Guidelines on
Penile Curvature

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1. INTRODUCTION

1.1 Aim

The aim of this guideline is to provide the practising urologist with the most recent evidence on the diagnosis and management of penile curvature in order to assist in his/her decision-making process.

Penile curvature is a common urological disorder which can be congenital or acquired. Congenital curvature is briefly discussed in these guidelines as a distinct pathology in the adult population without any other concomitant abnormality present (such as urethral abnormalities). For paediatric congenital penile curvature, please refer to the EAU Guidelines on Paediatric Urology, Chapter on Congenital Penile Curvature.

Acquired curvature is mainly secondary due to La Peyronie's disease (referred to as Peyronie's disease in this text), but can also be due to the healing process of a penile fracture.

1.2 Publication history

The first version of the EAU Guidelines on Penile Curvature was published in 2012. In this 2015 version, the text has been significantly reduced so that only key information is included and re-formatted according to the EAU template for non-oncology Guidelines, so that all Guidelines follow a similar format.

A quick reference document (pocket guidelines) is available, both in print and in a number of versions for mobile devices, presenting the main findings of the penile curvature guidelines. These are abridged versions which may require consultation together with the full text versions. All available material can be viewed and downloaded for personal use at the EAU website. The EAU website also includes a selection of EAU Guidelines articles as well as translations produced by national urological associations: http://www.uroweb.org/guidelines/online-guidelines/.

This document was peer-reviewed prior to publication.

1.3 Panel composition

The EAU Guidelines on Penile Curvature were written by the EAU Male Sexual Dysfunction Panel. Members of this Panel have been selected based on their expertise to represent the professional treating patients suffering from penile curvature.

2. METHODS

References used in this text are graded according to their Level of Evidence (LE) and Guidelines are given a Grade of Recommendation (GR). In this 2015 EAU Guidelines compilation, all standard information on LE and GR has been taken out of the individual Guidelines topics for the sake of brevity. The methodology section (see the introduction chapter of the complete book) outlines the LE and GR criteria which are used throughout the Guidelines, according to a classification system modified from the Oxford Centre for Evidence-based Medicine Levels of Evidence.

A systematic literature search of the Medline database was performed. The controlled vocabulary of the Medical Subject Headings (MeSH) database uses the specific term 'penile induration' for Peyronie's disease. There is no specific MeSH term for congenital penile curvature. In order to identify relevant articles, the search included the MeSH terms 'congenital abnormalities', 'penis abnormalities' and 'male' as well as the free text term 'congenital penile curvature'. The search included all relevant articles published up to July 2014. A total of 199 articles were identified for congenital penile curvature while this number was 1806 for Peyronie's disease. The panel reviewed and selected the articles with the highest evidence available. However, in several subtopics only articles with low levels of evidence were available and discussed accordingly.

3. THE GUIDELINE
3A CONGENITAL PENILE CURVATURE

3A.1 Epidemiology/aetiology/pathophysiology

Congenital curvature is rare: one well-performed study reports an incidence of less than 1% [1] while there are reports from studies with poor quality which claim that it is more common with prevalence rates of 4-10% in the absence of hypospadias [2].

Congenital penile curvature results from disproportionate development of the tunica albuginea of the corporal bodies and is not associated with urethral malformation. In the majority of cases the curvature is ventral but can be lateral and rarely dorsal.

3A.2 Diagnostic evaluation

Taking medical and sexual history are usually sufficient to establish the diagnosis of congenital penile curvature. Patients usually present after reaching puberty as the curvature becomes more apparent with erections, and severe curvature can make intercourse difficult or impossible. Physical examination during erection (autophotograph or after intracavernosal injection of vasoactive drugs) is useful to document curvature and exclude other pathologies [3].

3A.3 Disease management

The treatment of this disorder is surgical correction deferred until after puberty. Surgical treatments for congenital penile curvature generally share the same principles as in Peyronie's disease (presented in detail in the next section). Nesbit procedure with excision of an ellipse of the tunica albiginea is the gold standard of treatment but many other techniques have been described and employed. Plication techniques are widely used including techniques producing a de-rotation of the corporal bodies [4]. Most of the time, dissection of the dorsal neurovascular bundle is needed in order to avoid loss of sensation and ischaemic lesions in the glans [5-7].

Conclusions for treatment	**LE**
Medical and sexual history are usually sufficient to establish the diagnosis of congenital penile curvature. Physical examination during erection is useful for documentation of the curvature and exclusion of other pathologies.	3
Surgery is the only treatment option which is deferred until after puberty and can be performed at any time in adult life. Nesbit and plication techniques are the standard treatment in congenital penile curvature with high correction rates.	3

3B PEYRONIE'S DISEASE

3B.1 Epidemiology/aetiology/pathophysiology

*3B.1.1 **Epidemiology***

Epidemiological data on Peyronie's (PD) disease are limited. Prevalence rates of 0.4-9% have been published, with a higher prevalence in patients with erectile dysfunction (ED) and diabetes [8-15]. The typical age of a patient with PD is 55-60 years.

*3B.1.2 **Aetiology***

The aetiology of Peyronie's disease is unknown. However, an insult (repetitive microvascular injury or trauma) to the tunica albuginea is the most widely accepted hypothesis on the aetiology of the disease [16]. A prolonged inflammatory response will result in the remodelling of connective tissue into a fibrotic plaque [16-18]. Penile plaque formation can result in curvature which, if severe, may prevent vaginal intromission.

*3B.1.3 **Risk factors***

The most commonly associated comorbidities and risk factors are diabetes, hypertension, lipid abnormalities, ischaemic cardiopathy, ED, smoking, and excessive consumption of alcohol [10, 14, 19, 20]. Dupuytren's contracture is more common in patients with Peyronie's disease affecting 9-39% of patients [11, 21-23] while 4% of patients with Dupuytren's contracture reported Peyronie's disease [22].

3B.1.4 ***Pathophysiology***

Two phases of the disease can be distinguished [24]. The first is the acute inflammatory phase, which may be associated with pain in the flaccid state or painful erections and a palpable nodule or plaque in the tunica of the penis; typically a penile curvature begins to develop. The second is the fibrotic phase with the formation of hard palpable plaques that can be calcified, which also results in disease stabilisation. With time, penile curvature is expected to worsen in 30-50% of patients or stabilise in 47-67% of patients, while spontaneous improvement has been reported by only 3-13% of patients [19, 25, 26]. Pain is present in 35-45% of patients during the early stages of the disease [27]. Pain tends to resolve with time in 90% of men, usually during the first 12 months after the onset of the disease [25, 26].

In addition to physiological and functional alteration of the penis, affected men also suffer significant distress. Validated mental health questionnaires have shown that 48% of men with Peyronie's disease have mild or moderate depression, sufficient to warrant medical evaluation [28].

Conclusions	**LE**
Peyronie's disease is a connective tissue disorder, characterised by the formation of a fibrotic lesion or plaque in the tunica albuginea, which leads to penile deformity.	2b
The contribution of associated comorbidities or risk factors (e.g. diabetes, hypertension, lipid abnormalities and Dupuytren's contracture) to the pathophysiology of Peyronie's disease is still unclear.	3
Two phases of the disease can be distinguished. The first phase is the acute inflammatory phase (painful erections, 'soft' nodule/plaque), and the second phase is the fibrotic/calcifying phase with formation of hard palpable plaques (disease stabilisation).	2b
Spontaneous resolution is uncommon (3-13%) and most patients experience disease progression (30-50%) or stabilisation (47-67%). Pain is usually present during the early stages of the disease but tends to resolve with time in 90% of men.	2a

3B.2 Diagnostic evaluation

The aim of the initial evaluation is to provide information on the presenting symptoms and their duration (erectile pain, palpable nodules, curvature, length, rigidity, and girth) and erectile function status. It is mandatory to obtain information on the distress provoked by the symptoms and the potential risk factors for ED and Peyronie's disease. A disease-specific questionnaire (PDQ) has been designed to collect data, and it has been validated for use in clinical practice [29]

Major attention should be given to whether the disease is still active, as this will influence medical treatment or the timing of surgery. Patients who are still likely to have an active disease are those with short symptom duration, pain during erection, or a recent change in penile curvature. Resolution of pain and stability of the curvature for at least 3 months are well-accepted criteria of disease stabilisation and patients' referral for surgical intervention when indicated [25].

The examination should start with a routine genitourinary assessment, which is then extended to the hands and feet for detecting possible Dupuytren's contracture or Ledderhose scarring of the plantar fascia [26]. Penile examination consists generally of a palpable node or plaque. There is no correlation between plaque size and the degree of curvature [30]. Measurement of length during erection is important because it may have impact on treatment decisions [31].

An objective assessment of penile curvature with an erection is mandatory. This can be obtained by a home (self) photograph of a natural erection (preferably) or using a vacuum-assisted erection test or an intracavernosal injection using vasoactive agents [32]. Erectile function can be assessed using validated instruments such as the International Index of Erectile Function (IIEF) although this has not been validated in Peyronie's disease patients [33]. Erectile dysfunction is common in patients with Peyronie's disease (> 50%) but it is important to define whether it pre- or post-dates the onset of Peyronie's disease. It is mainly due to penile vascular disease [19, 30]. The presence of ED and psychological factors may impact on the treatment strategy [34].

Ultrasound (US) measurement of the plaque's size is inaccurate and it is not recommended in everyday clinical practice [35]. Doppler US may be required for the assessment of vascular parameters [34].

3B.2.1 ***Recommendations for the evaluation of Peyronie's disease***

	LE	GR
Medical and sexual history in patients with Peyronie's disease must include duration of the disease, penile pain, change of penile deformity, difficulty in vaginal intromission due to deformity, and erectile dysfunction.	2b	B
Physical examination must include assessment of palpable nodules, penile length, extent of curvature (self-photograph, vacuum-assisted erection test or pharmacological-induced erection) and any other possibly related diseases (Dupuytren's contracture, Ledderhose disease).	2a	B
PDQ may be useful for establishing individual baseline scores and determining symptom changes with time and the effect of treatment	2a	B
US measurement of the plaque's size is inaccurate and operator dependent. It is not recommended in everyday clinical practice.	3	C
Doppler US is required to ascertain vascular parameters associated with erectile dysfunction.	2a	B

PDQ = Peyronie's disease-specific questionnaire; US = ultrasound.

3B.3 Disease management

3B.3.1 ***Non-operative treatment***

Conservative treatment of Peyronie's disease is primarily focused on patients in the early stage of the disease [26, 36]. Several options have been suggested, including oral pharmacotherapy, intralesional injection therapy and other topical treatments (Table 1). Shockwave treatment of calcified plaques and clostridial collagenase injection in patients with densely fibrotic or calcified plaques have been also suggested [24, 37]. Clostridium collagenase is the only drug approved for the treatment of Peyronie's disease by the FDA. No single drug has been approved by the European Medicines Agency (EMA) for the treatment of Peyronie's disease at this time. The results of the studies on conservative treatment for Peyronie's disease are often contradictory making it difficult to provide recommendations in the everyday, real-life setting. This is due to several methodological problems including uncontrolled studies, limited number of patients treated, short-term follow-up and different outcome measures [37]. Moreover, the efficacy of conservative treatment in distinct patient populations in terms of early (inflammatory) or late (fibrotic) phases of the disease is not yet available.

Table 1: Non-operative treatments for Peyronie's disease

Oral treatments
Vitamin E
Potassium para-aminobenzoate (Potaba)
Tamoxifen
Colchicine
Acetyl esters of carnitine
Pentoxifylline
Phosphodiesterase type 5 inhibitors (PDE5i)
Intralesional treatments
Steroids
Verapamil
Clostridium collagenase
Interferon
Topical treatments
Verapamil
Iontophoresis
Extracorporeal shock wave treatment (ESWT)
Traction devices
Vacuum devices

3B.3.2 ***Oral treatment***

3B.3.2.1 Vitamin E

Vitamin E (tocopherol, a fat-soluble compound that acts as a natural antioxidant to reduce the number of oxygen-free radicals produced in energy metabolism) is commonly prescribed by the majority of urologists at

once or twice daily doses of 400 IU because of its wide availability, low cost and safety [38]. A double-blind, placebo-controlled crossover study failed to show a significant effect on penile deformity or plaque size [39]. Moreover, there is conflicting evidence as to long-term cardiovascular effects of vitamin E usage at large doses, which urologists use for penile deformity treatment [40].

3B.3.2.2 Potassium para-aminobenzoate (Potaba)

Potassium para-aminobenzoate is thought to exert an antifibrotic effect through an increase in oxygen uptake by the tissues, a rise in the secretion of glycosaminoglycans, and an enhancement of the activity of monoamine oxidases [41]. Preliminary studies reported an improvement in penile curvature, penile plaque size, and penile pain during erection [42]. In a prospective double-blinded controlled study in 41 patients with Peyronie's disease, Potaba (12 g/day for 12 months) improved penile pain significantly, but not penile curvature or penile plaque size [43]. In another similar study in 103 patients with Peyronie's disease, Potaba decreased penile plaque size significantly, but had no effect on penile curvature or penile pain [44]. However, the pre-existing curvature under Potaba remained stable, suggesting a protective effect on the deterioration of penile curvature. Treatment-emergent adverse events are nausea, anorexia, pruritus, anxiety, chills, cold sweats, confusion and difficulty concentrating, but no serious adverse events were reported [45].

3B.3.2.3 Tamoxifen

Tamoxifen is a non-steroidal oestrogen receptor antagonist modulating transforming growth factorβ1 (TGFβ1) secretion by fibroblasts. Preliminary studies reported that tamoxifen (20 mg twice daily for 3 months) improved penile pain, penile curvature, and reduced the size of penile plaque [46]. However, a placebo-controlled, randomised study (in only 25 patients, at a late stage of the disease with a mean duration of 20 months) using the same treatment protocol, failed to show any significant improvement in pain, curvature, or plaque size in patients with Peyronie's disease [47].

3B.3.2.4 Colchicine

Colchicine has been introduced into the treatment of Peyronie's disease on the basis of its anti-inflammatory effect [48]. Clinical data should be interpreted with caution since they come from only uncontrolled studies. Preliminary results showed that half of the men given colchicine (0.6-1.2 mg daily for 3-5 months) found that painful erections and penile curvature improved, while penile plaque decreased or disappeared in 50% out of 24 men [49]. In another study in 60 men (colchicine 0.5-1 mg daily for 3-5 months with escalation to 2 mg twice daily), penile pain resolved in 95% and penile curvature improved in 30% [48]. Similar results have been reported in another uncontrolled retrospective study in 118 patients [50]. Reported treatment-emergent adverse events with colchicine are gastrointestinal effects (nausea, vomiting, diarrhoea) that can be improved with dose escalation [48].

The combination of vitamin E and colchicine (600 mg/day and 1 mg every 12 hours, respectively) for 6 months in patients with early-stage Peyronie's disease resulted in significant improvement in plaque size and curvature, but not in pain compared to ibuprofen 400 mg/day for 6 months [51].

3B.3.2.5 Acetyl esters of carnitine

Acetyl-L-carnitine and propionyl-L-carnitine are proposed to inhibit acetyl coenzyme-A and produce an antiproliferative effect on human endothelial cells. This may eventually suppress fibroblast proliferation and collagen production, thus reducing penile fibrosis. In a randomised, double-blind study in 48 patients with early-stage Peyronie's disease, patients were randomised to acetyl-L-carnitine (1 g twice daily) compared to tamoxifen (20 mg twice daily). After 3 months, acetyl-L-carnitine was significantly more effective than tamoxifen in pain and curvature reduction and inhibition of disease progression, but not in penile plaque size reduction (both drugs significantly reduced plaque size) [52]. Tamoxifen induced significantly more side-effects.

Finally, the combination of intralesional verapamil (10 mg weekly for 10 weeks) with propionyl-l-carnitine (2 g/day for 3 months) significantly reduced penile curvature, plaque size, and disease progression compared to intralesional verapamil combined with tamoxifen (40 mg/day) for 3 months [53].

3B.3.2.6 Pentoxifylline

Pentoxifylline is a non-specific phosphodiesterase inhibitor which down-regulates TGFβ1 and increases fibrinolytic activity [54]. Moreover, an increase of nitric oxide levels may be effective in preventing progression of Peyronie's disease or reversing fibrosis [55]. Preliminary data from a case report showed that pentoxifylline (400 mg three times daily for 6 months) improved penile curvature and the findings on US of the plaque [55]. In another study in 62 patients with Peyronie's disease, pentoxifylline treatment for 6 months appeared to stabilise or reduce calcium content in penile plaques [56].

3B.3.2.7 Phosphodiesterase type 5 inhibitors

The rationale for the use of phosphodiesterase type 5 inhibitors (PDE5I) in Peyronie's disease comes from animal studies showing that they can reduce the collagen/smooth muscle and collagen III/I ratios and increase the apoptotic index in the Peyronie's disease-like plaque [57]. In a retrospective controlled study, daily tadalafil (2.5 mg for 6 months) resulted in statistically significant ($p < 0.05$) resolution of septal scar in 69% of patients compared to 10% in the control group (no treatment). However, this study included patients with isolated septal scars without evidence of penile deformity [58]. Therefore, no recommendation can be given for PDE5I in patients with Peyronie's disease.

3B.3.3 ***Intralesional treatment***

Injection of pharmacologically active agents directly into penile plaques represents another treatment option. It allows a localised delivery of a particular agent that provides higher concentrations of the drug inside the plaque. However, delivery of the compound to the target area is difficult to ensure particularly when a dense or calcified plaque is present.

3B.3.3.1 Steroids

Intralesional steroids are thought to act by opposing the inflammatory milieu responsible for Peyronie's plaque progression via inhibition of phospholipase A2, suppression of the immune response and by decreasing collagen synthesis [59]. In small, non-randomised studies, a decrease in penile plaque size and pain resolution was reported [60, 61]. In the only single-blind, placebo-controlled study with intralesional administration of betamethasone, no statistically significant changes in penile deformity, penile plaque size, and penile pain during erection were reported [62]. Adverse effects include tissue atrophy, thinning of the skin and immunosuppression [60].

3B.3.3.2 Verapamil

The rationale for intralesional use of verapamil (a calcium channel antagonist) in patients with Peyronie's disease is based on in-vitro research [63, 64]. A number of studies have reported that intralesional verapamil injection may induce a significant reduction in penile curvature and plaque volume [65-69]. These findings suggested that intralesional verapamil injections could be advocated for the treatment of non-calcified acute phase or chronic plaques to stabilise disease progression or possibly reduce penile deformity, although large scale, placebo-controlled trials have not yet been conducted [68]. Side-effects are uncommon (4%). Minor side-effects include nausea, light-headedness, penile pain, and ecchymosis [68]. However, in the only randomised, placebo-controlled study, no statistically significant differences on plaque size, penile curvature, penile pain during erection or plaque 'softening' were reported [70]. Younger age and larger baseline penile curvature were found to be predictive of favourable curvature outcomes in a case-series study [71].

3B.3.3.3 Clostridium collagenase

Clostridium collagenase(CCH) is a chromatographically purified bacterial enzyme that selectively attacks collagen, which is known to be the primary component of the Peyronie's disease plaque [72-74]. Clostridium collagenase is now approved by the Food and Drug Administration (FDA) for PD in adult men with a palpable plaque and a curvature deformity of at least 30° at the start of therapy. Findings from two independent, double-blind, placebo controlled studies, reveal the efficacy and tolerability of CCH for improving the co-primary outcomes of physical penile curvature and the psychological subject reported PD symptom bother domain of the PDQ in adults with PD. Participants were given up to four treatment cycles of CCH or placebo and were then followed for 52 weeks. Overall, of 551 treated men with CCH 60.8% were global responders compared with 29.5% of 281 who received placebo. The most commonly reported side-effects were penile pain, penile swelling, and ecchymosis at the site of injection [75]. Of note, CCH is available in the US only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) because of the risks of serious adverse reactions, including penile and other serious penile injury. CCH should be administered by a healthcare professional who is experienced in the treatment of male urological diseases. The REMS requires participating healthcare professionals to be certified within the program by enrolling and completing training in the administration of CCH treatment for Peyronie's disease. The REMS also requires healthcare facilities to be certified within the program and ensure that CCH is dispensed only for use by certified healthcare professionals [76].

3B.3.3.4 Interferon

Interferon α-2b has been shown to decrease fibroblast proliferation, extracellular matrix production and collagen production from fibroblasts and improved the wound healing process from Peyronie's disease plaques in-vitro [77]. Intralesional injections (5×10^6 units of interferon α-2b in 10 mL saline, two times per week for 12 weeks) significantly improved penile curvature, plaque size and density, and pain compared to placebo [78, 79].

Side-effects include myalgias, arthralgia, sinusitis, fever and flu-like symptoms. They can be effectively treated with non-steroidal anti-inflammatory drugs before interferon injection.

3B.3.4 ***Topical treatments***

3B.3.4.1 Topical verapamil

There is no evidence that topical treatments applied to the penile shaft result in adequate levels of the active compound within the tunica albuginea. Verapamil gel has been used in this context [80]. Iontophoresis - now known as transdermal electromotive drug administration (EMDA) - has been introduced to try and overcome limitations on the local uptake of the drugs themselves. Small studies using Iontophoresis with verapamil 5 mg and dexamethasone 8 mg resulted in inconsistent results [81, 82].

3B.3.4.2 Extracorporeal shock wave treatment

The mechanism of action involved in shock wave treatment (ESWT) for Peyronie's disease is still unclear, but there are two hypotheses. In the first hypothesis, shock wave therapy works by directly damaging and remodelling the penile plaque. In the second hypothesis, SWL increases the vascularity of the area by generating heat resulting in an inflammatory reaction, with increased macrophage activity causing plaque lysis and eventually leading to plaque resorption [83]. Most uncontrolled studies failed to show significant improvements in patients with Peyronie's disease [84-86]. In a prospective, randomised, double-blind, placebo-controlled study, four weekly treatment sessions of ESWT, with each session consisting of 2000 focused shock waves, resulted in significant improvement only for penile pain [87].

3B.3.4.3 Traction devices

The application of continuous traction in Dupuytren's contracture increases the activity of degradative enzymes [88]. This initially leads to a loss of tensile strength and ultimately to solubilisation. It is followed by an increase in newly synthesised collagen [88]. This concept has been applied in an uncontrolled study, including 10 patients with Peyronie's disease. The FastSize Penile Extender was applied as the only treatment for 2-8 hours/day for 6 months [89]. Reduced penile curvature of 10-40° was found in all men with an average reduction of 33% (range: 51-34º). The stretched penile length increased 0.5-2.0 cm and the erect girth increased 0.5-1.0 cm, with a correction of hinge effect in four out of four men. Treatment can be uncomfortable and inconvenient due to use of the device 2–8 h daily for an extended period, but has been shown to be tolerated by highly motivated patients [22]. There were no serious adverse events, including skin changes, ulcerations, hypoesthesia or diminished rigidity.

In another prospective study, there was a significant reduction in penile curvature (mean 20 degrees reduction). Erectile function and erection hardness also improved significantly. The percentage of patients who were not able to achieve penetration decreased from 62% to 20% ($P < 0.03$). Importantly, the need for surgery was reduced in 40% of patients who would otherwise have been candidates for surgery and simplified the complexity of the surgical procedure (from grafting to plication) in 1 in 3 patients [90].

3B.3.4.4 Vacuum devices

The application of vacuum devices follows the same principles as traction devices with the drawback of being non-continuous precluding remodelling of the plaque. Their efficacy has been assessed in an uncontrolled study (31 patients completed the study) [91]. Half of the patients were satisfied with the outcome and the remaining had their curvature corrected surgically.

3B.3.4.5 Recommendations for non-operative treatment of Peyronie's disease

	LE	GR
Conservative treatment for Peyronie's disease is primarily aimed at treating patients in the early stage of the disease. It is an option in patients not fit for surgery or when surgery is not acceptable to the patient.	3	C
Oral treatment with potassium para-aminobenzoate may result in a significant reduction in penile plaque size and penile pain as well as penile curvature stabilisation.	1b	C
Intralesional treatment with verapamil may induce a significant reduction in penile curvature and plaque volume.	1b	C
Intralesional treatment with clostridium collagenase showed significant decreases in the deviation angle, plaque width and plaque length.	1b	B
Intralesional treatment with interferon may improve penile curvature, plaque size and density, and pain.	1b	C
Topical verapamil gel 15% may improve penile curvature and plaque size.	1b	C
Iontophoresis with verapamil 5 mg and dexamethasone 8 mg may improve penile curvature and plaque size.	1b	C
Extracorporeal shock-wave treatment fails to improve penile curvature and plaque size, and should not be used with this intent, but may be beneficial for penile pain.	1b	C
Penile traction devices and vacuum devices may reduce penile deformity and increase penile length.	2b	C
Intralesional treatment with steroids is not associated with significant reduction in penile curvature, plaque size or penile pain. Therefore, intralesional treatment with steroids cannot be recommended.	1b	B
Oral treatment with vitamin E and tamoxifen are not associated with significant reduction in penile curvature or plaque size and should not be used with this intent.	2b	B
Other oral treatments (acetyl esters of carnitine, pentoxifylline, colchicine) are not recommended.	3	C

3B.3.5 ***Surgical treatment***

Although conservative treatment for Peyronie's disease should resolve painful erections in most men, only a small percentage will experience any significant straightening of the penis. The aim of surgery is to correct curvature and allow satisfactory intercourse. Surgery is indicated in patients with penile curvature that does not allow satisfactory intercourse and it is associated with sexual bother [92]. Patients must have a stable disease for at least 3 months, although a 6-12 month period has also been suggested [93].

The potential aims and risks of surgery should be discussed with the patient so that he can make an informed decision. Specific issues that should be mentioned during this discussion are the risks of penile shortening, ED, penile numbness, the risk of recurrent curvature, the potential for palpation of knots and stitches underneath the skin, and the potential need for circumcision at the time of surgery [24]. Two major types of repair may be considered for both congenital penile curvature and Peyronie's disease: penile shortening and penile lengthening procedures [94].

Penile shortening procedures include the Nesbit wedge resection and the plication techniques performed on the convex side of the penis. Penile lengthening procedures are performed on the concave side of the penis and require the use of a graft. They aim to minimise penile shortening caused by Nesbit or plication of the tunica albuginea or correct complex deformities. Penile degloving with associated circumcision (as a means of preventing post-operative phimosis) is considered the standard approach for all types of procedures [94]. However, recent data suggest that circumcision is not always necessary e.g. in cases where the foreskin is normal pre-operatively [95]. Finally, in patients with Peyronie's disease and ED not responding to medical treatments, the surgical correction of the curvature with concomitant penile prosthesis implantation should be considered [96].

Choosing the most appropriate surgical intervention is based on penile length assessment, curvature severity and erectile function status, including response to pharmacotherapy in cases of ED [24]. Patient expectations from surgery must also be included in the pre-operative assessment. There are no standardised questionnaires for the evaluation of surgical outcomes [92]. Data from well-designed prospective studies are scarce, with a low level of evidence. Most data are mainly based on retrospective studies, typically noncomparative and non-randomised, or on expert opinion [24, 97].

3B.3.5.1 Penile shortening procedures

In 1965, Nesbit was the first to describe the removal of tunical ellipses opposite a non-elastic corporal segment to treat congenital penile curvature [98]. Fourteen years later, this technique became a successful treatment option, also for Peyronie's disease [99]. This operation is based on a 5-10 mm transverse elliptical excision of the tunica albuginea or approximately 1 mm for each 10° of curvature [94]. The overall short- and long-term results of the Nesbit operation are excellent. Complete penile straightening is achieved in more than 80% of patients [100]. Recurrence of the curvature and penile hypoesthesia are uncommon (about 10%) and the risk of postoperative ED is minimal [94, 101]. Penile shortening is the most commonly reported outcome of the Nesbit procedure [101]. However, shortening of only 1-1.5 cm has been reported for about 85% of patients, which is rarely the cause for post-operative sexual dysfunction [99, 102]. Patients often perceive the loss of length as greater than it actually is [100, 101]. It is therefore advisable to measure and document the penile length peri-operatively, both before and after the straightening procedure, whatever the technique used. Only one modification of the Nesbit procedure has been described (partial thickness shaving instead of conventional excision of a wedge of tunica albuginea) [103].

Plication procedures actually share the same principle as the Nesbit operation but are simpler to perform. Many of them have been described as Nesbit modifications in the older literature. They are based on single or multiple longitudinal incisions on the convex side of the penis closed in a horizontal way, applying the Heineke-Miculicz principle, or plication is performed without making an incision [104-109]. Another modification has been described as the '16 dot' technique with minimal tension under local anaesthesia [110]. The use of non-absorbable sutures reduced recurrence of the curvature. Results and satisfaction rates are similar to the Nesbit procedure [94]. However, a lot of different modifications have been described and the level of evidence is not sufficient to recommend one method over the other.

3B.3.5.2 Penile lengthening procedures

Tunical lengthening procedures entail an incision in the short (concave) side of the tunica to increase the length of this side, creating a tunical defect, which is covered by a graft. However, plaque removal may be associated with high rates of postoperative ED due to venous leak [111].

Devine and Horton introduced dermal grafting in 1974 [112]. Since then, a variety of grafting materials and techniques have been reported (Table 2) [113-127]. Unfortunately, the ideal material for grafting has yet to be identified. In addition, grafting procedures are associated with ED rates as high as 25%. Despite excellent initial surgical results, graft contracture and long-term failures resulted in a 17% re-operation rate [128].

Vein grafts have the theoretical advantage of endothelial-to-endothelial contact when grafted to underlying cavernosal tissue. Saphenous vein is the most common vein draft used, followed by dorsal penile vein [94]. In the first case, a secondary incision for graft harvesting is avoided. Postoperative curvature (20%), penile shortening (17%) and graft herniation (5%) have been reported after vein graft surgery [118, 123, 126]. Tunica vaginalis is relatively avascular, easy to harvest and has little tendency to contract due to its low metabolic requirements [116].

Dermal grafts are commonly associated with contracture resulting in recurrent penile curvature (35%), progressive shortening (40%), and a 17% re-operation rate at 10 years [129]. Cadaveric pericardium (Tutoplast®) offers good results by coupling excellent tensile strength and multi-directional elasticity/expansion by 30% [127]. In a retrospective telephone interview, 44% of patients with pericardium grafting reported recurrent curvature, although most of them continued to have successful intercourse and were pleased with their outcomes [127, 129].

Small intestinal submucosa (SIS, a collagen-based xenogenic graft derived from the submucosal layer of the porcine small intestine) has been shown to promote tissue-specific regeneration, and supports the growth of endothelial cells. Small intestinal submucosa acts as a scaffold to promote angiogenesis, host cell migration and differentiation, resulting in tissue structurally and functionally similar to the original. It has been used successfully to repair severe chordee and Peyronie's disease, without significant contraction or histological alterations, but data are limited [124].

More recently the use of buccal mucosa grafts (BMG) has been advocated. BMG provided excellent short-term results, suggested by the fast return of spontaneous erections and prevented shrinkage, which is the main cause of graft failure. It also proved to be safe and reproducible, thus representing a valuable treatment option for PD [115].

Tunical incision, preferably with grafting, offers an excellent surgical option for men with curvatures over 60° as well as patients with an hourglass deformity and good erectile function that are willing to risk a higher rate of postoperative ED [130]. The presence of pre-operative ED, the use of larger grafts, age more than 60 years, and ventral curvature are considered poor prognostic factors for functional outcome after grafting surgery [96]. Although the risk for penile shortening is significantly less compared to the Nesbit or plication procedures, it is still an issue and patients must be informed accordingly [94]. The use of geometric principles introduced by Egydio helps to determine the exact site of the incision, and the shape and size of the defect to be grafted [117].

The use of a penile extender device on an 8- to 12-hour daily regimen has been advocated as an effective and safe treatment for loss of penile length in patients operated on for Peyronie's disease [131].

Table 2: Types of grafts used in Peyronie's disease surgery

Autologous grafts
Dermis
Vein grafts
Tunica albuginea
Tunica vaginalis
Temporalis fascia
Buccal mucosa
Allografts
Cadaveric pericardium
Cadaveric fascia lata
Cadaveric dura matter
Cadaveric dermis
Xenografts
Porcine small intestinal submucosa
Bovine pericardium
Porcine dermis
Synthetic grafts
Gore-Tex
Dacron

3B.3.5.3 Penile prosthesis

Penile prosthesis implantation is typically reserved for the treatment of Peyronie's disease in patients with ED, especially when they are not responders to phosphodiesterase type 5 inhibitor (PDE5I) [94]. Although all types of penile prosthesis can be used, the implantation of inflatable penile prosthesis seems to be most effective in these patients [132].

Most patients with mild-to-moderate curvature can expect an excellent outcome simply by cylinder insertion. In cases of severe deformity, intra-operative 'modelling' of the penis over the inflated cylinders (manually bent on the opposite side of the curvature for 90 seconds, often accompanied by an audible crack) has been introduced as an effective treatment [133, 134]. If there is a residual curvature of less than 30°, no further treatment is recommended, as the prosthesis will act as a tissue expander and will result in complete correction of curvature in a few months [133]. While this technique is effective in most patients, a Nesbit/plication procedure or plaque excision/incision and grafting may be required in order to achieve adequate straightening [135-137].

The risk of complications (infection, malformation, etc) is not increased compared to the general population. However, a small risk of urethral perforation (3%) has been reported in patients with 'modelling' over the inflated prosthesis [134].

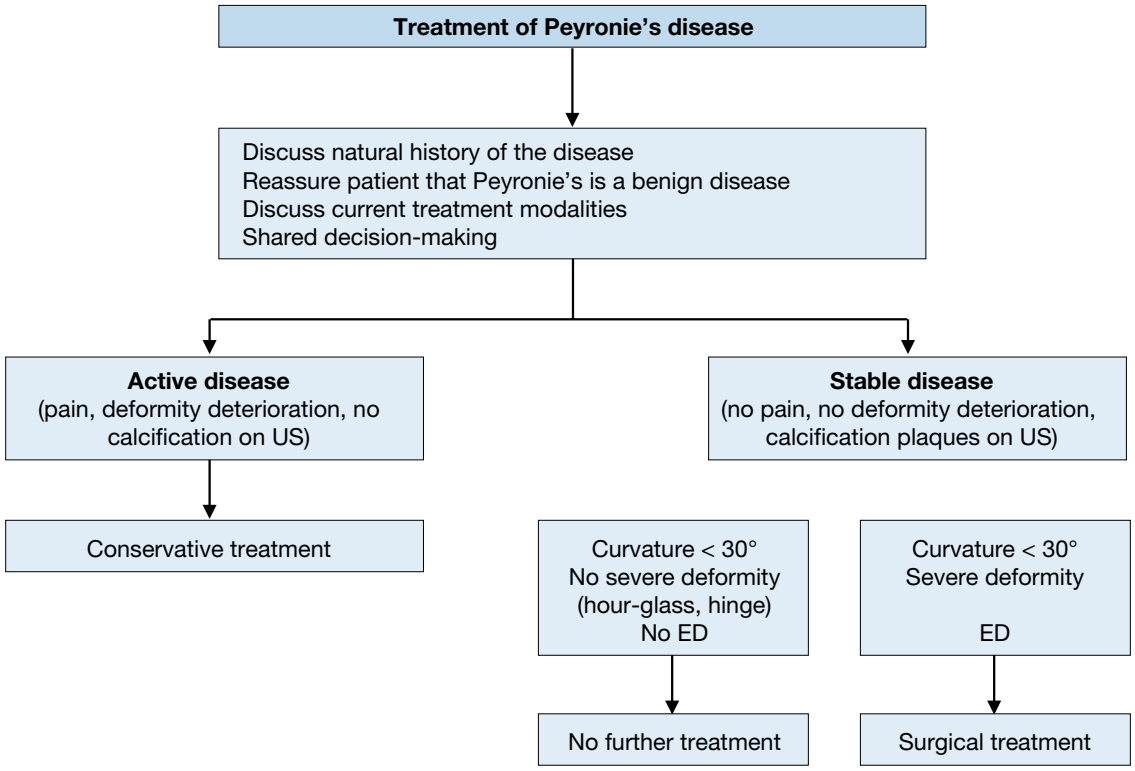
Table 3: Results of surgical treatments for Peyronie's disease (data from different, non-comparable studies) [99, 101-127, 129, 130]

	Tunical shortening procedures	Tunical lengthening procedures	
	Nesbit	**Plication**	**Grafts**
Penile shortening	4.7-30.8%	41-90%	0-40%
Penile straightening	79-100%	58-100%	74-100%
Persistent or recurrent curvature	4-26.9%	7.7-10.6%	0-16.7%
Post-operative erectile dysfunction	0-13%	0-22.9%	0-15%
Penile hypoesthesia	2-21%	0-21.4%	0-16.7%
Technical modifications	1	At least 3	Many types of grafts and techniques used

3B.3.5.4 Treatment algorithm

The decision on the most appropriate surgical procedure to correct penile curvature is based on pre-operative assessment of penile length, the degree of the curvature and erectile function status. If the degree of curvature is less than 60°, penile shortening is acceptable and the Nesbit or plication procedures are usually the method of choice. This is typically the case for congenital penile curvature. If the degree of curvature is over 60° or is a complex curvature, or if the penis is significantly shortened in patients with a good erectile function (with or without pharmacological treatment), then a grafting procedure is feasible. If there is ED, which is not responding to pharmacological treatment, the best option is the implantation of an inflatable penile prosthesis, with or without an associated procedure over the penis (modelling, plication or even grafting plus the prosthesis). The treatment algorithm is presented in Figure 1.

Figure 1: Treatment algorithm for Peyronie's disease



US = Ultrasound; ED = erectile dysfunction.

The results of the different surgical approaches are presented in Table 3. It must be emphasised that there are no randomised controlled trials available addressing surgery in Peyronie's disease. The risk of erectile dysfunction seems to be greater for penile lengthening procedures [24, 94]. Recurrent curvature implies

either failure to wait until the disease has stabilised, a reactivation of the condition following the development of stable disease, or the use of re-absorbable sutures that lose their strength before fibrosis has resulted in acceptable strength of the repair [94]. Accordingly, it is recommended that only non-absorbable sutures or slowly reabsorbed absorbable sutures be used. Although with non-absorbable sutures, the knot should be buried to avoid troublesome irritation of the penile skin, this issue seems to be alleviated by the use of slowly re-absorbed absorbable sutures [101]. Penile numbness is a potential risk of any surgical procedure involving mobilisation of the dorsal neurovascular bundle. This will usually be a neuropraxia, due to bruising of the dorsal sensory nerves. Given that the usual deformity is a dorsal deformity, the procedure most likely to induce this complication is a lengthening (grafting) procedure for a dorsal deformity [94].

3B.3.5.5 Recommendations for the surgical treatment of penile curvature

	LE	GR
Surgery is indicated when Peyronie's disease is stable for at least 3 months (without pain or deformity deterioration), which is usually the case after 12 months from the onset of symptoms, and intercourse is compromised due to deformity.	3	C
Penile length, curvature severity, erectile function (including response to pharmacotherapy in case of erectile dysfunction) and patient expectations must be assessed prior to surgery.	3	C
Tunical shortening procedures, especially plication techniques are the first treatment options for congenital penile curvature and for Peyronie's disease with adequate penile length, curvature < 60° and absence of special deformities (hour-glass, hinge).	2b	B
Grafting techniques are the preferred treatment option for patients with Peyronie's disease and normal erectile function, with no adequate penile length, curvature > 60º and presence of special deformities (hour-glass, hinge).	2b	B
Penile prosthesis implantation, with or without any additional procedure (modelling, plication or grafting), is recommended in Peyronie's disease patients with erectile dysfunction not responding to pharmacotherapy.	2b	B

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5. CONFLICT OF INTEREST

All members of the EAU Penile Curvature Guidelines Panel have provided disclosure statements on all relationships that they have that might be perceived to be a potential source of a conflict of interest. This information is publically accessible through the European Association of Urology website. This document was developed with the financial support of the European Association of Urology. No external sources of funding and support have been involved. The EAU is a non-profit organisation, and funding is limited to administrative assistance and travel and meeting expenses. No honoraria or other reimbursements have been provided.