occurred, the attending neurologist or cardiologist was contacted and photocopies of original reports, letters, laboratory tests, and electrocardiograms were obtained to document these possible events. The possible events were then judged by an independent event committee consisting of an intensive care specialist, a cardiac surgeon, and a neurologist who were blinded for treatment allocation.

Stroke was defined as focal brain injury, detected by standard neurological examination, persisting for more than 24 hours, combined with an increase in disability of at least 1 grade on the Rankin Scale.16 Myocardial infarction was considered present when 2 of the following criteria were met: chest discomfort lasting at least 30 minutes, creatine kinase–MB/creatinine kinase ratio greater than 0.1, and development of abnormal new Q waves in the electrocardiogram.

We also assessed anginal status at 5 years, defined according to the Canadian Cardiovascular Society17 and Braunwald classification.18 Finally, we reassessed quality of life with the EuroQol and Short Form–36 questionnaires. The EuroQol questionnaire generates a single score ranging from −1 to +1, reflecting the worst imaginable quality of life and +1 reflecting the best imaginable quality of life.19 The Short Form–36 questionnaire comprises 8 different domains, all ranging from 0 to 100. Higher scores indicate higher levels of functioning or well-being.20

Data Acquisition
Each participant’s general practitioner received a letter to inquire whether any cardiovascular events had occurred during the last 5 years. When the general practitioner had confirmed that the patient was still alive, a consultant (D.v.D.) invited the patient by telephone to participate in the 5-year follow-up of the study. The anginal status and use of antianginal medication was assessed by the consultant. The occurrence of cardiovascular events according to the patients themselves was

Box. Description of Neuropsychological Tests*

Rey Auditory Verbal Learning (Verbal Memory)
The learning list consists of 15 meaningful monosyllabic words, which are presented in 5 trials. Each trial ends with a free recall of the words. After a period of 20 minutes following the fifth trial, the participant is requested to recall as many words as possible (delayed recall). The mean variables used are the total number of correct words in the 5 trials and the total number of correct words on delayed recall.

Grooved Pegboard (Motor Capacity)
A test for manual dexterity. It is a highly sensitive test for studying improvement in motor functions following stroke. Time to completion is scored.

Trail-Making Test Parts A and B (Divided Attention)
A test procedure in which shifting between concepts is operationalized.

Stroop Color Word Test (Selective Attention)
This test consists of subtasks that measure, first, the speed at which color names are read; second, the speed at which colors are named; and third, the speed at which the color of the printing ink is named when there is interference from the printed color name.

Self-ordering Tasks (Working Memory)
The procedure consists of 3 tasks: digit span, missing item scan, and randomization task. The task measures immediate memory and verbal working memory.

Symbol Digit Modalities Test (Information Processing)
The participant has to fill in blanks that corresponds to a key in which a symbol corresponds to a digit. The test measures speed of simple information processing. The number of filled blanks in a fixed time is scored.

Line Orientation Test (Visuospatial Capacity)
This test measures spatial perception ability by requiring participants to match angled lines to an array of lines with varying slopes.

Continuous Performance Task (Sustained Attention)
A computerized test for sustained attention. The test requires the participant to react to a visual target. The median of reaction time is recorded.

Visuospatial Working Memory Test (Visual Working Memory)
The participant has to fill in as accurately possible a visuospatial target on a sheet of paper.

*The neuropsychological domain assessed is given in parentheses after the test name.
CABG indicates coronary artery bypass graft.

Table 1. Baseline Participant Characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Off-Pump Group (n = 142)</th>
<th>On-Pump Group (n = 139)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD), y</td>
<td>61.7 (9.2)</td>
<td>60.8 (8.8)</td>
</tr>
<tr>
<td>Education, mean (SD), y</td>
<td>9.3 (2.4)</td>
<td>9.7 (2.8)</td>
</tr>
<tr>
<td>Men</td>
<td>94 (66.2)</td>
<td>98 (70.5)</td>
</tr>
<tr>
<td>Vessel involvement</td>
<td></td>
<td></td>
</tr>
<tr>
<td>One-vessel disease</td>
<td>43 (30.3)</td>
<td>31 (22.3)</td>
</tr>
<tr>
<td>Two-vessel disease</td>
<td>71 (50.0)</td>
<td>70 (50.4)</td>
</tr>
<tr>
<td>Three-vessel disease</td>
<td>28 (19.7)</td>
<td>38 (27.3)</td>
</tr>
<tr>
<td>Normal left ventricular function</td>
<td>109 (76.8)</td>
<td>110 (79.1)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>13 (9.2)</td>
<td>23 (16.5)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>57 (40.1)</td>
<td>61 (43.9)</td>
</tr>
<tr>
<td>Pulmonary disease</td>
<td>12 (8.5)</td>
<td>14 (10.1)</td>
</tr>
</tbody>
</table>

*Data are expressed as No. (%) unless otherwise indicated.

The presence or absence of cardiovascular events could be determined in all 281 participants: in 279 (99.3%) through their general practitioner and, if alive, confirmed by the patients themselves. Twenty-one patients (7.5%) had died. Of the surviving 260 patients, 259 (99.6%) were contacted by telephone. Their anginal status was documented and 235 (90.4%) agreed to undergo neuropsychological testing. Five patients (1.9%) were unable to undergo neuropsychological testing because of severe dementia (n = 3) or because of a stroke (n = 2). They were included in the cognitive analyses and considered to have cognitive decline.

Post hoc logistic regression analysis was used to identify codeterminants of cognitive decline at 5 years. All reported P values are 2-sided, and P < .05 was set as the threshold for statistically significant findings. All analyses were performed using SPSS software, version 10.1 (SPSS Inc, Chicago, Ill).

RESULTS

Characteristics of the Patients and Treatment Assignments

Between March 1998 and August 2000, 139 patients were randomly assigned to undergo on-pump surgery and 142 patients to undergo off-pump surgery. The flow of the patients throughout the trial is shown in Figure 1 and their baseline characteristics are summarized in Table 1. The mean number of grafts per patient was 2.6 in the on-pump group and 2.4 in the off-pump group. The mean interval between surgery and the 5-year follow-up was 62 months (SD, 3 months) in both patient groups (P = .98).

Completeness of Follow-up

The presence or absence of cardiovascular events could be determined in all 281 participants: in 279 (99.3%) through their general practitioner and, if alive, confirmed by the patients themselves. Twenty-one patients (7.5%) had died. Of the surviving 260 patients, 259 (99.6%) were contacted by telephone. Their anginal status was documented and 235 (90.4%) agreed to undergo neuropsychological testing. Five patients (1.9%) were unable to undergo neuropsychological testing because of severe dementia (n = 3) or because of a stroke (n = 2). They were included in the cognitive analyses and considered to have cognitive decline.

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Twenty-one (16.2%) of the surviving patients in the off-pump group and 19 (14.6%) of the surviving patients in the on-pump group underwent neuropsychological testing at home because they were not able to travel to the hospital. Nine patients (3.5%) completed fewer neuropsychological tests during postoperative assessment than at baseline because of a lack of motivation or
exhaustion. In the analyses, they were considered to have decreased performance on the missing tests (worst-case score). Cognitive status remained unknown in 41 patients (14.6% of all patients). Reasons for a failed neuropsychological assessment are shown in Figure 1.

Cognitive Outcomes
When applying the standard definition of cognitive decline (20% decline in 20% of the main test variables), 62 (50.4%) of 123 patients in the off-pump group and 59 (50.4%) of 117 patients in the on-pump group had cognitive decline (absolute difference, 0%; 95% confidence interval, −12.7% to 12.6%; P = .99).

Using the alternative, more conservative definition of cognitive decline, 41 patients in the off-pump group (33.3%) and 41 patients in the on-pump group (35.0%) had cognitive decline (absolute difference, −1.7%; 95% confidence interval, −13.7% to 10.3%; P = .79).

The results per neuropsychological test variable are presented in Table 2.

<table>
<thead>
<tr>
<th>Test Main Variable</th>
<th>Off-Pump Group</th>
<th>On-Pump Group</th>
<th>Absolute Difference Between Groups, % (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rey auditory verbal learning Total score, trials 1 to 5</td>
<td>36 (30-43)</td>
<td>35 (27-42)</td>
<td>−0.25 (1.03)</td>
<td>.86</td>
</tr>
<tr>
<td>Rey auditory verbal learning Delayed recall score</td>
<td>6 (5-8)</td>
<td>7 (5-9)</td>
<td>0.13 (1.09)</td>
<td>.95</td>
</tr>
<tr>
<td>Grooved pegboard Time, dominant hand, s</td>
<td>106 (95-118)</td>
<td>107 (96-122)</td>
<td>−0.24 (0.63)</td>
<td>.99</td>
</tr>
<tr>
<td>Trail-Making Test parts A and B Time, trail B, s</td>
<td>83 (62-115)</td>
<td>89 (66-119)</td>
<td>−0.40 (0.94)</td>
<td>.79</td>
</tr>
<tr>
<td>Sternberg memory comparison Time, 4-character chart, s</td>
<td>59 (50-69)</td>
<td>57 (48-72)</td>
<td>−0.02 (0.85)</td>
<td>.99</td>
</tr>
<tr>
<td>Stroop color word test Time C – time B, s</td>
<td>43 (31-61)</td>
<td>46 (33-59)</td>
<td>−0.24 (0.83)</td>
<td>.77</td>
</tr>
<tr>
<td>Symbol digit modalities test Total score</td>
<td>41 (32-50)</td>
<td>41 (33-52)</td>
<td>−0.04 (0.63)</td>
<td>.99</td>
</tr>
<tr>
<td>Line orientation test Total score</td>
<td>24 (21-28)</td>
<td>26 (22-28)</td>
<td>0.09 (0.81)</td>
<td>.61</td>
</tr>
<tr>
<td>Continuous performance task Mean reaction time, ms</td>
<td>544 (491-616)</td>
<td>514 (465-567)</td>
<td>0.21 (0.76)</td>
<td>.01</td>
</tr>
<tr>
<td>Visuospatial working memory test Average distance, cm</td>
<td>0.4 (0.0-1.1)</td>
<td>0.7 (0.3-1.1)</td>
<td>−0.24 (1.19)</td>
<td>.96</td>
</tr>
<tr>
<td>Overall postoperative change (mean of change scores)</td>
<td>−0.09 (0.41)</td>
<td>−0.06 (0.35)</td>
<td>.49</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviation: IQR, interquartile range.
*Standardized change scores reflect improvement in performance from baseline to 5 years after surgery.
†P values (by 2-sample t tests) are for comparison of standardized change scores between the off-pump and on-pump groups.

<table>
<thead>
<tr>
<th>Outcomes after Off-Pump vs On-Pump Coronary Bypass Surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Events</td>
</tr>
<tr>
<td>-----------------</td>
</tr>
<tr>
<td>First event during 5-year follow-up*</td>
</tr>
<tr>
<td>Death from any cause</td>
</tr>
<tr>
<td>Stroke</td>
</tr>
<tr>
<td>Myocardial infarction</td>
</tr>
<tr>
<td>Repeated coronary revascularization</td>
</tr>
<tr>
<td>Bypass surgery</td>
</tr>
<tr>
<td>Angioplasty</td>
</tr>
<tr>
<td>Any first event at 5 years</td>
</tr>
<tr>
<td>All cardiovascular events at 5 years†</td>
</tr>
<tr>
<td>Death</td>
</tr>
<tr>
<td>Due to cardiovascular causes</td>
</tr>
<tr>
<td>Due to noncardiovascular causes</td>
</tr>
<tr>
<td>Stroke</td>
</tr>
<tr>
<td>Fatal</td>
</tr>
<tr>
<td>Nontfatal</td>
</tr>
<tr>
<td>Myocardial infarction</td>
</tr>
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</tr>
<tr>
<td>Angioplasty</td>
</tr>
</tbody>
</table>

Abbreviation: CI, confidence interval.
*Only the first cardiovascular event that occurred in a patient is included in this analysis.
†All cardiovascular events are included in this analysis.
The overall change in performance (ie, overall improvement; mean of the 11 standardized change scores) was −0.09 in the off-pump group and −0.06 in the on-pump group (P = .49).

In univariable logistic regression analyses, older age, lower level of education, and a preoperative history of stroke or transient ischemic accident were risk factors for cognitive decline at 5 years (according to the more conservative definition; P < .01 for all). In a multivariable model, only older age and lower level of education were associated with cognitive decline. Female sex, diabetes, peripheral vascular disease, hypertension, number of coronary bypass grafts, and intraoperative use of a side-biting clamp were not risk factors for long-term cognitive decline.

Cardiac Outcomes
Cardiovascular events at 5 years are shown in Table 3 and Figure 2. Thirty patients assigned to undergo off-pump surgery (21.1%) and 25 patients assigned to undergo on-pump surgery (18.0%) had experienced a cardiovascular event (absolute difference, 3.1%; 95% confidence interval, −6.1% to 12.4%; P = .55). The number of patients with recurrent angina was 23 (17.7%) in the off-pump group and 16 (12.3%) in the on-pump group (absolute difference, 5.4%; 95% confidence interval, −3.3% to 14.0%; P = .23).

Quality of Life
In both groups, 124 patients (95.4% of the surviving patients) completed the quality-of-life questionnaires. There were no differences between the 2 groups in the overall measure of quality of life and in 7 of the 8 subdomains (Table 4). Only in the domain of role limitations due to physical health problems did the on-pump group do slightly better than the off-pump group. In both groups, patients had a significantly better quality of life compared with their preoperative status (all domains).

COMMENT
The present study is the first large randomized trial reporting long-term cognitive outcomes after off-pump vs on-pump CABG surgery. Using the standard definition at 5 years, we found that half of our patients had cognitive decline after both surgical strategies. We were unable to demonstrate any benefit from avoiding cardiopulmonary bypass on long-term cognitive outcomes. Concurrently, there were no differences in cardiovascular event rate, angina, and quality of life.

To date, no adequately powered randomized study has demonstrated a benefit of off-pump surgery on cognitive outcome. In the Octopus Study, we found a trend toward better cognitive outcome 3 months after surgery, but this difference disappeared at 12 months and now appears to remain absent at 5 years. This is remarkable because several studies have demonstrated that off-pump CABG surgery is associated with less cerebral embolization than on-pump CABG surgery.4,21

The present results suggest that factors other than cardiopulmonary bypass may be responsible for cognitive decline, such as anesthesia and the generalized inflammatory response that is associated with major surgical proce-
The present study has several limitations. Sixteen patients did not receive the assigned treatment. Analyses based on actual treatment received, however, showed results that are comparable with the intention-to-treat analyses (available from authors on request). The results of this trial cannot be extrapolated to older patients with more advanced coronary artery disease or a higher preoperative risk. The patients included in the Octopus Study represent only 11% of all CABG procedures performed during the recruitment period. The mean age of the trial patients was 61 years, and the majority had single- or double-vessel disease. Both cognitive decline and stroke occur more frequently in elderly persons. A recent study in 120 elderly high-risk CABG surgery patients did not show a difference in cognitive outcome 3 months after off-pump and on-pump surgery, but this study did not report long-term outcomes. Cohort studies have indicated that off-pump CABG surgery may prevent strokes, but a sufficiently powered randomized study to confirm this would require the inclusion of a larger patient sample and has not been conducted yet. Because of the small number of participants in the present study, the absolute differences in the outcome measures were associated with wide confidence intervals. Therefore, significant differences in outcome favoring one surgical approach may have been missed.

The loss to cognitive follow-up in our patients was 14.6%, which is very satisfactory compared with other studies reporting long-term cognitive outcomes. More than half of this loss to follow-up was due to mortality, and the dropout rate and baseline characteristics of the remaining patients were largely similar across the groups. Less than 4% of the patients lost motivation for cognitive follow-up after their surgery. A relationship between loss to follow-up and cognitive outcome may therefore be present in only a very small proportion of the patients. We conclude that in low-risk patients undergoing CABG surgery, avoiding the use of cardiopulmonary bypass had no effect on cognitive or cardiac outcome 5 years after the procedure.

Author Contributions: Dr van Dijk had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: van Dijk, Hijman, Borst, Jansen, Grobbée, de Jaegere, Kalkman. Acquisition of data: van Dijk, Spoer, Nathoe. Analysis and interpretation of data: van Dijk, Grobbée, Kalkman. Drafting of the manuscript: van Dijk. Critical revision of the manuscript for important intellectual content: Spoer, Hijman, Nathoe, Borst, Jansen, Grobbée, de Jaegere, Kalkman. Statistical analysis: van Dijk, Kalkman. Obtained funding: van Dijk, Grobbée, Kalkman. Administrative, technical, or material support: Spoer. Study supervision: Hijman, Kalkman.

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