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Giuseppe M. SANGIORGI, Alessandra PIZZUTO, Nicholas DIEHM, Francesco GRECO, Ferdinando FUSCO, Gaetano CHIRICOLO, Alberto VISMARA, Vincenzo ALTIERI, Alberto CEREDA, Sante BONGO

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Endovascular Therapy For Erectile Dysfunction: A State of the Art Review

Giuseppe Sangiorgi[1*], Alessandra Pizzuto[1], Nicholas Diehm[2], Francesco Greco[3], Ferdinando Fusco[4], Gaetano Chiricolo[1], Alberto Vismara[3], Vincenzo Altieri[3], Alberto Cereda[5], Sante Bongo[5]

*ORCID ID 0000-0001-5862-1967

[1] *Division of Cardiology, Department of Systemic Medicine, University of Tor Vergata, Rome, Italy*
[2] *Vascular Institute Central Switzerland, Aarau, Switzerland*
[3] *Department of Urology, Humanitas Gavazzeni, Bergamo, Italy*
4 Department of Urology, University "Luigi Vanvitelli", Caserta, Italy
[5] *Division of Cardiology, Clinica San Gaudenzio, Novara, Italy*

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Address for correspondence: Giuseppe Sangiorgi, MD, FESC, FSCAI, FSICI-GISE
Division of Cardiology
Department of Systemic Medicine
University of Rome Tor Vergata
Via Montpellier 1, 00133 Rome Italy
Email: gsangiorgi@gmail.com

Abstract

Erectile dysfunction (ED) is defined as the inability to attain or maintain penile erection sufficient for successful sexual intercourse. ED carries a notable influence on quality of life, with significant implications for family and social relationships. Because atherosclerosis of penile arteries represents one of the most frequent causes of ED, patients presenting with it should always be investigated for potential coexistent coronary or peripheral disease. Up to 75% of patients with ED have a stenosis of the iliac-pudendal-penile arteries, supplying perfusion of the male genital organ. Recently the potential treatment of this pathological condition by percutaneous approaches has emerged with good angiographic results and with a significant improvement in symptoms and quality of life. This review will focus on the normal anatomy and physiology of erection, the pathophysiology of ED, the relation between ED and cardiovascular diseases and, lastly, on new treatment modalities aimed at restoration of normal erectile function.

Key words. Erectile dysfunction; Paclitaxel Eluting Balloon; Sirolimus Eluting Balloon; Venous embolization; Low-intensity Extracorporeal Shock Wave;

"Success is stumbling from failure to failure with no loss of enthusiasm."
– Winston S. Churchill

Introduction

Erectile dysfunction (ED) is defined as consistent or recurrent inability to attain and/or maintain penile erection sufficient for sexual satisfaction (1). The term ED has recently replaced the term "impotence", because sexual desire, orgasm function and ejaculation may be normal, but the patient is unable to have or maintain an erection. To exclude temporary disorders, the patient must have experienced ED for at least 3 months, except in cases of ED secondary to trauma or surgery (2). Depression, shame, decreased self-esteem and relationship problems are commonly reported symptoms and experiences of people suffering from ED. ED is a common disorder, affecting almost 40% of men over 40 years of age, with varying degrees of severity and with increasing frequency with age (3). It may result from psychological, neurologic, hormonal, arterial, venous or cavernosal impairment or from a combination of these factors.

This review will briefly summarize the normal physiology of erection, the pathophysiology of ED, the relations between ED and cardiovascular diseases focusing on new treatment modalities for vasculogenic ED from mechanical percutaneous revascularization to low-intensity extracorporeal shock wave (LI-ESWT) therapies.

Penis Anatomy and Physiology of Erection

The penis is made up of an attached root and a pendulous body. The root consists of three bodies of erectile tissue: two crura and the bulb, attached to the pubic arch (crura) and perineal membrane (bulb) *(Figure 1, Panel A-B-C)*.

Near the border of the pubic symphysis the bilateral crura continue as the corpora cavernosa throughout the body of the penis, while the bulb, that lies between the two crura, narrows anteriorly and continues as the corpus spongiosum. During penile erection, all 3 erectile bodies, which are highly specialized vascular structures, become engorged with blood. The corpora cavernosa are enveloped in a thick fibrous tunica albuginea, which is comprised of a longitudinal running superficial layer of fibres and a deep layer of circular oriented fibres. The corpus spongiosum is penetrated by the urethra as it traverses the body of the penis. The corpora cavernosa are composed of trabecular smooth muscle, which constitutes approximately 40–50% of tissue cross-sectional area, and extracellular matrix consisting predominantly of collagen types I, III, and IV, and elastin; endothelial cells and neurons play critical roles in maintaining and regulating vascular smooth muscle cell tone (4).

The hypogastric iliac artery, a branch of the common iliac artery, provides penile arterial blood supply through the internal pudendal artery and its sub-branches: the common penile artery which splits into the bulbourethral (which supplies the glans and the distal part of the urethra), dorsal and cavernosal arteries. The latter lie in the middle of the corporal bodies and give rise to the helicine resistance arteries which open directly into the lacunar spaces and feed the individual trabeculae. The penis is drained by three groups of veins including superficial,

intermediate and deep (5). The superficial veins primarily drain penile skin, and they can communicate with the deep dorsal veins. The intermediate veins primarily consist of the deep dorsal vein and prostatic venous plexus. The venous drainage of the penis relies mainly on the deep dorsal vein under the fascia penis. Then, the deep dorsal vein drains to the prostatic venous plexus. The deep veins primarily consist of crural veins, draining the deep cavernous tissue.

A physiological penile erection requires normal vascular, neurological and tissue responses. Penile erection is initiated after central processing and integration of tactile, visual, olfactory, and imaginative stimuli and the final response is mediated by coordinated spinal activity in the autonomic pathways to the penis and in the somatic pathways to the perineal striated muscles. The central regulation of penile erection involves many transmitters, the details of which are not completely known (4,6). Nerve impulses cause the release of neurotransmitters from the cavernous nerve terminals and of relaxing factors from the endothelial cells in the penis, resulting in the relaxation of smooth muscle in the arteries and arterioles supplying the erectile tissue and a severalfold increase in penile blood flow. At the same time, relaxation of the trabecular smooth muscle increases the compliance of the sinusoids, facilitating rapid filling and expansion of the sinusoidal system. The sub-tunica venular plexuses are thus compressed between the trabeculae and the tunica albuginea, resulting in almost total occlusion of venous outflow. These events trap the blood within the corpora cavernosa and raise the penis from a flaccid to an erect position, with an intracavernous pressure of approximately 100 mmHg. Detumescence can be the result of a cessation of neurotransmitter release, the breakdown of second messengers by phosphodiesterase's, or sympathetic discharge during ejaculation. Contraction of the trabecular smooth muscle re-opens the venous channels, the trapped blood is expelled, and flaccidity returns.

In order to have a normal erection, several components are required: a) a functioning nervous system; b) a good arterial flow; c) healthy corpora cavernosa; d) the ability to block the venous blood spill.

A complex balance between the central and peripheral nervous systems and the integrity of the penile vasculature determines the ability to pass from flaccid state to erection. The response of the central nervous system to sexual stimulation is mediated by the hypothalamus through dopamine release, with production of impulses through the spinal cord to stimulate the erection process. Furthermore, the same process can be achieved through a direct tactile stimulation of the penis through the production of erectile stimuli to the sacral cord by excitatory sensory neurons at the level of the S2-S4 region. Therefore, efferent neurons emerge through the neural foramen sacral forming synapses with postganglionic fibres and non-adrenergic non-cholinergic (NANC) fibres in the hypogastric plexus. These fibres run through the cavernous nerves at the level of the corpora cavernosa and generate reflexes (central or local starting impulses) that cause the release of nitric oxide (NO) at the level of the corpora cavernosa. The NO is further released by the vascular endothelium in response to parasympathetic stimulation and the release of acetylcholine, linked to increased wall stress due to the increase of blood flow in the cavernous sinusoids. The NO activates at this level the release of guanylate cyclase *(Figure 2 - Panel A)* by smooth muscle cells by increasing the conversion of guanosine triphosphate into cyclic guanosine monophosphate (cGMP). Through a protein kinases mediated cascade, hyperpolarization of the cell membrane and intracellular calcium

sequestration occurs leading to release of smooth muscle cells of the corpora cavernosa and arterial vasodilation. The swelling of the cavernous sine waves simultaneously causes compression of the venous plexus in the tunica albuginea, resulting in venous outflow obstruction and maintaining the erectile phase. The phosphodiesterase-5 compounds are the mediators of the return to the state of penile detumescence through cGMP hydrolysis. The pro-erectile parasympathetic mechanism is offset by adrenergic sympathetic fibres which run in the cavernous nerves. The release of norepinephrine from sympathetic neurons stimulates and maintains the flaccidity through the release of alpha-1 G-protein receptors on smooth muscle cells of the cavernous sinusoids which in turn activates a calcium decrease in intra-cytoplasmic reticulum and relaxation of smooth muscle cells themselves *(Figure 2 – Panel B)*.

A detailed review of biochemical and molecular mechanisms involved in vascular smooth muscle cells tone of penile corpora cavernosa has been published by Gratzke et al (4).

Clinical Meaning and Epidemiology of Erectile Dysfunction

Erectile dysfunction is a common medical disorder that primarily affects men older than 40 years of age and it is becoming a major problem with many implications for the ageing population. Its worldwide prevalence has been predicted to increase from 152 million cases in 1995 to 322 million by the year 2025 (7). Despite the magnitude of this problem many patients suffering from ED do not explicitly seek medical help, commonly because of embarrassment, fear or lack of information about the therapeutic possibilities.

The first large study on ED epidemiology was the Massachusetts Male Aging Study (MMAS), a community based, random sample observational survey of noninstitutionalized men 40 to 70 years old conducted from 1987 to 1989 in cities and towns near Boston, Massachusetts (8). This study documented a combined prevalence of minimal, moderate and complete impotence of 52% between 40 and 70 years of age; specific prevalence for mild, moderate and severe ED was respectively 17.2%, 25.2% and 9.6%. In a German epidemiological study performed in Cologne in men aged between 30 and 80 years, the prevalence of ED was found to be 19.2%, with an age related increase from 2.3% to 53.4% (9). The prevalence of erectile dysfunction is age dependent, increasing from 2-9% in men between the ages of 40 and 49 years, to 20–40% in men aged 60–69 years. In men older than 70 years, prevalence of erectile dysfunction ranges from 50% to 100% (10).

ED incidence (new cases / year per 1000 males) was reported to be 26 in the MMAS (3), 65.6 (median follow up 2 years) in a Brazilian study (11) and 19.2 (median follow-up 4.2 years) in a Dutch study (12).

A cross-sectional study conducted in Italy (12) found that 12.8% of the 2010 men interviewed reported ED, of whom 70% reported partial and 30% complete ED. The prevalence increased with age, from 2% in men aged 18–39 years to 48% in those > 70 years.

Erectile Dysfunction and Cardiovascular Diseases

Among the different pathogenic mechanisms of ED, vascular aetiology is the most common cause (*Table 1*) (2). As a known symptom of atherosclerotic lesions, ED shares the same modifiable risks factors with coronary artery disease and peripheral artery disease including

hypertension, diabetes, dyslipidaemia, cigarette smoking, obesity, metabolic syndrome, and sedentary behaviour. Published data evidence an increased prevalence of ED, in cardiovascular patients, and, conversely, an increased prevalence of CVD in patients with ED (13).

ED it is an independent risk factor for future cardiovascular events, being a potential useful marker for cardiovascular disease (14,15). In this setting, ED would represent an early clinical evidence of a diffuse, largely vascular disease, being ‘‘the tip of the iceberg’’ of pre-clinical cardiovascular disorders (16).

The prevalence of hypertension in ED population is higher than in people without ED and vice versa, a high prevalence of ED is generally observed in hypertensive patient populations (17). Both antihypertensive drugs and hypertension alone can deteriorate erectile function. High blood pressure is characterized by increased peripheral sympathetic activity, which maintains an elevated vasoconstrictor tone and decreases the endothelium-dependent vasodilation in arteries leading to consequent alterations in vessel architecture and diminished dilatory capacity; moreover vascular remodelling could also occur at the corporal level, progressing to ED by altering mechanical properties of erectile tissue (17).

Epidemiologic data report that up to 75% of diabetic patients have a lifetime risk of developing ED (8) and ED in diabetics is more common than retinopathy or nephropathy (18). Moreover the pathophysiology of ED is accelerated in diabetic patients: its onset occurs at an earlier age, presenting within 10 years of the diabetic onset in more than 50% of patients with any type of diabetes (19). Anatomopathological analysis of penile specimens from diabetic men with ED demonstrated ultrastructural changes in the cavernous arteries, cavernous smooth muscle, and impaired endothelium-dependent relaxation of the corporeal smooth muscle (4). In 12% of type 1 diabetic men, ED was the first symptom of diabetes (30). Gazzaruso et al. (20)found a higher prevalence of ED in diabetic patients with silent CAD than those without any evidence of myocardial ischemia, moreover ED was associated with higher major cardiovascular morbidity and mortality in diabetic patients with silent CAD.

An association between ED and hyperlipidaemia has been found in several clinical studies. High concentrations of low-density lipoprotein and low levels of high-density lipoproteins seem to be related to ED (21). In animal models of hypercholesterolemia, studies show both deficient endothelium- and neurogenic-dependent cavernosal relaxations, reversible by normalizing total plasma cholesterol levels through dietary changes (22).

Active and passive smokers are at higher risk of developing ED and the risk increases with the exposure (23). Moreover, this association is independent of cardiovascular disease (24). The increased risk of ED in smoking patients is also age dependent with a higher risk in smokers aged more than 50 years, which also suggests that cessation of smoking before middle age may avoid a significant increase in the risk of ED (24). The exact pathophysiology of ED in smokers is not completely clear but many factors may participate to its development as oxidative stress leading to impairment of the biosynthesis and degradation of NO, endothelial dysfunction and decreased endothelium-dependent vasodilatation, thickening of the vascular intimal-medial layer, increased blood coagulability, reduced serum antioxidants, and alteration of glucose and lipid metabolism.

Erectile Dysfunction and Coronary Artery Disease

About 46% of patients affected by ischemic heart disease is also suffering from ED, 75% of these patients have problems to attain an erection and 67% to maintain it (25).

The presence of ED has a similar or greater predictive value for future cardiovascular events than traditional risk factors such as a family history of ischemic heart disease, smoking, diabetes and hyperlipidaemia (26).

ED commonly accompanies silent heart disease (27) with an average time interval between the onset of ED and coronary heart disease by 2 to 5 years (class Ia) (27).

A recent metanalysis by Osondu et al (28) confirms an association between ED and subclinical cardiovascular diseases identified by different variables such as endothelial dysfunction with impaired flow mediated dilatation, carotid intimal medial thickness, coronary artery calcification, ankle-brachial index, underscoring the importance of aggressive cardiovascular disease risk assessment and management in patients affected as first onset by ED.

In addition, ED is predictive of obstructive arterial disease and stroke. In a population study in patients between 40 and 70 years, the addition of the ED to the Framingham risk score in a statistical model for multivariate analysis resulted in a reclassification of 5 out of 78 patients from low risk (<5%) to intermediate-risk (between 5% and 10%) (29). Therefore, ED can be particularly useful in cardiovascular risk stratification in patients whose risk may be underestimated compared to a stratification based only on the Framingham (30). A recent metanalysis by Guo et al. (13) clearly demonstrates that men with ED have a higher risk ($P < .001$) of coronary events than those without ED. Moreover, based on the data of the Prostate Cancer Prevention Trial, the number of cardiovascular events per man with ED (including death from myocardial infarction) is twice as high as compared with men without ED (31). Thus, ED's evaluation should include its degree of severity as a severe ED is associated with a higher risk of cardiovascular events, coronary heart disease, severity of coronary atherosclerosis and risk of obstructive peripheral artery disease (32-35). In this setting, IIEF (International Index of Erectile Function) (36)is a simple questionnaire with good sensitivity and specificity consisting of 15 questions that assess erectile function, orgasmic function, sexual desire, intercourse satisfaction, and overall satisfaction. The erectile function domain, which includes six questions (maximum score of 30), provides a reliable measurement for classifying the severity of ED as mild, moderate, or severe. A shortened version of this questionnaire, the IIEF-5 (SHIM questionnaire) (37), has been developed to provide an easier and more rapid diagnostic tool. It has high sensitivity and specificity and it consists of five questions (#5, 15, 4, 12, and 7 from the IIEF); its principal use is as a screening test for subjects with risk factors for ED and as an important tool during the follow up of patients after appropriate treatment. Subjects with a score of 21 or lower are diagnosed with ED (Table 2).

Guidelines for Therapeutic Management of Erectile Dysfunction

The American Urological Association and the European Urology Association have recently developed an evidence-based guidelines on management of erectile dysfunction (38,39), in order to offer to patients and their partners, a full understanding of the benefits and risks/burdens of the various management strategies. The first management strategy consists in

lifestyle modifications, including changes in diet and increased physical activity, which improve overall health and may improve erectile function (*Moderate Recommendation; Evidence Level: Grade C*). The second recommendation is that men affected ED should be informed regarding the treatment option of an FDA-approved oral phosphodiesterase type 5 inhibitor (PDE5i), including discussion of benefits and risks/burdens, unless contra- indicated. (*Strong Recommendation; Evidence Level: Grade B*). In addition, instructions should be provided to maximize benefit/efficacy, including the fact that dose-response effects across PDE5i medications are small and non-linear, and on demand dosing versus daily dosing for tadalafil appears to produce the same level of efficacy (*Strong Recommendation; Evidence Level: Grade C*). Moreover, the dose of PDE5i should be titrated to provide optimal efficacy (Strong Recommendation; Evidence Level: Grade B), and the use of nitrate-containing medications in combination with a PDE5i can cause a precipitous drop in blood pressure. As such, men taking nitrates regularly should not use PDE5i medications. Patients should also be informed regarding the treatment option of a vacuum erection device (VED), including discussion of benefits and risks/burdens. (*Moderate Recommendation; Evidence Level: Grade C*). Men with ED should be informed regarding the treatment option of either intraurethral (IU) alprostadil, or intracavernosal injection (ICI - with alprostadil, papaverine, phentolamine, and/or atropine) including discussion of benefits and risks/burdens, and an in-office test of both treatments options is recommendable (*Conditional Recommendation; Evidence Level: Grade C*). For men with ED, low-intensity extra-corporeal shock wave therapy, intracavernosal stem cell therapy and platelet-rich plasma therapy should be considered investigational (*Conditional Recommendation; Evidence Level: Grade C*). For young men with ED and focal pelvic/ penile arterial occlusion and without documented generalized vascular disease or veno-occlusive dysfunction, penile surgical arterial reconstruction may be considered (*Conditional Recommendation, Evidence Level: Grade C*), while penile venous surgery is not (*Moderate Recommendation, Evidence Level: Grade C*). Men with ED should be informed regarding the treatment option of penile prosthesis implantation, including discussion of benefits and risks/burdens (*Strong Recommendation, Evidence Level: Grade C*).

It is worth to note that both the urology guidelines do not mention the therapeutic possibilities related to mechanical revascularization with drug eluting balloon and/or drug eluting stents in case of atherosclerotic disease of pudendal arteries and/or endovascular embolization with microparticles cocktail in case of venous insufficiency.

Mechanical Revascularization for Erectile Dysfunction

Since the vast majority of patients with vascular ED (~ 75%) presents an arterial stenosis affecting the iliac-pudendal-penile arteries (10,26,40), interventional treatment of atherosclerotic disease in the internal iliac artery (IIA) and internal pudendal artery (IPA) may be a strategic approach to patients non-responding to current first-line oral phosphodiesterase-5 inhibitors (PDE5i) (41).

Recently, Wang and associates (42) performed a CT angiographic study of the pelvic region by identifying and proposing a classification comprehending 8 arterial segments where it is possible to find an atherosclerotic disease leading to vasculogenic ED. Of 921 lesions analysed, 12% were affecting the proximal pudendal artery, 29% the distal pudendal artery distal and

30% at the penile arteries, while the remaining lesions were distributed proximally or distally (*Figure 3*).

Only recently several studies have been published on ED percutaneous treatment using simple conventional plain old balloon angioplasty (POBA), paclitaxel drug eluting balloon (DEB), or angioplasty and stenting with drug-eluting stent (DES) *(Table 3).*

The ZEN trial (43), was the first of these studies; it was designed as a prospective, multicentre, single-arm trial that sought to evaluate the safety and feasibility of zotarolimus-eluting stent implantation in focal atherosclerotic lesions of the internal pudendal arteries among men with ED and a suboptimal response to phosphodiesterase-5 inhibitors. Between the 89 patients included in the trial and undergoing pelvic vessels angiography, 60 (67%) had critical stenosis of internal pudendal artery but only 33.7% (n = 30) had appropriate anatomical features suitable for endovascular approach. Target lesions were most prevalent in the distal IPA (24 lesions, 53.3%), followed by 6 lesions in the ostial IPA (13.3%), 5 proximal IPA lesions (11.1%), and 4 lesions in the mid-IPA (8.9%), with an average length of the segment affected by atheromatous disease of 17.6 ± 99 mm; 45 lesions were treated with stents with a 100% procedural success and without complications at 30 days (primary endpoint). The percentage of pre-procedural angiographically significant stenosis was 63.3%, reduced to 23.3% after the procedure (acute gain 1:13 ± 0:54), and it returned to 41.4% at 6 months (late loss 0:56 ± 0:57), with a restenosis incidence of 34.4% (n = 11). A non-significant increase in the peak systolic velocity Doppler of the penile arteries at 6 months (from 14.4 ± 10.7 to 22.5 ± 23.7 cm/s) was documented. Despite the moderate rate of flow increase and the significant incidence of restenosis, in the intention-to-treat analysis, the primary efficacy endpoint (improvement of erectile function pre- vs. post-procedural evaluated with all IIEF-5 Rating ≥4 in 50% of subjects) at 3 and 6 months was achieved in 59.3% of patients (95% confidence interval 38.8-77.6).

Subsequently, the team led by Dr.Wang (44) reported the results of 12 months follow up after angioplasty using POBA in 20 patients (23 lesions) affected from isolated internal pudendal artery stenosis (PERFECT-1) study, assessed by CT angiography (150 patients enrolled, 121 with stenosis of the iliac-penile axis, 34 with internal pudendal artery stenosis; 9 excluded for Doppler criteria, 5 for angiographic criteria). Three patients had bilateral stenosis. All stenoses were successfully treated with a balloon of average size of 1.6 mm (1.0-2.25 mm). Procedural success was 100% with a clinical success at one month (defined as a variation of the IIEF-5 score> 4 between pre- and post-angioplasty or normalization of the IIEF ≥22) by 75% at 3 months of 65 % and at 6 months of 60%. The IIEF-5 improved from a value of 10.0 ± 5.2 at enrolment at a value of 15.2 ± 6.7 ($p < 0.001$) at 1 month, and 15.2 ± 6.3 ($p < 0.001$) at 6 months. This study showed for the first time that internal pudendal artery angioplasty in patients with isolated stenosis is safe and effective.

The PERFECT-2 study (45) was a single-arm, single-centre trial, enrolled between December 2012 and January 2014, 22 patients suffering from ED and 34 isolated pudendal artery stenosis treated with POBA. Twenty out of 22 patients were treated with balloons of 1.5 mm. The mean lesion length was 11.1±9.0 mm (mean reference vessel diameter 1.7±0.4 mm). The primary endpoint was angiographic restenosis at 12-month CT angiography with a clinical endpoint of a ≥5 IIEF-5 score at follow-up compared with baseline. *Late loss* in this study was 0.32 ± 0.60 and a binary restenosis occurred in 14 of the 34 treated lesions (41%). At 1 year,

sustained clinical success was achieved in 11 of 22 patients. However, it has to be emphasized that many patients had more than one lesion and the incidence of restenosis per patient was 59%.

The same authors have recently presented at the Transcatheter Therapy Meeting (TCT 2015, San Francisco, CA, USA, unpublished data), a prospective randomized study (the PERFECT-3) in which they enrolled 52 patients treated with drug eluting balloon (n = 20), DES (n = 12) or POBA (n = 20) and who had focal artery stenosis of the internal pudendal artery *(Figure 4)*. The primary endpoint was the rate of binary restenosis in the segment treated assessed on angiography or CT control, while the secondary endpoint was the percentage of stenosis at eight months associated with clinical success (defined as a variation of the IIEF score -5> 4 between pre- and post-process or normalization of the same ≥22 to 6 months). It is important to note that in this study, enrolment in the DES group was prematurely discontinued for a high restenosis rate; this result together with that of ZEN trials suggests that this type of treatment is not effective in this district. This notion is probably to be referred to a different tissue response of the penile vessels implant of metallic stent or to a size of the vessels treated significantly lower than those of the coronary district (which in itself involves a higher rate of restenosis). Conversely, the use of drug-coated balloons may be favourable as documented with a clinical success of 85% in patients with vascular ED linked to an internal pudendal artery stenosis.

In a subsequent trial, the PERFECT-4 study, Wang et al (46) randomized 44 ED patients undergoing angioplasty for penile arteries with an RVD ⩾1.5 mm to plain balloon angioplasty versus additional anti-restenotic treatment with PEB. The RVD was 1.8 mm in the plain angioplasty group and 1.9 mm in the group treated with DCBs. At 8 months, binary in-segment restenosis by CTA was 40% in the plain angioplasty group vs 48% in the DCB group. Given that there were no significant differences in restenosis rates comparing conventional angioplasty with DCB, elastic recoil may be the most important mechanism of failure subsequent to angioplasty of these small-calibre arteries. To prevent elastic recoil, DES are recommended over bare metal stents.

In this setting, a recent study by Diehm et al. (47) evaluated the incidence of elastic recoil in patients presenting with erectile dysfunction (ED) undergoing endovascular revascularization of the pudendal or penile arteries. They analysed 21 ED patients (mean age 58.3±9.3 years) undergoing minimally invasive revascularization of 31 arteries. ED lesions included the pudendal arteries (n=27) and the penile artery (n=4). Mean lesion length was 20.6±13.9 mm. Early recoil was defined as an MLD reduction >10%. Elastic recoil with >10% lumen compromise was treated with drug-coated balloons, while severe elastic recoil (>30%) required drug-eluting stents (DES). Elastic recoil was observed in all 31 lesions and resulted in a mean lumen compromise of 21.2%. Severe (>30%) recoil was observed in 14 arteries, which underwent DES therapy. There were no differences in the restenosis rate or clinical outcomes of lesions treated with DCB angioplasty compared to the patients treated with a stent, even though the follow-up was very short. A commentary published by Wang et al. (48) underlined that severe elastic recoil reported by Diehm et al. developed exclusively in lesions in the internal pudendal artery. It is worth to note that in that study the average reference vessel diameter of the pudendal artery was larger (2.6 mm) compared to that of the penile artery (2.0 mm), and the average lesion length was much longer (23 mm vs. 4 mm, respectively), which

suggests that the severity of elastic recoil might be related to lesion length and plaque burden, implying at the same time that more detailed studies are needed to fully understand the mechanisms involved in elastic recoil in these small-diameter arteries. Furthermore, different studies with sirolimus-eluting balloon are currently enrolling pts to evaluate the efficacy in the long-term follow-up of percutaneous revascularization of vasculogenic ED.

More recently, Diehm and colleagues published outcomes in a 50 patient all-comers cohort undergoing endovascular revascularization for arteriogenic ED (49). Patients were treated by means of plain balloon angioplasty (16%), PEB angioplasty (27%), or drug-eluting stent (55%) implantation. The primary feasibility outcome measure was the incidence of a minimum clinically relevant improvement (MCRI) of ≥4 in the 6-question International Index of Erectile Function Questionnaire (IIEF-6) score at 12 months. Clinical effectiveness was defined as improvement in erectile function as quantified in the mean difference (MD) of the IIEF-15 score at 3 and 12 months as well as the mean changes in IIEF-15 questions 3 and 4. In that study, procedural success was achieved in 98% of 50 patients. At 12 months, 65% of patients achieved a minimum clinically relevant improvement in the IIEF-6 score. The overall IIEF-15 score, as well as scores for questions 3 and 4, improved in 65%, 57% and 60% of patients, respectively. Change in the overall IIEF-15 score at 12 months was consistent among subgroups, except for elderly patients [MD −5.0 (95% CI −9.7 to −0.2), p=0.041] and those with hypertension [MD −11.0 (95% CI −20.5 to −1.5), p=0.025], who showed less improvement.

A review and systematic metanalysis about safety and efficacy of endovascular therapy in the treatment of arterial insufficiency has been published (50). The arterial insufficiency cohort contained 162 patients most commonly treated via stenting of the internal pudendal artery (40.1%; n=65). The study found an overall clinical success rate of 63.2% in AI patients. Complications occurred in 4.9% of patients (n=8), with 4 considered to be mild and 4 considered to be severe. The authors concluded that endovascular therapy for medically refractory ED is safe and may provide a treatment alternative to more invasive surgical management, even though conclusions are limited by the heterogeneity of clinical success definitions among the included studies.

Our personal experience is in agreement with these results (51). We evaluated 112 patients with ED in whom a positive dynamic doppler after prostaglandin injections was positive in 64 (57%). Those patients were then submitted to selective pudendal angiography that demonstrated a critical stenosis of the proximal internal pudendal artery in 36 (44%) and in the distal internal pudendal artery in 46 (56%). Paclitaxel eluting balloon (PEB) was utilized in all lesions with a procedural success of 96%. An IIEF-5 score greater than 22 was observed in 81% of patients at 8 months follow up with a clinical success in 89% defined as delta IIEF ≥ 4 (*Figure 5, Panel A and B)*. More recently, Sirolimus Eluting Balloon (SEB) was also utilized by our group for treatment of pudendal and dorsalis penis arteries in 41 pts with a good success rate in the mid-term FU as demonstrated by a 6 mos clinical success rate (Delta IEF-5 basal vs. FU) greater than 72% (*Figure 6*). A practical approach for evaluation and treatment of pts affected by ED and seen in the cardiologic out-patient setting is provided in *Figure 7*.

Endovascular Embolization for Venous Endoleak ED

Veno-occlusive dysfunction of the corpora cavernosa leads to venogenic erectile dysfunction. It can result from several pathophysiologic processes (large venous channels, degenerative changes or traumatic injury to the tunica albuginea, structural alterations in the fibroelastic components, insufficient trabecular smooth muscle relaxation, and acquired venous shunts). In the past, the primary surgical options for venous leakage was ligation of the dorsal veins (both superficial and deep) and its collaterals. However, the reported long-term success was not greater than 25% in different series (52,53). The reasons for the low success rate were thought to be the inability to ligate all the defective veins, as small vein branches cannot be observed during surgery and some proximal veins cannot be ligated due to the exposure problem. Moreover, early development of collateral veins of the corpora cavernosum may be related to long-term failure of surgical ligation. Conversely, patients with isolated crural vein leakage can benefit from crural ligation surgery despite identification of the origin site of the crural vein is important for the success of this procedure (54). However, the crural vein generally involves a long segment of the crus, and ligation of the crus tip may be inadequate (55).

To increase the success rate of venous leakage treatment, several authors (52,56) have resorted to endovascular direct embolization of deep dorsal veins and the periprostatic venous plexus by different embolic particles (57) for patients with isolated deep dorsal vein leakage (Figure 5 B, Panel A, B, C). However, it is important to note that according to a recent CT cavernosography study results, isolated and focal venous leakage is rare in ED, so candidates for endovascular embolization should be highly selected (58). Still, there are reports of long-lasting efficacy in selected cases. Therefore, the validity of surgical ligation or endovascular embolization depends on highly select candidates, well-designed procedure plan, and operation technique.

Conclusions

Atherosclerotic and venous disease of the penile vessels can cause ED in subjects with cardiovascular risk factors and this should therefore always be sought in patients with a high cardiovascular risk profile (uncontrolled diabetes, cigarette smoking, uncontrolled hypertension, dyslipidaemia) or who are suffering from ischemic heart disease. In patients suffering from ED, a careful medical history collection with adoption of a simple screening tests such as IIEF-5 can then unmask atherosclerotic disease of the iliac-penile circulation. This should be part of the routine screening in patients presenting at any cardiology outpatient clinic. In cases of a positive dynamic echo-Doppler showing reduced arterial flow or increased venous flow, a penile angio-CT can provide a clear identification of the segments affected by atherosclerotic disease or venous leakage. Different non-invasive and invasive strategies may then be proposed for vasculogenic erectile dysfunction treatment. The strongest evidence relies on percutaneous revascularization of pudendal arteries while other treatment modalities such as endovascular venous embolization still need extensive testing clinical settings in order to be ultimately introduced in routine clinical practice. However, it is possible that in a near future a different combination of these therapies, tailored for a specific single patient, will have a synergistic effect for complete restoration of erectile function. In the meantime, it is strongly desirable the creation of multidisciplinary groups composed by

urologists, andrologists, cardiovascular physicians and radiologists, to offer to male patients affected by ED a correct diagnostic and therapeutic approach for their disease.

Table 1
Aetiology of Erectile Dysfunction

Vascular 60-80%	Neurological 10-20%	Drug related 10-15%	Hormonal 5-10%
• Arteriosclerosis • Smoking • Hyperlipidaemia • Hypertension • Diabetes • Peyronie's disease • Pelvic fractures • Perineal vascular trauma • Fracture of corpora cavernosa • Heterotopic renal transplantation • Leriche's syndrome • Aorto-iliac or aorto-femoral bypass • Radiotherapy sequelae • Priapism sequelae	• Stroke • Sleep apnoea syndrome • Alzheimer's disease • Parkinson's disease • Brain tumour • Spinal cord trauma • Compressive cause (herniated disk) • Demyelinating disease (multiple sclerosis) • Tumour cause (spinal cord tumour) • Spinal infarction • Infectious diseases • Myelomeningocele • Degenerative diseases • Iatrogenic damage • Diabetic neuropathy • Alcoholic neuropathy • Postsurgical sequelae • Prostatectomy • Cystectoymy • Transurethral resection of the prostate • Spinal cord surgery • Rectal amputation	• Sympathomimetics: clonidine, methyldopa, reserpine, guanethidine • β-Adrenergic blockers: propranolol, pindolol, atenolol, metoprolol • Diuretics: spironolactone, thiazides • Antipsychotics & neuroleptics: phenothiazines, thioxanthenes, thioridazines, butyrophenones • Antidepressants: tricyclic antidepressants, tetracyclic antidepressants, MAOIs, SSRIs • Anxiolytics: benzodiazepines • Decrease or block the action of testosterone: antiandrogens, estrogens, anabolic drugs, steroids, spironolactone, ketoconazole, digoxin, clofibrate, cimetidine • Increase prolactin levels: cimetidine, metoclopramide, phenothiazines • Opiates: endorphins, tricyclic antidepressants, methyldopa	• Estrogen excess • Iatrogenic exogenous • Liver diseases • Estradiol- or hCG-producing tumors • Hyperprolactinemia • Iatrogenic drug-induced • Pituitary tumor • Hypogonadism • Hypogonadotropic • Thyroid dysfunction • Adrenal dysfunction • Cushing's syndrome or disease • Adrenal insufficiency • Severe undernutrition

Table 2
IIEF-5 (SHIM) Score Questionnaire

PLEASE REFER TO THE PAST 2 MONTHS

QUESTION	ANSWER	SCORE
1. How do you rate your confidence that you could get and keep an erection?	Very Low Low Moderate High Very High	1 2 3 4 5
2. When you had erections with sexual stimulation, how often were your erections hard enough for penetration (entering your partner)?	No sexual activity Almost never or never A few times (much less than half the time) Sometimes (about half the time) Most times (much more than half the time) Almost always or always	0 1 2 3 4 5
3. During sexual intercourse, how often were you able to maintain your erection after you had penetrated (entered) you partner?	Did not attempt the intercourse Almost never or never A few times (much less than half the time) Sometimes (about half the time) Most times (much more than half the time) Almost always or always	0 1 2 3 4 5
4. During sexual intercourse, how difficult was it to maintain your erection to completion of intercourse?	Did not attempt intercourse Extremely difficult Very difficult Difficult Slightly difficult Not difficult	0 1 2 3 4 5
5. When you attempted sexual intercourse, how often was it satisfactory for you?	Did not attempt intercourse Almost never or never A few times (much less than half the time) Sometimes (half of the time) Most times (much more than half the time) Almost always or always	0 1 2 3 4 5
SCORE: Add the numbers corresponding to questions 1–5		

Score 0-5 = severe ED; Score 5-10 = Moderate ED; Score 10-15 = Light ED Score >15 = No ED

Table 3
Different Studies Published Related to Percutaneous Revascularization for Erectile Dysfunction

Author	Year	Study Type	Pts #	Stenotic Segment	Follow-up (mos)	Procedural Success (%)	Utilized Device
Castaneda-Zuniga et al. (40)	1982	Clinical Case	2	IIA	18	100	POBA
Van Unnik et al. (41)	1984	Clinical Case	1	EIA	ND	100	POBA
Goldwasser et al. (42)	1985	Clinical Case	1	IIA	ND	100	POBA
Rogers et al. (50)	2012	Prospective, Non-Randomized	30	IPA	12	100	DES
Wang et al. (51)	2014	Prospective, Non-Randomized	20	IPA	12	100	POBA
Wang et al. *	2014	Prospective, Non-Randomized	48	CIA, IIA, EIA, IPA, PA, AO	ND	65	POBA
Wang et al. (53)	2015	RCT	52	IPA	12	100	DES vs.DEB vs.POBA
Wang et al. (52)	2016	RCT	50	IPA	12	100 vs.96	PEB vs.POBA
Sangiorgi et al. (58)	2018	All-Comers Registry	84	IPA	12	98	DEB
Diehm et al. (54)	2018	Prospective, Non-Randomized	21	IPA, PA	3	100%	POBA, DEB, DES
Diehm et al. (56)	2019	All-Comers Registry	50	IIA, IPA, IGA, CPA, DPA, CA	12	98	POBA, DEB, DES

RCT: Randomized Clinical Trial; Ao-IL: Aorto Iliac artery; CIA: Common Iliac Artery; EIA: External Iliac Artery; IIA: Internal Iliac Artery; AO: Obturatory Artery; PA: Penile Artery; IPA: Internal Pudendal Artery, IGA: Inferior Gluteal Artery, CPA: Common Penile Artery, DPA: Dorsal Penile Artery, CA: Cavernosal Artery; POBA = plain old balloon angioplasty; DES = drug eluting stent; DEB = drug eluting balloon;
*Presented at TCT Meeting 2016, Not Published

Table 4
Suggested Training for Endovascular Treatment of Vasculogenic Erectile Dysfunction

Imaging Modality	Arterial ED	Venous ED	Case Load
Dynamic Penile Doppler	Not necessary/ Urologist supervision	Not necessary/ Urologist supervision	At least 50 exams
Angio-CT	✓	✓ (venous cavernosography with direct contrast injection in the corpora cavernosa) Urologist supervision	At least 30 arterial and 10 venous cavernosography cases to understand penile vessel anatomy
Pudendal Angiography	✓	✓ (only utilized for embolization which needs to be done with direct echo-guided puncture)	At least 10 arterial cases to understand angiographic projections and 5 cases for venous embolization

FIGURE LEGENDS

Figure 1. Adapted from (59)

Panel A - Normal anatomy of pelvic vascularization. The internal pudendal artery arises either from the internal iliac artery (ipogastric artery - 80% of the cases) or from the obturatory artery.

Panel B - From the internal pudendal artery - at the level of penis basis - arise the dorsal artery of the penis, the cavernous artery and the circumflex artery which in turn are distributed within the cavernous bodies and give origin to bulbar arteries within the spongious body where the bulbouretral artery originates.

Panel C – Transverse section of the penis in the resting and during erection state. It is worth to note that the latter is characterized by a dilatation of the spongious tissue vascular sinusoids with consequent penis swelling and subsequent squeezing of the sub-albugineous veins to interrupt blood outflow with erection maintenance for the entire sexual intercourse.

Figure 2. Adapted and modified from (60)

Panel A - Molecular Mechanism of Penile Smooth-Muscle Contraction. Norepinephrine from sympathetic nerve endings, endothelins, thromboxane A2 and prostaglandin F_{2a} from the endothelium, activate receptors on smooth-muscle cells to initiate the cascade of reactions that results in elevation of intracellular calcium concentrations and smooth-muscle contraction. Protein kinase C is a regulatory component of the calcium-independent, sustained phase of agonist- induced contractile responses.

Panel B - Molecular Mechanism of Penile Smooth-Muscle Relaxation. Cyclic AMP (cAMP) and cyclic GMP (cGMP), the intracellular second messengers mediating smooth-muscle relaxation, activate their specific protein kinases, which phosphorylate certain proteins to cause opening of potassium channels, closing of calcium channels, and sequestration of intracellular calcium by the endoplasmic reticulum. The resultant fall in intracellular calcium leads to smooth- muscle relaxation. Sildenafil inhibits the action of phosphodiesterase (PDE) type 5, thus increasing the intracellular concentration of cGMP. Papaverine is a nonspecific phosphodiesterase inhibitor. GTP denotes guanosine triphosphate, and eNOS endothelial nitric oxide synthase.

Figure 3.

Eight-zone Angio-CT Classification System of Pelvic Atherosclerotic Disease. *Panel A Anteroposterior Projection. Panel B Lateral Projection.* Zone 1: Common Iliac Artery; Zone 2: Internal Iliac Artery; Zone 3: Anterior Division of Internal Iliac Artery; Zone 4A: Proximal Internal Pudendal Artery; Zone 4B: Distal Internal Pudendal Artery; Zone 5A: Dorsal Penile Artery; Zone 5B: Cavernosal Artery; Zone 6: Obturator Artery. Fifty-nine percent of atherosclerotic lesions are located in Zone 4B (29%) and 5A (30%). The other 30% in Zone 4A (12%), Zone 5 B (14%) and Zone 6 (4%). The minority in Zone 1, 2 and 3 (11%) (88).

Figure 4.

Results of PERFECT-3 study in the three randomizations groups (DEB, DES and POBA). It is important to outline that the enrolment in the DES group was interrupted early for significantly higher restenosis rate compared to POBA and DEB groups. DEB - drug eluting balloon, DES drug eluting stent, POBA plain old balloon angiography, IIEF-5 international index of erectile function.

Figure 5

Personal Case examples. **5A** *Panel A:* CTO of the Left Internal Pudendal Artery of a 59 yo male, diabetic not responder since 1 year to PDE-5i. *Panel B:* The pudendal artery was recanalized with Gaia 1 wire, followed by POBA 1.5x20 at 8 atm and by SEB 2.0x20 at 12 atm for 1 minute. *Panel C:* Multiple stenosis (arrows) of a left internal pudendal artery in the proximal, mid and distal segments of a 67 yo male not responding to PDE-5i since 2 years before. Note that the distal part of the artery is hypo-perfused and not clearly visible. *Panel D:* Final angiography after implantation of a DES Onyx 2.5x12 at 12 atm in the proximal segment, POBA 2.0x20 at 8 atm + PEB 2.0x20 at 12 atm in the mid segment and POBA 2.0x20 at 8 atm + PEB 2.0x20 at 8 atm in the distal segment. *Panel E:* Final angiography to evaluate the distal segments and filling of the cavernous body (white asterisk).

5B Personal Case Example. *Panel A:* Selective venography by direct echo-guided micro-kit puncture of the deep dorsal vein showing the right and left vein plexus. *Panel B:* Preparation of embolic cocktail with 1 cc of 3% Aethoxysclerol® and 2 cc of Histoacril®. The injection should be done under Valsalva manoeuvre to avoid distal embolization and immediately followed by 3% glucosate flush of the micro-puncture sheet to avoid its occlusion. *Panel C*: Complete embolization of the plexus at selective control venography.

Figure 6.

Proposed schematic diagram for evaluation, inclusion criteria and treatment of pts affected by vasculogenic erectile dysfunction

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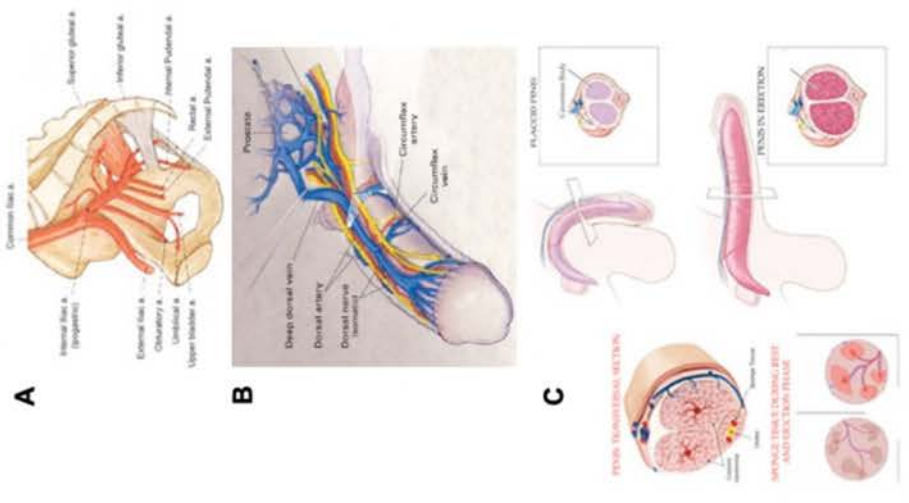

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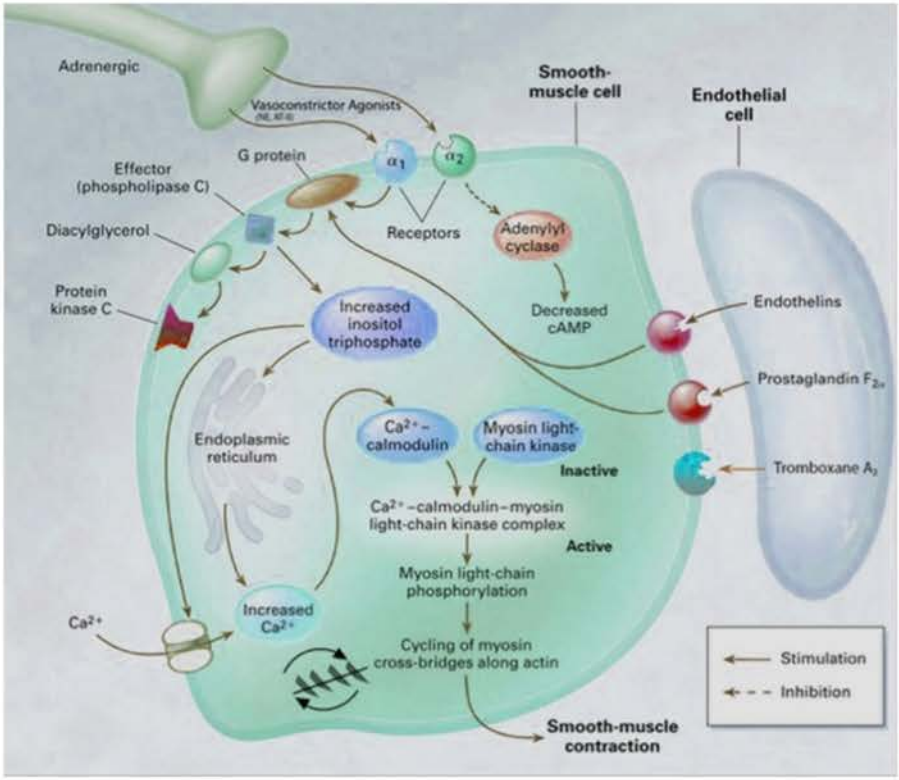

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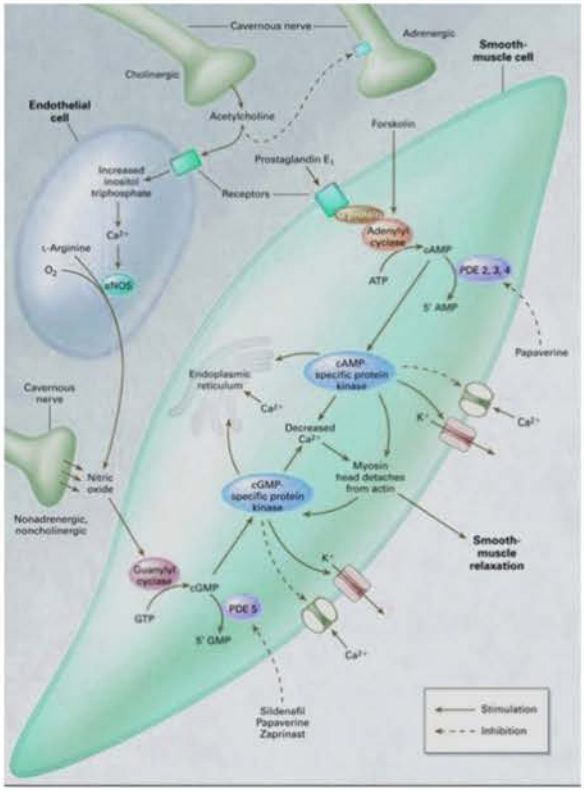

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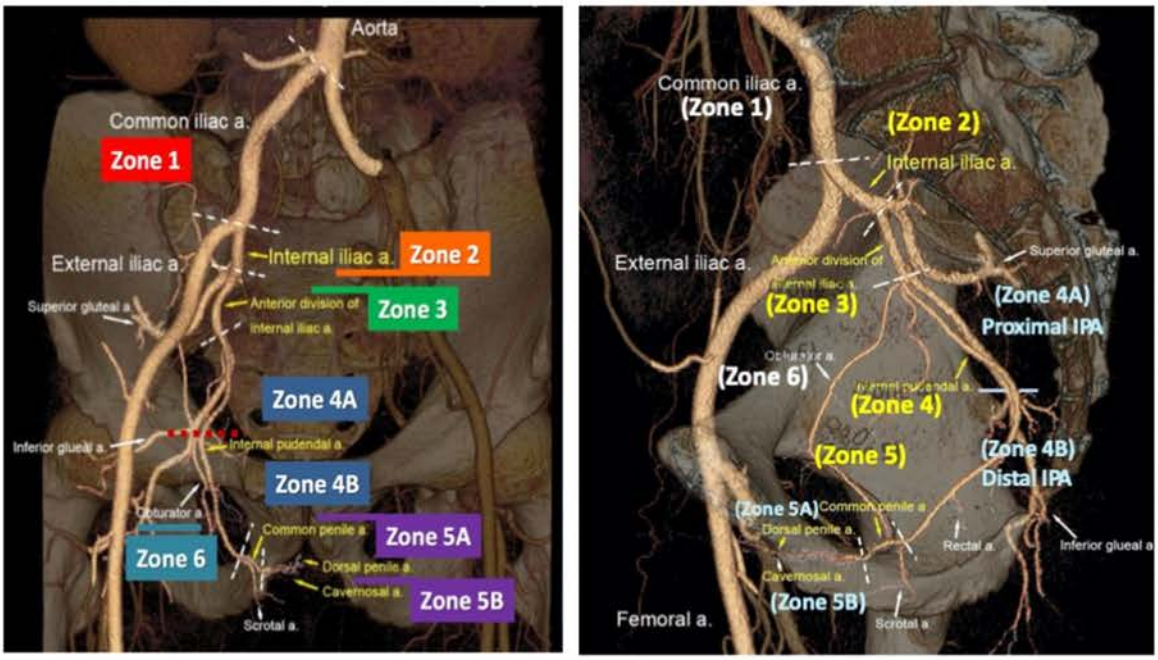

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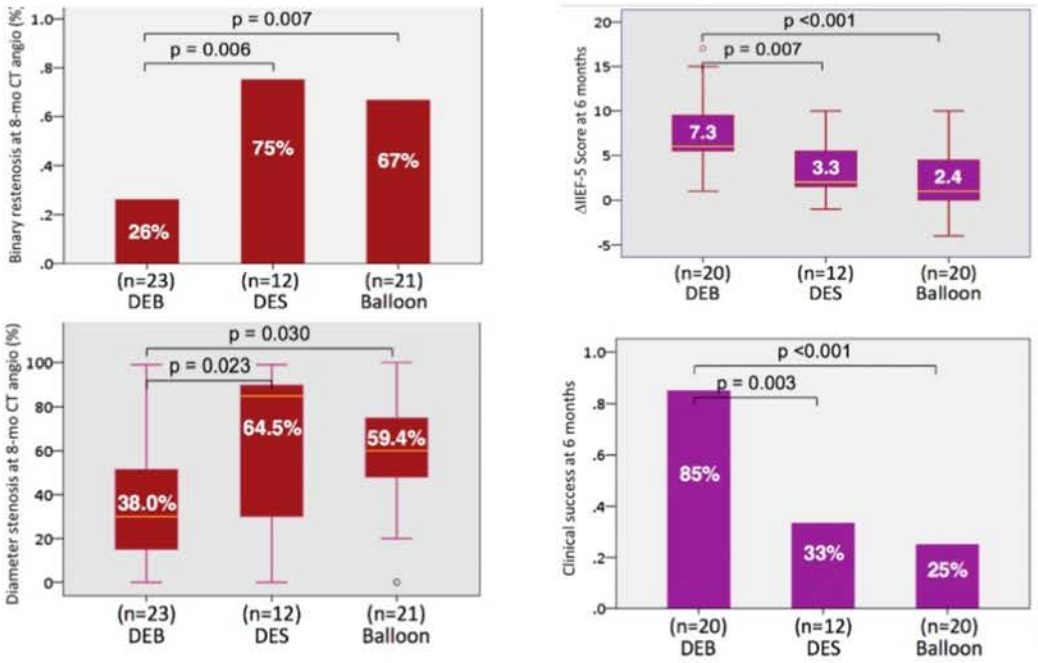

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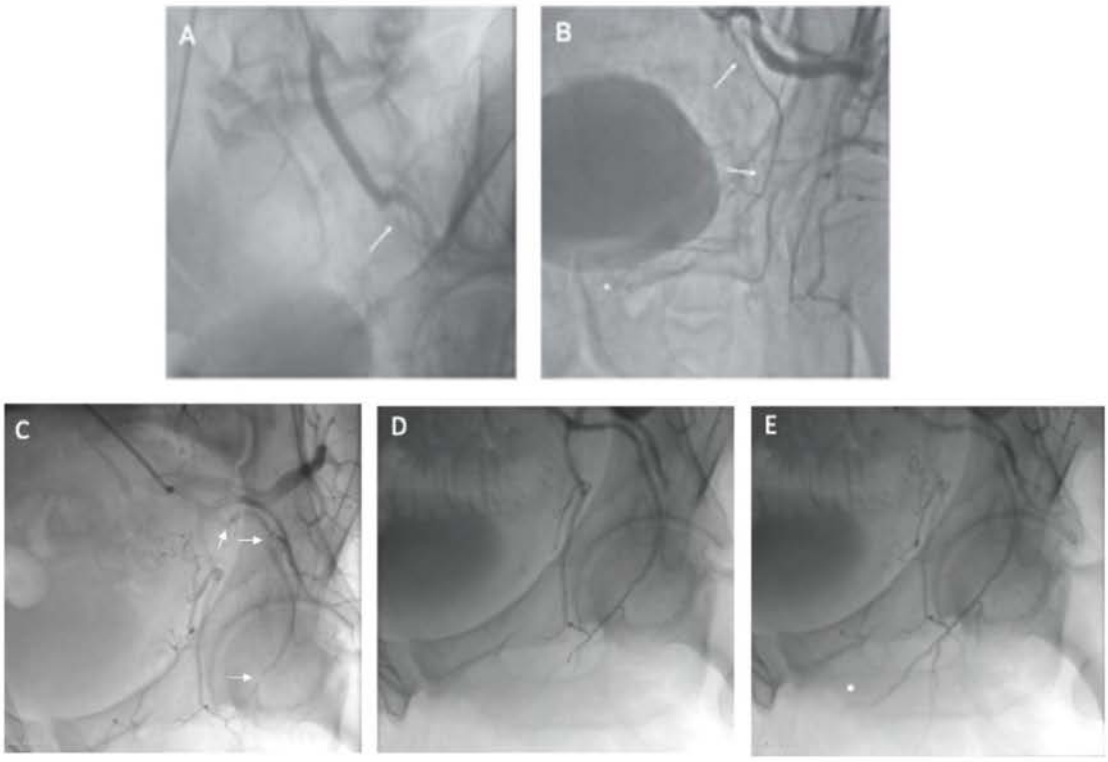

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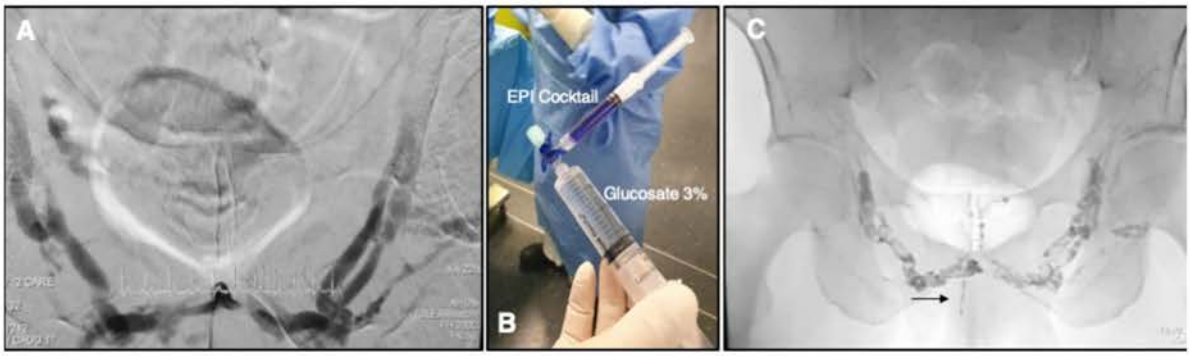
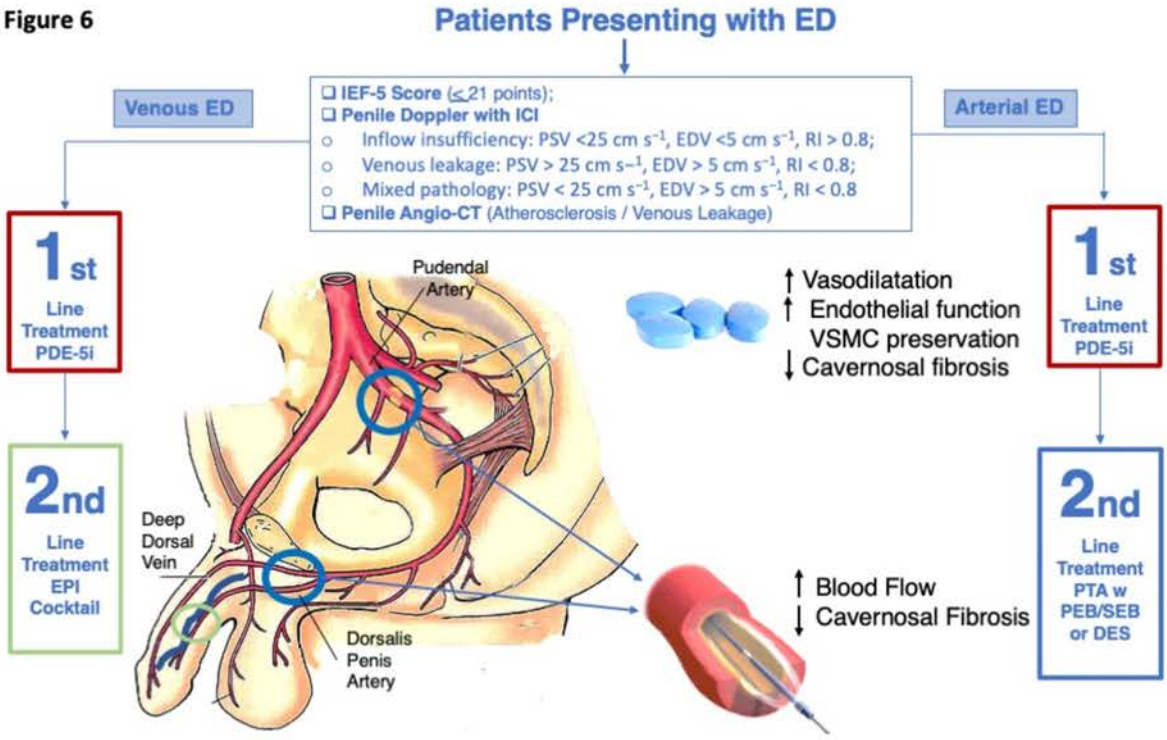


Figure 5B

Figure 6



ICI = Intracavernous Injection; VSMC = Vascular Smooth Muscle Cells; PDE-5i = Phospodiesterase-5 Inhibitors; PTA = Percutaneous Transluminal Angioplasty; EPI = Embolic Particles Injection with 3% Aethoxysclerol® and Histoacril®; PEB/SEB = Paclitaxel/Sirolimus Eluting Baloon; DES = Drug Eluting Stent