Randomized Control Study of the IntraVascular UltraSound vs. angiography for the evaluation and treatment of carotid artery stenoses.

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Aims and objectives

Carotid artery stenting (CAS) is a viable alternative treatment to carotid endarterectomy. Stroke is one of the most important complications of CAS and is mostly caused by intra-procedural distal embolization of plaque components (1). In order to prevent procedure related cerebrovascular accidents, a careful assessment of carotid plaque morphology is required.

Large studies demonstrated that necrotic core, mainly if superficial and surrounded by a thin or ruptured fibrous cap, is the predominant histological finding in carotid plaque related to cerebrovascular accidents (2). So, it is fundamental to have a technique able to identify vulnerable and prone to rupture plaques (3-4).

Duplex UltraSound (US) proved to be a good technique to identify necrotic cores plaques; in fact, hypoechogenic signals are associated with a predominant lipidic core, correlated with an higher risk of embolization and stroke during carotid artery interventions (2-5-6).

Nevertheless, use of transcutaneous US remains highly subjective and operator-dependent.

Multislice spiral Computed Tomography (msCT) and High Resolution Magnetic Resonance (HR-MR) are able to identify lipid-rich tissues, calcifications and thrombus with high diagnostic accuracy, except for small plaques which remain undetectable (2).

IntraVascular UltraSound (IVUS) and Virtual Histology - IVUS (VH-IVUS) have been extensively validated in the coronary arteries imaging, with a high vessel and plaque resolution, which is essential in the endovascular procedures planning (7). As CTA and MRA, VH-IVUS is able to demonstrate the proportion of hard and soft plaque constituents and the amount of fibrous and necrotic lipid core. Thus this technique may provide useful information on how the plaque may behave at the moment of treatment and which stent should be deployed (2-7).

Even if the diagnostic accuracy of VH-IVUS for the imaging of the carotid arteries resulted good in many available studies, it is lower in resolution and does not provide three-dimensional images, when compared to diagnostic techniques such as CTA or MRA, which are widely used for the carotid arteries imaging (8-10). VH-IVUS has, however, the advantage of the real-time intraprocedural evaluation over both CTA and MRA

The primary aim of this prospective study is to evaluate the usefulness of IVUS in the identification of otherwise un-noticed complications during carotid stenting. The secondary aim is the evaluation of the impact of IVUS-assisted stenting in the procedural outcomes and long-term patency rates.
Methods and materials

Patient selection

A randomized prospective evaluation was performed on 60 Patients at high surgical risk who underwent CAS during a 14-month period.

The institutional review board at our institution fully approved the treatment protocol. All eligible patients were invited to participate in the study with an information letter. Based on the written and spoken information, the patient made the decision whether or not to join the study. The informed consent was obtained from each participating patient. Patients were informed of their right to withdraw from the study at any time. The study was conducted in accordance with the current version of the Declaration of Helsinki.

Patient population

All patients were sorted using Duplex Ultrasound evaluation as primary diagnostic tool.

Fiftyfour patients (90 %) were evaluated by pre-procedural Magnetic Resonance Angiography (MRA) integrated with HR-MR for plaque characterization; 6 (10 %) Patients underwent Computed Tomography Angiography (CTA) for MR contraindications.

Patients presenting stenoses higher than 85% were excluded from the study, as to avoid significant blood flow reduction to the brain during the IVUS catheter passage or thraumatism due to the catheter-to-plaque attritus. Patients which presented carotid post-CAS or post-CEA restenoses or stenosis determined by an etiology different than atherosclerosis (e.g. post-attinic stenoses, post-surgery stenoses, stenoses determined by neoplasms), were not enrolled in the study.

Patients were matched by age, risk factors and plaque pattern, and divided in two groups: in group 1 VH-IVUS evaluation was performed during the CAS procedure, before and after the stent deployment; in group 2 a conventional CAS procedure, without the use of VH-IVUS, was carried out. IVUS-assisted CAS was performed in 30 Patients (50%), angiography-only CAS was performed in 30 Patient (50%).

Data about total procedure time, fluoroscopy time and success rate was collected for all the 60 patients treated. All Patients underwent a 5-day anti-aggregation therapy with ASA (100 mg / day) and clopidogrel (75 mg / day) or Ticlopidin (500 mg/die) before the procedure.

Statistical methods
Analysis of the data gathered from this retrospective study was descriptive. Simple descriptive statistics (n, mean, median, SD, minimum and maximum for continuous variables, and n and percentage for discrete variables), graphs, and patient listings were used to evaluate and summarize the data. X² test was used for the p values calculation.

**CAS procedure**

All procedures were carried out in an angiographic suite and performed by the same interventional radiologist. Procedural and fluoroscopy times have been measured starting from the arterial puncture to the sheath removal. Common femoral artery access was obtained using Seldinger technique and guide catheter access into the common carotid artery was obtained using a 7-Fr 10 cm-long introducer sheath (Terumo, Tokyo, Japan). A diagnostic angiography was performed in order to confirm the carotid plaque location, stenosis degree and to evaluate the anatomy and patency of the intracranial.

5000 IU of heparin were administered intravenously to maintain the Active Coagulation Time (ACT) between 200 and 250 seconds. Distal embolism prevention was carried out using a cerebral protection device during both IVUS guided and angiography-only procedures.

The Gray-Scale IVUS and VH-IVUS evaluations were performed using a 20-MHz IVUS probe (Eagle Eye, Volcano Therapeutics, Rancho Cordova, CA). The IVUS catheter was washed with saline solution prior to its placement into the internal carotid artery through the guide catheter. After the gain optimization, the IVUS catheter was retrieved from the distal third of the internal carotid artery at a speed of 1.0 mm/sec using a motorized pull-back device. A 360° rotational and two dimensional longitudinal ultrasound was performed for a plaque composition and stenosis degree assessment, the examination was recorded on a DVD. This evaluation was also performed after stent deployment and compared during the procedure with the pre-stent one to assess wall integrity, stent-wall apposition and stent expansion.

Stent type and size were primarily chosen on the basis of the pre-procedural MRA or CTA. In the Group 1 procedures, the pre-stenting IVUS findings were evaluated during the procedure in order to confirm or disprove the pre-procedural stent choice.

Only two types of stents were used in this trial: an open-cell nitinol one (Vivexx, Bard Medical, Covington, USA) and a closed-cell medical steel one (Carotid Wallstent, Boston Scientific, Natick, USA). The open cell stent was used for calcific-fibrous plaques, the closed-cell one for mixed-lipidic ones. The embolic protection device used was EPI Filter Wire EZ (Boston Scientific, natick, USA) in all the procedures but one, in which a Spider FX (Covidien, Dublin, Ireland) was used.
In both groups, a diagnostic angiography was performed after the stent deployment and the embolic protection device retrieval, as to evaluate the angiographic outcome of the procedure and the extra and intra-cranial vessels patency and blood flow.

All patients underwent a post-procedural neurological evaluation 24 hours after the procedure and were discharged one day after the treatment, with a 6 weeks double anti-aggregation therapy.

Technical success was defined as a residual stenosis lower than 30%.

**Follow up**

Neurological status and blood pressure of every patient were monitored for at least 24 hours, with a Duplex US examination before the discharge.

Follow-up was performed at 1, 3, 6 months and each year after the procedure by Duplex US evaluation.

Mean follow up period was $23 \pm 5.3$ months (minimum 15 - maximum 28). A lifelong antiplatelet therapy was administered to each patient while clopidogrel or ticlopidin were administered for 6 weeks.
Fig. 1: (A) Post procedural IVUS Grey Scale showed a suboptimal stent expansion (B) A stent further dilatation was performed, with good final result in IVUS scan.

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Fig. 2: IVUS imaging shows (A) an high lipid plaque at the origin of the internal carotid artery and (B) the following stent deployment. (B) An intraluminal lesion was identified at
the distal end of the stent with a substantially hypoechoic ultrasound pattern at IVUS Grey Scale, corresponding to ruptured plaque material protrusion through stent cells caused by plaque squeezing.

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Fig. 3: Carotid plaque debris showed in figure 2, removed by local manual aspiration using a 6 Fr 90 cm long guide catheter.

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Results

Technical success was achieved in all patients. The VH-IVUS evaluation performed after stent deployment showed a not optimal stent-to-wall apposition, which was not evident at the fluoroscopic evaluation, in 2 patients (3 %), leading to a postdilation (Fig 1). (Fig 1).

The VH-IVUS evaluation led to a stent type change in 3 patients (5 %): 2 close-to-open cell, 1 open-to-close cell. After VH-IVUS plaque evaluation stent changes in size and/or length were not required in any case.

In one Patient, during after-stenting VH-IVUS evaluation, an intraluminal lesion at the distal third of the stent was observed. This lesion presented ultrasonographic characteristics suggestive for ruptured plaque material protrusion through stent cells, caused probably by a plaque "squeezing" by the stent; it appeared at the post-stent IVUS evaluation as an hypoechoic protrusion (Fig. 2). It was decided to perform a manual aspiration with a 6 Fr 90 cm long guide catheter (Mach 1™ Guide Catheter, Boston Scientific Corporation, Natick, United States). A subsequent Grey-scale IVUS demonstrated the success of the manual aspiration and fragments of embolic plaque material were found in the EPD filter after its retrieval (Fig. 3). The patient was relocated to the Stroke Unit as a precaution and was discharged three days after the procedure; no peri-procedural neurological symptomatology had arisen.

Mean fluoroscopy time resulted longer in VH-IVUS guided procedures (IVUS group procedure lengthened of 10.3 ± 5 minutes).

A peri-procedural self-resolving transient ischemic attack was observed in one patient (1.6%) which underwent VH-IVUS assisted procedure. No other peri-procedural or long-term cerebrovascular accidents (e.g. transient ischemic attack, ipsilateral minor or major stroke, death, acute myocardial infarction) were observed. Difference among the two groups resulted not significant (p<0.05).

At the 14 months follow up, 3 (5%) significant (> 70%) restenoses, which required a secondary angioplasty, were observed; two cases (3%) were observed in the angiography-guided-only group and one case in the IVUS-assisted group. The fference between the two groups resulted not significant (p<0.05).
Conclusion

IVUS has been exhaustively described as a valid diagnostic tool for the intra-procedural evaluation of the coronary plaque morphology for the percutaneous transluminal angioplasty and stenting real-time assistance (7-10). There are currently no definitive evidences of its usefulness in CAS procedures, even if some studies are available (11-12).

Whenever a pre-procedural CT- or MR-angiography is not available, the angiographic evaluation typically requires a multiplanar assessment for an accurate vessel measurement and an adequate stent choice; moreover, the angiography offers a vessel luminography, with few or none informations about the morphology and composition of the atherosclerotic plaque. A pre-procedural duplex ultrasound evaluation is highly operator-dependant, and certain plaques, as the highly calcific ones, are poorly evaluated through this technique. These limitations may be addressed by IVUS. The 360° IVUS vessel Imaging may reduce the need to perform calibrated angiogram runs for stent sizing; the need of a lower number of angiogram runs may, moreover, lead to a reduction of the overall administered contrast media volume and of the radiation exposure (2,7).

In our study, the careful pre-procedural assessment of vessel size, plaque morphology and aortic arch obviated the need of the diagnostic calibrated angiograms; this resulted in comparable values of contrast media administration between the two groups and a higher procedural time and radiation exposure, as well as procedural overall costs, in the IVUS-assisted group.

In our experience, VH-IVUS evaluation led to stent type change only in 3 patients (5%), with no change in the size and length, indicating a satisfying concordance with CTA or MRA about the stent choice; though these results are preliminary and need to be confirmed by observations on higher samples, we believe that VH-IVUS, although flawed by a lower spatial resolution and bidimensional output, may offer a satisfying pre-procedural evaluation of plaque ultrastructure and morphology even in carotid plaques.

Undeniably, IVUS has the advantage of a real-time procedural evaluation over MRA and CTA, which may be useful when treating plaques which are highly prone to rupture, such as the inflamed ones, or whenever the operator needs to counter-check the fluoroscopic images for undiagnosed residual stent deformity and suboptimal wall stent apposition (7,8,11,12). In this study IVUS assessment resulted useful after stent deployment in two cases, in which poor stent expansion, which was not evident at the fluoroscopic evaluation, was found. Some authors, such as Inglese et al. and Clark et al, believe that the early identification and resolution of a not optimal stent expansion may determine a reduction in the in-stent restenosis rate (2,13). In our study, however, the restenosis rate did not significantly differ between the two groups.
The comparison of pre- and post-CAS IVUS examination, moreover, led to an unexpected result in one case, in which a focal plaque protrusion through the stent cells, determined by a plaque compression by the stent, was observed. This complication, which otherwise would have been unnoticed, was readily solved by intraprocedural manual aspiration of the debris and, thus, a potentially dangerous intraprocedural embolic complication was prevented.

Though this study provides preliminary results, to our knowledge this is the first randomized prospective study in which IVUS is used for the CAS intraprocedural evaluation. The main limitation of this study is the small number of enrolled patients, which should be increased in order to confirm the resulted data.

CONCLUSIONS

Though not recommendable as a routine evaluation during CAS, IVUS may result useful for the real-time control of CAS of challenging plaques such as "soft", lipidic or prone to rupture ones, or whenever an intra-procedural morphologic evaluation is required for the choice of the appropriate stent type, and the prevention of embolic complications.
References


