Durability of endovascular treatment for intracranial aneurysms
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De novo aneurysm formation and growth of untreated aneurysms

5-year MRA follow-up in a large cohort of patients with coiled aneurysms and review of the literature

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ABSTRACT

Background and purpose
Rate of development of de novo intracranial aneurysms and of growth of untreated additional aneurysms is largely unknown. We performed MRA in a large patient cohort with coiled aneurysms at 5 years follow-up.

Methods
In 276 patients with coiled intracranial aneurysms and 5 ± 0.5 years follow-up MRA (totaling 1332 follow-up patient-years), additional aneurysms were classified as unchanged, grown, de novo or incomparable with previous imaging. We calculated 5-year cumulative incidence of de novo aneurysm formation and growth of untreated aneurysms. We searched PubMed and EMBASE databases for studies assessing aneurysm development and growth.

Results
In 50 of 276 patients (18%), 75 additional aneurysms were present at follow up MRA. Of these 75, 2 were de novo (both 3 mm), 58 were unchanged, 5 had grown from 1-3 mm (7.9% of 63 known additional aneurysms, 95%CI: 1.3- 14.6%), and 10 were incomparable. Five-year cumulative incidence for developing a de novo aneurysm was 0.75%. Four additional aneurysms in 3 patients were treated. Ten previous studies reported annual incidences of growth of additional aneurysms ranging from 1.51% to 22.7%, and 5 studies reported annual incidences of de novo aneurysm formation ranging from 0.3 to 1.8%.

Conclusions
In general, MRA screening of patients with coiled aneurysms within the first 5 years after treatment to detect de novo aneurysms and growth of additional aneurysms does not seem beneficial, both in terms of preventing SAH and for detection of aneurysms that need treatment.
INTRODUCTION

In patients with a symptomatic intracranial aneurysm, additional aneurysms are frequently found and new aneurysms may develop with time.\textsuperscript{1-5} Additionally found aneurysms that are small are often left untreated because of unfavorable location or geometry together with a low anticipated chance of rupture.

The incidence of development of de novo aneurysms and rate of growth of untreated additional aneurysms has been the subject of several studies. These studies differ in design and results. An important drawback is the lack of fixed follow-up intervals in most studies that impedes assessment of incidence of development and growth of aneurysms. Because growth rate of aneurysms in not constant over time, recalculating annual incidences from the total period of follow up is inaccurate.\textsuperscript{6}

Proven aneurysm growth is considered a risk factor for rupture since aneurysm size is directly related to the risk of rupture and growing aneurysms may be regarded as unstable.\textsuperscript{7,8}

We assessed the incidence of de novo aneurysm formation and determined the natural history of additional untreated aneurysms in a large cohort of patients with coiled intracranial aneurysms after a follow-up period of 5 years. In addition, we provide an overview of relevant other studies in perspective to our results.

METHODS

Patients
Institutional Review Boards of the 7 participating medical centers (Academic Medical Center Amsterdam, Leiden University Medical Center, Maastricht University Medical Center, Slotervaart Ziekenhuis Amsterdam, St. Elisabeth Ziekenhuis Tilburg, University Medical Center Utrecht, and VU Medical Center Amsterdam, all in the Netherlands) approved the study protocol. All participants provided written informed consent.

From the databases of the centers, we retrieved all patients with a ruptured or unruptured intracranial aneurysm that was coiled since January 1995. Patients with adequate aneurysm occlusion (complete occlusion or a small neck remnant) at 6 months angiographic follow-up, according to occlusion status recorded in the databases and radiological reports were selected to participate in a study to assess long-term stability of coiled intracranial aneurysms (LOTUS). Inclusion criteria for LOTUS were: follow-up duration more than 4.5 years, current age between 18 and 70 years, independent functional state and no contra-indications for 3T MRI.
Eligible patients received a letter with an invitation to participate in LOTUS. Patients who did not respond to the invitation letter were contacted by phone.

For the purpose of the present study, we selected those patients included in the LOTUS study that had a follow up MRA 5 ± 0.5 years after treatment. Our group has previously reported the first 65 patients.\(^9\) We extended the number of patients to obtain more reliable data.

Figure 1. Flow chart showing patient and aneurysm selection
MR imaging follow-up protocol
MR imaging examinations were performed centrally in 2 centers on a 3T system (Intera R10; Philips Medical Systems, Best, The Netherlands) by using the sensitivity encoding (SENSE) phased-array head coil (MR Imaging Devices, Gainesville, FL, USA). MR imaging protocol included Axial T2-weighted fast spin echo and multiple overlapping thin slab acquisition 3D time-of-flight (MOTSA 3D-TOF) MRA sequences. Detailed descriptions of the imaging parameters have been described previously. Images were processed into maximum intensity projections and volume rendered 3D images of the circle of Willis. Total MR imaging examination time was 20 minutes.

MR imaging and MRA evaluation
MR images were evaluated independently by 2 experienced neuroradiologists in 3 of the participating centers with discrepancies resolved in consensus. Presence, location and largest diameter of additional aneurysms were compared with conventional, CT or MR Angiography at the time of coiling or at 6 months follow-up. Additional aneurysms were classified as unchanged, grown, de novo, or incomparable with previous imaging.

Data analysis
Proportions of patients with additional aneurysms, patients that developed a de novo aneurysm, and proportions of previously known additional aneurysms that had grown, were calculated with 95% confidence interval (CI). Characteristics of patients with additional aneurysms were compared with patients without additional aneurysms. Patient- and aneurysm characteristics of patients with grown additional aneurysm were compared to patients with no aneurysm growth. The sample t-test was used for comparison of means and relative risks (RR) were calculated for proportions. Clinical implication of the 5-year-follow-up MRA in terms of treatment advice and change of follow-up imaging policy was described.
Literature search and study eligibility

We searched PubMed and EMBASE databases until April 2010. The following key words as MESH terms and text words were used: “Intracranial aneurysm” in “AND” combination with “additional,” “growth,” “new”, and “novo” in “OR” combinations. Studies were included if: (1) prevalence or incidence of growth of untreated intracranial aneurysms or de novo aneurysm formation was assessed, (2) sample size was >50. To assess eligibility, the reviewer (S.P.F.) screened titles and abstracts and reviewed relevant full-text articles on inclusion criteria. Reference lists of relevant studies were searched for additional studies.

Table 1. Patient- and aneurysm characteristics of 276 patients with follow-up MRA 5 years after coiling, of 50 patients with additional aneurysms, and of 4 patients with grown additional aneurysms

<table>
<thead>
<tr>
<th></th>
<th>276 patients/300 coiled aneurysms</th>
<th>50 patients/75 additional</th>
<th>4 patients/5 grown</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>5 ± 0.5 years</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td>191 (69%)</td>
<td>41 (82%)</td>
<td>2 (50%)</td>
</tr>
<tr>
<td>Mean age (yrs)</td>
<td>54.4</td>
<td>55.0</td>
<td>53.0</td>
</tr>
<tr>
<td>median, range</td>
<td>55, 23-70</td>
<td>55, 40-70</td>
<td>51, 49-66</td>
</tr>
<tr>
<td>History of SAH</td>
<td>235 (78%)</td>
<td>41 (77%*)</td>
<td>2 (50%)</td>
</tr>
<tr>
<td>Follow-up (yrs)</td>
<td>4.8</td>
<td>4.7</td>
<td>4.9</td>
</tr>
<tr>
<td>median, range</td>
<td>4.8, 4.5-5.5</td>
<td>4.8, 4.5-5.5</td>
<td>5.0, 4.7-5.3</td>
</tr>
</tbody>
</table>

SAH: subarachnoid hemorrhage

* 41 of 53 coiled aneurysms in 50 patients with additional aneurysms were ruptured and 12 unruptured.
RESULTS

Patient and aneurysm characteristics
Of 1808 intracranial aneurysms in 1675 patients that were coiled in the 7 participating centers in the Netherlands, 1287 with 1412 aneurysms had 6 months follow-up angiography and 1066 (75%) aneurysms in 971 patients were adequately occluded at this first angiographic follow-up. Of these 971 eligible patients with 1066 aneurysms, 157 (16%) could not be traced, and 274 could not be included for a variety of reasons (Figure 1). The remaining 540 patients were invited to participate in the study and 140 declined (participation grade 74%).

Of 400 patients with 440 coiled aneurysms participating in LOTUS, 75 patients (19%) had 101 additional aneurysms. Of 400 patients, 276 with 300 coiled aneurysms had a follow-up duration of 5 years ± 6 months (totaling 1332 follow-up patient-years); the follow-up interval of the remaining 124 participants was 5.5 -12.9 years. The 276 patients with 300 coiled aneurysms and 1332 follow-up patient years are the subject of this study. Fifty of these patients had 75 additional aneurysms. Patient- and aneurysm characteristics of all 276 patients and the 50 patients with additional aneurysms are displayed in Table 1.

Additional aneurysms on 5-year follow-up MRA
In 50 of the 276 patients (18.1%, 95%CI 13.6-22.7%), 75 additional aneurysms were found. Additional aneurysms were more often present in women (RR 2.03, 95% CI 1.03 - 3.98); other patient characteristics were comparable. Thirty-six patients had 1 additional aneurysm, 8 patients had 2, and 6 patients had 3 or more additional aneurysms. Characteristics of 75 additional aneurysms are displayed in Table 2.

Ten of 75 additional aneurysms (13%) were classified as incomparable: No previous imaging was available in 7 additional aneurysms and in another 3 the projection of the initial angiogram did not allow verification of their presence. The remaining 65 additional aneurysms could be compared with previous imaging; 58 (89.2%, 95%CI 81.7-96.8%) were unchanged, and 2 (3.1%, 95%CI 0.8-10.6%) were de novo. Five of 63 previously known untreated aneurysms had grown (7.9%, 95%CI:1.3-14.6%). The 58 unchanged additional aneurysms were present in 41 patients.Sizes ranged from 1-7 mm.

The 5 additional aneurysms in 4 patients that had grown had the following characteristics: The first patient, a 45 year old man had 5 additional aneurysms of which a pericallosal artery aneurysm had increased in size from 1.5 to 2.5 mm.
second patient, a 49 year old woman also had 5 additional aneurysms, of which a right internal carotid artery tip aneurysm had increased from 3 to 6 mm (Figure 2). This aneurysm is scheduled for coiling. The third patient, a 66 year old man had a posterior communicating artery aneurysm that increased in size from 2 to 3 mm. The fourth patient, a 53 year old woman had two additional aneurysms that both had increased in size; a posterior inferior cerebellar artery aneurysm had grown from 2 to 3 mm and a basilar tip aneurysm had grown from 4 to 6 mm. The basilar tip aneurysm was subsequently coiled. Patient gender and age were not predictors for aneurysm growth (Table 2). Size of the additional aneurysm was also not a predictor for aneurysm growth; mean size of aneurysms without growth was 2.6 mm and of aneurysms with growth 2.8 mm.

Five years after coiling, 2 de novo aneurysms were found in 2 of 276 patients (0.7%, 95% CI 0.2-2.6%); one 3 mm middle cerebral artery aneurysm in a 56 year old woman and one 3 mm basilar tip aneurysm in a 66 year old man. Cumulative 5-year incidence of de novo aneurysm formation was 0.75% (95% CI 0.2-2.7%); 2 de novo aneurysms in 1332 patient-years.

| Table 2. Characteristics of 75 additional aneurysms detected on 5-year follow-up MRA in 50 of 276 patients |
|----------------------------------|-----------------|-----------------|---------|----------|------------|
| 75 additional aneurysms          | unchanged       | grown           | de novo | incomparable |
| Mean aneurysm size               | 2.5 mm          |                 |         |           |            |
| median, range                    | 2.0, 1.7 mm     |                 |         |           |            |
| **Aneurysm location**            |                 |                 |         |           |            |
| Anterior cerebral artery         | 7 (9%)          | 6               | 1       | 0         | 0          |
| Middle cerebral artery           | 24 (32%)        | 18              | 0       | 1         | 5          |
| Internal carotid artery          | 27 (36%)        | 22              | 2       | 0         | 3          |
| Posterior circulation            | 17 (23%)        | 12              | 2       | 1         | 2          |
| **Total**                        | 75              | 58              | 5       | 2         | 10         |

ACA: anterior cerebral artery; MCA: middle cerebral artery; ICA: internal carotid artery
Clinical implications of 5-year MRA follow-up

Of 75 additional aneurysms, 2 left middle cerebral artery aneurysms in 1 patient classified as incomparable with previous imaging were clipped. Two grown additional aneurysms were coiled in 2 patients: 1 on the internal carotid artery tip and 1 on the basilar tip. Thus, after 5 year MRA follow-up, 3 of 276 patients were advised treatment for an additional aneurysm (1.1%, 95% CI 0.4-3.1). Both de novo aneurysms were left untreated, follow-up imaging is scheduled. In 8 patients with 8 additional aneurysms (2.9%, 95%CI:0.9-4.9%) treatment was judged not indicated by the treating multidisciplinary team because of small size, but extended follow-up imaging was advised. Other patients with additional aneurysms were not planned for extended imaging follow-up, because it was judged unnecessary by the treating multidisciplinary team in the clinical context of the individual patient.

Figure 2. 49-year-old woman with a coiled ruptured basilar tip aneurysm and 5 small additional aneurysms at presentation. A; Right carotid artery angiogram at presentation shows additional aneurysms on the carotid artery tip of 3 mm and on the posterior communicating artery of 1 mm (arrow), both left untreated. B; MRA after 5 years shows some growth of the carotid tip aneurysm. C; Repeated right carotid artery angiogram confirmed growth of the carotid artery tip aneurysm to 6 mm. The posterior communicating artery aneurysm had not grown. The patient is scheduled for coiling of the carotid tip aneurysm.
Other studies reporting de novo aneurysms and growth of untreated aneurysms

Searching the literature yielded 12 relevant studies (Table 3). Three studies of 610, 102, and 112 patients with clipped aneurysms reported additional aneurysms on imaging follow-up, one study reported additional aneurysms on imaging follow-up of 65 patients with coiled aneurysms, and 8 studies reported additional aneurysms on imaging follow-up in selected cohorts of 57-321 patients with known untreated additional aneurysms.

Proportions of growth of additional aneurysms were described in 10 studies, with backward calculations of these proportions to annual risks, which ranged from 1.51% to 22.7%. Growth rate of additional aneurysms was assessed in 2 studies, with a recalculated annual rate of 0.31 and a range of 0.12-1.3 mm. Risk factors for aneurysm growth were assessed in 9 studies. Additional aneurysm sizes ≥5 mm, ≥8 mm, and ≥10 mm were predictors for growth in 4 studies. Patients with multiple additional aneurysms had higher chance of aneurysm growth in 3 studies, smoking was a predictor for aneurysm growth in 2 studies, and female gender in another 2 studies. The following predictors for aneurysm growth were found in 1 study each: advanced patient age, or family history of SAH, alcohol abuse, and aneurysms with multiple lobes. Each of the 4 large vessels have been suggested to be at higher risk for growth in different studies; the anterior cerebral-, internal carotid-, middle cerebral-, and basilar artery.

De novo aneurysm formation was reported in 5 studies, with recalculated annual risks ranging from 0.3-1.8%. Risk factors for new aneurysm formation were assessed in 4 studies. Smoking was a predictor for de novo aneurysm formation in 2 studies, and female gender, multiple aneurysms and follow-up duration >9 years were risk factors in 1 study each.
Table 3. Characteristics and outcome of studies reporting on growth and de novo formation of intracranial aneurysms

<table>
<thead>
<tr>
<th>First author</th>
<th>Year</th>
<th># patients</th>
<th>Mean FU yrs (range)</th>
<th># of PY</th>
<th>Type of imaging</th>
<th>Total # add AA</th>
<th>Mean add AA size (mm(range))</th>
<th># grown AA/pt (annual risk growth untreated AA)</th>
<th>Rate of AA growth (mm/yr)</th>
<th># de novo AA/pt (annual risk novo)</th>
<th>Significant risk factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>David CA³</td>
<td>1999</td>
<td>102</td>
<td>4.4 (2.6-9.7)</td>
<td>443</td>
<td>DSA</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>8/6 (1.8%)</td>
<td>multiple AA</td>
</tr>
<tr>
<td>Juvela S²</td>
<td>2001</td>
<td>94</td>
<td>18.9 (12.2-8.0)</td>
<td>1789</td>
<td>DSA</td>
<td>111</td>
<td>5.1 ±4.1</td>
<td>30/39 (2.37%)</td>
<td>0.31±0.86</td>
<td>19/15 (0.64%)</td>
<td>smoking, female</td>
</tr>
<tr>
<td>Tsutsumi K⁴</td>
<td>2001</td>
<td>112</td>
<td>9.3 (3.0-1.0)</td>
<td>1041</td>
<td>DSA</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>9/9 (0.89%)</td>
<td>FU&gt;9yrs</td>
</tr>
<tr>
<td>Phan TG¹⁰</td>
<td>2002</td>
<td>57</td>
<td>4.2 (1.4-7.5)</td>
<td>239</td>
<td>MRA</td>
<td>62</td>
<td>5 (2-15)</td>
<td>4/4 (1.67%)</td>
<td>-</td>
<td>-</td>
<td>AA size, multiple lobes</td>
</tr>
<tr>
<td>Yonekura M¹¹</td>
<td>2004</td>
<td>321</td>
<td>1.2 (0.5-3.0)</td>
<td>385</td>
<td>MRA/CTA/DSA</td>
<td>380</td>
<td>&lt;5</td>
<td>22/- (5.71%)*</td>
<td>-</td>
<td>-</td>
<td>female, old age, multiple AA, ACA, basilar a.</td>
</tr>
<tr>
<td>Matsubara S²</td>
<td>2004</td>
<td>140</td>
<td>1.5 (-)</td>
<td>207</td>
<td>CTA</td>
<td>166</td>
<td>4.1 (2-20)</td>
<td>10/9 (2.5, 8, 17.6%)†</td>
<td>-</td>
<td>-</td>
<td>AA size, basilar a., ICA</td>
</tr>
<tr>
<td>Wermer MJ¹</td>
<td>2005</td>
<td>610</td>
<td>8.9 (2.3-8.8)</td>
<td>5078</td>
<td>CTA</td>
<td>59</td>
<td>-</td>
<td>13/- (22.2, 20.0%)#</td>
<td>0.12-1.3</td>
<td>19/14 (0.37-1.20%)</td>
<td>smoking, multiple AA</td>
</tr>
<tr>
<td>Miyazawa N¹³</td>
<td>2006</td>
<td>130</td>
<td>2.4 (0.8-5.8)</td>
<td>317</td>
<td>MRA</td>
<td>159</td>
<td>4.2 ±2.1</td>
<td>16/14 (5.05%)*</td>
<td>-</td>
<td>-</td>
<td>AA size, family history</td>
</tr>
<tr>
<td>Wermer MJ⁵</td>
<td>2006</td>
<td>93</td>
<td>1.1 (0.7-2.2)</td>
<td>102</td>
<td>CTA/MRA</td>
<td>117</td>
<td>3</td>
<td>3/3 (2.04%)*</td>
<td>-</td>
<td>-</td>
<td>history of SAH combined with family history</td>
</tr>
<tr>
<td>Burns JD⁴</td>
<td>2009</td>
<td>165</td>
<td>3.9 (1.2-0.5)</td>
<td>647</td>
<td>MRA</td>
<td>172</td>
<td>4.9 (3.1-6.0)</td>
<td>14/- (2.17%)†</td>
<td>-</td>
<td>-</td>
<td>AA size</td>
</tr>
<tr>
<td>Sprengers MF⁹</td>
<td>2009</td>
<td>65</td>
<td>5.1 (4.9-5.3)</td>
<td>332</td>
<td>MRA</td>
<td>24</td>
<td>3.1 (1-6)</td>
<td>1/1 (1.51%)*</td>
<td>-</td>
<td>1/1 (0.3%)§</td>
<td>-</td>
</tr>
<tr>
<td>So, TY¹⁵</td>
<td>2010</td>
<td>208</td>
<td>1.8 (0.1-1.4)</td>
<td>549</td>
<td>DSA</td>
<td>285</td>
<td>1.8 (1-6)</td>
<td>95/- (22.7, 35.2, 47.7%)#§</td>
<td>-</td>
<td>-</td>
<td>alcohol abuse</td>
</tr>
</tbody>
</table>

FU: follow-up; PY: patient years; AA: aneurysms; pt: patient; -: not reported; ACA: anterior cerebral artery; ICA: internal carotid artery; MCA: middle cerebral artery

*not reported, but calculated by the authors as number of events/number of FU years of patients with additional AA

† cumulative incidence after 1, 2 and 3 years

‡ cumulative incidence after 5 and 10 years

§ not reported, but calculated by the authors as number of events/number of patient years
DISCUSSION

Imaging follow-up 5 years after coiling to detect de novo aneurysm formation has a very low yield. The cumulative 5-year incidence in our cohort was only 0.75%. Some previous studies found higher annual incidences up to 1.8%. However, unlike our study, these studies had no fixed follow-up period but wide follow-up intervals, making it difficult to assess the true timing of development of de novo aneurysms. Three studies had a much longer follow-up of 9-19 years. As can be expected with longer follow-up, more de novo aneurysms were detected in these studies.

Growth of untreated aneurysms in our study was more frequent than development of de novo aneurysms with a 5-year incidence of 7.9%. Other studies found widely ranging annual incidences of 1.51% to 22.7%. We could not find a risk factor for aneurysm growth, but in previous studies a consistent risk factor for growth of additional aneurysms was aneurysm size (≥5, ≥8, and ≥10 mm in different studies), and presence of multiple aneurysms. In our series, all but one additional aneurysm were smaller than 7 mm. Two of 4 patients in our series with grown aneurysms had 5 additional aneurysms.

The concern of growth of untreated aneurysms is the increased risk of rupture, because size is an important determinant of the risk of rupture and possibly also because enlarging aneurysms are unstable. In a meta-analysis for the risk of rupture of unruptured intracranial aneurysms, annual incidence of SAH from an unruptured aneurysm was 1.2% in studies with a mean follow-up duration of <5 years, 0.6% in studies with mean follow-up duration of 5-10 years, and 1.3% in studies with a mean follow-up duration of >10 years. Juvela et al more recently found a comparable annual rupture rate of 1.3%. Long-term follow-up data from the ISAT study suggest an annual rupture rate from de novo and known additional aneurysms in patients with a clipped aneurysm to be 0.036% each (3 events in 8447 person-years). Miller et al estimated the incidence of rupture of de novo aneurysms to be 0.06% per patient-year in patients with a clipped aneurysm.

Combining the data from our study and the very low rupture risk from additional aneurysms suggests that the risk of de novo aneurysm formation and significant enlargement of additional untreated aneurysms is low, with subsequently an extremely low risk of SAH from these aneurysms. This low risk seems particularly true for the first 5 years and probably also for the first 10 years. Therefore, screening of all patients...
within the first 5 years after aneurysm treatment does not seem beneficial, both in terms of preventing SAH and for detection of aneurysms that need treatment.

Cost-effectiveness analyses for periodic screening for detection of grown and de novo aneurysms in patients with a history of SAH and clipping, proved that screening was not cost-effective, mostly dependent on screening-induced fear in patients.\textsuperscript{20}

A limitation of our study is that 13\% of additional aneurysms (10 aneurysms in 7 patients) could not be compared with previous imaging, and were considered ‘not comparable’. It is therefore possible that we underestimated the incidence of de novo aneurysm formation and growth of untreated aneurysms in our patient cohort. This problem will most likely not occur in future studies, since in current practice patients are more frequently followed with MRA, resulting in complete imaging of cerebral vessels. A second limitation is that the low rate of grown and de novo additional aneurysms did not allow for reliable identification of risk factors for aneurysm growth and formation of de novo aneurysms. Risk factors found in other studies are female gender, smoking, aneurysm size $>5$ mm, and the presence of multiple additional aneurysms.\textsuperscript{1-3,5,10-14}

**CONCLUSION**

MRA 5 years after coiling to detect de novo aneurysms and growth of additional untreated aneurysms has a low yield in terms of treatment consequences. In general, MRA screening 5 years after coiling seems not necessary based on our data. However, it is possible that some patients are at higher risk and may benefit from screening such as young patients with multiple aneurysms, patients with a positive family history, or patients with proven growth of additional aneurysms.
Chapter 4 5-year incidence of de novo aneurysm formation and growth of untreated aneurysms

REFERENCES


