Durability of endovascular treatment for intracranial aneurysms
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Summary of findings and implications
SUMMARY OF FINDINGS

Coiling is increasingly used as treatment for intracranial aneurysms with favorable short-term outcome. Concern exists about long-term reopening and the inherent risk of recurrent subarachnoid hemorrhage (SAH), and long-term imaging follow-up is advocated. It is currently unknown for how long and how often coiled aneurysms need to be followed and what subgroups carry a higher or lower risk for reopening. In this thesis, we have presented studies to start solving this issue.

In CHAPTER 2, we have performed a systematic review of literature regarding imaging outcome of coiled intracranial aneurysms. We found 42 studies reporting on imaging follow-up of over 50 patients with coiled intracranial aneurysms, totaling more than 8000 aneurysms with follow-up. Directly post-coiling, about 90% of aneurysms are adequately occluded. On imaging follow-up, reopening was seen in 21% of aneurysms. Because follow-up duration of included studies varied widely, and most studies lacked fixed follow-up duration, we could not determine timing of reopening. Approximately half of reopened aneurysms are retreated, and in the other half retreatment is judged not necessary; not possible due to unfavorable morphology, or not indicated in the clinical context of the individual patient. Aggregation of data of included studies showed that location of the aneurysm in the posterior circulation and aneurysm size >10 mm are possible risk factors for early and late reopening combined and for retreatment.

Previous studies reported contradicting results in addressing the question of timing of aneurysm reopening. Some have found more reopened aneurysms with longer follow-up duration, and some claim that virtually all reopenings occur early after coiling. These discrepancies are confusing in clinical practice; if more first-time reopenings are found with longer follow-up, prolonged imaging would be mandatory to detect late-onset reopenings. On the other hand, if adequately occluded aneurysms at 6 months do not reopen later, extended follow-up is not necessary. In CHAPTER 3 we performed a long-term multicenter follow-up study (LOTUS) focusing on patients with adequate aneurysm occlusion on first angiographic follow-up 6 months after coiling (approximately 80% of all coiled aneurysms). We performed MR Angiography at 3 Tesla in 400 patients with 440 aneurysms mean 6 years after coiling. We concluded that, if an aneurysm is adequately occluded after 6 months, the chance of reopening needing retreatment in the next 4.5-12.9 years is very low (<1%). Late aneurysm reopening in this large subgroup of coiled aneurysms occurred in only 3%. Dependent
and independent risk factors for reopening were aneurysm size ≥ 10 mm (odds ratio 4.7) and location on the basilar tip (odds ratio 3.9).

Apart from assessment of occlusion status of coiled aneurysms, imaging follow-up of patients after coiling is also performed for detection of de novo aneurysms and growth of pre-existent untreated intracranial aneurysms. A substantial part of patients with coiled intracranial aneurysms have multiple aneurysms and often these additional aneurysms remain untreated due to small size. With the increasing awareness that an aneurysm might be the expression of a general disease of the intracranial arteries, these patients may develop aneurysms de novo later in life. Little is known about the pace of growth of untreated additional aneurysms and the frequency and timing of development of new aneurysms, making it impossible to assess the need for and optimal timing of long-term imaging follow-up for these aneurysms. In CHAPTER 4, we have investigated the 5-year incidence of growth and development of de novo aneurysms in 276 patients with coiled aneurysms. We found de novo aneurysm formation in less than 1% of patients 5 years after coiling. Although known additional aneurysms showed growth in 8% during 5 years, most growth was minimal, and treatment or additional follow-up was judged not necessary in the majority of patients with grown aneurysms. The yield of 5-year MR follow-up screening to detect additional aneurysms that need treatment was very low (1%). Thus, from the 2 studies presented in chapter 3 and 4, we found no benefit of screening after 5 years, both for detection of late reopening and for detection of de novo aneurysms or growth of additional aneurysms.

It is thought that long-term follow-up screening for coiled aneurysm reopening and formation of new aneurysms of patients may work two-sided; it may cause relieve if no such findings are present, but it may also cause anxiety if small additional aneurysms are found that are left untreated. In CHAPTER 5, we asked participants in our long-term MRA follow-up study after coiling to fill out questionnaires concerning mood and anxiety. Of 120 participants that filled out the questionnaires, half of the patients reported a problem with anxiety or depression at the time of screening. Patients with coiled intracranial aneurysms that were screened with MRI more than 5 years after coiling are more anxious or depressed at the time of screening and 3 months thereafter compared to Dutch general population norms. A negative screening result, although positive news for the patient, did not substantially decrease anxiety or depression after 3 months, but provided a subjective feeling of relieve in most participants and no patients regretted participation. Surprisingly, a screen-positive result did not influence quality of life, nor did it cause a subjective feeling of increased fear for SAH in most
patients. Hence, the decision to subject patients with a coiled intracranial aneurysm to long-term follow-up should be made considering clinical relevance only, and follow-up is not recommended for the sole purpose of reassuring the patient.

In CHAPTER 6, we studied the subgroup of 20% of patients with coiled aneurysms that are incompletely occluded at first angiographic follow-up after 6 months. Long-term clinical and angiographic outcome may be very different from their adequately occluded counterparts. We have conducted a retrospective study of 124 patients with incompletely occluded aneurysms. We assessed long-term clinical and angiographic outcome and retreatment, but focused on the occurrence of late adverse events due to rebleeds from the incompletely occluded aneurysm, and complications from additional treatments and extended follow-up. We concluded that a strategy of imaging follow-up and retreatment when possible leads to a low incidence of serious adverse events. Rebleeding and progressive mass effect of the aneurysm were equally often responsible for these events, and we encountered no complications from additional treatment or angiographic follow-up. Posterior circulation aneurysms were overrepresented in our cohort, and growing large and giant basilar tip aneurysms were mainly responsible for increasing mass effect by continuous growth, causing brain stem compression with grim short-term prognosis.

Aneurysms with intraluminal thrombus presenting with mass effect form a very small subgroup of endovascular treated intracranial aneurysms (4% in our patient cohort), with well understood worse angiographic and clinical outcome compared to aneurysms without intraluminal thrombus. Because of the scarcity of these aneurysms, presently this group has never been described as a separate entity. In CHAPTER 7, we performed a retrospective study of 56 patients with partially thrombosed aneurysms presenting with mass effect that were endovascular treated, either with selective coiling or with occlusion of the parent vessel. Thirty aneurysms were treated by selective coiling and 26 were treated by parent vessel occlusion. The results of parent vessel occlusion were much better than those of selective coiling. After parent vessel occlusion, aneurysms remained permanently occluded and most aneurysms decreased in size with time with relief of symptoms of mass effect in most patients. After primary coiling, additional treatments were often needed during follow-up, and some aneurysms kept growing, sometimes with progressive and devastating symptoms of mass effect. For partially thrombosed aneurysms, parent vessel occlusion is the preferred therapy. When parent vessel occlusion is not tolerated or not possible, surgical options should be considered before proceeding with coiling.
CONCLUSIONS

Before we conducted this thesis, we have formulated the following aims:

- To systematically review the literature on angiographic outcome and retreatment after coiling of intracranial aneurysms
- To evaluate the yield and psychological effect of MRA screening >5 years after coiling in patients with adequate aneurysm occlusion at first angiographic follow-up after 6 months
- To assess long-term clinical and angiographic outcome in patients with incomplete aneurysm occlusion at first angiographic follow-up 6 months after coiling
- To assess long-term clinical and angiographic outcome after endovascular treatment of patients with partially thrombosed intracranial aneurysms

After conducting the studies presented in this thesis, we can conclude that:

- Of all coiled intracranial aneurysms, 21% shows reopening on imaging follow-up and 10% is retreated. Possible risk factors for early and late reopening combined are aneurysm location in the posterior circulation and aneurysm size > 10 mm.
- In the first 5-10 years after coiling, late aneurysm reopening, defined as first-time reopening after the 6 months angiographic follow-up, is rare. In addition, de novo aneurysm formation and clinically significant growth of additional aneurysms is also rare. Thus, the yield of follow-up MRA 5-10 years after adequate coiling is very low, in terms of finding aneurysms re-openings and additional aneurysms that need treatment. Long-term imaging follow-up may be considered in the clinical context of the individual patient, for example young patients with multiple aneurysms or patients with large posterior circulation aneurysms, but it is not recommended for the sole purpose of reassuring the patient.
- A strategy of prolonged imaging follow-up and retreatment when possible is recommended in patients with coiled intracranial aneurysms that are incompletely occluded at first angiographic follow-up. Additional treatments and angiographic follow-up have a very low complication rate. Coiled large and giant basilar tip aneurysms may need more frequent follow-up to timely detect growth and reopening, also after stable occlusion during some years.
• Partially thrombosed aneurysms that present with mass effect and are treated with selective coiling have high chance of reopening, multiple treatments with possible complications, and continuous growth, compared to partially thrombosed aneurysms treated with parent vessel occlusion. Parent vessel occlusion should be the endovascular treatment of choice for these aneurysms, and coiling should only be considered if there is no other surgical treatment option. Frequent and prolonged imaging follow-up is recommended for coiled partially thrombosed aneurysms.
IMPLICATIONS

Follow-up imaging of coiled intracranial aneurysms beyond the 6-month interval

For all coiled aneurysms, the first imaging follow-up after 6 months is a crucial point in time. We propose further imaging follow-up schedules after coiling to be divided in subgroups as follows:

Adequately occluded coiled aneurysms at 6 months

The vast majority of patients in this large subgroup, comprising approximately 80% of all coiled aneurysms, may be considered cured. Keeping in mind the very low annual risk of rupture from additional aneurysms and adequately occluded aneurysms, described in previous literature, screening in the first 5-10 years does not seem beneficial. Selected patients may benefit from screening after 5 years, such as young patients with multiple aneurysms, patients with positive family history or patients with very large or giant posterior circulation aneurysms. Whenever long-term imaging is considered, the imaging method of choice is MRA, preferably at 3 Tesla without administration of contrast material. Any risk of complications of the method of imaging, as with 3 vessel angiography, outweighs the low expected yield. MRA at 3 Tesla without administration of contrast material not only has negligible risk but also provides images of all cerebral vessels simultaneously allowing detection of de novo aneurysms and assessment of growth of additional untreated aneurysms.

Incompletely occluded coiled aneurysms at 6 months

If aneurysm reopening is detected at first angiographic follow-up, additional treatment of the coiled aneurysm should be considered. Both retreated and not retreated reopened aneurysms should have extended imaging follow-up beyond the 6 month interval, for example initially with a 2-year interval, and later every 3-5 years. For coiled large and giant basilar tip aneurysms and for coiled partially thrombosed aneurysms, more frequent imaging follow-up is recommended.
Recommendations for future research

It remains uncertain whether long-term imaging follow-up after adequate coiling is beneficial beyond the first 5-10 year interval. In addition, cost-effectiveness of periodic imaging follow-up in high-risk patient subgroups is yet to be clarified.

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. Whether patients with minimal growth (1 or 2 mm) of a small additional aneurysm may benefit from extended imaging follow-up is currently unknown.