Interventional treatment of noncoronary atherosclerotic pathologies: an update about what the cardiologists should know

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Introduction

The multidisciplinary and systemic nature of vascular atherosclerosis has been the concern of many specialists including general and vascular surgeons, angiologists, diabetologists, radiologists and cardiologists, depending on both the local circumstances and national traditions. Non-coronary angioplasty, proclaimed in 1988 as “the new endoluminal vascular surgery”, is becoming a field of interest for many interventional cardiologists, who should be aware of both the gross and microscopic arterial anatomy.

Two types of arteries have to be distinguished, the muscular and elastic ones, and the difference between them is histologically found in the medial layer. Muscular arteries are characterized by a prevalence of smooth muscle cells in the medial layer of the artery: most small arteries, including the external iliac, the renal, the femoral and coronary arteries are of this muscular type, with the only exception being the internal thoracic arteries. Elastic arteries show densely packed multiple elastic laminae in the medial layer with a poorly defined internal elastic lamina. All large proximal arteries, including the aorta, the pulmonary artery, the proximal segments of the brachiocephalic trunk, the carotids, the subclavian, the internal thoracic and the common iliac arteries are of this elastic type. A transitional type, such as the proximal part of the common iliac arteries, has also been described: it is characterized by a smooth muscle component sandwiched between multiple parallel elastic laminae with a well-defined internal elastic lamina.

Depending on the arterial morphologic types, in advanced atherosclerosis, the atherosclerotic process leads to different basic types of lesions: lumen narrowing of the muscular arteries due to a final negative vessel remodeling and aneurysmal disease of the elastic arteries caused by outward expansion of the vessel wall. As a result, the coronary, iliac and femoral arteries, that are the targets of most intravascular interventions, usually require the same kind of knowledge. Peripheral vascular interventional techniques require specific skills and the complexity of the procedures dictate that formal learning curve programs (i.e. training in diagnostic and therapeutic cardiovascular medicine as well as diagnostic angiography) become the standard means of learning.

The clinical profile of noncoronary atherosclerosis is similar to the coronary profile. It is traditionally classified into three types: acute or chronic ischemia and aneurysmal disease.
Acute arterial ischemia is usually due to intrinsic (i.e. embolization from a distant arterial source, sudden thrombosis superimposed upon stenosis, aneurysmal disease and aortic dissection) or extrinsic causes (i.e. direct or iatrogenic injuries, mechanical compression and hypercoagulable states). Atherosclerosis is the fundamental process in the pathogenesis of chronic critical arterial ischemia, even though inflammatory arteritis (e.g., thromboangiitis obliterans) or diabetic distal angiopathy may occasionally be responsible. Finally, extensive atherosclerotic changes and destruction of the vessel wall should be reserved for a localized abnormal dilation (i.e. aneurysm) of the aorta that acquires either a spherical or saccular shape (Table I).

Over the past 2-3 years, industrial technology has developed several new devices and techniques for dealing with these different atherosclerotic manifestations (Table II), and some of these have made significant advances with clinically more impressive results.

This review is an update on the evaluation and treatment of noncoronary artery diseases and suggests future applications in this complex and extensive field which is encountered by cardiologists every day in the real word.

Clinical acute arterial ischemia category and specific lesion treatment based on its site

Extracranial carotid and other supra-aortic arterial lesions. Acute ischemic stroke is the second most common cause of death worldwide, exceeded only by ischemic heart disease, and better immediate results and clinical outcome have been reported in such patients with recanalization of the underlying occlusive arterial lesions. Thrombolysis is a potentially attractive form of therapy because it gives the opportunity for a prompt restoration of the vessel patency and it may help to prevent long-term neurological sequelae. The only widely approved recanalization medical therapy is the intravenous infusion of alteplase within 3 hours of stroke onset. Recently, to overcome the limits of intravenous thrombolysis for the treatment of acute stroke, the potential role of intra-arterial thrombolysis has been investigated, and the results of first generation agents, such as streptokinase and urokinase were positive. In particular, second generation thrombolytic agents, such as alteplase, were found to be relatively safe and in the near future, the use of third generation agents, such as reteplase, lanoteplase and

Table I. Spectrum of the manifestations of atherosclerotic pathology in the vascular tree.

<table>
<thead>
<tr>
<th>Arterial District</th>
<th>Acute Pathology</th>
<th>Chronic Pathology</th>
<th>Aneurysmal Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brachiocephalic arteries</td>
<td>Acute stroke</td>
<td>Cerebrovascular disease</td>
<td>Brachiocephalic aneurysms</td>
</tr>
<tr>
<td>Thoracic aorta</td>
<td>Acute dissection</td>
<td>–</td>
<td>Thoracic aneurysm</td>
</tr>
<tr>
<td>Renal arteries</td>
<td>Embolic ischemia</td>
<td>Ischemic nephropathy</td>
<td>Renal artery aneurysm</td>
</tr>
<tr>
<td>Visceral arteries</td>
<td>Intestinal infarct</td>
<td>Angina abdominis</td>
<td>Splenic aneurysms</td>
</tr>
<tr>
<td>Abdominal aorto-iliac arteries</td>
<td>Acute dissection</td>
<td>Chronic occlusion</td>
<td>Abdominal-iliac aneurysm</td>
</tr>
<tr>
<td>Femoro-popliteal trunk</td>
<td>Lower limb ischemia</td>
<td>Chronic lower limb ischemia</td>
<td>Femoral aneurysm</td>
</tr>
<tr>
<td>Tibio-peroneal trunk</td>
<td>Lower limb ischemia</td>
<td>Chronic lower limb ischemia</td>
<td>–</td>
</tr>
</tbody>
</table>

Table II. Use of different techniques according to the specific arterial district.

<table>
<thead>
<tr>
<th>Technique</th>
<th>Brachiocephalic</th>
<th>Thoracic</th>
<th>Renal</th>
<th>Visceral</th>
<th>Abdominal</th>
<th>Iliac</th>
<th>Femoro-popliteal</th>
<th>Tibio-peroneal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thrombolysis</td>
<td>+++</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>Rheolytic thrombectomy</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+++</td>
<td>+</td>
</tr>
<tr>
<td>Stent</td>
<td>+++</td>
<td>+</td>
<td>+++</td>
<td>+++</td>
<td>+</td>
<td>+++</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Stent graft</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+++</td>
<td>+</td>
<td>+++</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Rotational thrombectomy</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+++</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Directional atherectomy</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Brachytherapy</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Drug-eluting stent</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Angiogenesis</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

+++ very useful; ++ used without uncertain outcome; + abandoned use or use under scrutiny; - not used.
tenecteplase should result in a further advantage in terms of lysis rates with limited systemic adverse effects. The report by Lutsep et al.3 in 2002 provided an early insight into the feasibility and safety of percutaneous aspiration thrombectomy using a 7F guiding catheter and a 60 ml syringe in order to establish a continuous suction pressure that was to be close to a perfect vacuum (<760 mmHg). Similarly, the only commercially available pulsatile isovolumetric pump, i.e., the rheolytic thrombectomy device (AngioJet, Possis Medical, Inc., Minneapolis, MN, USA), has been shown to be promising for rapid, large-burden thrombus removal (according to the Bernoulli principle) in cases of internal carotid artery thrombosis, allowing immediate access to the intracranial circulation for additional thrombolytic therapy4.

Intra-arterial thrombolysis of other acute supra-aortic vessel occlusions has also been proposed, but the cost-effectiveness of this approach has high resource implications5,6 and recently, to overcome these drawbacks, rotational thrombectomy devices, such as 8F Rotarex (Straub Medical AG, Wangs, Switzerland), have been successfully utilized by interventional endovascular specialists in the subclavian artery to reduce recanalization time5.

Infrarenal abdominal aorta and iliac arterial lesions. Acute occlusion of the infrarenal abdominal aorta and iliac artery are infrequently observed and their clinical presentation may vary from acute limb ischemia, neurological symptoms of the lower extremities, abdominal pain, sexual dysfunction, and secondary systemic hypertension. The natural history is also variable, ranging from rapid spontaneous improvement to progression to tissue death. Factors favoring a benign prognosis include the presence of preexisting collateral (i.e., a preexisting history of claudication), the presence of an audible arterial flow at Doppler and the absence of neurological changes at the time of presentation. Factors predicting a more morbid prognosis include the absence of preexisting arterial disease (as in embolic or traumatic arterial occlusion), the absence of detectable Doppler signals, and the presence of neurological changes and of muscular rigidity.

For nearly 40 years, elective management included immediate heparinization, balloon embolectomy and conventional surgical reconstruction with synthetic grafts or extra-anatomic bypass7. Recently, intra-arterial catheter-based thrombolysis has proved to be a safe and attractive alternative to surgery, obviating the need for operative intervention in 36% of patients and drastically reducing the rate of major complications (4 to 10%)8. Currently, percutaneous management includes the thrombus aspiration catheter, rheolytic thromboembolectomy9 and direct stenting without thrombolysis10.

It is important that visceral and limb revascularization procedures be performed early and expeditiously in the face of deteriorating clinical findings.

Femoro-popliteal and below-knee arterial lesions. Intra-arterial thrombolysis is an alternative to balloon embolectomy for the treatment of acute lower limb ischemia: it has a complete success rate of 69 to 86%, with a primary patency rate ranging from 75 to 87% at 2 years11-15. Despite these results, hospitalization costs seem to be higher than for surgery and subsequent surgical revascularization is common both for native artery and bypass graft occlusions, as suggested by Weaver et al.14 and Korn et al.15. Recently, reteneplase has proved to be a valid alternative to urokinase with a technical success rate of 87% and a major complication rate of 16%16.

Currently, percutaneous treatment includes the thrombus aspiration catheter or rheolytic thromboembolectomy17. The latter seems to be the most attractive technique with a technical success rate ranging from 88.4 to 90% and primary patency rates of 79 and 60% at 6 months and 2 years respectively18,20.

Clinical chronic critical arterial ischemia category and specific lesion treatment based on its site

Extracranial carotid arterial lesions. Prospective randomized studies, such as the NASCET (North American Symptomatic Carotid Endarterectomy Trial)21, the ECTS (European Carotid Surgery Trial)22 and the ACAS (Asymptomatic Carotid Atherosclerosis Study)23 have demonstrated the superiority of traditional carotid endarterectomy over medical treatment for both symptomatic and asymptomatic patients with ≥ 60% stenosis involving the internal carotid artery. However, carotid endarterectomy is not without its inherent risks of stroke and perioperative deaths and their reported combined rates are lower in studies with a single author affiliated with a surgery department (2.3%)23 and higher in studies in which the patients are assessed by neurologists after surgery (7.7%).

Carotid angioplasty and stenting have been recommended by some clinicians as an alternative to carotid surgery. This has provoked considerable discussion and controversies. At present, there is no consensus, and indications vary considerably among interventionists, whether they be radiologists, cardiologists or vascular surgeons. The reason is that comparative data and especially long-term results are lacking. In spite of this, some early considerations may be made. Firstly, with a combined minor and major stroke and procedure-related death rate of 5.07%, the risk of carotid stent placement is below that recommended in the American Heart Association guidelines for carotid endarterectomy which should be < 6% for patients with transient ischemic attacks and < 7% for patients with symptomatic strokes, whereas it is uncertain whether the risk rate would be below the recommended 3% for asymptomatic patients25. Secondly, in spite of the fact that an impressive number of case control studies and clinical
trials have established an acceptable rate of complications (Table III)\textsuperscript{26-31}, there are no conclusive suggestions for performing carotid artery stenting rather than surgery, and the concept of “widespread” that creates the concern has to be abhorred. This notwithstanding, endovascular stent placement for carotid occlusive disease is becoming popular and most skeptics and critics of carotid stenting are also becoming aware that cerebral protection may play an important role by reducing the procedural embolization risks, especially if their design and use can be improved without sacrificing the procedure time or threatening to dislodge plaque (Table IV)\textsuperscript{31-38}. However, despite the 30-day results of the SAPHIRE trial (Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy)\textsuperscript{39} that reports an advantage for angioplasty and stenting, no agreement exists about the indications and real superiority of carotid stenting over surgery.

As regards the risk of restenosis related to myointimal hyperlasia, the advent of stent use at the carotid bifurcation has reduced it to 8\%\textsuperscript{40,41} and parenchymatous hemorrhagic complications have been reported very rarely\textsuperscript{42}. Moreover, a new combined pharmaceutical and catheter-based scenario, i.e., the use of abciximab to abort impeding stroke during carotid angioplasty, is in the pipeline\textsuperscript{43}.

**Table III.** Summary of the most recent trials on carotid angioplasty and stenting.

<table>
<thead>
<tr>
<th>Author</th>
<th>No. patients</th>
<th>Minor stroke (%)</th>
<th>Major stroke (%)</th>
<th>Deaths (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jordan et al.\textsuperscript{26}, 1997</td>
<td>107</td>
<td>6.5</td>
<td>0.9</td>
<td>3.7</td>
</tr>
<tr>
<td>Jordan et al.\textsuperscript{27}, 1998</td>
<td>109</td>
<td>–</td>
<td>7.7</td>
<td>0.9</td>
</tr>
<tr>
<td>Jordan et al.\textsuperscript{28}, 1998</td>
<td>312</td>
<td>4.1</td>
<td>8.6</td>
<td>1.1</td>
</tr>
<tr>
<td>Wholey et al.\textsuperscript{29}, 1998</td>
<td>2048</td>
<td>3.08</td>
<td>1.32</td>
<td>1.37</td>
</tr>
<tr>
<td>Brooks et al.\textsuperscript{30}, 2001</td>
<td>104</td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Kastrup et al.\textsuperscript{31}, 2003</td>
<td>100</td>
<td>2</td>
<td>2</td>
<td>1</td>
</tr>
</tbody>
</table>

Summarizing, only high-risk patients, recurrent carotid stenosis after surgery and a difficult neck have been advocated and continue to be considered as a potential area for the use of this percutaneous procedure. On the other hand, soft plaques seem to be an absolute contraindication according to the ICAROS study (Imaging in Carotid Angioplasty and Risk of Stroke) in which 71.4\% of complications after carotid stenting occurred in patients with a duplex scan gray scale median assessment < 25 (very soft echolucent plaque)\textsuperscript{44}.

**Other supra-aortic arterial lesions.** The aortic arch classically gives rise to three main vessels: the innominate artery or brachiocephalic trunk that usually has two branches (the right common carotid artery and the right subclavian artery from which the right vertebral artery originates), the left carotid artery, and the left subclavian artery from which the generally dominant left vertebral artery originates. It is the function of these supra-aortic vessels to supply the brain and upper limbs with blood. Both vascular territories compete for the flow distribution in case of a proximal lesion, and the patient may suffer from symptoms of the brain or the arms. Chronic arterial insufficiency of the subclavian, innominate and vertebral arteries is subtle, varying from the absence of clinical signs (subclavian steal phenomenon), to symptoms of an impaired perfusion of the posterior cerebral circulation (subclavian steal syndrome) and arm discomfort upon exertion. The arm symptoms are more severe when the obstruction is located distally to the origin of the vertebral artery because of the poor collateral blood flow via branches of the thyrocervical and costocervical trunk, whereas vertebrobasilar insufficiency symptoms become evident when the dominant vertebral artery is supplied by a stenotic subclavian artery. Besides atherosclerotic disease, subclavian artery obstruction may be caused by other disease processes such as fibromuscular dysplasia, neurofibromatosis, arteritis, radiation damage,

<table>
<thead>
<tr>
<th>Author</th>
<th>No. patients</th>
<th>Neuroprotection</th>
<th>Minor stroke (%)</th>
<th>Major stroke (%)</th>
<th>Deaths (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parodi et al.\textsuperscript{32}, 2000</td>
<td>25</td>
<td>Filter protection</td>
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<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Henry et al.\textsuperscript{33}, 2000</td>
<td>150</td>
<td>Balloon-distal occlusion</td>
<td>1.2</td>
<td>0</td>
<td>2.3</td>
</tr>
<tr>
<td>Reimers et al.\textsuperscript{34}, 2001</td>
<td>84</td>
<td>Reversal flow system</td>
<td>0.5</td>
<td>0</td>
<td>1.9</td>
</tr>
<tr>
<td>Tubler et al.\textsuperscript{35}, 2003</td>
<td>54</td>
<td>Balloon-distal occlusion</td>
<td>1.03</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Guimaarans et al.\textsuperscript{36}, 2002</td>
<td>164</td>
<td>Filter protection</td>
<td>1.1</td>
<td>3.1</td>
<td>0</td>
</tr>
<tr>
<td>Schluter et al.\textsuperscript{37}, 2002</td>
<td>93</td>
<td>Balloon-distal occlusion</td>
<td>1.8</td>
<td>0.2</td>
<td>0</td>
</tr>
<tr>
<td>Cremonesi et al.\textsuperscript{38}, 2003</td>
<td>442</td>
<td>Reversal flow system</td>
<td>0.5</td>
<td>0.3</td>
<td>0.8</td>
</tr>
<tr>
<td>Kastrup et al.\textsuperscript{31}, 2003</td>
<td>896</td>
<td>Filter protection</td>
<td>0.5</td>
<td>0.3</td>
<td>0.8</td>
</tr>
</tbody>
</table>
post-traumatic scarring and compression syndromes (thoracic outlet obstruction). Among the brachiocephalic vessels, the left subclavian artery is the most commonly affected by atherosclerosis. The surgical intrathoracic approach, requiring sternotomy, has been withdrawn because it was associated with significant morbidity. Extra-anatomic carotid-subclavian or subclavian-subclavian bypass avoids sternotomy but may have a lower long-term patency rate than intrathoracic aorto-carotid bypass or endarterectomy. Angioplasty and stenting of the subclavian artery are well established and effective procedures with a high technical success rate (ranging from 84 to 94.3%), a low complication rate (varying between 16 and 17.8%), and a good secondary patency rate (72%). On the contrary, the effectiveness in treating subclavian occlusion is lower, ranging form 46 to 100% with a restenosis rate of 50%.

Innominate artery stenosis and short occlusion are also currently treated well with angioplasty and stenting with success rates of 96.4% for angioplasty and 100% for stent implantation and a good primary patency rate at 6 months (about 98%).

**Coronary-subclavian steal syndrome.** An important issue for the interventional cardiologist is the subclavian coronary steal syndrome: with the increased use of the internal mammary artery for myocardial revascularization, the potential for the recurrence of angina pectoris in patients who have, or in whom high-grade stenosis or occlusion of the subclavian artery develops, exists because of the coronary-subclavian steal syndrome. The coronary-subclavian steal syndrome involves the siphoning of blood from the myocardium through an internal mammary artery graft because of a proximal subclavian artery stenosis or occlusion, and results in myocardial ischemia. The incidence of this syndrome in patients undergoing internal mammary artery grafting for coronary artery bypass is estimated to be 0.44%. The use of duplex scanning and 99mTc-sestamibi has been suggested as an adjunct for the evaluation of the coronary-subclavian steal syndrome.

In the modern era surgical revascularization has been replaced by angioplasty and stenting of the subclavian artery when a tight stenosis of the subclavian artery and instrumental proof of myocardial ischemia are observed and high technical success and good patency rates have been demonstrated by a recent report.

All patients undergoing cardiac catheterization prior to coronary artery bypass grafting in which use of the internal mammary artery is anticipated should be evaluated for the presence of upper extremity and cerebrovascular ischemia, the presence of cervical or supraclavicular bruits, and an upper extremity blood pressure differential of ≥ 20 mmHg. Patients with these findings or with evidence of diffuse atherosclerotic vascular disease should have brachiocephalic arteriography at the time of coronary arteriography to identify significant subclavian artery occlusive disease. When this is demonstrated, the use of the internal mammary artery as a free graft instead of an in situ graft or the use of saphenous vein grafts is indicated. Patients in whom recurrent angina develops following coronary artery bypass grafting that included an internal mammary artery graft should have coronary arteriography to evaluate the presence of the coronary-subclavian steal syndrome, and brachiocephalic arteriography.

**Renal artery lesions.** There are two main etiologies of renal artery stenosis, i.e., atherosclerosis (90%) and fibromuscular dysplasia. These types of lesions, even if discovered incidentally in asymptomatic patients, are usually diagnosed in the following situations: 1) renovascular hypertension detected in 0.5 to 5% of patients with sudden onset, accelerated or difficult to control hypertension, or hypertension without a family history, or hypertension which does not respond to medical treatment, or sudden onset of renal insufficiency during captopril therapy, 2) renal insufficiency, which is present in 10 to 15% of cases, and 3) recurrent pulmonary edema without left ventricular dysfunction. The natural history of these lesions is to progress, and atrophy of the kidney has been reported in more than 20% of patients with over 60% renal artery stenosis.

Medical treatment may be proposed to reduce blood pressure, but the lower the arterial pressure, the lower the perfusion, and the renal failure may subsequently worsen. Surgical treatment has demonstrated its superiority over medical therapy. However, surgical revascularization is associated with a perioperative mortality of 1 to 6.1% and an associated morbidity > 20%. For these reasons, the endovascular treatment of renal artery disease is now a well accepted revascularization technique and the treatment of choice, offering both high procedural success and low restenosis rates (Table V). Not all patients with renal artery stenosis will

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**Table V.** Summary of the results of the most recent trials on angioplasty and stenting of the renal artery.

<table>
<thead>
<tr>
<th>Author</th>
<th>No. patients</th>
<th>Success (%)</th>
<th>Restenosis (%)</th>
<th>Benefit (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>White et al.56, 1997</td>
<td>100</td>
<td>99</td>
<td>19</td>
<td>76</td>
</tr>
<tr>
<td>van de Ven et al.57, 1999</td>
<td>43</td>
<td>88</td>
<td>14</td>
<td>–</td>
</tr>
<tr>
<td>Yutan et al.58, 2001</td>
<td>86</td>
<td>89</td>
<td>31</td>
<td>52</td>
</tr>
<tr>
<td>Rocha-Singh et al.59, 2002</td>
<td>51</td>
<td>98.9</td>
<td>–</td>
<td>94</td>
</tr>
</tbody>
</table>


benefit from angioplasty or surgery. For this reason, it is not sufficient to diagnose the presence of renal artery stenosis, but one also has to evaluate its functional significance. At sonography, renal artery stenosis can be detected with a sensitivity and specificity > 90% by an experienced investigator. A combination of Doppler parameters making use of both the direct and indirect signs of stenosis should be used. The reversibility of hypertension or impaired renal function (i.e. the presence of renovascular hypertension or azotemia) after the successful correction of renal artery stenosis may be assessed by measuring the segmental artery resistance indices. It has been proposed that a resistance index > 0.80 makes a treatment effect highly unlikely, and angioplasty or surgery should not be considered for these patients60,61.

Unfortunately, there is still no consensus on the ideal diagnostic test for the selection of patients with a high probability of a beneficial outcome following renal stenting and the selection criteria for such patients who may need percutaneous treatment are still lacking and vary considerably between different institutions. In view of the above, the outcome of renal angioplasty and stenting in so far as hypertension and renal function are concerned cannot be easily explained: a recent report62 observed significant reductions in systolic and diastolic blood pressure, and a modest increase in the calculated glomerular filtration rate. Other authors63,64 reported a maximum cure rate approximating 10% for hypertension, with a 40% rate of improvements, whereas with regard to the ischemic kidney some improvement in renal function has been observed in 35% of patients with outcomes related to the pretreatment serum creatinine levels. Stenting seemed to be more effective than percutaneous transluminal angioplasty both with regard to the hypertension cure rate and to the renal function improvement.

The outcomes of renal angioplasty and stenting in patients with fibromuscular dysplasia are currently much better than those of patients with renal atherosclerosis: arterial hypertension was cured or improved in 74-95% of patients, and renal failure in 86% of the patients; a stable renal profile was achieved in 14% of the patients65-67.

Moreover, even though the effectiveness of primary or direct stentings68, of the protection device69 and of alternative contrast media during renal angioplasty70 has been reported, their absolute role has still not been extensively and sufficiently investigated.

Infrarenal abdominal aorta and aorto-iliac bifurcation lesions. There are several forms of atherosclerotic processes in the aorto-iliac region that may be summarized as follows: 1) isolated and focal lesions of the infrarenal abdominal aorta, 2) localized disease of the aortic bifurcation involving the lower part of the abdominal aorta and the common iliac arteries, and 3) lesions of the origin of both common iliac arteries. The numerous options currently available for the treatment of infrarenal and aorto-iliac occlusive diseases have led to considerable controversy as to the optimal method of revascularization in such patients71. Both the aorto-iliac endarterectomies and the aorto-bifemoral grafting procedures have traditionally been regarded as the "gold standard" treatment, but these surgical interventions are associated with a substantial procedure-related risk for the patients. The low morbidity, the option of repeating the procedure and the good immediate and long-term results render the endoluminal therapies a valid alternative to surgery or even the first treatment to offer to patients with infrarenal abdominal aorta or aorto-iliac stenoses, whereas bilateral iliac total occlusions involving the aorto-iliac bifurcation are generally not considered as an indication for percutaneous treatment71. The kissing balloon angioplasty and stenting techniques seem well adapted to treat aorto-iliac bifurcation lesions and even infrarenal abdominal aortic lesions. With regard to stent types, there is a common consensus to use only the balloon-expandable stents because they may be positioned precisely72.

Current literature shows a percutaneous primary technical success of nearly 100% with a primary patency rate ranging from 86 to 100% at 3 years73-76. Although little truly definitive data are available, there is a lot of evidence on the effectiveness of primary stenting77, combined excimer laser-assisted recanalization and stenting of aorto-iliac occlusions (primary patency rate 86.8% at 2 years)78 and on the use of intravascular ultrasound to assist aorto-iliac stenting in order to decrease the restenosis rate to 0% in comparison with 25% for angiographic guidance alone79.

Iliac artery lesions. Percutaneous transluminal angioplasty is a well-established treatment and has proved to be an effective technique for symptomatic iliac artery stenoses and short occlusions.

Stent placement after uncomplicated angioplasty (primary stenting) has been subsequently advocated as a routine means of improving the initial technical success rate and as an attempt to decrease the risk of long-term failure. Recently, direct iliac stenting without antecedent dilation has been recommended to reduce the procedural time, costs and radiation exposure; however, there is no definite evidence in support of less vessel injury with this approach over primary stenting. Percutaneous angioplasty and stenting of iliac artery stenoses has been performed with a 90.2% technical success rate and a primary patency rate of 73 and 76% at 1 and 2 years80,82, whereas chronic iliac artery occlusion has been treated by stenting with a technical success rate ranging from 97 to 100% and primary and secondary patency rates varying from 52 to 79.4% and 66 to 97.7% at 3 years84,85, respectively.

Recently, intravascular ultrasound has been proven to increase the primary and secondary patency rates to 100% at 6 years86, whereas combined iliac artery stent-
ing and common femoral endarterectomy has been suggested as a less invasive surgical approach than conventional aorto-femoral bypass grafting85.

**Femoro-popliteal and below-knee arterial lesions.**

The femoral and popliteal arteries are considered together because the anterograde approach, the results and the complications are generally the same. The role of angioplasty and conventional stenting in the treatment of atherosclerotic disease in the femoro-popliteal arteries has been extensively evaluated in randomized trials (Table VI)88-91. Whereas it has been accepted that percutaneous interventions at the iliac level are efficacious, there is more debate regarding the femoro-popliteal level, where the long-term results are not always favorable. The failure rate of femoro-popliteal catheter-based procedures correlates with the type (stenosis vs occlusion) and location (femoral vs popliteal) of the treated lesion, the status of the distal run-off (focal vs diffuse occlusive disease), and the severity of limb ischemia.

At present, the endovascular specialists prefer different types of stents for different purposes.

Balloon-expandable stainless-steel stents are not indicated at the femoral site because of the crushing effect they may be subjected to. In view of their flexibility, coil stents have been suggested for soft femoral lesions92,93 and in the popliteal district, showing a restenosis rate of 14.4% and a primary patency rate of 84.7% at 4 years93. The nitinol stents are preferred in the joint, whereas the bare-metal stents are preferred in case of fibrocalcific plaques due to their high radial force.

In an attempt to improve the patient outcome, especially for femoro-popliteal obstruction, some investigators have begun to evaluate Duplex ultrasound-guided angioplasty and the use of stent grafts and alternative forms of endovascular procedures such as thermal laser angioplasty, vibrational angioplasty, cryoplasty, and new kinds of atherectomy devices. The use of Duplex ultrasound-guided angioplasty in patients at high risk for contrast-induced complications showed a lower technical success and similar 12-month patency rates to those of standard angioplasty94. The stent graft technology has been proven to be effective in the short-mid term, especially for short occlusions with a primary patency rate of 49 to 73.2% and an occlusion rate of 28.6 to 72%95-97 at 1 year. Thermal laser angioplasty has been proved to be effective, with successful recanalization of the superficial femoral artery in 80% of cases and a primary patency rate of 50% at 1 year98. It has also been suggested that vibrational angioplasty, using coronary equipment, improves the recanalization rate in long chronic femoral occlusions with a 100% technical success rate and acceptable patency rates at 9 months99. Moreover, an interesting and promising technique seems to be cryoplasty: the angioplasty balloon is inflated with pressurized nitrous oxide which cools to a temperature of -10°C, freezing the plaque and inducing apoptosis. The preliminary results of the first human trial demonstrated a restenosis rate of 12% and a reduction in the rate of meaningful dissection to around 6% when compared to the 40–45% of standard percutaneous transluminal angioplasty (Laird J, 2003, personal communication). Finally, two rotational atherectomy devices, the Rotarex catheter (Straub Medical AG, Waing, Switzerland) and the Xtrak (Xtrak Medical, Inc., Salem, NH, USA) have shown encouraging early results in recanalizing acute, subacute17 and chronic100 femoro-popliteal occlusions. However, larger and longer follow-up studies are required to assess their real effectiveness.

Femoral bifurcation lesions, as well as any other bifurcation lesion regardless of its localization (i.e., coronary, renal, iliac, femoral and tibio-peroneal trunk), need to be held in due consideration. In fact, the percutaneous treatment of lesions located at an arterial bifurcation always gives rise to several problems. In particular, the femoral bifurcation is the most ambiguous and challenging arterial lesion for percutaneous treatment for two main reasons: firstly, the joint location exposes the stent to compression; secondly, accidental damage of the deep femoral artery may threaten the functionality of the foot because the collateral circulation of the lower limbs mainly depends on this artery. Consequently, surgical endarterectomy is preferable when common femoral disease extends to the deep and superficial femoral arteries, because the bifurcation may be easily surgically accessed without any significant risks.

The use of below-knee percutaneous revascularization is becoming the primary choice of treatment in pa-
tients with chronic limb ischemia and distal lesions including focal stenosis and short occlusions. Standard angioplasty and stenting has been improved by the use of coronary stents and the Bolia subintimal re-
canalization technique achieving a cumulative limb sal-
vage rate ranging from 60-88% at 12 months to 94% at 5 years. On the basis of these findings, some authors recommend that percutaneous transluminal an-
gioplasty be attempted, whenever possible, for initial the treatment of patients presenting with critical, limb-
threatening ischemia due to isolated or multiple stenoses of below-knee arteries.

Dialysis fistula access-related vascular problems. Hemodialysis-dependent patients require reliable vascular access. The preferred type of access has been the direct internal arterio-venous fistula such as the Brescia-Cimino type. When a direct arterio-venous fistula is not possible because of iatrogenic vessel injury, obesity or other factors, or when the arterio-venous fistula fails, synthetic polytetrafluoroethylene or heterologous grafts are used. The forearm is the preferred site of ac-
cess, but the brachium, thigh, neck and other sites have been used.

Vascular problems in association with arterio-ve-
nous fistulae or conduits include needle-puncture-relat-
ed false aneurysms, anastomotic stenoses, proximal ve-
nous stenoses and thromboses. When a decreased or absent flow or a high venous resistance are found at dialysis, complete thrombosis of the subclavian vein or access-related stenosis are the more common causes of failure. Local fibrinolytic therapy for complete throm-
bosis of the subclavian vein is constantly successful in these cases, always demonstrating a stenosis in the vein wall. Percutaneous transluminal angioplasty has been applied to failing access-related stenosis since 1980: appropriate lesion selection and the use of the proper size high-pressure or cutting balloons may be expected to yield patency for approximately 1 year. These inter-
terventional procedures should be considered in all such patients as the treatment of choice in order to pre-
serve any single access and to minimize the number of surgical procedures.

Clinical aneurysmal disease category and specific lesion treatment based on its site

Extracranial carotid and brachiocephalic aneurys-
mal lesions. Extracranial carotid and other brachio-
cephalic aneurysms due to the atherosclerotic process are quite rare. In the past 5 years, with the advances in stent graft technology, dacron-covered bare-metal stents or polytetrafluoroethylene-coated nitinol stents have been proposed for the treatment of aneurysms of these arterial districts and many case re-
ports in the world literature have referred successful treatment both for the carotid and subclavian-innomi-
nate arteries, with a reduction in the perioperative risk of surgical repair, and primary and secondary patency rates at 29 months of 68 to 89 and 100%, respectively.

Infra-abdominal visceral and popliteal aneurysmal lesions. Infra-abdominal visceral and popliteal aneu-
rysmal lesions are relatively uncommon diseases. They may present incidentally and be asymptomatic or fol-
lowing complications such as rupture, compression or thromboembolism. Until some time ago, their treat-
ment was exclusively surgical, but the operative risks were high, particularly when surgery was required on an emergency basis. Recently, it has been suggested that splenic artery aneurysms may benefit from endovascular repair with stent grafts, allowing the aneurysm to be excluded and thus preserving organ perfusion. Exclusion and preservation of organ supply is also the goal of treatment of renal artery aneurysms. Atherosclerotic renal artery aneurysms constitute up to 25% of all infra-abdominal visceral aneurysms with an incidence ranging between 0.1 and 2.5% in angiographic series. They are relevant because rupture carries a mortality of 80% and surgery is aggravated by a high morbidity and mortality. The Jomed (Jomed, Ulestraten, The Netherlands) covered stent has been successfully used to treat this kind of aneurysm in single case reports. Isolated common and external iliac aneurysms constitute only 2% of aneurysms of an atheromatous origin and 1.5% of infra-abdominal ones, whereas aneurysms of the internal iliac artery are very rare (0.4% of all intra-abdominal aneurysms). Despite the improvements in surgery, the mortality and morbidity remain high, and presently percutaneous treatment of iliac aneurysms seems to be an effective alternative to surgery with a satisfactory mid-term outcome. Satisfactory early results achieved by percutaneous endovascular treatment of popliteal aneurysms using the Hemobahn endograft (WL Gore & Associates, Flagstaff, AZ, USA) have also been reported, but the clinical durability will require a longer follow-up and additional evaluation in a greater number of patients. Consequently, to date, the popliteal aneurysm is still a surgical indication, except for high-risk patients.

Thoracic and abdominal aorta aneurysmal lesions. Thoracic and abdominal aortic aneurysmal disease has been diagnosed ever more frequently since the past two decades. This observation is probably related to the ag-
ing of the population as well as to the extensive use of ultrasoundography and computed or magnetic scanning for different pathologies. Although an aortic aneurysm may occasionally cause distal embolization, rupture remains the most common and deadly complication. Elective re-
placement with a synthetic graft has proved to be the most appropriate method for the prevention of aneurysm rupture for nearly 40 years, but it has been associated with a high postoperative mortality and morbidity. Moreover, aortic aneurysms present a diagnostic chal-
lenge as well as a difficult clinical decision regarding the appropriate time of elective surgical intervention.

Recently, endoluminal grafting of the thoracic and abdominal aortic aneurysms has fast become an alternative treatment to the historically standard surgical repair since Parodi et al.114 first demonstrated its technical feasibility, the basic idea being to replace the surgical suture by a different element for fixation of the fabric graft to the arterial wall. This technique blends stent and graft technologies and allows placement of a vascular graft from a remote access (i.e., femoral or axillary surgery atherectomy) under fluoroscopic guidance. The main advantage of this new approach is its less invasive nature, whereas the main concerns are the potential neck dilation and device migration over time.

Classical indications for thoracic aortic aneurysm endovascular repair include aneurysms with a proximal neck distal to the left subclavian artery and at least 2 cm in length and no more than 3.5 cm in width, and a distal cuff of similar dimensions: tortuosity, angularity, or stenosis of the iliac system as well as the presence of a mural thrombus or calcification at the proximal or distal landing site are considered relative contraindications. The ideal patients for abdominal aortic aneurysm endovascular repair must have a proximal infrarenal undilated aortic segment 0.5-1.5 cm in length, a sufficient caliber of the common and external iliac artery to allow passage of the introducer sheath, an angle between the suprarenal aorta and the proximal neck < 60°, and no aberrant inferior mesenteric or accessory renal artery included in the segment of aorta to be excluded. Indications and selection criteria for the endovascular repair of both thoracic and abdominal aortic aneurysms are continuing to evolve and, due to technical and material advances, an increase in the percentage of patients suitable for such intervention is likely in the near future.

Due to these limitations, several details should be considered before recommending the widespread use of this technique. Firstly, measurements of the diameters and lengths are crucial and they have to be obtained using enhanced computed tomography scans or magnetic resonance imaging; secondly, access problems need to be worked out; thirdly, for an uncomplicated outcome, the accuracy of the deployment of the self-expanding stent graft should always be checked by means of intravascular ultrasound115; finally, microembolizations, which are the main and worst problems associated with this procedure.

In addition to their use for the elective repair of the descending thoracic aortic and abdominal aortic aneurysms (Table VII)116-123, during the last years, endovascular grafts have been implanted to treat a variety of arterial lesions including ruptured aneurysms of both the thoracic and abdominal aorta (Table VIII)124-127, type B128 and type A aortic dissections in combination with open repair129, and traumatic or iatrogenic aortic injuries. These endovascular grafts have facilitated successful treatment in many patients and have permitted correction of limb life-threatening lesions in selected patients for whom treatment would have otherwise been impossible or difficult. This is particularly true for subjects with severe comorbid medical illnesses, scarring from previous operations or multorgan trauma.

On the other hand, the anatomic characteristics of the patients represent the only key component for the selection criteria for the endoluminal treatment of aneurysmal lesions. Besides, even in low-risk patients,
standard vascular repairs have associated morbidity, and the quality of life following such treatment may be impaired by scar pain, sexual dysfunction and other problems. Nowadays, the standard limits of endograft implantation have been progressively overcome. In fact, supra-subclavian fixation has presently become feasible without ischemic complications and associated aneurysms of the common iliac arteries (> 16 mm in diameter), which in the past excluded endoluminal repair of the abdominal aneurysm, are now being treated by extending the flared cuff inside (the so-called “bell bottom” technique) to preserve the internal iliac artery circulation, thus avoiding the need for endovascular coil embolization.

Modified endoprostheses with a long uncovered stent segment, which are suitable for suprarenal and across the left aortic arch vessel fixation, had a low endoleak rate (about 10% at 1 year) and a lower mortality and morbidity than open surgery.

Nevertheless, the debate about the real effectiveness of the endovascular repair of aortic aneurysms is far from concluded, since a lot of doubts and limitations still remain. On the one hand, the incidence of adverse events (i.e., myocardial infarction, renal failure, aortoenteric fistulae, pseudoaneurysm formation, bowel ischemia and graft infection), although lower in endovascular than open surgery, is still relevant and stent graft migration in cases of a large proximal or complex neck still occurs. On the other hand, delayed paraplegia after thoracic and thoracoabdominal aneurysm repair and renal artery infarction occur in 10 and 8.3% of cases respectively. Moreover, type I and type II endoleaks are diagnosed in 19 and 49% of patients respectively. The risk of late failure is about 3% per year, further increasing the cost of endovascular repair in comparison to open surgery despite the shorter hospital stay and fewer intensive care admissions. However, although the operative mortality rate for the elective repair of aortic aneurysms has decreased markedly over the past several decades (declining from 21% in early surgical surveys to < 5% reported in modern studies), the value and limitations of endovascular grafting for the treatment of aneurysmal lesions in low-risk patients still has to be proved, whereas their use in high-risk patients and in those with iatric aneurysms or traumatic false aneurysms and arterio-venous fistulae already appear to be justified, because the endovascular grafting transforms a sometimes complicated and potentially dangerous procedure into a simple and a safe one. Moreover, in cases of traumatic lesions, this procedure may be combined with the endovascular control of bleeding of secondary branches by using detachable balloons, coils, occlusion stents or the injection of fluids that solidify within the body.

Recently, the use of 16-22F sheaths and the Prostar XL Percutaneous Vascular Surgery Device (PVS, Perclose, Redwood City, CA, USA), with 46.2-96% successful groin wound repair rates, are opening a new horizon for the totally percutaneous endovascular repair of both thoracic and abdominal aortic aneurysms. These instruments allow the treatment of vascular aneurysms without the need of directly exposing the access site through an extensive incision.

**Problems related to endovascular procedures: restenosis and reoclusion**

The success of percutaneous endovascular interventions in the systemic circulation for the treatment of atherosclerotic disease is variable depending on the vascular segment (Table IX). Different strategies are beginning to be proposed to really control this phenomenon, the most attractive of which are brachytherapy and drug-eluting stents.

<table>
<thead>
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<th>Table IX. Restenosis rate according to the different arterial segments.</th>
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<tr>
<td>Artery</td>
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<td>-------------------------</td>
</tr>
<tr>
<td>Brachiocephalic</td>
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<tr>
<td>Renal</td>
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<tr>
<td>Aorto-iliac</td>
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<td>Femoro-popliteal</td>
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<td>Tibio-peroneal</td>
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Brachytherapy with gamma-radiation, inducing positive remodeling, has been recently proposed for the treatment of carotid in-stent restenosis and in the aorto-iliac district. The femoro-popliteal arteries are the most widely investigated: the Vienna 2-Trial demonstrated a cumulative patency rate at 1 year of 63.6% with brachytherapy after percutaneous transluminal angioplasty in de novo femoral lesions compared to 35.3% with percutaneous transluminal angioplasty alone, whereas the PARIS trial (Peripheral Artery Radiation Investigational Study) obtained an angiographic restenosis rate at 6 months of 17.2% and a clinical restenosis rate of 13.3% at 1 year. The only relevant clinical drawback to this technique is late thrombosis or occlusion that occurred in 27% of such patients, subsequently requiring a prolonged antithrombotic therapy.

Following the exceptional results in the coronary circulation, the use of drug-eluting stents is starting to be extensively investigated for the femoro-popliteal arteries. The 6-month results of the first series using the SMART-sirolimus coated stent showed an in-stent percent diameter stenosis of 22.6% compared to 30.9% in the uncoated stent group.

**Summary**

Noncoronary interventional procedures are an established method of treatment in a variety of medical conditions. To summarize, the following specific mor-
phologic and clinical conditions in patients with non-
coronary vascular disease should be seriously consid-
ered as indications for these procedures as the ther-
apeutic strategy of first choice: 1) lower extremity is-
chemia due to iliac and/or femoro-popliteal stenosis or 
short occlusion; 2) renovascular hypertension, renal in-
sufficiency and transplant renal artery stenosis; 3) 
abdominal angina, sitophobia (fear of eating because of 
the anticipated symptoms), and profound weight loss 
due to mesenteric ischemia; 4) subclavian steal syn-
drome and vertebralbasilar insufficiency; 5) dialysis ac-
cess-related stenosis; 6) thoracic and/or abdominal aor-
tic aneurysms, and iliac and/or popliteal aneurysms 
when they are morphologically suitable for endovascu-
lar repair.

New horizons and conclusions

With the increasing prevalence of atherosclerotic 
vascular disease in our community, difficult manage-
ment decisions are arising when patients develop si-
multaneous symptoms from different arterial sites. On 
the one hand, the severity and the progressive nature of 
the arterial occlusive disease sometimes render surgical 
or percutaneous therapy impossible, resulting in persist-
ent, disabling symptoms or limb loss. On the other 
hand, the outcomes following combined operations 
such as integrated minimally invasive approaches (i.e. 
bypass grafting and angioplasty) have yielded conflict-
ing results. Consequently, the need for alternative ther-
apy is compelling. Significant research has focused on 
developing therapeutic angiogenesis and, after an ex-
tensive experimental phase in animals, the intramuscu-
lar vascular endothelial growth factor was first pro-
posed for treatment in humans by Baumgartner et al.153 
with an increase in the pain-free walking time and the 
angiographic appearance of new visible collateral ves-
sels. Recently, Vale et al.154 have demonstrated clinical 
improvement and ulcer regression in 72% of 55 pa-
thents. Laitinen et al.155 experimented intra-arterial trans-
catheter adenovirus-mediated gene transfer after percu-
taneous angioplasty and observed a significant devel-
opment of collateral vessels. These results confirm the 
report of Kalka et al.,156 who studied the augmentation 
of endothelial progenitor cells by vascular endothelial 
growth factor gene transfer, accomplishing not only ther-
apeutic angiogenesis but also vasculogenesis. In the 
near future, therapeutic angiogenesis, using both 
human embryonic or autologous bone marrow stem 
cells157, may represent an exciting potential arsenal in
interventional laboratories for the treatment of non-
coronary atherosclerotic pathologies.

In conclusion, as never previously imagined, the en-
thusiasm for noncoronary interventional procedures is 
growing rapidly among cardiologists, who are to be-
come more familiar with peripheral vascular diseases, 
acquiring knowledge of their natural history, vascular 
anatomy, pathophysiology, and therapeutic alterna-
tives.

Why should a cardiologist perform noncoronary 
procedures? Firstly, due to very frequent association of 
peripheral vascular disease with coronary artery dis-
eease, it is very common for an interventional cardiolo-
gist to encounter significant peripheral vascular disease 
in a patient who requires a coronary interventional pro-
ceedure. Secondly, the cardiologist has the best training 
for the management of atherosclerotic risk factors. If 
for no other reason, it has been well established that
disease in one region frequently influences other re-
gions: e.g. renovascular disease and suboptimally con-
trolled arterial hypertension will unfavorably affect the 
symptoms of coronary artery disease, congestive heart 
failure and cerebrovascular disease. Thirdly, their close 
historical association with the principal manufacturers 
of coronary and peripheral balloons and stents may 
have high resource implications both at the institute and 
at the hospital, also offering the best patient care for 
complex interventional procedures and stimulating ed-
uational activities and research.

However, at present, only a few integrated cardio-
vascular centers are following this multidisciplinary 
approach in our country. In particular, no attention is 
being directed toward the development of these skills 
during postgraduate study and after board certification 
in cardiology.

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