CAROTID Atherosclerosis – Natural History and Complications

Prof. Pavel Poredoš, MD, PhD

Department for Vascular Disease
University Medical Centre Ljubljana
Slovenia
DECLARATION OF CONFLICT
OF INTEREST

• No conflict of interest to declare
THE PREVALENCE OF CAROTID STENOSIS

- **moderate** (50-70%)
  - < 70 years – 3.6%
  - > 70 years – 9.3%

- **severe** (70-99%)
  - ≥ 65 years – 1.7% *(deWeerd M et al, Stroke 2009)*

- **stenosis ≥ 50%**
  - 50-59 years – 1.0%
  - > 70 years – 10.0% *(Touze E, Rev Neural 2008)*
CLINICAL CONSEQUENCES OF CAROTID ATHEROSCLEROSIS

• For 15-30% of acute ischaemic stroke is responsible extracranial carotid stenosis
  

• Asymptomatic carotid stenosis (ASCS) has an average annual risk of stroke up to 2% per year (it is about half of that of any stroke) and the risk for coronary events is around 7%.

  Streifler I, J Neural Transm 2011
CLINICAL CONSEQUENCES OF CAROTID ATHEROSCLEROSIS

• In symptomatic patients (TIA, minor stroke), the risk of stroke is exceeding 20% in 3 months.
  Sheehan OC et al, Stroke 2010

• Annual stroke mortality is around 0.6% whereas the overall mortality is estimated to be 4-7%.
  Redgrave JN, Curr Opin Neurol 2007

• Therefore the natural history of asymptomatic carotid stenosis is quite benign.

The data gained are from the period before optimal medical treatment.
The data on the risk of stroke in pts. with carotid atherosclerosis were mostly retrieved a few decades ago (before optimal medical treatment) and are probably overestimating the real nowadays risk.

Findings indicate a shift toward lower risk comparing observations from older and recent trials, resulting from better medical treatment in the last period.

A gradual reduction of annual risk of ASCS from 2.5% in the mid 1980s to 1% by 2008.


A better natural history for patients with asymptomatic carotid stenosis in recent years.
NATURAL HISTORY OF CAROTIDATHEROSCLEROSIS
ACST study – 10-year follow up

• of the 3,210 pts, 50% have died

• even in younger groups (<75 years) 44% of males were dead

• stroke was the underlying cause in only 10%

• cardiovascular cause was responsible for almost 50% of total mortality

Streifler Jy, J Neural Transm 2011
FACTORS PREDICTING THE RISK OF ISCHEMIC CV EVENTS IN ASYMPTOMATIC CAROTID ATHEROSCLEROSIS

- severity of stenosis
- progressive stenosis
- structure of plaques
- risk factors of atherosclerosis: SBP, cholesterol, diabetes, smoking, age
- contralateral symptomatic carotid stenosis or occlusion
- silent ipsilateral cerebral infarctions
- microembolic signals identified by transcranial Doppler
- serum creatinine
THE DEPENDANCE OF \textbf{CV EVENTS} ON THE STRUCTURE OF PLAQUES

STABLE CAROTID PLAQUE

US – HYPERECHOIC
VIDEODENSITOMETRIC CHARACTERISTICS
HIGH GSM 0 \rightarrow 255
HISTOLOGY – FIBROS TISSUE WITHOUT INFLAMMATION

Baroncini et al, Cardiovascular Ultrasound, 2006
VULNERABLE CAROTID PLAQUE

US-HYPOECHOIC (echolucent)

VIDEODENSITOMETRIC CHARACTERISTICS

LOW GSM: 0 - 255

HISTOLOGY – HIGH LIPID CONTENT
INFLAMMATORY CELLS

Baroncini et al, Cardiovascular Ultrasound 2006

LOW GSM (<32) IS RELATED WITH 5-TIME HIGHER RISK FOR ASYMPTOMATIC AND SYMPTOMATIC CEREBRAL INSULT
MORPHOLOGIC PRESENTATION OF Atherosclerotic Plaques Using US Photodensitometry

Image region

Image colouring (10 contours)

Dark area close to lumen : Yes
Patient Status : D (Str.)
Discrete white blobs : Yes
Type of Plaque : Type 2
Percentage of stenosis 1.99% : 70

1 comp. All plaque
Percent. : 30.73 15.53 %
Area mm2: 18.91
Red black distance : 0.19
Run length GLD : 721.912
GSM : 7.45533
GRADE OF CAROTID STENOSIS AND THE RISK OF STROKE

• The risk of CV events increases as the grade of stenosis increases – up to 94%.
  – average annual risk of ASCS (≥50%) is about 2%
  – in ASCS ≥ 80% - annual risk of stroke is 6%

• Patients with more severe stenosis had more severe stroke.

MICROEMBOLI - PREDICTORS OF CV EVENTS

• Embolism from stenotic extracranial carotid lesions is important pathomechanism of cerebral infarction.

• Asymptomatic microembolic signals (MES) detected by transcranial Doppler in middle cerebral artery reflect plaque activity (stability) and predict CV events.

• The studies indicated that pts. without MES have only about 1% risk of annual stroke and those with MES around 15%.

Liapis CD et al, Stroke 2001

• Using MES detection, it is possible to identify pts. at high risk of CV events who may benefit from revascularization.
HOW TO PREVENT PROGRESSION OF CAROTID ATHEROSCLEROSIS AND COMPLICATIONS?

• Current “best” medical therapy:
  • modification of risk factors

• Invasive procedures:
  • CEA
  • CAS
MEDICAL THERAPY

• **Hypertension** is the most important modifiable RF
  – all antihypertensive agents have positive effects on the incidence of stroke  
  
  Goldstein LB et al, American guidelines, Stroke 2006

• **Cholesterol:**
  – SPARCL trial – 4731 pts with TIA or recent stroke (up to 6 months)
    80 mg of atorvastatin
    33% RR reduction in late stroke in pts with carotid atherosclerosis and
    16% RR in whole group
  – **HPS study:** 17,265 pts without CV disease
    simvastatin 40 mg
    significant RR of CV events: first stroke was reduced for 25% and ischemic for 30%

Therefore, **statins reduce primary and secondary CV events.** However, there is no definite answer regarding the effectiveness of statins on incidence of CV events related to asymptomatic carotid stenosis.
RR reduction of stroke detected in the CARE, LIPID, and HPS studies

Kaste M, AHA Journals, 2002
MODIFICATION OF RISK FACTORS

• Smoking cessation – imperative
• Regulation of blood-glucose level in diabetics (HbA$_1^C$<7%)
• Antiplatelets:
  - aspirin – primary prevention
  - aspirin+dipyridamole – secondary stroke prevention
  - aspirin+clopidogrel – in pts. with proven symptomatic disease in other arterial beds
SYMPTOMATIC CAROTID STENOSIS AND THE RISK OF STROKE

• Within 24h after TIA or minor stroke, the risk of stroke is – 5% - and within 3 months, the risk is exceeding - 20%.
  
  Rothwell PM, Eur J Vasc Endovasc Surg 2008

• About 15-20% of stroke patients reported preceding TIA.
  
  Rothwell PM et al, Neurology 2005

• The time window for prevention of stroke is short – 40% of stroke related to TIA occur during the first week after TIA.
  
  Rothwell PM et al, Neurology 2005

• A meta-analysis confirmed that 37% of pts. with symptomatic carotid stenosis had early recurrent stroke.
  
  Lovett JK et al, Neurology 2004

• Ipsilateral ischemic stroke is in pts. with ≥ 50% symptomatic stenosis during a 30-day period 100 times greater than that in pts. with similar asymptomatic stenosis.
  
  Rothwell PM et al 2008
SHORT TIME – WINDOW for recurrent stroke in pts. with symptomatic stenosis

Cumulative risk of stroke following a TIA or minor stroke in the Oxford Vascular Study 1709 pts.

Rothwell PM, Eur J Vasc Endovasc Surg, 2008
MEDICAL TREATMENT OF SYMPTOMATIC CAROTID STENOSIS

- Benefits of medical treatment of symptomatic carotid stenosis in high risk period were indicated in the EXPRESS and SOS-TIA study. 


- early initiation of medical treatment (up to 1 day) after TIA or minor stroke (aspirin or clopidogrel, simvastatin, antihypertensive drugs) is associated with 80% reduction in the risk of early recurrent stroke.
MEDICAL TREATMENT OF SYMPTOMATIC CAROTID STENOSIS

- Antiplatelet drugs represent the basis of preventive measures.
  - aspirin is indicated in all pts. with TIA or minor stroke
  - EXPRESS study indicated that aspirin+clopidogrel would be more effective in acute phase
  - the MATCH trial showed a trend towards benefit of aspirin+clopidogrel vs. clopidogrel alone

Diener HC et al, Lancet 2004

- CARESS trial confirmed significant reduction of microembolic signals on dual therapy vs. monotherapy and fewer recurrent stroke in dual therapy.

Markus HS et al, Circulation 2005

These studies suggest that combination of antiplatelet treatment is likely to reduce the risk of early recurrent stroke prior to endarterectomy
BLOOD PRESSURE REGULATION IN SYMPTOMATIC CAROTID ATHEROSCLEROSIS

- Blood pressure lowering has been shown to be effective in secondary prevention of stroke.
- Gradual BP lowering is beneficial and safe in pts. with unilateral stenosis.
- Caution is needed in blood pressure lowering in pts. with severe atherosclerosis.
- Increasing stroke risk in pts. with bilateral ≥70% stenosis with low systolic BP.
- Aggressive BP lowering (SBP <120 mmHg) prior to endarterectomy may be harmful in pts. with bilateral carotid stenosis.

Rothwell PM, Eur J Vasc Endovasc Surg 2008
Invasive treatment (CEA) of symptomatic carotid stenosis is still a golden standard for prevention of stroke.

Advances in medical therapy have challenged the indication for invasive treatment of pts. with ASCS.

Already in the past (the mid 90s) most studies showed no definite benefit in ASCS for endarterectomy in comparison to medical therapy.

Only the ACAS trial showed the benefit of endarterectomy in pts. with ASCS. The risk was reduced to 1% annual rate, which is comparable to the effect of current medical treatment.
PREVENTION OF CV EVENTS WITH INVASIVE TREATMENT OF CAROTID STENOSIS

• The observed benefit is in ASCS, inspite of excellent surgical skill, limited and NNT to prevent one stroke in 2 years is high: 67-83. However, in symptomatic pts., it is <10.

  Streifler JY, J Neural Transm 2011

• The results of carotid artery stenting of ASCS have been so far incoherent.


• Therefore, for pts. with asymptomatic carotid stenosis, medical treatment is an optimal option. A subgroup of pts. who clearly benefit from CEA or CAS cannot be clearly determined by existing evidence.
TAKE HOME MESSAGE

• Asymptomatic carotid stenosis is a relatively benign disease.

• Most of pts. with carotid atherosclerosis are dying because of cardiovascular complications and not because of CV events.

• Complications referring to ASCS are not related only to the degree of stenosis but also to the structures of atherosclerotic plaque and to atherosclerotic lesions in other territories.

• Natural history of ASCS is influenced by medical treatment and annual risk of CV events is recently only about 1%. (In the mid 80s it was 2-3%).
• In pts. with **symptomatic** carotid stenosis **3-month risk is exceeding 20%**. Most of CV events appear the first week after TIA or minor stroke.

• Current **“best” medical therapy** significantly reduces the progression of carotid atherosclerosis and prevents CV events in ASCS as well as in symptomatic pts.

• **Early initiation of medical treatment** (particularly dual antiplatelet) reduces the risk of early recurrent stroke.