Abstract

Atherosclerosis disease of the carotid is one of the major reasons for stroke and a leading cause for morbidity and mortality. An accurate diagnosis and severity quantification of the disease is therefore needed to prevent symptoms and decide the appropriate treatment. The most important indicator for the risk of symptoms is the Degree of Stenosis (DS). Very recently, a new score was proposed, called Enhanced Activity Index (EAI), which is more complex but more accurate than DS. EAI, however, only takes into account medical information about the patient.

In this work, other factors besides the medical ones, e.g., age, gender, expected costs and effects of surgery to the patient, are considered together with EAI in order to improve the information available for the decision making process of endarterectomy. Quality-Adjusted Life Years (QALY), and its respective Incremental Cost-Effectiveness Ratio (ICER), when compared to medical therapy, will be considered.

The optimal EAI cut-off for endarterectomy is computed under the Receiver Operating Characteristics (ROC) framework. A Graphical User Interface (GUI) is described to help the medical staff in the decision making process. The optimal decision point is adjusted according to population characteristics, inherent to the ROC curve, patient information and economic aspects.

Complementary analysis of medical outputs, in a comparative perspective of different strategy therapies, is assessed and quantified in terms of the life expectancy, QALY and ICER are included in the overall Computer Aided Decision (CAD) tool for endarterectomy decision making purposes.

The method is tested with real data acquired at Instituto Cardiovascular de Lisboa and Department of Vascular Surgery, Hospital de Santa Maria, Lisbon. The created tool outputs coincide results to the ones presented in different studies of the bibliography. This preliminary approach to the problem lead to promising results that strongly suggest its application at medical facilities in clinical practice. Nevertheless, it would be interesting to incorporate both the EAI and the economical information in a global index.

1 Introduction

The atherosclerotic disease, which is the main cause of stroke, is one of the main causes of morbidity and mortality in developed countries like Portugal. Stroke is regarded as the first cause of morbidity and continued incapacity in Europe and is also the second most common cause of dementia. It is also responsible for temporary and permanent disabilities with strong socio-economic impact.

The correct indication of treatment to a patient is crucial, in order to obtain the best possible results in the recovery of the patient. Endarterectomy is one alternative of surgical treatment to remove the atherosclerotic plaque that, despite the great results in terms of health recovery, has an associated risk to the patient. Also, it is considered an expensive alternative of treatment when compared to medical therapy. Hence, an accurate evaluation of the need for this intervention is critical to save the patient’s life, when it is needed, and at the same time to avoid its use when it is not absolutely necessary, subtracting the patient to the risk of surgery and reduce unnecessary costs.

Previous work presented the EAI, calculated through a software tool to aid diagnosis using clinical data and ultrasound images of the carotid artery of the patient to assess the state board and calculate an indicator of instability or danger, and therefore the risk of stroke. This indicator is however only medical and does not account for the economic factors of the decision to submit a patient to endarterectomy. Moreover, it provides no notion about life expectancy to the patient after surgery or associated incremental quality of life.

We present further a software tool to assess clinical decision support to the physician that provides an advanced ROC analysis, estimates of expected costs and effects for the patient in various scenarios. The results are presented in terms of Life Expectancy, QALY and ICER. The referred indicators and ROC analysis (that provides an optimal cut-off point for the decision) should be analysed together with the objective risk of stroke, obtained by the EAI, developed by Instituto Superior Técnico and the Faculdade de Medicina da Universidade de Lisboa. This information will assist the decision making process of indicating a patient to endarterectomy, as the adequate treatment for carotid atherosclerosis.

For the case of carotid atherosclerosis, we represent in Figure 3 the steps in the diagnosis and treatment workflow for a carotid atherosclerosis patient. Considering that a patient can resort a health service when coming from the decision of primary or private health providers, a specialty consultation is performed to better assess the health state of the patient. Also, a patient can arrive at the emergency health services because of a symptomatic situation. It is defined a diagnosis strategy where imaging tests are performed, as well as, other laboratory tests needed. Ultrasound imaging has become a standard procedure for medical diagnosis worldwide and treatment options for carotid artery disease will depend on the severity of stenosis (narrowing) of the artery, whether the patient is symptomatic or asymptomatic and general health or other conditions affecting the patient [38]. Eco-Doppler enables, from the morphological point of view, the quantification of carotid stenosis by the measurement of the longitudinal cut, which compares the minimum luminal diameter with the carotid bulb diameter (European method) or with the distal internal carotid (American method) [25]. According to the diagnosis result, if the patient does not have atherosclerosis, no further action is needed, despite a re-evaluation consult in 2 to 5 years. When a patient is diagnosed with stenosis, it can be divided into mild, moderate, severe and quasi-occlusive stenosis. With this information, the physician can decide whether to perform medical therapy, based on antiplatelet therapy, antihypertensive treatment and lipid-lowering therapy [14], or surgery. For
both options mentioned, the patient will need to be re-evaluated every 6 months to assess the condition of the disease.

Figure 3: Workflow enhancing the possible outcomes for carotid atherosclerosis diagnosis.

Despite the Asymptomatic Carotid Atherosclerosis Study [23] referring that patients with asymptomatic carotid stenosis of 60% or greater reduction in diameter and whose general health makes them good candidates for elective surgery will have a reduced 5-year risk of ipsilateral stroke, a meta-analysis of individual patients data from the European Carotid Surgery Trial (ECST) [40] and the North American Symptomatic Carotid Endarterectomy Trial (NASCET) [2], showed that surgery was harmful in patients with less than 30% stenosis, of no benefit in those with 30 to 49% stenosis, of some benefit for 50 to 69% stenosis, and highly beneficial for those with 70% or more stenosis without near-occlusion [36]. A typical symptomatic NASCET patient is a patient within 120 days from the last symptomatic event.

Figure 4: Representation of atherosclerosis time line and narrowing [26].

2 Treatments for carotid atherosclerosis

There are several factors that must be evaluated for the selection of treatment for the carotid disease. Among these are severity of stenosis of the artery and consequent narrowing of the artery, as shown in Figure 5, whether the patient is symptomatic or asymptomatic and general health or other conditions affecting the patient. Symptomatic disease in the carotid circulation encompasses a spectrum of presentations from transient ischemic attacks to embolic or thrombotic stroke and, at times, is paradoxical in that the degree of collateral circulation may allow severe carotid lesions to present with only minimal symptoms [3]. Any consideration of surgery for symptomatic carotid disease must be based on objective comparison of surgical morbidity and results with both the natural history of the disease process and the best available medical therapy [3]. Asymptomatic severe carotid stenosis is generally accepted to refer to atherosclerotic narrowing of the proximal internal carotid artery exceeding approximately 50% to 60% diameter reduction in the absence of symptoms of ipsilateral stroke or Transient Ischemic Attack (TIA) [34]. The mentioned risk factors must be controlled, like arterial blood pressure, recommendation for smoking cessation, regular and appropriated physical exercise, dietetic control [20]. Medical treatment can also include platelet aggregation inhibitors (acetylsalicylic acid or other agents).

Surgical alternatives to medical therapy represent specific interventions for carotid artery disease. It is of most importance the correct plaque classification, in order to select the best treatment alternative for a patient. The NASCET [2] and ECST [40] studies developed in the late 90’s allowed a objective analysis of the advantages and disadvantages of endarterectomy in the carotid atherosclerosis disease. They classified the carotid stenosis in terms of its transversal fraction of the artery occupied by the plaque, despite of the determination is different in each study [5]. The NASCET study was used as reference for the majority of studies performed after.

2.1 Carotid Endarterectomy (CEA)

Follow-up from the medical therapy or conventional therapy groups from randomized trials of carotid endarterectomy allows to understand the relation between carotid artery stenosis and subsequent stroke [27]. CEA is the surgical procedure that consists in the removal of atherosclerotic plaque from the carotid artery to restore greater blood flow to the brain [42], like is shown in Figure 6. The atherosclerotic plaque formation is responsible for the appearance of neurologic symptoms due to embolization of plaque components or blood flux reduction. Several studies refer the morphology of the plaque to be a characteristic positively related to symptoms, as well as the patient’s clinical history and his degree of stenosis.

CEA is one of the most common types of vascular surgery performed in the United States with over 117000 cases done annually [13]. The expected benefits of CEA to reduce the risk of stroke depend on the presence of neurologic symptoms and the degree of carotid artery stenosis [32]. It consists, in its conventional approach, of exposing and mobilizing the carotid bifurcation, place clamps in the common carotid artery (CCA), external carotid artery (ECA) and internal carotid artery (ICA), identified in Figure 6. Thereafter, it is performed a longitudinal arteriotomy in the internal carotid, with the removal of all the stenotic lesion, connection of the intima connection margins and arteriotomy closure [5].

Figure 5: In the left is shown the location of the right carotid artery in the head and neck. In the center is a cross-section of a normal carotid artery that has normal blood flow. On the right is shown a carotid artery that has plaque buildup and reduced blood flow.

Figure 6: Technique of carotid endarterectomy. An atherosclerotic lesion involving the common carotid artery (CCA), internal carotid artery (ICA), and external carotid artery (ECA) is demonstrated on the left panel. The middle panel demonstrates plaque removal following a longitudinal incision of the vessel. The right panel shows the arteriotomy repair with the use of a patch [35].

On the basis of the results of numerous published randomized trials, CEA has been established as the “gold standard” in the treatment of stenotic lesions of the extracranial carotid arteries [18]. This procedure is indicated by the Asymptomatic Carotid Surgery Trial (ACST) for patients which are younger than 75 years old and have a degree of stenosis superior than 70%, reducing the net 5-year stroke risk from about 12% to about 6% (including the 3% perioperative hazard) [12]. Possible reasons that justify the heterogeneity of opinions in clinical practice include the lack of acuity to detect asymptomatic patients with high risk of neurologic complications, continuous development in medical treatment which is believed to be much more efficient nowadays, or even financial motivations [22].

Benefit from endarterectomy depends not only on the degree of carotid stenosis, but also on several other clinical characteristics such as delay to surgery after the presenting event. Ideally, the procedure should be done within 2 weeks of the patient’s last symptoms [36]. It is not a surgery absent of risk, being associated with cardiovascular and technique associated risks, having also the possibility of restenosis after a well succeeded surgery [5].
2.2 Plaque classification scores

Carotid artery atherosclerosis is one of the main causes of stroke. It is of major importance that correct diagnosis of patients is performed, as most situations that reveal complications arise from asymptomatic plaques, more than symptomatic ones. Though Degree of Stenosis (DS) is a proven marker of plaque vulnerability, it is widely recognized that better risk markers for cerebrovascular events are needed [41]. It is, none the less, referred in many studies to be a good indicator of the risk of stroke [40]. The scheme already presented 3 addresses the groups related to the degree of stenosis diagnosed in patients by the NASCET.

Activity Index (AI) is an objective parameter of plaque echostructure that positively correlates with symptoms. AI may contribute to better selection for treatment of patients with carotid artery disease [30]. A previous study showed that a set of ultrasonographic parameters associated with degree of stenosis, were important determinants of a profile of unstable carotid plaques associated with neurological symptoms [29]. It was then given a different weight to each parameter, being AI an objective parameter that correlates with plaque instability and clinical activity [30]. It brought objectivity in the assessment of carotid plaque structure using high definition ultrasonography.

There was, even though, the need to classify and identify a subset of plaques, considered "dangerous" for its associated high risk, as they are relevant for the indication for endarterectomy. Enhanced Activity Index (EAI) is a quantitative diagnostic measure that was developed as a score to classify asymptomatic plaques [37], being a diagnostic tool that allows to predict neurologic complications. As a consequence, the identification of a set of active plaques, that have a high neurological risk associated, helps in the indication for treatment. It results from a study [37] that enabled to identify several characteristics of a plaque, considering it as "active" by taking into account a set of parameters that are statistically relevant for separating symptomatic and asymptomatic lesions.

3 Receiver Operating Characteristic Plots (ROC)

ROC curve analysis became of great use in radar detection and experimental psychology [8]. They were suggested to be used in medical decision making, in 1967, and were used in studies of medical imaging devices, back in 1969 [45]. The selection of the optimal cut-off when binary decisions are involved and one of two classes should be selected, is another aspect of its use. In Computer-Aided Design (CAD) systems this tool is extensively used in the performance evaluation of the involved classifiers. The use of ROC plots in medical decision making is commonly used as a tool which provides a direct visual comparison between tests on a common scale, does not require selection of a particular decision threshold because the whole spectrum of possible decision thresholds is included [45]. It is a useful technique for organizing classifiers and visualizing their performance [10], as well as a statistical tool to support medical decisions based on Sensitivity and Specificity analysis.

3.1 Evaluation of Receiver Operating Characteristic Plots

It is important to understand that when representing the results of a diagnostic test, most often, the populations overlap, as the discrimination between them is not perfect, like the representation in Fig. 7.

We have two populations representing, for example, the group of the population with a disease, and the other, without the disease. For every possible cut-off that one selects, four outcomes are possible: To correctly classify an individual as healthy, True Negative (TN); to correctly classify an individual as unhealthy, True Positive (TP); to classify an individual as healthy when, in fact, he is unhealthy, False Negative (FN); finally, to classify an individual as unhealthy when, in fact, he is healthy False Positive (FP). Hence, one easily associates Sensitivity to the TP fraction and the Specificity to the TN fraction. ROC curves can be defined as a parametric curve, being the Sensitivity a function of 1 – Specificity as shown in Fig. 8. For every possible cut-off, a different point represents a pair with singular sensitivity/specificity. Only the entire spectrum of this point provides a complete analysis of test accuracy [45].

To better understand the dynamic of ROC plots, Figure 8 (b) presents four points of analysis. Together, these points represent extreme situations of ROC analysis, gathering also the best and worst case scenarios. Point a) is the best possible result. It represents a test with perfect discrimination with a ROC curve that passes through the upper left corner (Sensitivity=1 and Specificity=1). A curve that passes through point c) misses all classifications (Sensitivity=0 and Specificity=0). It represents a classifier that indicates a healthy patient as diseased, and a diseased patient as healthy. Point b) represents a classification of all individuals as asymptomatic, regardless of score (Sensitivity=1 and Specificity=0). Finally, point d) represents a classification of all patients as asymptomatic, regardless of score (Sensitivity=0 and Specificity=1). Therefore, the closer the ROC curve is to the upper left corner, the higher is the overall accuracy of the test [45]. The problem under analysis is about Sensitivity/Specificity values between 0 and 1, that results in the representation of a curve which demands further evaluation criteria for the selection of the appropriate cut-off value.

Figure 8: Receiver Operating Characteristic curves.

The procedure, and underlying criterion, to select an optimal cut-off is crucial for the final performance of the classifier [19]. Therefore, a test where two populations do not overlap, meaning that there is perfect discrimination, would result in a curve balanced completely to the upper left corner, where there is a maximum in sensitivity and specificity (100%). Knowing that a criterion should reflect the statistics associated with each group, it also should depend on other objective and subjective factors relevant in the whole process. The optimal cut-off primarily depends on the true distributions of both populations but also on the consequences associated with the decision making procedure, failing an endarterectomy on a patient from the symptomatic group is probably, from a clinical and medical point of view, severer than making a surgical intervention on a subject from the asymptomatic group.

Different cut-off criteria exist in the literature. Youden’s Index is considered the most commonly used global index of diagnostic accuracy [9]. Criteria and rates like accuracy, efficiency, precision, Likelihood Ratio, Positive Predictive Value and Negative Predictive Values allow a better understanding of ROC interpretation. Accuracy measures the ability of a test to discriminate between two subclasses of subjects. Efficiency is the number of correctly classified individuals, with the possibility of being presented as a percentage value. Precision indicates the reproducibility of the quantitative results of a classifier. Likelihood ratio is the expression of whether a test result usefully changes the probability that a condition (such as a disease state) exists. Positive and Negative predictive values are the post-test probabilities, which combines intrinsic accuracy and the prevalence (p) of the disease. The prevalence of the disease for the Portuguese reality was studied in 1991 by José Fernandes e Fernandes, Luis Mendes Pedro et al. [16]. The study showed a global prevalence for the referred disease of 31.8%, from a population of 1143 patients of the Vascular Laboratory. This prevalence is representative of a population of patients sent to Instituto Cardiovascular de Lisboa (ICVL).
by other health services like Neurology or Cardiology.
Next section introduces the economic evaluation theme, to understand the fundamentals of economic evaluations. This will allow to explain concepts like QALY and ICER, used further.

## 4 Economic Analysis

Evaluation of surgical procedures for carotid atherosclerotic treatment are possible in an economics perspective. It would be interesting to support the decision making process for endarterectomy in a wider perspective, complementing the medical aspects with economic and other related information.

The decision to commit resources to one use instead of another is always difficult. Scarcity of people, time, facilities, equipment and knowledge demand a sustained answer to the allocation of resources for at least three reasons [7]:

- Without systematic analysis it is difficult to identify clearly the relevant alternatives;
- The viewpoint assumed in an analysis is important;
- Without some attempt at measurement, the uncertainty surrounding orders of magnitude can be critical.

Hence, any consideration made about value for money based on economic evaluation minimizes the chances of an important alternative being excluded from consideration, or a new programme being compared to an inefficient baseline, offering the possibility of comparing between programme costs and resulting benefits. The extent to which they may contribute is based on the viewpoints considered for the analysis.

There are some limitations in economic evaluations due to the importance of the distribution of costs and consequences among different patient or population groups. This aspect is not usually incorporated into the analysis. Also, the different forms of analysis available have different approaches and different criteria, resulting in different discussions and conclusions.

### 4.1 Types of economic analysis and the concept of costs

Economic evaluations may be divided in Cost-Effectiveness Analysis (CE Analysis), Cost-Utility analysis (CUA) and Cost-Benefit analysis (CBA). It is of most importance that when performing an economic study, the author identifies explicitly the perspective of the study, whether it is individual, provider, payer or patient [7].

Economic analysis is more common and what are the costs considered, for example, are addressed through utility and willingness to pay [7].

#### 4.1.1 Quality-adjust Life Years for Endarterectomy

The concept of QALY has the advantage of measuring health outcome, simultaneously capture gains from reduced morbidity (quality gains) and reduced mortality (quantity gains), and combining these into a single measure [7]. It can be understood as the relative desirability of each treatment alternative, by the meaning of the life years gained by an intervention, comparing to the life deterioration of not performing medical treatment (or even comparing to applying another strategy of treatment).

To ensure the correct QALY concept, the quality weights must be based on preferences, with a correct scale implementation where the ends are fixed by death (with a value of 0) and perfect health (with a value of 1). The calculation of the QALYs for an intervention is made by the quality weight attributed to a health state, multiplied by the time (usually in years) that the patient stays in that state.

The appropriate comparison between two health care programmes or interventions is in terms of ICER [7]. This is the most popular method of presenting the results of cost-effectiveness and cost-utility analysis. By definition, ICER represents the cost needed to produce an additional QALY and is presented as the ratio between additional costs per QALY gains.

## 5 Literature Review

It is consensual that the correct diagnosis of the atherosclerotic plaque is of most importance to perform a sustainable decision for endarterectomy. Nevertheless, the correct classification of an individual as symptomatic or asymptomatic associating medical diagnosis, hospital characteristics at the time of decision, economic aspects and other logistic variables, may result in an improvement for endarterectomy decision making supported with economic analysis and ROC analysis.

### 5.1 Economic Analysis of Carotid Atherosclerosis Treatments

This section aims at understanding, from literature, which type of economic analysis is more common and what are the costs considered, for endarterectomy purposes. The QALYs used in the literature are presented, in order to understand the utility values considered for endarterectomy and associated states of health. For carotid atherosclerosis there are medical therapy and surgery as treatment possibilities. Many studies present comparisons between CEAs and CAS. Economic evaluations are commonly used to assess the characteristics of these two procedures, most of the times, trying to realize which one is more efficient than the other, cost-effective or simply compare costs and benefits. Table 1 summarizes the studies gathered in the context of economic analysis of endarterectomy. It was enhanced the type of costs considered in each study and how they were collected, the methodology used and the main conclusions of the authors.

As shown in Table 1, several methodologies were adopted and most of the studies presented are CE Analysis. We shall highlight the type of costs considered, the effects in terms of QALY and the ICER, when presented.

Firstly, the type of costs considered differ, as some studies collected costs from discharge records and others used direct reference costs, as
Table 1: Review of Economic studies for Carotid Endarterectomy

<table>
<thead>
<tr>
<th>Author and Title</th>
<th>Year</th>
<th>Costs Considered</th>
<th>Methodology</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mahoney et al. [44]</td>
<td>2011</td>
<td>CEA vs. CAS</td>
<td>A Markov analysis model was created to evaluate the relative cost-effectiveness of CAS and CEA.</td>
<td>Procedural costs. Cost of morbidity, quality adjusted life expectancy. QALY values were evaluated, rather than charges.</td>
</tr>
<tr>
<td>Young et al. [44]</td>
<td>2010</td>
<td>CEA vs. BMT</td>
<td>Patients with an acutely ischemic deficit for CEA but not for CAS.</td>
<td>Outpatient procedures costs. Rehabilitation costs. Direct medical costs.</td>
</tr>
<tr>
<td>Cost-effectiveness of CEA vs. CAS for patients with increased surgical risk [44]</td>
<td>2007</td>
<td>CEA vs. CAS</td>
<td>A Markov analysis model was created to evaluate the relative cost-effectiveness of CAS and CEA.</td>
<td>Carotid stenting is not economically attractive alternative to CEA.</td>
</tr>
<tr>
<td>Kilaru et al. [44]</td>
<td>2003</td>
<td>CEA vs. CAS</td>
<td>A Markov analysis model was created to evaluate the relative cost-effectiveness of CAS and CEA.</td>
<td>Outpatient procedures costs. Rehabilitation costs. Direct medical costs.</td>
</tr>
</tbody>
</table>

Despite the QALYs scale being from 0 to 1, QALYs values in Table 2 are above 1 because they were multiplied by the average life expectancy for the patients. Some studies presented are comparisons between endarterectomy and carotid stenting, but Henriksson et al. [14] presented a study that compares endarterectomy to the best medical treatment (BMT) available. Mahoney et al. [11] [21] evaluated the cost-effectiveness of carotid stenting versus carotid endarterectomy using data from the SAPPHIRE trial. Patients were followed for a 1-year period and life expectancy, quality-adjusted life expectancy and health care costs beyond the follow-up period were estimated. The ICER for stenting compared with endarterectomy was $6,555 per QALY gained. We shall also consider the CREST trial (Carotid Revascularization Endarterectomy versus Stenting Trial) analysis made by Khan et al. [17]. They estimated the QALYs associated with each treatment modality, by adjusting for the incidence of each quality-adjusted outcome (QALY weights of ipsilateral stroke, Myocardial Infarction, death, and postprocedure QALYs) and ICER was estimated for the 4-year period after the procedure. These led to 0.702 QALY for CEA (ranging from 0.0 [death] to 0.815 [no adverse events]). Kilaru et al. [2003], presented a study that compared two types of surgery: CEA and CAS. The analysis was performed for immediate and long-term costs associated, in the form of a CE Analysis. The authors determined a long term service rate in QALYs and lifetime costs for a hypothetical 70-year-old cohort undergoing CEA and CAS. However, the concept of cost-saving does not completely represents the initial purpose and the analysis of cost-effectiveness was not entirely discussed. Young et al. verified that LOS increased with age and average cost associated with CEA was $10,965 [43]. However, the study does not mention which aspects were taken into consideration. Also in 2010, Young et al. [44] presented a cost-effectiveness analysis of carotid artery stenting compared to carotid endarterectomy in symptomatic subjects who were suitable for either intervention. Direct Medicare costs were used [2007 USD] and considered characteristics of a asymptomatic 70-year-old cohort. The results mentioned that lifetime costs were $35,200 and QALYs were 9.64 for CEA. In the case of CAS lifetime costs were $52,900 and...
the associated QALY gain was 8.97.

6 Problem Formulation

Our goal is to correctly classify a patient into specific populations and consequently, choose the appropriate decision threshold value for the decision making process. It is also important to consider a more flexible evaluation of patients, given the physiological experience, time line and economic aspects. A methodological framework is proposed.

The decision point will, from now on, be referred as cut-off. For every possible cut-off point or criterion value you select to discriminate between the two populations, there will be some cases with the disease correctly classified as positive (TPF = True Positive fraction), but some cases where the disease will be classified as negative (FNP = False Negative fraction). On the other hand, some cases without the disease will be correctly classified as negative (TNF = True Negative fraction), but some cases without the disease will be classified as positive (FPF = False Positive fraction) [24]. The referred classifications are usually presented in a contingency table, also called confusion matrix [11].

The Sensitivity of a diagnostic test, also called True Positive Rate (TPR), is defined as
\[
\text{Sens} = \frac{TPR}{TP+FN} = \frac{TP}{TP+FN}.
\]

It can be understood as the probability of classifying a subject as positive, when the disease is present. Specificity [37] is defined as \(\text{Spec} = 1 - \text{FPR} \) where \(\text{FPR} = \frac{FP}{FP+TN} \). It is the probability that a test result will be negative when the disease is not present.

In the specific case of endarterectomy, a binary classification problem, two cases are considered: \(\delta_0\) and \(\delta_\lambda\) containing the subjects that will present symptoms in the future and that will continue asymptomatic, respectively. The main goal concerning endarterectomy is to decide what class a given subject belongs to. Based on the respective Enhanced Activity Index (EAI) score, patients are classified as symptomatic or asymptomatic. Hence, it is expected with real data that the distributions overlap, as one rarely observes a perfect separation between the two groups.

A close analysis of cut-off criteria is necessary in order to correctly decide which criterion is most appropriate for different situations. The Descending Diagonal Intersection Criterion (DDIC) and Youden’s criterion, already addressed in [19] are two examples of how one can select the most appropriate cut-off. They will now be analysed in a graphical receiver operating characteristic approach. For the present work, it is necessary to understand cut-off selection by the need of correctly classifying patients as symptomatic or asymptomatic, but also, to adjust that classification with economic aspects. We introduce a possibility that considers different weighing in Sensitivity(TPR) and Specificity (1-FPR) values, providing adjusted cut-off values.

6.1 ROC Geometrical Approach

ROC curves are used in medicine as a way to analyse the performance of diagnostic tests. This allows the determination of the cut-off value for distinguishing, for example, between positive and negative test results. Diagnostic testing is almost always a tradeoff between sensitivity and specificity and ROC curves provide a graphical representation of this tradeoff [33].

Since both Sensitivity, \(S(c)\), and Specificity, \(S(c)\), depend on the cut-off parameter, the ROC curve can be defined as the following parametric curve, \(s(c) : R \rightarrow R^2\), where \(s(c) = (1 - S(c), S(c))\).

We plot a point representing these rates on a two dimensional graph. The graphical representation of these sensitivity/specificity pairs, when the densities are fixed but the cut-off \(c\) is changed, represent the ROC curve.

To better understand the dynamic of ROC plots, Figure 9 presents four points of analysis. Together, these points represent extreme situations of ROC analysis, gathering also the best and worst case scenarios. Point a) is the best possible result. It represents a test with perfect discrimination with a ROC curve that passes trough the upper left corner (Sensitivity=1 and Specificity=1). A curve that passes through point c) misses all classifications (Sensitivity=0 and Specificity=0). It represents a classifier that indicates a healthy patient as diseased, and a diseased patient as healthy. Point b) represents a classification of all individuals as symptomatic, regardless of score (Sensitivity=1 and Specificity=0). Finally, point d) represents a classification of all patients as asymptomatic, regardless of score (Sensitivity=0 and Specificity=1). Therefore, the closer the ROC curve is to the upper left corner, the higher is the overall accuracy of the test [45]. The problem under analysis is about Sensitivity/Specificity values between 0 and 1, that results in the representation of a curve which demands further evaluation criteria for the selection of the appropriate cut-off value. Criteria for the computation of an optimal cut-off value are described next.

**Descending Diagonal Intersection Criterion (DDIC)**

From the ROC perspective, this criteria sets the optimal cut-off in the interception point between the ROC curve and the descending diagonal. This criterion may be formulated as
\[
\text{TPR} + \text{FPR} = 1 \tag{1}
\]

The interception of the ROC curve with the line at 90 degrees to the no-discrimination line is considered as an heuristic method to investigate the cut-off providing the best discriminative power of the test (or predictive method), maximizing the TPR and minimizing the FPR. In general medical applications, the cost associated with TPR is different from FPR, hence weighting them differently is a useful feature. Accordingly, let us consider the cost variable \(\lambda\) in our criterion, and expand equation 1, such that
\[
\lambda \times \text{TPR} + (1 - \lambda) \times \text{FPR} = \lambda \tag{2}
\]

From a geometrical point of view, this criterion maximizes the vertical distance from the ROC curve to the non-discriminative diagonal. The optimal cut-off, \(c^*\), is computed by finding the stationary point of \(J(c)\) with respect to \(c\), \(\frac{dJ(c)}{dc} = 0\) which leads to
\[
\frac{dTPR(c)}{dc} = \frac{dFPR(c)}{dc} \tag{3}
\]

This means that the tangent to the ROC curve at the optimal cut-off, under the Youden criterion, has a unitary slope.
Once again, in order to consider adjustments to cut-off selection, \( \lambda \) is considered in the criterion as a weighting factor. Eq. 3 can be written as:

\[
\frac{d}{dc} \frac{TPR(c)}{FPR(c)} = \frac{1 - \lambda}{\lambda}
\]  

(4)

Figure 11 is the graphical representation of the result presented by Eq. 4. For different relative values of TPR and FPR, Youdens’s consideration for cut-off selection will behave according to different slopes for the tangent to the cut-off point on the ROC curve.

### 6.2 Considerations for Carotid Endarterectomy

For the present analysis, we do not intend to have a complete description of all economic aspects related to endarterectomy or building an all inclusive cost estimate of the procedures, follow-up clinic visits and diagnosis. Our goal is to have a general perspective of its associated diagnostic costs, procedural costs and effects allowing to support a better interpretation of the ROC curve and consequent indication, or not, of the patient to surgery. Figure 12 represents the analysis that our methodology intends to replicate.

We will incorporate the age (and gender) influence in the decision making process in terms of utility. Table 3 from the study presented by Mahoney et al. [21], represents the utility values that shall be considered for the present analysis. Nevertheless, the average life expectancy in Portugal, with values updated in the 30th of May (2012) by INE (Instituto Nacional de Estatística) and PORData (Base de dados de Portugal Contemporâneo), is 76.4 years for men and 82.3 years for women [31] and shall be considered.

With the presented points of analysis, this work will allow to complete the decision making process with a more informed basis, together with Enhanced Activity Index. The tool presented in the next section will use the economic information presented previously and enables the physician to gather information about the patient, the outcomes of the selected treatment and the ICER of each decision.

### 7 Computational Implementation and Results

For the presented model, the intent was to include information about the patient and economical aspects together with Enhanced Activity index, which indicates the plaque activity provided by the classification framework. Like this, not only the diagnosis information would be taken into account, but also economical. A correct interpretation of the results will enable to decide whether endarterectomy is the right treatment for a specific patient, in a specific time frame.

It was important to take into account patient age, wether he was symptomatic or asymptomatic and its gender. With this three aspects, one can associate new information to the decision making process. This information includes the possibility of understanding the costs associated with both endarterectomy, and medical therapy as alternative, the life expectancy of the patient and the quality-adjusted life years for each alternative. We also present the “no treatment alternative”, in order to better assess the increment in life expectancy that both endarterectomy and medical therapy provide.

For an adaptive ROC analysis, the GUI should present a ROC curve representative of the Portuguese Private Health Providers reality. The available dataset contains 146 plaques, from a cross-sectional study of 99 patients (75 males and 24 females with a mean age of 68 years [41-88] acquired at Instituto Cardiovascular de Lisboa and Department of Vascular Surgery, Hospital de Santa Maria, Lisbon. They result from the diagnosis of carotid atherosclerosis and the ground truth of this database is that 44 were symptomatic plaques and the remaining 102 were asymptomatic [38]. In this part of the GUI, there is the interest of assessing the costs associated with Enhanced Activity Index, patient and economical aspects together with an index that indicates the plaque activity provided by the classification framework.
ficiency, accuracy, positive predictive value and negative predictive value are also important to understand the relevance of the decision made.

Like this, using the software Matlab, from MathWorks, Inc. (1984-2012), Version R2012a, we were able to create a graphical user interface (GUI) to perform the analysis. Figure 13 presents the interface created.

![Figure 13: Image of the GUI created in Matlab.](image)

### 7.1 Instructions and available tools

The structure of the interface is simple and is now explained, dividing the subject by the ROC curve analysis and the economic information.

For the economic analysis, the user will only need the age, gender and patient status (asymptomatic - no event, or, symptomatic). This last input is made in a pop-up menu with the alternatives represented in Figure 14.

Each of this options has an utility associated and enables the presentation of life expectancy for the patient, QALYs and estimated costs. All these results are presented to the possibility of endarterectomy and to medical therapy in form of a static text. The GUI is supposed refresh the results, each time one selects the patient status. Hence, it is advised for the user to firstly fill the patient’s age, selecting the patient’s status lastly.

![Figure 14: Image of the pop-up menu for Gender and Patient Status Selection.](image)

When the referred fields are completed, a pop-up window will is shown to indicate QALY and ICER associated to patient information and health condition. This calculations were calculated based in the utilities and effects presented in Section 6.2. The costs will include pre-treatment expenses (imaging, lab tests and consultation costs) and procedural costs (endarterectomy, hospitalization and inpatient care).

![Figure 15: Image of the pop-up window for QALY and ICER presentation, when age and patient status are indicated.](image)

For the advanced ROC analysis, the user shall select the criteria to assess the optimal cut-off point. Four possibilities are available, as demonstrated by Figure 16. This selection, made in check boxes on the Best Operating Point Criteria block, will represent a dot in the ROC curve in red, blue, magenta and cyan, respectively representing the best operating point for the selected criteria. The referred weighing is made in the field Lambda Value, that represents the factor of weighing differently sensitivity and specificity.

![Figure 16: Image of the check box menu for cut-off selection criteria.](image)

It is also available the possibility of drawing a line representing a fixed sensitivity, which presents also the respective cut-off point (interception of the ROC curve with the Fixed Sensitivity line). The results will be presented in a table, en the button Evaluate is pressed. Each time the parameters are changed and the evaluate button is pressed, new results on the table are presented and the dots on the ROC curve for the criteria will be repositioned.

The toolbox in the top of the GUI’s window also includes some other tools. It contains a data cursor, to navigate through the ROC curve, assessing the TPR (Sensitivity - yy axle) and FPR (1-Specificity - xx axle) values. Also zoom and pan tools are available, in order to select a specific region of the curve. Figure 17 is illustrative.

![Figure 17: Image of the available ROC tools.](image)

With the presented interface, the physician can support the decision in hand with statistical data. The relevance of ones decision, will be sustained by sensitivity and specificity of a representative data base, as well as, by the accuracy, positive predictive value and negative predictive value of the optimal operating point. The group of information gathered in the GUI of advanced ROC analysis, together with EAI (or Degree of stenosis, for example) will constitute a useful tool in the decision making process for endarterectomy.

### 7.2 Results

Nowadays, the selection of patient to endarterectomy is made based on diagnosis information together with the experience/knowledge of the physician. The degree of stenosis and the associated risk of atherosclerosis to the patient is the index considered. We pretend to assess the Incremental Cost-Effectiveness Ratio, base on the costs (C) and Effects (E), measured in QALYs for our model, together with the advanced ROC analysis. It is important to understand interpreting the information is simple and results in a suggestion of the best treatment option for the patient. It is usual to consider approximately 35000€ per QALY threshold, when considering an alternative cost-effective compared to another. Table 4 represents some examples of hypothetical patients.

<table>
<thead>
<tr>
<th>Age</th>
<th>Gender</th>
<th>Patient Status</th>
<th>Treatment</th>
<th>QALYs</th>
<th>Cost per QALY</th>
<th>ICER</th>
</tr>
</thead>
<tbody>
<tr>
<td>65</td>
<td>Male</td>
<td>Asymptomatic</td>
<td>CEA</td>
<td>9.6</td>
<td>9.4</td>
<td>47.680€</td>
</tr>
<tr>
<td>72</td>
<td>Male</td>
<td>Asymptomatic</td>
<td>CEA</td>
<td>3.7</td>
<td>33.379€</td>
<td>123.517€</td>
</tr>
<tr>
<td>73</td>
<td>Male</td>
<td>Asymptomatic</td>
<td>CEA</td>
<td>3.6</td>
<td>55.902€</td>
<td>159.846€</td>
</tr>
<tr>
<td>65</td>
<td>Male</td>
<td>MI</td>
<td>CEA</td>
<td>9.48</td>
<td>5.909€</td>
<td>56.045€</td>
</tr>
<tr>
<td>70</td>
<td>Male</td>
<td>MI</td>
<td>CEA</td>
<td>5.28</td>
<td>20.449€</td>
<td>107.939€</td>
</tr>
<tr>
<td>65</td>
<td>Female</td>
<td>Asymptomatic</td>
<td>CEA</td>
<td>14.41</td>
<td>12.534€</td>
<td>180.635€</td>
</tr>
<tr>
<td>65</td>
<td>Female</td>
<td>MI+Major Stroke</td>
<td>CEA</td>
<td>14.01</td>
<td>13.591€</td>
<td>190.471€</td>
</tr>
</tbody>
</table>

Example of an asymptomatic male patient
It is presented now an hypothetical 65-year-old asymptomatic male patient with high degree of stenosis (superior to 70%) or equivalent EAI. From the exposed in the bibliographic review, this type of patient is not consensual about the benefit of surgical treatment. From Table 4 it is possible to observe that the difference in QALYs from the endarterectomy to the medical therapy is minimal and the costs differential is high. This results represent an ICER of approximately 48000€ and surgery is considered cost-effective when compared to medical treatment.

\[
ICER = \frac{C(Surgery) - C(MedicalTherapy)}{E(Surgery) - E(MedicalTherapy)} = 47679.6 \quad (5)
\]

From the ROC analysis, if the patient has an EAI superior to 78 (0-100), surgery is the recommended treatment (by Youden’s index), as the economic information presented above already suggested. If the ROC analysis is performed considering that asymptomatic patients have higher associated risk in surgery, attributing a higher weighing to Sensitivity (using a Lambda value of 0.6) will ensure that only patients with higher EAI (82 or superior) will be indicated to surgery.

Let's now evaluate a situation where a patient is older (72 and 73 years old) and also asymptomatic. Despite the high ICER, for a 72-year-old patient, the surgery is cost-effective. However, for a 73-year-old-patient the ICER is 159846.55€ with a cost per QALY of 55902.13€. This situation allows to interpret that surgery in an asymptomatic patient with severe stenosis is not cost effective if the patient is 72 years or older, as it will represent a cost per QALY superior to the threshold of 35000€.

**Example of a symptomatic male patient**

It is now analysed the situation of symptomatic male patients, victims of myocardial infarction. Patients with these characteristics are indicated to surgery, with a ICER between 56045.47€ and 107939.42€ and a cost per QALY between 5909.85€ and 20449.27€. It is important to remind that these results take into account the life expectancy of 76.4 years to male patients.

On the contrary, patients above 71 years old with a myocardial infarction plus major stroke occurrence, will represent a cost per QALY higher that 35000€, being medical therapy the most adequate treatment.

Together with ROC analysis, using Youden’s index or DDIC, the cut-off will be of 78 and 82 respectively. For this, regarding that the symptomatic situation enhances endarterectomy as the most appropriate treatment, lower cut-off values (lambda of 0.4) will be adequate. This represents higher specificity and lower sensitivity values for the optimal cut-off, indicating a wider selection of patients for surgical treatment. Every symptomatic male patient with an EAI equal, or superior, to 69 (by Youden’s index - magenta) or 77 (by DDIC criterion - cyan) will be indicated to surgery.

**Example of a female patient**

In Table 3 it is possible to see that the utilities used to quantify each health state for women, are similar. The main difference is in life expectancy, which is 82.3 years for women. Like this, it is expected that cost per QALY values, for the ages studied before in men, will be lower. Nevertheless, differences in QALYs between surgical treatment and medical therapy is low, leading to high ICER values.

ICER values, for a 65-year-old patient go from 180635.84€ (asymptomatic) to 190471.79€. This values are extremely high, when compared to ICER values in men of this age. These ICER values suggest that surgery is not cost-effective when compared to medical therapy. In this case, a ROC analysis with higher weighing of sensitivity will narrow patient indication to surgery. An evaluation like this is coherent with the low increment in QALY compared to medical therapy. The results table for optimal cut-off criteria shown in Figure 18, are representative of a cut-off selection appropriate to this situation, where only female patients with an EAI of 83 or higher (for Youden’s index - magenta) are indicated for endarterectomy.

**Figure 18**: Results for a female patient. Youden’s index optimal cut-off - magenta. DDIC optimal cut-off - cyan.

### 8 Discussion of the results

The results presented by the created tool corroborate literature references about the cost-effectiveness of endarterectomy in patients with asymptomatic carotid artery stenosis [14]. Considering a willingness-to-pay of 35000€ per QALY, male patients older than 72 years old are indicated to medical therapy, instead of endarterectomy. Also, in our consideration, a higher sensitivity for the optimal operating point (with a lambda value of 0.6) is the most indicate. It represents that only patients with higher values of EAI (or Degree of stenosis) will be selected to surgery, avoiding a riskier treatment solution with higher costs to patients with lower EAI (between 70 and 81).

In the case of symptomatic male patients, ROC analysis has a preponderant part in the decision making process. Despite the indication of high cost per QALY in patients older than 72 years old, the risk of other symptomatic occurrences is high and surgical treatment should be considered. The adjustment made to find the optimal cut-off for this situation, by using a lambda of 0.4 will include a wider spectrum of symptomatic patients, with EAI of 69 or higher.

Female patients represent high ICER values for the ages analysed (65 to 70, which represent the median age of endarterectomy patients in Europe). Like this, higher lambda values will compensate this fact, by determining higher cut-off values, as endarterectomy does not constitute a better alternative than medical therapy.

The difference in cut-off selection represents different values in sensitivity and specificity. When the lambda value assigns equal importance to sensitivity and specificity, both criteria have similar results, with differences around 2%. If we assign different weighing (with lambda values different of 0.5), the differences go from 2% to 10%. It is important to highlight that DDIC has, for the examples presented above, higher accuracy and, generally, Sensitivity and Specificity.

The results presented could be improved in terms of specifying and detailing all the relevant costs associated to endarterectomy. To present a full economic analysis for the Portuguese reality, would be useful to register direct and indirect costs. The collection of cost data during a period of 12 months, for example, would enable an analysis considering seasonizing and resource availability during the year. This type of review is interesting to understand the fluctuations existent in periods like holidays and their impact in the costs of the procedure.

Also, when analysing patients younger than 65 years old, which is the retirement age, no adjustment was made for loss of productivity. The tool provided only considers direct costs associated to diagnosis and treatment.

Another point of interest would be to relate age with differences detected in costs. There is evidence in the literature [43] that indicates a direct relation between age and the length of hospitalization, having direct influence in the total cost of the treatment.

With the presented results it is demonstrated that a correct analysis of a ROC curve, demonstrative of the carotid atherosclerosis reality, together with economic information creates an informed decision making process. In the hypothetical examples created, it was shown that some situations demand a correct adaptation of the cut-off value for patient selection to endarterectomy, according to the available information about the patient and the expected effect that surgery will provide in terms of quality of life.

### 9 Conclusions and Further work

This article intended to complete the information implied in EAI with economic factors, to better assess the decision making process of indicating a patient to endarterectomy.

Based on a literature review about ROC curves and economic evaluations for endarterectomy, a broader tool was proposed to enable the analysis of factors like age, gender, expected costs and effects of surgery to the patient together with the already existent index. This tool was created using the software Matlab and, by the use of Receiver Operating Curves, it was intended to understand the behaviour of an existing data base of 146 atherosclerotic plaques, demonstrative of carotid atherosclerosis population that resorted the Portuguese private health care provider ICVL. Using adequate criteria that was analysed, it is suggested an op-
timal cut-off point for patient indication to surgery, based on their EAI (or DS). The complement of this information presents the associated effects of endarterectomy, in terms of Quality-Adjusted Life Years, and its respective Incremental Cost-Effectiveness Ratio when compared to medical therapy, taking into account patient age, gender, and condition.

The objectives outlined were achieved and when having a previous diagnosis and respective atherosclerosis index, like EAI, the physician is able to assess if the score attributed by the index determines wether the best therapeutic approach is endarterectomy or waiting to monitor the condition. If the score is higher than the optimal cut-off presented by the ROC analysis, the physician can understand if endarterectomy is cost-effective and determine if it is the most adequate treatment for the patient. The results presented corroborate previous indications of the bibliography, even in asymptomatic patients, where it is not consensual the benefit of carotid endarterectomy. It is plausible to affirm that the analysis created is consistent and useful for clinical practice assistance in the decision making process.

Nevertheless, it would be interesting to incorporate both the EAI and the economic information together in a global index. To present a full economic analysis for the Portuguese reality, would be useful to register direct and indirect costs and conclude the effectiveness of endarterectomy. The collection of cost data during a period of 12 months, for example, would enable an analysis considering seasoning and resource availability during the year. This type of review is interesting to understand the fluctuations existent in periods like holidays and their impact in the costs of the procedure. Also, to divide the outcomes in terms of QALY by age groups would allow an adjustment in terms of questions like productivity and associated loss to society. The relation between age and the length of hospitalization has direct influence in the total cost of the treatment, being the association of age to the costs a point of interest.

The combination of the created tool with the existing software for EAI calculation would simplify the decision making process. The inclusion of its usage as common practice in health care providers should be tested and further studies including cost-effectiveness analysis of more treatment possibilities, like CAS, would represent an additional step. In terms of value added to the scientific community, we consider that the present work is the initial step to suggest a broader software for carotid atherosclerosis diagnosis.

References


[12] D. Hodby. Dollars and sense: the economics and outcomes of patients undergoing carotid endarterectomy at present work is the initial step to suggest a broader software for carotid atherosclerosis index, like EAI, the physician is able to assess if the score attributed by the index determines whether the best therapeutic approach is endarterectomy or waiting to monitor the condition. If the score is higher than the optimal cut-off presented by the ROC analysis, the physician can understand if endarterectomy is cost-effective and determine if it is the most adequate treatment for the patient. The results presented corroborate previous indications of the bibliography, even in asymptomatic patients, where it is not consensual the benefit of carotid endarterectomy. It is plausible to affirm that the analysis created is consistent and useful for clinical practice assistance in the decision making process.

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