9. The Icaros Trial: Concepts and Outline

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Abstract

Even though it is generally accepted that the composition and the characteristics of the plaque may be influential on the outcome of Carotid Endarterectomy (CEA) and Carotid Stenting (CAS), especially in case of CAS where the plaque is not removed but remodelled, indication to either one of the two procedures is mostly based, both in trial and in the clinical practice, on the percentage of stenosis and the presence or absence of pre-procedural neurological symptoms, while the features of the plaque are somehow disregarded and ignored. The reason for this is understandable; in fact the percentage of stenosis, as well as the presence or not of symptoms, are easy to identify and quantify, while the plaque is usually defined as "very soft" or "pretty homogeneous", etc. which makes the parameter rather undetermined and consequently unreliable. With the ***ICAROS Study****, we have introduced a method which allows us to numerically quantify, on the basis of the GSM (Grey Scale Median) of the duplex scan image, the characteristics of the plaque so that this variable can be utilised in an easy and reliable way for the correct indication to CAS.*

Introduction

• It is generally agreed that severe (≥ 70%) stenoses of the carotid bifurcation in symptomatic and asymptomatic patients should be treated for the prevention of cerebral embolism. Carotid Endarterectomy (CEA) has been adopted since many years in a large number of patients world-wide with excellent early and late post-operative results [1].

• More recently Carotid Artery Stenting (CAS) has been introduced as an alternative procedure to CEA and is now being performed with increasing frequency. Recent publications on large series of patients, report very encouraging post-procedural early results comparable to those achievable with CEA, especially when brain protection devices are used [2, 3, 4]. Nevertheless, the role of this technique is strongly debated among vascular surgeons and endovascular interventionalists because of the potential risks.

• The North American Symptomatic Carotid Endarterectomy (NASCET) and ECT trials, have demonstrated the efficacy and safety of Carotid Endarterectomy (CEA) in the prevention of cerebral embolism from carotid artery bifurcation plaque with high-grade stenoses (≥70%) in asymptomatic patients, if the mortality and morbidity following intervention are lower than 6% [5, 6]. The Asymptomatic Carotid Atherosclerosis Study (ACAS) furthermore has established that surgical treatment is advisable also for asymptomatic patients with carotid stenosis >60%, if the cumulative mortality/morbidity rate is less than 3%. These studies have identified this treatment as the gold standard [7, 8].

• On the other hand, it is generally agreed that a longer follow-up is required for CAS before any definitive conclusion can be drawn concerning safety and that multicentre randomised studies, which compare CEA with CAS, would be highly recommended.

• The general consensus is that CAS remains an investigational procedure and that it is necessary that large series of patients be studied, following a rigid protocol, with comparable results and long term follow-ups [9].

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• The results of CEA, plus the identification of those patients who would most benefit from this kind of procedure, have been definitely recognised. Any major or minor contra-indication to conventional surgical treatment (such as: carotid restenosis, neck irradiation, high internal carotid lesions, pulmonary disease, congestive heart failure, recent stroke, etc.) were initially referred as indication to CAS [10], while the progressively more and more sophisticated and minimally invasive techniques for CAS, may have led to a widening of indication of this procedure in an increasing number of patients, sometimes with low risk lesions of the carotid bifurcation, introducing a bias in the statistical analysis. Good results of CAS could be obtained treating patients at lower risk of stroke.

• The establishment of the Carotid Revascularization Endarterectomy vs. Stent Trial (CREST), a multicenter randomised trial, to compare the efficacy of CAS vs. CEA in symptomatic patients with a carotid stenosis over 50%, is very appropriate. The duration of the study will be four years [11].

• It should be noticed that the morphology of the plaque, which is the parameter that marks the history of the atherosclerotic disease and ultimately will influence the percentage of stenosis and appearance of symptoms, is not considered among the criteria for indication to either one of the two procedures.

The importance of the plaque

• In clinical practice carotid plaques are recognised as atherosclerotic lesions currently identified as "soft plaques, lipidic or fibro-lipidic, haemorrhagic or colliquated; ulcerated, with thrombus inside". The high risk of stroke for some of these lesions is intuitive and even evident but not demonstrated. Indication for treatment of the carotid bifurcation lesions is often based only on the duplex scan examination, which is a very inexpensive, reliable and non-invasive diagnostic technique, which provides an accurate evaluation of the morphology of the plaque.

• The majority of post-CAS complications are mostly related to brain embolisation and it is to be highly suspected that the composition of the plaque could be influential on the release of particles from the plaque, which is ultimately the potential for brain embolism and appearance of transient or definitive neurological deficits [12]. The morphology and the composition of the plaque may play a major role in identifying subgroups of patients at higher or lower risk for brain embolisation during CAS and therefore for the selection of patients to be submitted to the stenting procedure [13].

• The information that we may obtain from the characteristics of the plaque and the risk of brain embolisation during CAS, is of outmost importance not only for clinical and ethical reasons but also for economical and legal implications [14, 15].

• The peri-operative stroke/death rate following carotid CAS is quite variable in different reports, especially when brain protection devices are applied and high neurological complication rates are thought to be due to embolic particles released from the carotid plaque during the endoluminal manoeuvre [16, 17]. To reduce the risk of embolization, several brain protection devices have been proposed and adopted and in some cases, very promising results have been reported [18, 19]. Nevertheless, it should be noticed that whatever brain protection device is used, no protection throughout the entire procedure is provided [20].

• Duplex scan analysis of the carotid bifurcation can give in a simple, reliable, inexpensive and non-invasive manner, important information concerning the morphology and composition of the plaque and the data processed through a standardisation procedure, can finally provide the GSM value [21, 22].

• GSM (Grey Scale Median) is a simple and quantifiable parameter, like the rate of stenosis or symptomatology, which depicts the morphology and composition of the plaque. It is operator and machine independent and is intended to evaluate the echogenicity of the plaque [23]. The GSM is obtained freezing the image of the plaque on the duplex scan machine and transferring it to a PC.

• A photo-editor software will standardise the image. Colour information is recorded and blood and adventitia are referred respectively as the values 0 and 180 of a grey scale ranging from 0 (black) to 255 (fully white). After this standardisation procedure is completed, the software calculates the median of the grey scale value of the pixels contained in the outlined plaque.

GSM could therefore represent the third parameter with rate of stenosis and neurological symptoms, on which to base the decision for the indication to CAS [24].

The Icaros registry

The **ICAROS Study** that we have introduced, is a registry which utilises the **I**maging in **C**arotid **A**ngioplasty in order to assess the **R**isk of **S**troke.

ICAROS correlates the risk of brain embolisation with the echographic characteristics of the plaque, by correlating the pre-procedural GSM of the plaque and the post-procedural events (death, stroke, TIA, silent brain infarct, MI).

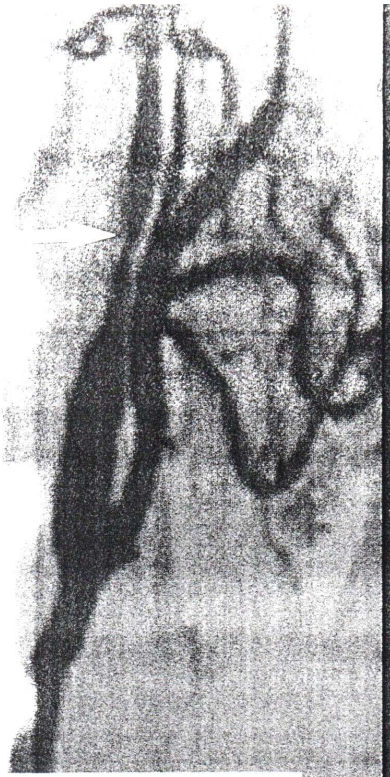


Fig. 1a. A case of restenosis at the distal end of previous CEA.

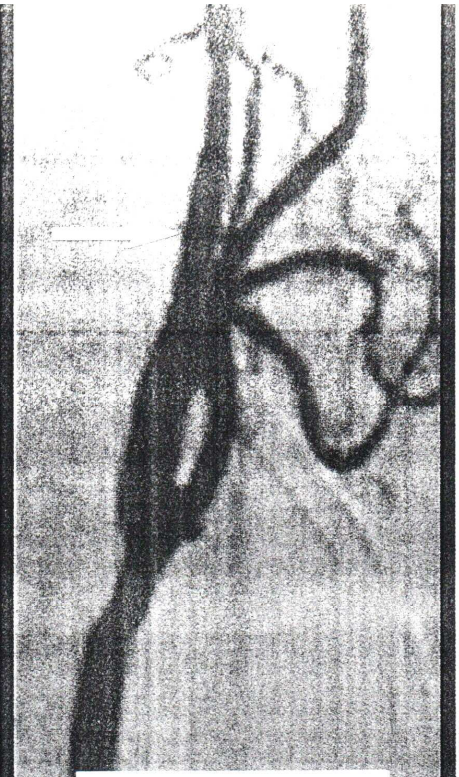


Fig. 1b. Good dilatation on control angiography.

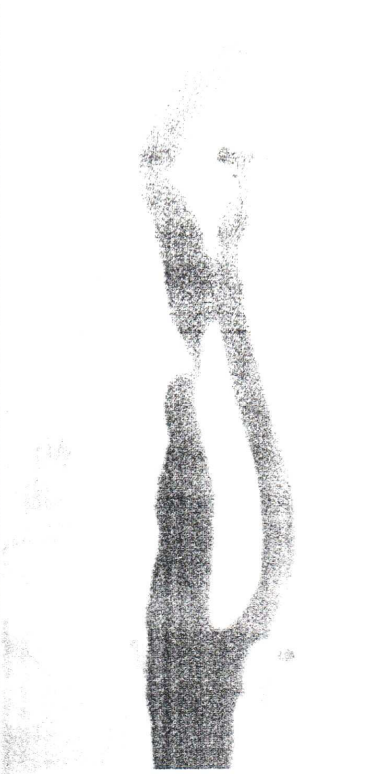


Fig. 2. A sub-occlusive stenosis of the ICA.

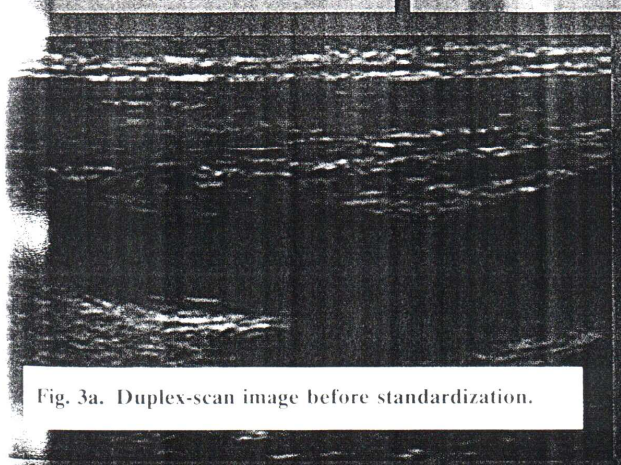


Fig. 3a. Duplex-scan image before standardization.

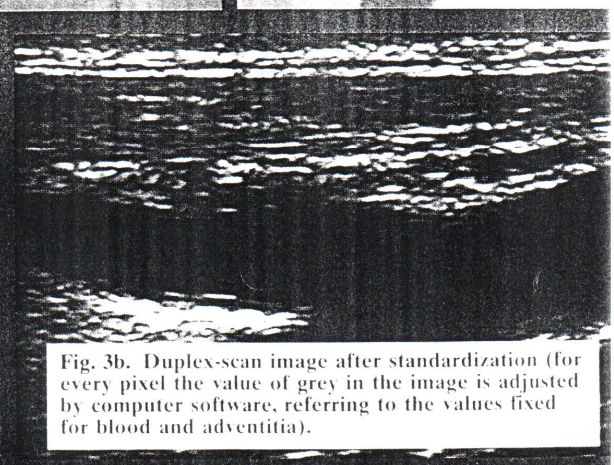


Fig. 3b. Duplex-scan image after standardization (for every pixel the value of grey in the image is adjusted by computer software, referring to the values fixed for blood and adventitia).

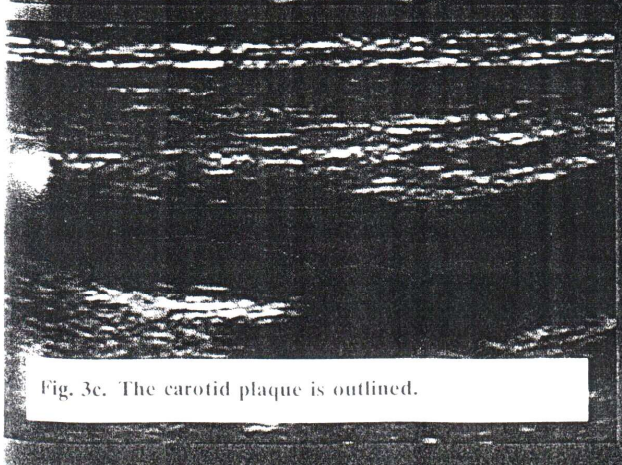


Fig. 3c. The carotid plaque is outlined.

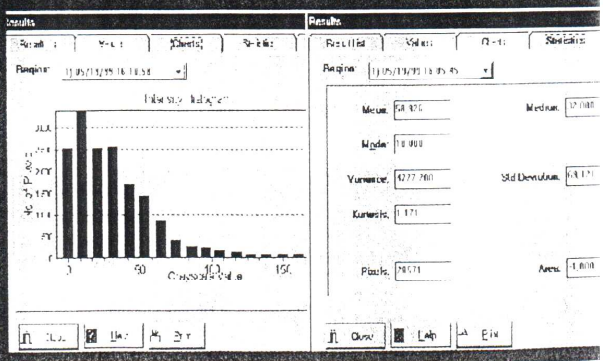


Fig. 3d. The computer analyses the distribution of the grey values of the plaque, fixing the GSM index.

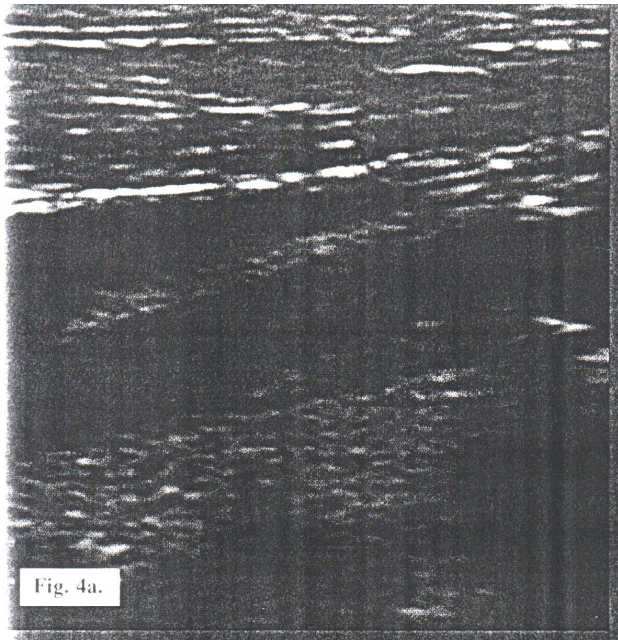


Fig. 4a.

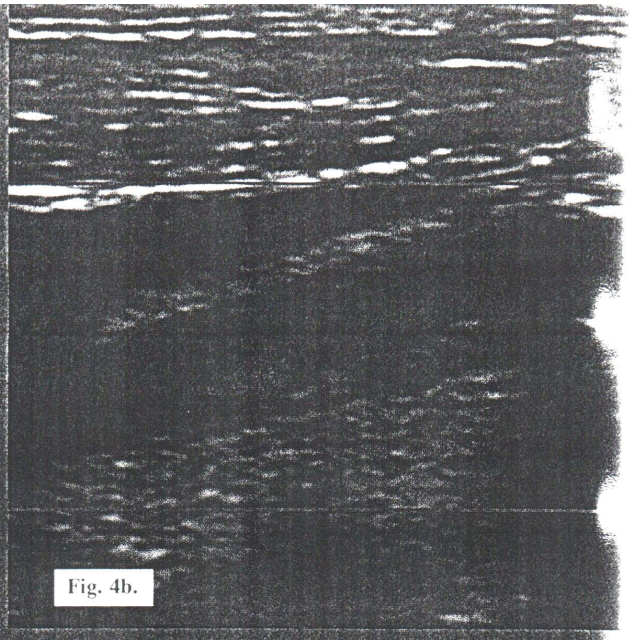


Fig. 4b.

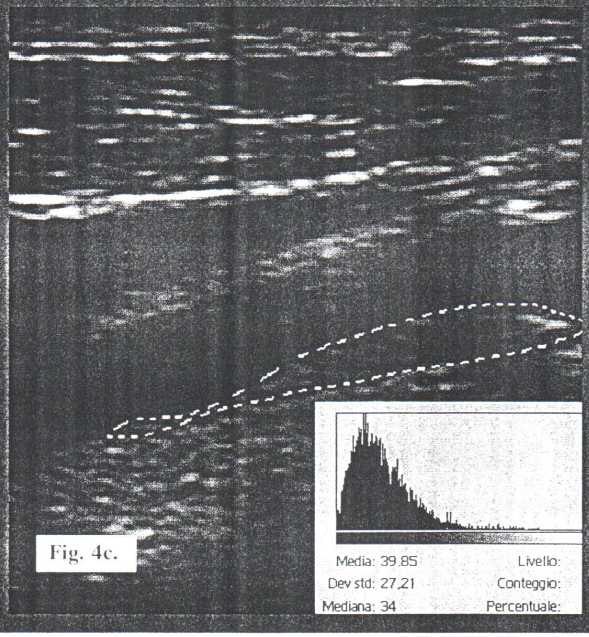
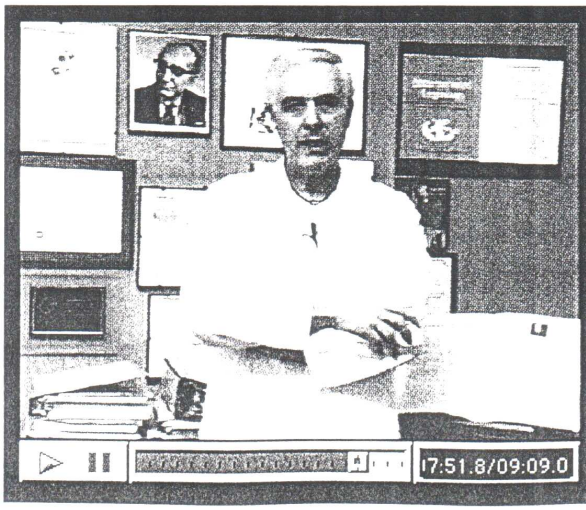


Fig. 4c.

Fig. 4. Another carotid plaque is outlined and the ISM is calculated.





• This procedure allows a stratification of the patients, with reference to the risk of brain embolisation, on the basis of the echogenicity of the plaque.

Collecting different experiences on carotid stenting from several clinical centres world-wide, correlation will be investigated between characteristics of the plaque (as recorded by duplex and defined by GSM index) and the outcome after CAS procedure.

• All Centers performing CAS can enter patients in the ICAROS Registry, following their own indications and techniques, just reporting carefully the following data on the Registry Data Form:

• Patients history, physical and neurological examination, blood tests, EKG and cardiac evaluation, duplex, brain CT (or MR), angio.

• Description of the endovascular procedure with information on devices used and complications, if any.

• Detailed description of the neurological events

• Duplex scan, CT or MR controls to be performed within a week from procedure.

• Follow-up with physical and duplex scan examinations to be at 1, 6 and 12 months from procedure.

• All data concerning pre-procedural duplex-scan images of the plaque will be recorded and stored on video or magneto-optical disk and collected by the Referring Center for standardisation for identification of the GSM index. An immediate feed-back of information will be provided with the Center that has sent in the data. Analysis of the filtered particles (number, size and composition) will be provided when available.

Conclusions

The preliminary results have proved that the **ICAROS Study** is:

– Feasible.

– Reliable by providing a numeric quantification of the GSM.

– Reproducible through the normalisation of the images collected from the various Centres participating in the Study.

If the **ICAROS end-points** will be proved, characterisation of the carotid plaque will be a reliable parameter for indication to CAS.

References

1. Zarins C. K. Carotid endarterectomy: The gold standard. *J. Endovasc. Surg.* 1996; *3*: 10-5.
2. Gomez C. R., Roubin G. S., Vitek J.J. *et al.* Safety of carotid artery stenting in NASCET patients. *Neurology* 1998; *50*: 76A.
3. Wholey M.H., Wholey M., Bergeron P., Diethrich E. B., Henry M., Laborde J.C., Mathias K., *et al.* Current global status of carotid artery stent placement. Catheterization & Cardiovasc Diagn. *44* (1): 1-6, 1998.
4. Hassen-Khodja R., Sala F., Declemy S., Pittaluga P., Batt M. Angioplastie Carotidienne: Donnees de la Litterature. *Journal des Maladies Vasculaires 23* (4) : 243-50, 1998.
5. North American Symptomatic Carotid Endarterectomy Trial Collaborators. Beneficial effect of carotid endarterectomy in symptomatic patients with high-grade carotid stenosis. *N. Eng. J. Med.* 1991; *325* (7) : 445-53.
6. European Carotid Surgery Trialists' Collaborative Group. MRC European Carotid Surgery Trial: Interim results for symptomatic patients with severe (70-99%) or mild (0-29%) carotid stenosis. *Lancet* 1991; *337*: 1235-43.
7. Executive Committee for the Asymptomatic Carotid Athero-Sclerosis Study. Endarterectomy for asymptomatic carotid artery stenosis. *JAMA* 1995; *273* (28): 1421-8.
8. Hobson R.W. II, Weiss D.G., Fields W.S., *et al.* Efficacy of carotid endarterectomy for asymptomatic carotid stenosis. *N. Eng. J. Med.* 1993; *328* (4) :221-7.
9. Bequemin J.P., Qvarford P., Castier Y., Melliere D. Carotid angioplasty: Is it safe? *J. Endovasc. Surg.* 1996; *3*: 35-41.
10. Diethrich E.B. Indication for Carotid Artery Stenting: A Preview of the Potential Derived from Early Clinical Experience. *J. Endovasc. Surg.* 1996; 3: 132-9.
11. Hobson R.W., Brott T., Ferguson R., Roubin G., Moore W., Kuntz R., Howard G. Ferguson J. CREST. *Cardiovasc. Surg.* 1997; 5 (5) : 457-9.
12. Ohki T., Marin M.L. *et al.* Ex vivo human carotid artery bifurcation stenting: Correlation of lesions characteristics with embolic potential. *J. Vasc. Surg.* 1998; *27* (3): 463-71.
13. Carr S. C., Cheanvechai V., Virmani R., Pearce W.H. Histology and clinical significance of the carotid atherosclerotic plaque: Implications for endovascular treatment. *J. Endovasc. Surg.* 1997; *4*: 321-5.
14. Aburahma A.F., Covelli M. A., Robinson P. A., Holt S.M. The role of carotid duplex ultrasound in evaluating plaque morphology: Potential use in selecting patients for carotid stenting. *Endovasc. Surg.* 1999; *6*: 59-65.
15. Reid D.B. Carotid plaque characterization: Helpful to endarterectomy and endovascular surgeons. *J. Endovasc. Surg.* 1998: 246-250.
16. Theron J., Courtheoux P., Alachkar F., Maiza D. New triple coaxial catheter system for carotid angioplasty with cerebral protection. *AJNR* 1990; *11*: 869-874.
17. Kachel R. Results of balloon angioplasty in the carotid arteries. *J. Endovasc. Surg.* 1996; *3*: 22-30.
18. Henry M., Amor M., Chati Z., Foliguet B., *et al.* Protected carotid angioplasty and stenting. Presented at the Transcatheter Cardiovascular Therapeutics; Washington DC, Sept. 1999.
19. Parodi J.C. An alternative method for preventing emboli during carotid stenting. Presented at the 26th Annual Symposium-Vascular and Endovascular Surgery; New York, Nov. 1999; XVIIA2.1
20. Ohki T., Roubin G.S., Veith F.J., Iyer S.S., Brady E. Efficacy of a filter device in the prevention of embolic events during carotid angioplasty and stenting: an ex vivo analysis. *J. Vasc. Surg.* 1999; *30*: 1034-44.
21. El-Barghouty N., Geroulakos G., Nicolaides A., Androulakis A., Bahal V. Computer assisted carotid plaque characterization. *Eur. J. Vasc. Endovasc. Surg.* 1995; *9* (4) : 389-93.
22. Biasi G.M., Sampaolo A., Mingazzini P.M., De Amicis P., El-Barghouty N., Nicolaides A.N. Computer analysis of ultrasonic plaque echolucency in identifying high risk carotid bifurcation lesions. Eur *J. Vasc. Endovasc. Surg.* 1999; *17*: 476-479.
23. Elatrozy T., Nicolaides A., Tegos T., Zarka A.Z., Griffin M., Sabetai M. The effect of B-mode ultrasonic image standardisation on the echodensity of symptomatic and asymptomatic carotid bifurcation plaques. *Int. Angiol.* 1998; *17*: 179-86.
24. Biasi G.M., Mingazzini P.M., Baronio L., Piglionica M.R., Ferrari S.A., Elatrozy T.S., Nicolaides A.N. Carotid plaque characterization using digital image processing and its potential in future studies of carotid endarterectomy and angioplasty. *J. Endovasc. Surg.* 1998; 5: 240-6.