

## Case of Asymptomatic Carotid Artery Stenosis in a Hypertensive Patient

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This is the case of a hypertensive patient with an asymptomatic carotid stenosis. This is a very common situation that neurologists have to manage.

The case is a 75-year-old man with an history of hypertension for 10 years, treated with amlodipine, 5 mg once a day, and perindopril, 8 mg once a day. His hypertension was considered to be controlled. He was also treated for a hyperlipidemia for 5 years with atorvastatin, 10 mg, once a day. His general practitioner recommended an echo-Doppler of cervical and intracranial arteries as part of a systematic screening because of his vascular risk factors. Echo-Doppler showed an atherosclerotic stenosis at the site of the left carotid bifurcation. On grayscale, this stenosis was characterized as a uniformly echogenic plaque (homogeneous plaque). On sonographic NASCET index (North American Symptomatic Carotid Endarterectomy Trial), there was a peak systolic velocity increase of 280 cm/s that translated to a high internal carotid artery/common carotid artery peak systolic velocity ratio of 4.5. Morphology and hemodynamic data were consistent with a severe carotid stenosis estimated about 70% per NASCET criteria.

A computed tomographic angiography, already planned by the general practitioner, confirmed a calcified severe stenosis of the bifurcation. The degree of narrowing was also estimated to be about 70% according to NASCET criteria. Contralateral internal carotid artery and intracranial arteries were normal. Arterial work-up was consistent with an isolated

severe asymptomatic left carotid stenosis. The patient had no previous history of cerebral vascular disease. His neurological examination was normal. His blood pressure was slightly elevated with systolic blood pressure of 160 mmHg and a diastolic blood pressure of 95 mmHg. His recent blood sample showed low-density lipoprotein cholesterol <1 g/L, and his glomerular filtration rate was normal.

This case addresses several issues, in particular estimation of the absolute risk of ischemic stroke ipsilateral to carotid stenosis and the need for prophylactic revascularization.

The issue of management of patients with asymptomatic carotid stenosis is very common because it is estimated that almost 1 million French people have an asymptomatic carotid stenosis of  $\geq 50\%$ . Of course, not all are aware of this condition.

### What Do We Know About the Need for Revascularization in Patients With an Asymptomatic Carotid Stenosis?

In 2 large randomized clinical trials conducted in the 1990s in patients with asymptomatic carotid stenosis, endarterectomy conferred an absolute risk reduction of only 1% per year compared with medical treatment. This translates into a large number needing treatment, about 100 patients require treatment to prevent 1 stroke in 1 year.<sup>1,2</sup> However, despite level I evidence (2 randomized clinical trials with similar results), no consensus exists as to whether asymptomatic carotid patients should be revascularized. Accordingly, there is considerable variation in clinical practice. The proportion of carotid revascularizations performed in asymptomatic patients varies from 0% in Denmark, 17% in the United Kingdom, 68% in Italy, and 90% in the United States (Figure 1).<sup>3,4</sup>

The controversy has intensified recently because of growing evidence that the annual risk of stroke in medically treated patients with asymptomatic stenosis has declined significantly during the past 20 years and is now <1% per year.<sup>5,6</sup> Therefore, it is uncertain whether the benefit of carotid surgery still justifies the procedural risk of stroke or death. It is also uncertain whether revascularization is good monetary value considering demands on health services.

The decreased risk of ipsilateral stroke in patients with asymptomatic carotid stenosis justifies focusing on medical treatment. Medical therapy for prevention of stroke in patients with carotid disease has evolved since these trials were performed. There is now more widespread use of statin therapy, more strict blood pressure control, and more effective antiplatelet regimes. In the ACST (Asymptomatic Carotid Surgery Trial) that compared medical treatment and endarterectomy in patients with asymptomatic carotid surgery, the proportion of patients on lipid-lowering therapy rose from <10% to >80%

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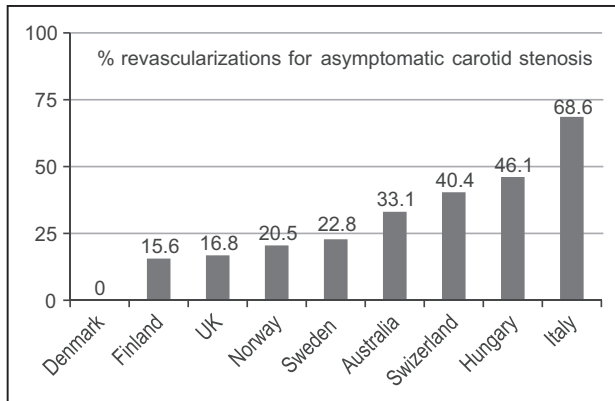
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**Figure 1.** Proportion of carotid revascularization (mainly using surgery) performed in patients with asymptomatic carotid stenosis in Europe and Australasia. Adapted from Vikatmaa et al<sup>9</sup> with permission of the publisher. Copyright © 2012, Elsevier. Authorization for this adaptation has been obtained both from the owner of the copyright in the original work and from the owner of copyright in the translation or adaptation.

during the study.<sup>7</sup> The relative risk reduction of nonperioperative stroke rate was similar in both groups, but the absolute benefit was smaller in patients on lipid-lowering therapy, because they had a lower risk of stroke than patients not taking lipid-lowering drugs. Randomized trials have shown that statins lower stroke risk in patients with cerebrovascular disease by about a third and halve the numbers requiring carotid revascularization.<sup>8,9</sup> In another study with follow-up of about 3700 patients in atherosclerotic clinic during a 20-year period with regular Doppler examinations, <10% were identified as having progression to occlusion.<sup>10</sup> Interestingly, 80% of occlusion occurred before 2002 corresponding to the era of widespread use of statins.<sup>10</sup> In addition, lifestyle modification, such as smoking cessation and reduction of body weight, may also have an impact on the event rate in patients with asymptomatic carotid disease.

Most patients in early trials of carotid surgery for asymptomatic carotid stenosis did not receive medical treatment that is now considered standard according to current national and international guidelines. Therefore, the small benefit of surgery in asymptomatic carotid stenosis observed in early trials is likely to have decreased further, obviating the need for endarterectomy in many patients with carotid disease. Therefore, it seems timely to assess whether endarterectomy combined with state of the art medical therapy improves long-term survival free of ipsilateral stroke (or periprocedural stroke or death) when compared with state of the art medical therapy alone.

### What About Specific Guidelines of Medical Treatment in Patients With Asymptomatic Carotid Stenosis?

There are few guidelines specifically dedicated to patients with carotid stenosis.<sup>11</sup> It is recommended to treat hypertension to maintain a blood pressure <140/90 mmHg but without specific target. In our case, our patient was already treated using perindopril and amlodipine. At this stage, we could add a third antihypertensive drug or increase the dose of perindopril or amlodipine. Our suggestion is to add a diuretic.

Always within these guidelines, patients who smoke should be advised to quit and to offer cessation intervention. In case of hyperlipidemia, a treatment with statin is recommended for all patients to lower low-density lipoprotein cholesterol level <1 g/L or even <0.7 g/L even though no randomized clinical trial have compared these targets. If the goal is not achieved, it is recommended to intensify therapy.

Diet and exercise are recommended and glucose-lowering drugs in case of diabetes mellitus but it is not known whether a very strict control of diabetes mellitus is useful in terms of prevention of events. Obviously, do not forget to add aspirin if the patient did not have aspirin before.

### Management for This Specific Patient

Because of uncertainties, each case must be discussed at a multidisciplinary team, including neurologists, neuroradiologists, and surgeons. In addition, physicians should try to ascertain the patients' preferences on treatment, as well as the reasons for these preferences. Finally, enrollment of patients in ongoing randomized clinical trials comparing revascularization to current optimal medical treatment (OMT) should be encouraged.

### Discussion of Case and Available Options

Professor Rossi: Having in mind that this plaque is a sign of atherosclerosis, which could be elsewhere. Many years ago, 1994, we reported that patients with atherosclerotic renovascular hypertension had an excess rate of carotid plaques. The same applies to coronary artery disease, so in the evaluation of the patient, I think you need to look at more than just one vascular bed.

You have stated that this patient was asymptomatic. That concerns me because symptoms cannot tell the whole story. If you do, for example, a magnetic resonance of the brain, you might see signals of previous ischemic events that were totally asymptomatic. In that case, I wonder if the definition of asymptomatic is still really there.

Professor Dominiczak: These are really good points and we would like some answers to those. Could we tackle all these points from Professor Rossi?

Dr Calvet: Regarding carotid stenosis, the asymptomatic status means that the patient did not suffer from an ischemic stroke due to carotid stenosis. Indeed, patients with a recent symptomatic carotid stenosis have a much higher risk of ipsilateral stroke justifying urgent revascularization. But it is true that the presence of silent brain infarction on computed tomography or magnetic resonance imaging (MRI) scan has also been related to future stroke risk. For instance, in the Asymptomatic Carotid Stenosis and Risk of Stroke Study,<sup>12</sup> an association between a higher stroke risk and silent brain infarction was found for embolic infarcts. These patients had a 3-fold excess risk of late ipsilateral stroke (1.0% versus 3.6%). However, the definition of infarction and topographical patterns has varied across studies making it difficult to standardize the impact of silent infarct, on the risk of stroke in patients with asymptomatic carotid surgery.<sup>13</sup> No large specific prospective magnetic resonance study assessed the association between silent brain infarction and future stroke risk in patients with asymptomatic carotid surgery. This makes it difficult to use such markers in current practice at the patient level.

Regarding the question about the extent of atherosclerosis, it is true that carotid stenosis is also a marker of atherosclerosis, especially of myocardial infarction. Cohort studies have shown that asymptomatic carotid stenosis is an independent risk factor for myocardial infarction<sup>14</sup> and that patients with bilateral carotid atherosclerosis are more likely to have a previous myocardial infarction and to die as a consequence of myocardial infarction compared with those with unilateral carotid stenosis.<sup>15</sup> We have also shown that the severity of cervicocephalic atherosclerosis is strong and an independent predictor of occult coronary stenosis of 50% or more in patients who had an ischemic stroke.<sup>16</sup> However, these associations cannot address the value of screening for occult coronary stenosis in patients with carotid stenosis. The potential benefit of such screening remains to be specifically assessed through a randomized clinical trial. Pending results of such trials, the decision to screen for other occult atherosclerotic stenosis should be individualized and addressed according to standard algorithms as suggested by guidelines. Above all, that concern emphasizes the need for OMT in all patients.

Professor Touyz: Just to follow, these are patients who are asymptomatic by definition, yet the general practitioner has undergone all these tests. I think the question that I would like to ask is, who do we screen? When do we screen? And should we screen? Because surely this is what is fundamental for all these patients who are apparently asymptomatic.

Professor Dominiczak: Before you answer, could I add to this? The huge variety between the way various European countries treat these patients is very interesting. But I wonder if you have, or somebody has, the data whether the primary referral is to surgeons or physicians? Because I think how aggressive the treatment is very much depends on whether it is a physician or surgeon. I know that in the United Kingdom, the vast majority of these patients would be with a physician and never see the surgeon. That is why it is below 18%. While in the United States, I presume, and maybe in France, they all go to a vascular surgeon and then the aggressive treatment follows because we know surgeons like to use the knife and be more aggressive. I think it would be extremely interesting to know clearly where they were referred for specialist care? This is not the first referral, but the second or third referral center. Is that known in these studies?

Dr Calvet: Unfortunately, the pathway of patients with asymptomatic carotid stenosis according to countries remains unknown. I do agree that it probably explains part of the differences as well as understanding of the concept of risk according to countries.

Professor Dominiczak: But I think we have an opportunity, as European Society of Hypertension, to design such a study. It could be a simple questionnaire to our European Society of Hypertension centers of excellence. What is the relationship between the referral pattern and the recommended type of treatment? I think it would be very interesting. So now you can tackle Professor Touyz's questions.

Dr Calvet: Current guidelines recommend that carotid revascularization in patients with asymptomatic carotid stenosis should only be used in highly selected cases but do not provide an evidence-based approach to guide such individual treatment decisions.<sup>11,17</sup> The absence of contemporary

evidence comparing optimal medical therapy to carotid surgery emphasizes the need for large trials in patients with asymptomatic carotid stenosis to assess which patients with asymptomatic carotid stenosis (if any) benefit from carotid surgery plus OMT when compared with OMT alone. Pending results from randomized clinical trials, it is quite impossible to answer this question and to identify a subgroup of patients for whom screening for asymptomatic carotid stenosis would be useful. For instance, the US preventive Services Task Force recommends against screening for asymptomatic carotid artery stenosis in the general adult population.<sup>18</sup>

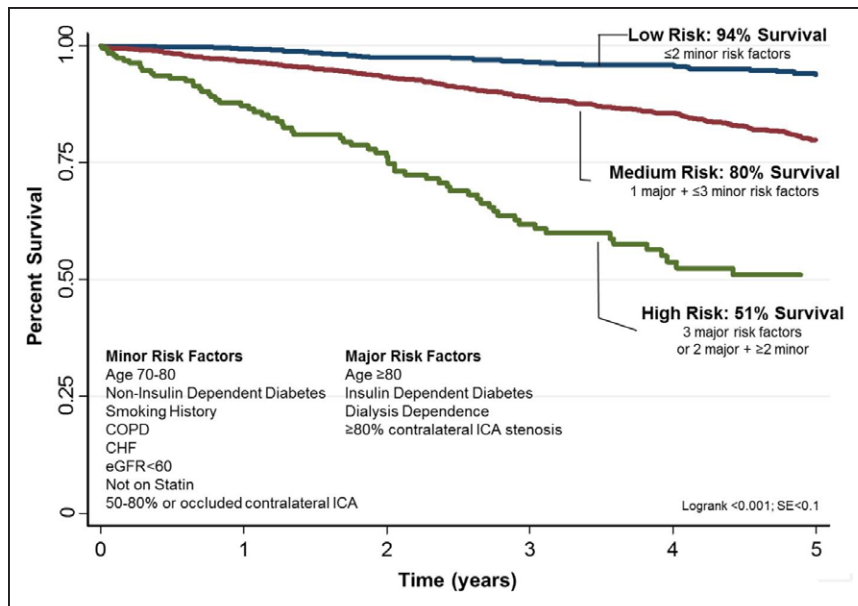
Dr Amar: I have a question. Basically, the point you are making is drugs can do very well. The problem is that we have all other evidence telling us that patients do not take drugs. So, the study shows that if you follow the patients and give them the good drugs, then maybe we do not need revascularizations. But in the real life, patients are lost to follow-up and so are there any studies that just looked at that?

Dr Calvet: The data we have so far refer to patients treated with medical treatment prescribed. We do not know whether they really take their medication or not. However, the decline of the risk of ipsilateral stroke observed during the last 30 years in patients with asymptomatic carotid stenosis is more likely to be related to improvement of treatment itself rather than patient compliance. However, future trials which will compare carotid revascularization plus OMT with OMT alone will also have to assess to what extent we can achieve the optimal goals of vascular prevention.

Professor Laurent: Thank you, David, for this illustrative case. In my opinion, the discussion is a little bit biased because the aging parameter seems to be lacking. At an age of 65, 75, and 85, life expectancy is different, and the perioperative and postoperative risks, which are around 2% to 3% as a mean, are increased by aging since the risk of cerebrovascular event depends on your age. Everything is discussed as if the risk of a cerebrovascular event is the same, at 65, 75, or 85. However, you must consider the age of the patient as a major parameter. A 70% stenosis is considered as a threshold for taking a decision and starting discussion. But how should we modulate our decision according to age and comorbidities?

Dr Calvet: Previous studies suggest that the benefit of surgery is greater in men aged less than 75, and no significant benefit was found among patients older than 75, but these later patients had a short life expectancy. Life expectancy is a critical factor in decision-making. Indeed, any condition that reduces life expectancy will limit any net potential benefit from revascularization. Therefore, models to predict survival in patients with asymptomatic carotid stenosis would be useful.

In this respect, Wallaert et al<sup>19</sup> examine factors associated with 5-year survival following carotid surgery in patients with asymptomatic stenosis in a large cohort of more than 4000 patients. In this study, patients with high-risk profiles, including age more than 80, insulin-dependent diabetes mellitus, dialysis dependence, and those with severe contralateral carotid stenosis, had a 5-year survival rate of 51%, whereas those with low-risk or medium-risk profile had a 5-year survival rate of 94% and 80%, respectively (Figure 2). In addition, patients with limited life expectancy are often at higher



**Figure 2.** Factors associated with 5-year survival after endarterectomy in patients with asymptomatic carotid artery stenosis. Reprinted from Wallaert et al<sup>19</sup> with permission of the publisher. Copyright © 2013, Elsevier. CHF indicates cardiac heart failure; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; and ICA, internal carotid artery.

risk for revascularization. In our current case, our patient is expected to live long enough to potentially benefit from revascularization (Figure 2).

**Dr Moodley:** I am Dr Moodley from Durban in South Africa. Where I come from, there is a lot of type 2 diabetes mellitus. When we get this type of patient, we would routinely do a glucose tolerance test. We would routinely also do computed tomography scanning of the brain. Because if we find previous lesions there, that will move us more toward intervening. Third, just a comment, the salicylic acid prevention ongoing. Do you recommend 75, 81, 150, or 300 mg of aspirin in a patient like this?

**Dr Calvet:** As done in secondary prevention of ischemic stroke, a usual dose between 75 and 160 mg once a day is recommended in that condition.

**Dr Moodley:** Would you be more aggressive with the low-density lipoprotein level?

**Dr Calvet:** Despite absence of specific randomized clinical trials in that population of patient, type 2 diabetes mellitus is a good reason to lower low-density lipoprotein cholesterol below 0.7 g/L rather than below 1 g/L (see above).

**Dr Turc:** You focused on carotid artery surgery; however, as compared to surgery, stenting was associated with a lower risk of procedural myocardial infarction in the CREST study (Carotid Revascularization Endarterectomy vs Stenting Trial). Do you not think that this should be taken into account?

**Dr Calvet:** It is true that in CREST which included patients with symptomatic and asymptomatic carotid stenosis, the significantly higher periprocedural risk of stroke in patients treated with stenting was partly offset by a lower periprocedural risk of myocardial infarction with stenting,<sup>20</sup> such that the combined 30-day risk of any death, stroke, or myocardial infarction (MI) was only slightly higher in the stenting group than in the surgery group. However, the rates of MI were much higher in CREST than in previous trials, which may reflect the reenrollment of more patients with cardiac disease, as well as a different process of screening for MI. Unlike European trial that compared stenting to surgery in symptomatic patients,

CREST did not require the presence of clinical symptoms for diagnosing MI. If silent MIs are included in the primary end point, then silent cerebral infarcts as detected by MRI should be included as well, which have been found to be much more frequent in patients treated with stenting.<sup>21</sup> The second reason why the inclusion of MI in the primary end point of CREST is debatable is that one cannot equate stroke with MI equally. CREST investigators found that stroke had a much greater and sustained impact on health-related quality of life than MI 1 year after the procedural period.<sup>22</sup>

**Professor Jennings:** I would like to add some support for medical therapy, along 2 lines. Number 1 is, most of the data we have talked about relates to rates of ipsilateral stroke, and you have already talked about the fact that quite often these people go on, and they have myocardial infarction. They also have contralateral stroke, quite often, too, and that kind of takes away the argument for local treatment of a systemic disease. A second point is, we have gone along with the logic, that if somebody has an asymptomatic disease, has MRI lesions of previous involvement, that this leads toward more likely wanting to intervene. But if you really believe that contemporary medical therapy works, there could be just as much an argument for that being a useful strategy for preventing future strokes.

**Dr Calvet:** I thoroughly agree with you. I focus on ipsilateral stroke because only ipsilateral stroke is expected to be avoided with surgery. But again, it is crucial to consider OMT in all patients with the aim to prevent all vascular events.

**Professor Guzik:** I think the point raised by Professor Laurent regarding age of the patient and consideration for procedural complications linked to that is very important. However, I came here to ask about additional clinical investigations that your list did not contain and which might be useful in follow-up. In particular, what do you think about the need to perform serial ultrasound testing for progression of the disease? What do you think is the place for that in such a patient?

**Dr Calvet:** Of course, there is a place for that. Several studies have reported an association between carotid stenosis

progression and the risk of ipsilateral stroke. In a cohort of 523 patients with 50% to 69% carotid stenosis, any progression to more over 1 year was associated with the occurrence of vascular events.<sup>23</sup>

In 1469 patients enrolled in the ACST, a fast (over 1 year) rate of progression (from less than 50% to 70% or more, or from 50% to 69% to 90% or more) of asymptomatic carotid luminal narrowing was associated with a 4-fold higher risk of ipsilateral stroke.<sup>24</sup>

Professor Guzik: When would you do the second test in this patient to be able to detect such potential risk?

Dr Calvet: Probably at least once a year.

Dr Bilo: Yes. Gregors Bilo from Milan. My first question was already anticipated. My second question was, what about the cases which are maybe not so common, but you can see occasionally a bilateral stenosis. Does it influence your management if you find in the second artery, a moderate or a severe stenosis?

Dr Calvet: On one hand, the presence of a contralateral stenosis is a predictive factor of an ipsilateral stroke and of any vascular events and also a predictive factor of procedural complication in case of revascularization. On the other hand, it is a major factor of a lower life expectancy (see above). Then, that kind of patient has a higher risk of dying before the end of the follow-up in the studies. This is another reason to consider OMT as a real option.

Dr Barigou: Thank you. Dr Barigou from Paris. I have a question about the use of anticoagulants in this condition. When we have an important plaque on the carotid artery, and with microembolic signals should it be recommended to use anticoagulant drugs to replace antiaggregants? The second question would be about the blood pressure targets. You say that we should be below 140/90 mmHg, but many studies show that in the outcome of stroke, the lower the better in many studies. So should we not target less than 135 over 85 mm mercury, and should we not provide treatment by diuretics like others in this room have said? Thank you.

Dr Calvet: I agree that lower is better, provided we do not have too severe a stenosis or tandem lesion. There is no reason why we should consider a different target for that kind of patient, except in a patient with cerebral hypoperfusion. Then, as previously discussed, a diuretic should be considered in that case. Screening for microembolic signal on transcranial Doppler is another very good opportunity to stratify the risk of ipsilateral stroke. In the Asymptomatic Carotid Emboli Study, the odds ratio for the risk of ipsilateral stroke for patients with asymptomatic carotid stenosis who had embolic signals was 5.6, which is very consistent with the recent meta-analysis that included 6 studies and more than 1000 patients.<sup>25</sup>

Dr Barigou: The question was about the use of anticoagulants in this type of patient.

Dr Calvet: There are no data that can recommend anticoagulant in that type of patient. One study suggested interest in combination therapy with clopidogrel and aspirin in patients with symptomatic carotid stenosis and microembolic signals waiting for revascularization.

Dr Sharabi: Yuri Sharabi, from Tel Aviv. We look at age, the comorbidities, and the progression of the plaque, but I was wondering how much emphasis do you put on the plaque

itself? For example, the PLOS article talked about meta-analysis, talked about carotid distensibility, how it adds to the re-stratification. Do you put a lot of weight on the structure, the distensibility, and the plaque itself, in decision-making?

Dr Calvet: Absolutely. Magnetic resonance techniques are now available that can visualize different characteristics of the atherosclerotic plaque. In addition to the lumen, the vessel wall and the atherosclerotic plaque itself can be imaged in detail as well. In particular, 2 recent meta-analyses showed that the presence of intraplaque hemorrhage on MRI strongly predicted ipsilateral stroke in patients with asymptomatic carotid stenosis.<sup>26,27</sup> Then, such technique can be used to better assess individual risk.

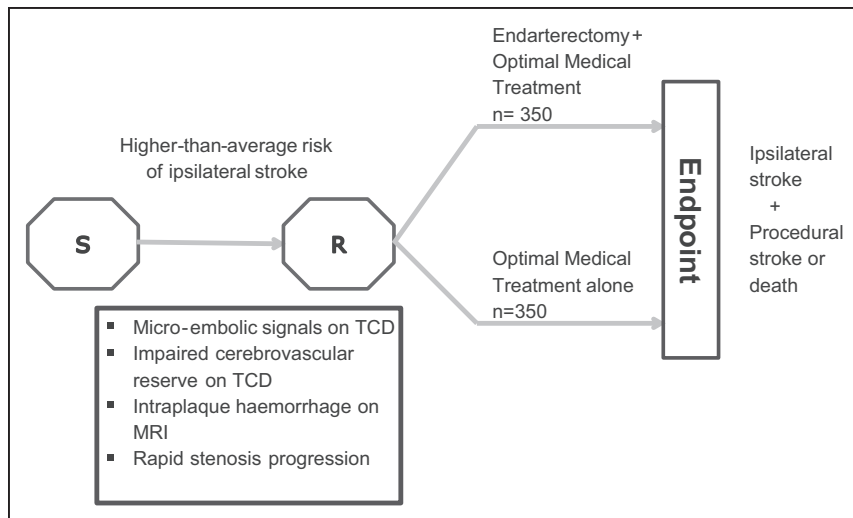
Professor Touyz: Yes, thank you. Just going back to the question about aspirin. Do you have any comments regarding blood pressure control and initiation of aspirin usage? Because there are some guidelines in terms of using aspirin only when blood pressure is actually controlled. So in this patient, where you have still got very high blood pressure, would you still start aspirin?

Dr Calvet: I believe that you refer to the risk of hemorrhage. However, in the specific situation of a patient with atherosclerotic carotid stenosis, aspirin initiation should not be delayed even though blood pressure is not well controlled.

Professor Dominiczak: Okay. I would like to come back to the patient you described, and ask what precisely happened to this particular patient? What have you done, and what has been the outcome of this particular patient. That is my question 1.

My question 2, which is sort of under family and friends management type of question, how many times would you normally do detailed MRI in a patient like this? I accept your data from the computed tomography, but in 2016, I would send the patient for MRI and maybe more than once, and I would like to know what you would do for your family and friends? That is a very good test in medicine.

Dr Calvet: Thank you very much for your question. I am going to give you my proposal for this patient. In France, we believe that the time has come to implement ultrasound or MRI-based predictors of stroke risk in randomized trials comparing carotid revascularization and medical therapy in patients with asymptomatic carotid stenosis. This trial, called ACTRIS (Endarterectomy Combined With OMT vs OMT Alone in Patients With Asymptomatic Severe Atherosclerotic Carotid Artery Stenosis at Higher-Than-Average Risk of Ipsilateral Stroke, <https://clinicaltrials.gov/ct2/show/NCT02841098>; Figure 3), will be the first trial to assess whether endarterectomy further reduces stroke risk in asymptomatic carotid stenosis patients at higher than average risk of stroke who receive OMT. Among potential predictive factors of ipsilateral stroke risk, we select those which have been consistently associated with an increased risk of ipsilateral stroke, are available in routine clinical practice, and can be standardized in a setting of a multicenter trial. Specifically, the presence of transcranial Doppler (TCD)-detected embolic signals, intraplaque hemorrhage on MRI, TCD-measured impaired cerebral vasoreactivity, or rapid stenosis progression has been all shown to increase at least 3-fold the risk of ipsilateral stroke, corresponding to an absolute risk of ipsilateral stroke risk >3% per year. To conclude, I



**Figure 3.** Design of ACTRIS trial. Endarterectomy combined with optimal medical therapy (OMT) vs OMT alone in patients with asymptomatic severe atherosclerotic carotid artery stenosis at higher than average risk of ipsilateral stroke. MRI indicates magnetic resonance imaging; R, randomization; S, screening; and TCD, transcranial Doppler.

would recommend the OMT in this patient as previously discussed, and at the same time, I would stratify his individual risk of ipsilateral stroke according to TCD and MRI plaque results. In case of the presence of at least 1 predictive factor, I would be happy to enroll the patient in ACTRIS. In the absence of any predictive factors, I would not recommend revascularization.

Dr Amar: In the protocol and also for the patient. What is rapid stenosis progression?

Dr Calvet: Rapid means within 1 year. Of course, echo-Doppler has to be repeated at least once a year in case of stability.

Dr Turc: Which proportion of patients with severe carotid stenosis do you expect to be reachable for the study?

Dr Calvet: Probably about 20% of patients. But we do not know if these predictive factors are really independent or not. Only microembolic signal and intraplaque hemorrhage have been shown to be independently associated with an increased risk in patients with symptomatic stenosis, so probably it should be the same thing for asymptomatic stenosis. By contrast, it is likely that a rapid progression is associated with intraplaque hemorrhage. Overall, we estimated that about one fifth of patients should be eligible.

Dr Tropeano: In this study, do you take into account echographic parameters of the plaque, like characteristic of the plaque.

Dr Calvet: Not directly for eligibility of patients but in an ancillary study. For decision-making, it is useful if you have a very heterogeneous plaque. But the concern is about the definition of heterogeneous plaque. Not all specialists agree with the definition, so that, in a multicenter trial, such a marker is not easy to use to select patients.

### Summary and Case Resolution

We reported the case of a 75-year-old man with a history of hypertension and hyperlipidemia for whom screening tests consistently demonstrated a 70% stenosis of the left internal carotid artery. This carotid stenosis was asymptomatic because the patient did not have any medical history of neurological deficit. During the Clinical-Pathological conference, we discussed the need for revascularization in addition to the OMT and additional investigations to better identify ipsilateral risk

of stroke in this patient. We concluded that because of uncertainty, enrollment of that kind of patient in ongoing trials comparing current medical treatment to revascularization plus OMT should be encouraged.

This patient had a high-resolution MRI of the carotid stenosis that did not identify intraplaque hemorrhage and Transcranial-Doppler that identified neither microembolic signal nor impaired cerebral vasoreactivity. We decided to reinforce medical treatment adding aspirin, diuretic, and increasing dose of statin and to perform another echo-Doppler within 1 year to check for a rapid progression of the stenosis.

### Disclosures

None.

### References

- Executive Committee for the Asymptomatic Carotid Atherosclerosis Study. Endarterectomy for asymptomatic carotid artery stenosis. *JAMA*. 1995;273:1421–1428. doi: 10.1001/jama.1995.03520420037035.
- Halliday A, Mansfield A, Marro J, Peto C, Peto R, Potter J, Thomas D; MRC Asymptomatic Carotid Surgery Trial (ACST) Collaborative Group. Prevention of disabling and fatal strokes by successful carotid endarterectomy in patients without recent neurological symptoms: randomised controlled trial. *Lancet*. 2004;363:1491–1502. doi: 10.1016/S0140-6736(04)16146-1.
- Vikatmaa P, Mitchell D, Jensen LP, Beiles B, Björck M, Halbakken E, Lees T, Menyhei G, Palombo D, Troëng T, Wigger P, Venermo M. Variation in clinical practice in carotid surgery in nine countries 2005–2010. Lessons from VASCUNET and recommendations for the future of national clinical audit. *Eur J Vasc Endovasc Surg*. 2012;44:11–17. doi: 10.1016/j.ejvs.2012.04.013.
- Wang FW, Esterbrooks D, Kuo YF, Mooss A, Mohiuddin SM, Uretsky BF. Outcomes after carotid artery stenting and endarterectomy in the Medicare population. *Stroke*. 2011;42:2019–2025. doi: 10.1161/STROKEAHA.110.608992.
- Naylor AR. What is the current status of invasive treatment of extracranial carotid artery disease? *Stroke*. 2011;42:2080–2085. doi: 10.1161/STROKEAHA.110.597708.
- Abbott AL. Medical (nonsurgical) intervention alone is now best for prevention of stroke associated with asymptomatic severe carotid stenosis: results of a systematic review and analysis. *Stroke*. 2009;40:e573–e583. doi: 10.1161/STROKEAHA.109.556068.
- Halliday A, Harrison M, Hayter E, Kong X, Mansfield A, Marro J, Pan H, Peto R, Potter J, Rahimi K, Rau A, Robertson S, Streifler J, Thomas D; Asymptomatic Carotid Surgery Trial (ACST) Collaborative Group. 10-year stroke prevention after successful carotid endarterectomy for asymptomatic stenosis (ACST-1): a multicentre randomised trial. *Lancet*. 2010;376:1074–1084. doi: 10.1016/S0140-6736(10)61197-X.

8. Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. *Lancet*. 2002;360:7–22. doi: 10.1016/S0140-6736(02)09327-3.
9. Sillesen H, Amarencu P, Hennerici MG, Callahan A, Goldstein LB, Zivin J, Messig M, Welch KM; Stroke Prevention by Aggressive Reduction in Cholesterol Levels Investigators. Atorvastatin reduces the risk of cardiovascular events in patients with carotid atherosclerosis: a secondary analysis of the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) trial. *Stroke*. 2008;39:3297–3302. doi: 10.1161/STROKEAHA.108.516450.
10. Yang C, Bogiatzi C, Spence JD. Risk of stroke at the time of carotid occlusion. *JAMA Neurol*. 2015;72:1261–1267. doi: 10.1001/jamaneurol.2015.1843.
11. Brott TG, Halperin JL, Abbara S, et al; American College of Cardiology; American Stroke Association; American Association of Neurological Surgeons; American College of Radiology; American College of Radiology; Society of NeuroInterventional Surgery; Society for Vascular Medicine; Society for Vascular Surgery. 2011 ASA/ACCF/AHA/AANN/AANS/ACR/ASNR/CNS/SAIP/SCAI/SIR/SNIS/SVM/SVS guideline on the management of patients with extracranial carotid and vertebral artery disease. A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, and the American Stroke Association, American Association of Neuroscience Nurses, American Association of Neurological Surgeons, American College of Radiology, American Society of Neuroradiology, Congress of Neurological Surgeons, Society of Atherosclerosis Imaging and Prevention, Society for Cardiovascular Angiography and Interventions, Society of Interventional Radiology, Society of NeuroInterventional Surgery, Society for Vascular Medicine, and Society for Vascular Surgery. *Circulation*. 2011;124:e54–e130. doi: 10.1161/CIR.0b013e31820d8c98.
12. Kakkos SK, Sabetai M, Tegos T, Stevens J, Thomas D, Griffin M, Geroulakos G, Nicolaidis AN; Asymptomatic Carotid Stenosis and Risk of Stroke (ACSRS) Study Group. Silent embolic infarcts on computed tomography brain scans and risk of ipsilateral hemispheric events in patients with asymptomatic internal carotid artery stenosis. *J Vasc Surg*. 2009;49:902–909. doi: 10.1016/j.jvs.2008.10.059.
13. Jayasooriya G, Thapar A, Shalhoub J, Davies AH. Silent cerebral events in asymptomatic carotid stenosis. *J Vasc Surg*. 2011;54:227–236. doi: 10.1016/j.jvs.2011.01.037.
14. Joakimsen O, Bonna KH, Mathiesen EB, Stensland-Bugge E, Arnesen E. Prediction of mortality by ultrasound screening of a general population for carotid stenosis: the Tromsø Study. *Stroke*. 2000;31:1871–1876.
15. Touzé E, Warlow CP, Rothwell PM. Risk of coronary and other non-stroke vascular death in relation to the presence and extent of atherosclerotic disease at the carotid bifurcation. *Stroke*. 2006;37:2904–2909. doi: 10.1161/01.STR.0000248764.51601.bb.
16. Calvet D, Touzé E, Varenne O, Sablayrolles JL, Weber S, Mas JL. Prevalence of asymptomatic coronary artery disease in ischemic stroke patients: the PRECORIS study. *Circulation*. 2010;121:1623–1629. doi: 10.1161/CIRCULATIONAHA.109.906958.
17. Goldstein LB, Bushnell CD, Adams RJ, et al; American Heart Association Stroke Council; Council on Cardiovascular Nursing; Council on Epidemiology and Prevention; Council for High Blood Pressure Research, Council on Peripheral Vascular Disease, and Interdisciplinary Council on Quality of Care and Outcomes Research. Guidelines for the primary prevention of stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2011;42:517–584. doi: 10.1161/STR.0b013e3181fcb238.
18. LeFevre ML; U.S. Preventive Services Task Force. Screening for asymptomatic carotid artery stenosis: U.S. Preventive Services Task Force recommendation statement. *Ann Intern Med*. 2014;161:356–362. doi: 10.7326/M14-1333.
19. Wallaert JB, Cronenwett JL, Bertges DJ, Schanzer A, Nolan BW, De Martino R, Eldrup-Jorgensen J, Goodney PP; Vascular Study Group of New England. Optimal selection of asymptomatic patients for carotid endarterectomy based on predicted 5-year survival. *J Vasc Surg*. 2013;58:112–118. doi: 10.1016/j.jvs.2012.12.056.
20. Brott TG, Hobson RW II, Howard G, et al; CREST Investigators. Stenting versus endarterectomy for treatment of carotid-artery stenosis. *N Engl J Med*. 2010;363:11–23. doi: 10.1056/NEJMoa0912321.
21. Bonati LH, Jongen LM, Haller S, et al; ICSS-MRI Study Group. New ischaemic brain lesions on MRI after stenting or endarterectomy for symptomatic carotid stenosis: a substudy of the International Carotid Stenting Study (ICSS). *Lancet Neurol*. 2010;9:353–362. doi: 10.1016/S1474-4422(10)70057-0.
22. Cohen DJ, Stolker JM, Wang K, Magnuson EA, Clark WM, Demaerschalk BM, Sam AD Jr, Elmore JR, Weaver FA, Aronow HD, Goldstein LB, Roubin GS, Howard G, Brott TG; CREST Investigators. Health-related quality of life after carotid stenting versus carotid endarterectomy: results from CREST (Carotid Revascularization Endarterectomy Versus Stenting Trial). *J Am Coll Cardiol*. 2011;58:1557–1565. doi: 10.1016/j.jacc.2011.05.054.
23. Balestrini S, Lupidi F, Balucani C, Altamura C, Vernieri F, Provinciali L, Silvestrini M. One-year progression of moderate asymptomatic carotid stenosis predicts the risk of vascular events. *Stroke*. 2013;44:792–794. doi: 10.1161/STROKEAHA.112.671461.
24. Hirt LS. Progression rate and ipsilateral neurological events in asymptomatic carotid stenosis. *Stroke*. 2014;45:702–706. doi: 10.1161/STROKEAHA.111.613711.
25. Markus HS, King A, Shipley M, Topakian R, Cullinane M, Reihill S, Bornstein NM, Schaafsma A. Asymptomatic embolisation for prediction of stroke in the Asymptomatic Carotid Emboli Study (ACES): a prospective observational study. *Lancet Neurol*. 2010;9:663–671. doi: 10.1016/S1474-4422(10)70120-4.
26. Gupta A, Baradaran H, Schweitzer AD, Kamel H, Pandya A, Delgado D, Dunning A, Mushlin AI, Sanelli PC. Carotid plaque MRI and stroke risk: a systematic review and meta-analysis. *Stroke*. 2013;44:3071–3077. doi: 10.1161/STROKEAHA.113.002551.
27. Saam T, Hetterich H, Hoffmann V, Yuan C, Dichgans M, Poppert H, Koeppel T, Hoffmann U, Reiser MF, Bamberg F. Meta-analysis and systematic review of the predictive value of carotid plaque hemorrhage on cerebrovascular events by magnetic resonance imaging. *J Am Coll Cardiol*. 2013;62:1081–1091. doi: 10.1016/j.jacc.2013.06.015.

## Case of Asymptomatic Carotid Artery Stenosis in a Hypertensive Patient

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