IJIR: Your Sexual Medicine Journal (2019) 31:177–194
https://doi.org/10.1038/s41443-019-0117-z

REVIEW ARTICLE

Clinical studies on low intensity extracorporeal shockwave therapy for erectile dysfunction: a systematic review and meta-analysis of randomised controlled trials

Ioannis Sokolakis[1] · Georgios Hatzichristodoulou[1]

Received: 13 November 2018 / Revised: 7 January 2019 / Accepted: 10 January 2019 / Published online: 21 January 2019

Abstract

The efficacy of low intensity extracorporeal shock wave therapy (LI-ESWT) for erectile dysfunction (ED) has received hard criticism and recently published meta-analyses were not able to provide further insights, nor specific recommendations. The aim of this systematic review and meta-analysis is to evaluate the efficacy of LI-ESWT for ED, identify the ideal treatment population and treatment protocol, and provide recommendations for future research in the field. A systematic research for relevant clinical studies published from January 2010 to September 2018 was performed, using the following databases: Medline, Embase, The Cochrane Library, Scopus, and Web of Science. Only clinical studies that investigated the efficacy of LI-ESWT for ED only, and reported primary outcomes using IIEF-EF scores/questionnaires were included. Both, randomised controlled trials (RCTs) and cohort studies were included, but the meta-analysis was performed only for sham-controlled RCTs. Ten RCTs including 873 patients were selected for the meta-analysis. Pooling data of these studies showed that LI-ESWT could significantly improve erectile function in men with ED regarding both patient-subjective outcomes (IIEF-EF: +3.97; 95% CI [2.09–5.84]; $p < 0.0001$, EHS ≥ 3: OR: 4.35; 95% CI [1.82–10.37]; $p = 0.0009$) and patient-objective outcomes (peak systolic velocity: +4.12; 95% CI [2.30–5.94]; $p < 0.00001$). In conclusion, the present meta-analysis provided results showing that LI-ESWT significantly improves erectile function in patients with vasculogenic ED.

Introduction

Low intensity extracorporeal shockwave therapy (LI-ESWT) for the treatment of erectile dysfunction (ED) was first introduced by Vardi et al. [1]. It has been proposed as a non-invasive, non-pharmacological treatment option for ED with minimal side-effects and as the first treatment option which attempts to improve erectile function by treating the underlying pathophysiology. As expected, it attracted the scientific community with increasing research activity in the last eight years, but also received hard criticism regarding the underlining mechanism of action.

The first clinical studies and RCTs had their limitations and the recently published systematic reviews with meta-analyses were not able to provide any further insights, nor specific recommendations. A recent survey among sexual medicine practitioners showed that 25% of them reported that they were unfamiliar with LI-ESWT. Moreover, 62% of the colleagues that were familiar with LI-ESWT have never recommended this treatment to a patient [2]. Recently, Fode et al. pointed out that there is no level 1 evidence available to support the use of LI-ESWT in any population of patients with ED, and its use should, therefore, be limited to clinical trials [3]. However, during the last 2 years additional well-designed RCTs, as well as studies investigating the ideal treatment protocol emerged.

In the current study, we aimed to perform a systematic review of the current literature to identify clinical studies on LI-ESWT for ED as the primary end-point. Moreover, we performed a meta-analysis of well-designed RCTs with the effects of LI-ESWT on erectile function as measured by the IIEF-EF score as primary end-point. The aim of this systematic review is to provide level 1a evidence regarding the efficacy of LI-ESWT for ED, identify the ideal treatment population and treatment protocol, and provide recommendations for future research in the field.

✉ Georgios Hatzichristodoulou
hatzichris_g@ukw.de

[1] Department of Urology and Paediatric Urology, Julius-Maximilians-University of Würzburg, Würzburg, Germany

Materials and methods

Search strategy

The Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) [4] and the Cochrane Handbook for Systematic Reviews of Interventions [5] were used as the framework for this systematic review. Between August 2018 and September 2018, the authors independently performed a systematic search in the following databases: Medline, Embase, The Cochrane Library, Scopus, and Web of Science. The keywords "shockwave", "shock wave", and "ESWT" were searched alone and in combination with the terms "erectile", "penis", "penile", "IIEF", "EHS", and "ED". Additionally, the reference lists were tracked backwards for further relevant articles, which were not listed in the databases mentioned above or were not identified during the research. Furthermore, we reviewed articles that were suggested by the "related citations in PubMed" option for the most recent articles. The search was performed for the time period from January 2010 (the year of the first published article regarding LI-ESWT for ED by Vardi et al. [1]) through September 2018. Our research was not restricted by language.

Inclusion and exclusion criteria

Only clinical studies that investigated the efficacy of LI-ESWT for ED only and reported primary outcomes using the IIEF-EF score/questionnaire were included. Both, randomised controlled trials (RCTs) and cohort studies were included in this study, but the meta-analysis was performed only for sham-controlled RCTs. Studies that were designed for pathological conditions other than ED (such as Peyronie's disease or chronic pelvic pain syndrome, or combination) were excluded. Although some of these studies included secondary outcomes for ED, they contain high risk of bias regarding the interpretation of these results [6, 7]. No limitation was placed on PDE5i consumption during the LI-ESWT treatment period. In case of multiple studies involving the same study population, only the last and most comprehensive article was included. Narrative reviews, editorial comments, letters to the editor, conference abstracts, experimental studies on animal models, and case reports were excluded.

Data extraction and synthesis

The initial screening of titles/abstracts and later of full articles was conducted by the authors (IS, GH) independently with predefined inclusion and exclusion criteria. Finally, any discrepancies were discussed between the two reviewers, in order to reach a consensus on eligibility for inclusion. A PRISMA flow chart of screening and selection results is presented in Fig. 1. The same authors independently extracted data from the included articles using a data collection form that was developed a priori. This included: first author and publication year, year of study, publication type, duration of follow-up, population, participant inclusion and exclusion criteria, sample size, setup parameters of the LI-ESWT generator, the model of LI-ESWT machine, treatment protocols, assessment tools, results regarding IIEF-EF score at baseline and at the final follow-up, minimal clinical important difference (MCID) in improvement of IIEF-EF [8], erection hardness score (EHS) at baseline and at the final follow-up and proportion of patients that

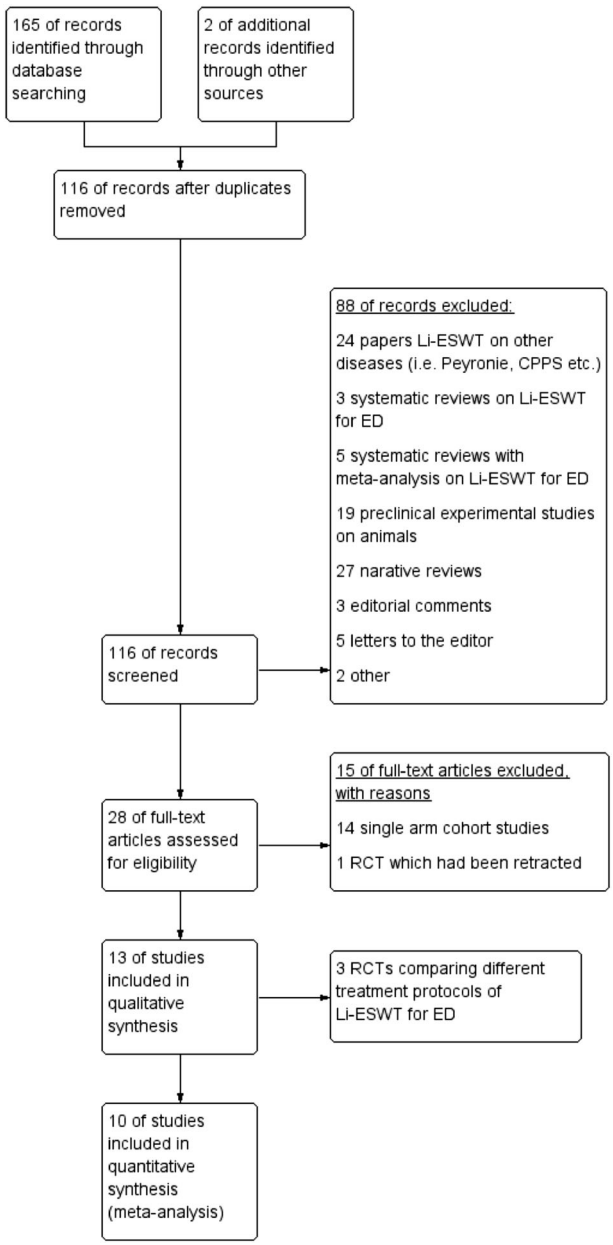

Fig. 1 PRISMA flow chart of screening and selection results

reached EHS ≥ 3 at study's end, penile hemodynamics (i.e., peak-systolic velocity, PSV) [9] at baseline and at final follow-up, and *p*-values were abstracted manually from each of the studies.

Quality assessment

The risk of bias in the included RCTs was assessed using the Cochrane Risk of Bias Assessment tool [10] in the domains of randomisation, allocation concealment, blinding (participants, investigators and outcome assessment), completeness of outcome data, selective outcome reporting, and other potential sources of bias. Domains were independently assessed by the authors (IS, GH). All discrepancies were resolved by discussion. A graph and a summary for risk of bias were generated with RevMan 5.3 software (Cochrane Collaboration, London, UK) (Fig. 2).

Meta-analysis

The extracted data were analysed using the RevMan 5.3 software (Cochrane Collaboration, London, UK). The primary outcome was the effect of LI-ESWT for ED as measured with the IIEF-EF score. Secondary outcomes were the changes regarding EHS and penile hemodynamics. The proper effect sizes and statistical analysis methods were chosen according to different data types and evaluation purposes. For continuous variables, the mean difference (MD) between groups with a 95% confidence interval [CI] were used. For dichotomous variables, odds ratio (OR) with a 95% CI were used. Between-study heterogeneity was assessed by standard χ^2 tests and the I^2 statistic. The data without significant heterogeneity ($p > 0.05$, $I^2 < 50\%$) were analysed by fixed-effects model. The data with heterogeneity, that could not be explained

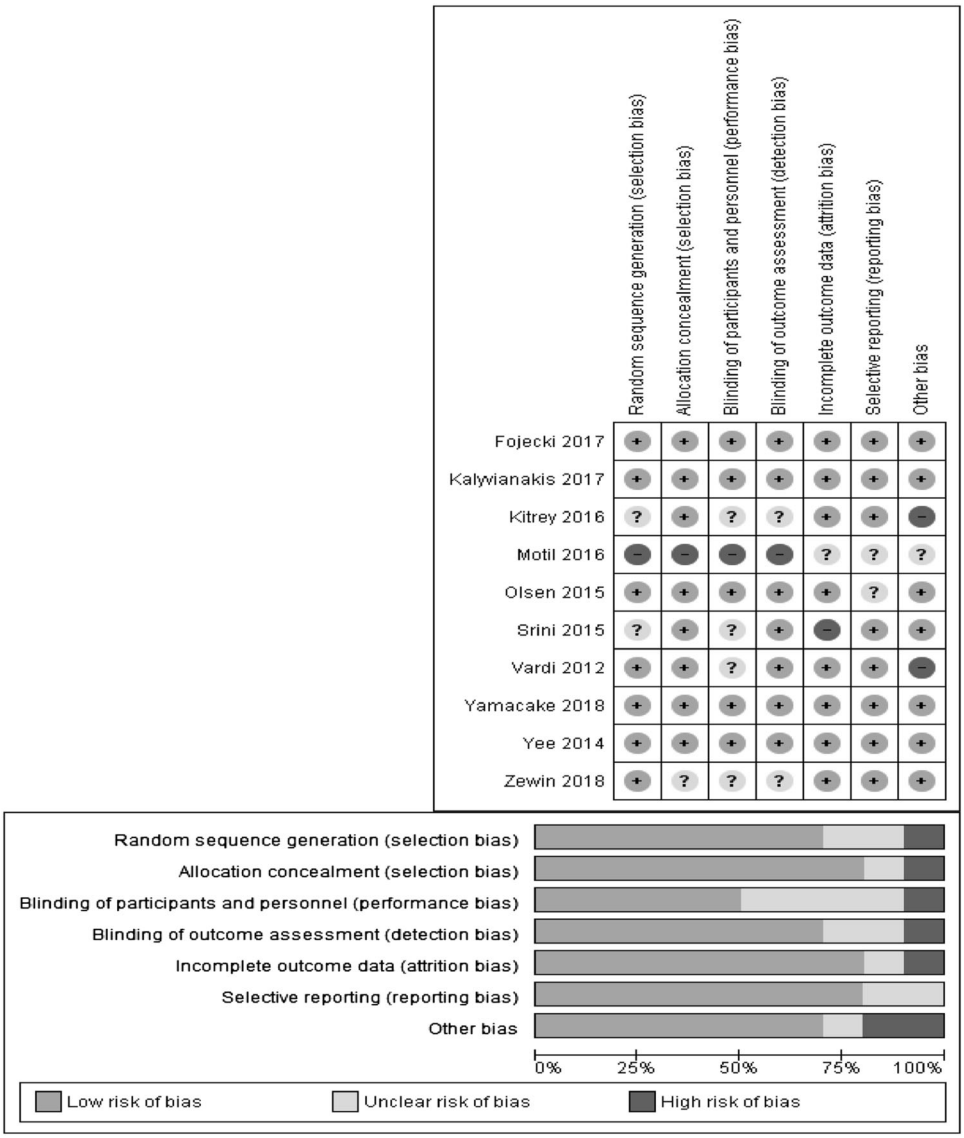

Fig. 2 Quality assessment of the 10 RCTs showed through a graph and a summary for risk of bias. RCTs, randomised controlled trials

otherwise, were analysed by random-effects model. The data that could not be analysed were described. The influence of individual studies on the overall summary estimates was examined by serially excluding each study in a sensitivity analysis. Results of the meta-analysis are presented in forest plots, with statistical significance set at p-value < 0.05. Publication bias was analysed with funnel plots.

Results

Current studies on LI-ESWT for ED

A total of 28 clinical studies with more than 2000 patients investigating the effects of LI-ESWT for ED as primary outcome were identified [1, 11–37]. Fourteen of these studies were single arm cohorts and 14 RCTs. The main characteristics of these studies including outcomes are shown in Tables 1 and 2 (cohorts and RCTs, respectively). One RCT was retracted from the journal for plagiarized data previously published in another study and was not included in the analysis [34]. Three RCTs were comparing different treatment protocols of LI-ESWT for ED [35–37]. Finally, 10 RCTs with a total of 872 patients that compared LI-ESWT with sham-control treatment were included for meta-analysis [24–33] (Fig. 1). The mean number of participants per study was 87 (range 20–139), the mean age was 58 (range 27–81) years, and the mean follow-up was 5.12 months (range 1–12).

Population

Most of the studies evaluated LI-ESWT in patients with vasculogenic ED (12 cohorts and 10 RCTs), either PDE5i-responders (the majority of the studies) [1, 14, 15, 19, 22–27, 29, 31–33] or PDE5i-non-responders [11–13, 16, 17, 21, 23, 28]. Most of the studies prohibited the usage of PDE5i during the treatment course. The majority of RCTs even set a washout period (2–4 weeks) for patients who had taken PDE5i before they started LI-ESWT. Vasculogenic ED was defined in the majority of the studies based on inclusion and exclusion criteria. They excluded patients with ED due to psychiatric, neurological, hormonal, or anatomical conditions, ED due to pharmacological treatment, and patients after pelvic surgery or irradiation. Two of the RCTs additionally defined vasculogenic ED using penile doppler duplex/triplex ultrasound [27, 31] and one using cardio-ankle vascular index (CAVI) [29]. From the remaining studies, one RCT investigated LI-ESWT in ED-patients post nerve-sparing radical cystectomy [33], one RCT in kidney transplant recipients with ED [32], one RCT in patients with organic ED [30], one cohort in ED-patients post radical prostatectomy [18] and one cohort with ED of miscellaneous aetiology [20].

Shockwave generators and treatment protocols

Different setup parameters and treatment protocols were used among these studies. The shockwave generator as well as the type of shockwave pulse produced was also different among the studies. Nine studies (4 cohorts and 5 RCTs) used an electrohydraulic shockwave generator, 11 (9 cohorts and 4 RCTs) used electromagnetic, 3 RCTs used piezoelectric and 1 RCT used electropneumatic generator. The majority of the generators (15) produced focused shockwaves (SW) (8 cohorts and 7 RCTs), 9 produced linear (5 cohorts and 4 RCTs), one semi-focused and one unfocused SW. The generators were provided from different manufacturers: Omnispec ED1000 (Medispec Ltd., Yehud, Israel): 9 studies; Duolith-SD1 (Storz Medical AG, Tagerwilen, Switzerland): 5, PiezoWave (Richard-Wolf GmbH, Knittlingen, German): 3, Renova/MoreNova (DirexGroup, Wiesbaden, Germany): 5/1; Dornier-Aries^2 (Dornier MedTech, Munich, Germany): 2 and Swiss-DolorClast (EMS; Electro Medical Systems S.A., Nyon, Switzerland): 1 study. The energy flux density (EFD) ranged between 0.05 mJ/mm^2 and 0.25 mJ/mm^2, with the majority of the studies using 0.09 mJ/mm^2 (19/27 studies). The number of shockwave pulses during each treatment ranged between 600 and 5000, with the majority delivering 1500 pulses/treatment (11/27 studies). The duration of the treatment course ranged between 1 and 9 weeks, with treatment sessions from 1 to a maximum of 5 times per week (usually 1 or 2 treatment sessions per week), delivering a total number of shockwave pulses between 3000 and 60,000 at the end of treatment. In studies that used focused shockwaves, shockwaves were applied at multiple sites of the penis including the crura (usually 4, 5, or 6 sites), while studies using linear shockwaves applied the treatment by continuous movement of the applicator on penile shaft and crura.

Assessment tools

The international index of erectile function (IIEF) with the erectile function domain (IIEF-EF) was the prevailing assessment tool of the effects of LI-ESWT for ED. Another frequently used assessment tool was the erection hardness score (EHS). Both assessment tools were found in the majority of the studies making it possible to perform further meta-analysis. Other tools, such as the sexual encounter profile (SEP), the Global assessment questionnaire (GAQ), maximal penile circumferential change, and the clinical global impression of change (CGIC) were not used consistently throughout the studies and thus not used for further meta-

Table 1 Single arm cohort studies on Li-ESWT for ED

Study	Study design	Li-ESWT setup	Li-ESWT protocol	IIEF change	Rate EHS ≥ 3	Other
Vardi et al. [1]	•Single arm cohort •PDE5i-responders •Vasculogenic ED •$N = 20$ •1, 6 month follow-up	•EFD: 0.09 mJ/mm^2 •Electrohydraulic •Focused SW •2 Hz •Omnispec ED1000	•2 /week •3 weeks treatment—3 weeks no treatment—3 weeks treatment •12 × 1500 pulses (18,000) •500 pulses at 5 points	+7.4	N/A	N/A
Gruenwald et al. [11]	•Single arm cohort •PDE5i-non-responders •Vasculogenic ED •$N = 29$ •1 or 2 month follow-up •Without PDE5i and with PDE5i	•EFD: 0.09 mJ/mm^2 •Electrohydraulic •Focused SW •2 Hz •Omnispec ED1000	•2 /week •3 weeks treatment—3 weeks no treatment—3 weeks treatment •12 × 1500 pulses (18,000) •500 pulses at 5 points	+3.5 (without PDE5i) +10 (with PDE5i)	72.4%	Penile endothelial function improved significantly
Bechara et al. [12]	•Single arm cohort •PDE5i-non-Responders •Vasculogenic ED •$N = 25$ •1, 3 month follow-up •With PDE5i	•EFD: 0.09 mJ/mm^2 •Electromagnetic •Linear SW •RENOVA	•1/week •4 weeks treatment •4 × 5000 pulses (20,000) •1800 were applied on the penis and 3200 were applied on the perineum	+9	N/A	SEP2: +41.7% SEP3: +35.5%
Chung and Cartmill [13]	•Single arm cohort •PDE5i-non-responders •Vasculogenic ED •$N = 30$ •1, 4 month follow-up	•EFD: 0.25 mJ/mm^2 •Electromagnetic •Focused SW •6 Hz •Duolith SD1 ultra	•2/week •6 weeks treatment •12 × 3000 pulses (36,000) •2000 on the penis 2 points and 1000 on the crura 2 points	+2.5 (≥5 points change (60%)	60%	N/A
Pelayo-Nieto et al. [14]	•Single arm cohort •PDE5i-responders •Vasculogenic ED •$N = 15$ •1, 6 month follow-up	•EFD: 0.09 mJ/mm^2 •Electromagnetic •Linear SW •RENOVA	•1/week •4 weeks treatment •4 × 5000 pulses (20,000) •1800 were applied on the penis and 3200 were applied on the perineum	+5.46	N/A	SEP3: +33.3%
Reisman et al. [15]	•Single arm cohort •PDE5i-responders •Vasculogenic ED •$N = 58$ •1, 3, 6 month follow-up •After 1 month with PDE5i	•EFD: 0.09 mJ/mm^2 •Electromagnetic •Linear SW •RENOVA	•1/week •4 weeks treatment •4 × 3600 pulses (14,400) •900 pulses at 4 points	+7.5	N/A	SEP2: +33% SEP3: +49%
Ruffo et al. [16]	•Single arm cohort •PDE5i-non-responders •Vasculogenic ED •$N = 31$ •1, 3 month follow-up	•EFD: 0.09 mJ/mm^2 •Electromagnetic •Linear SW •RENOVA	•1/week •4 weeks treatment •4 × 3600 pulses (14,400) •900 pulses at 4 points	+4.49	N/A	SEP2: +28% SEP3: +30%
Bechara et al. [17]	•Single arm cohort •PDE5i-non-responders •Vasculogenic ED	•EFD: 0.09 mJ/mm^2 •Electromagnetic •Linear SW •RENOVA	•1/week •4 weeks treatment •4 × 3600 pulses (14,400) •900 pulses at 4 points	+9.1	80%	SEP2: +38.4% SEP3: +53%

Table 1 (continued)

Study	Study design	Li-ESWT setup	Li-ESWT protocol	IIEF change	Rate EHS ≥ 3	Other
	•$N = 50$ •3, 6, 9, 12 month follow-up					
Frey et al. [18]	•Single arm cohort •Post prostatectomy ED •$N = 18$ •1, 12 month follow-up	•EFD: 0.15 mJ/mm^2 •Electromagnetic •Focused SW •6 Hz •Duolith SD1 T-Top	•2/week •6 weeks, treatment every other week •6 × 3000 pulses (18,000) •2000 on the penis 2 points and 1000 on the crura 2 points	+3.5 (1 month) +1 (12months)	N/A	N/A
Hisasue et al. [19]	•Single arm cohort •PDE5i-Responders •Vasculogenic ED •$N = 57$ •1, 3, 6 month follow-up (with and without PDE5i	•EFD: 0.09 mJ/mm^2 •Electrohydraulic •Focused SW •2 Hz •Omnispec ED1000	•2 /week •3 weeks treatment – 3 weeks no treatment – 3 weeks treatment •12 × 1500 pulses (18,000) •500 pulses at 5 points	N/A	57.1%	SHIM: +5 (with PDE5i, 64.2%) +4 (without PDE5i)
Ayala et al. [20]	•Single arm cohort •Miscellaneous ED •$N = 412$ •1 month follow-up	•EFD: 0.1 mJ/mm^2 •Electromagnetic •Focused SW •6 Hz •Duolith SD1	•1 /week •5 weeks treatment •5 × 3000 pulses (15,000) •500 pulses at 6 points	N/A	38.5%	N/A
Tsai et al. [21]	•Single arm cohort •PDE5i-non-responders •Vasculogenic ED •N = 52 •1, 3 month follow-up •With PDE5i	•EFD: 0.15 mJ/mm^2 •Electromagnetic •Focused SW •4 Hz •Duolith SD1 T-Top	•1 /week •12 weeks treatment •12 × 3000 pulses (36,000) •500 pulses at 6 points	N/A	67.3%	N/A
Chen et al. [22]	•Single arm cohort •PDE5i-Responders •Vasculogenic ED •N = 32 •1, 3 month follow-up	•EFD: 0.09 mJ/mm^2 •Electrohydraulic •Focused SW •2 Hz •Omnispec ED1000	•2 /week •3 weeks treatment—3 weeks no treatment—3 weeks treatment •12 × 1500 pulses (18,000) •500 pulses at 5 points	+6.41	71.88%	SEP2: +50% SEP3: +56.25%
Kitrey et al. [23]	•Single arm cohort •PDE5i responders and non-responders •Vasculogenic ED •$N = 156$ •24 months follow-up	•EFD: 0.09 mJ/mm^2 •Miscellaneous ESWT-Systems	•2 /week •3 weeks treatment—3 weeks no treatment—3 weeks treatment •12 × 1500 pulses (18,000) 500 pulses at 5 points	N/A	63.5% at 1 month and 34% at 2 years	N/A

Table 2 Randomized controlled trials (RCTs) on Li-ESWT for ED

Study	Study design	Li-ESWT setup	Li-ESWT protocol	IIEF change	Rate EHS ≥ 3	Risk of bias
Vardi et al. [24]	•Monocentric RCT •PDE5i-responders •Vasculogenic ED •Double-blinded, 2:1 randomised, sham-controlled •$N = 67$ (46 LiESWT, 21 control) •1 month follow-up	•EFD: 0.09 mJ/mm^2 •Electrohydraulic •Focused SW •2 Hz •Omnispec ED1000	•2/week •3 weeks treatment—3 weeks no treatment—3 weeks treatment •12 × 1500 pulses (18,000) •500 pulses at 5 points	+6.7	77.5%	Low risk of bias
Yee et al. [25]	•Monocentric RCT •PDE5i-Responders •Vasculogenic ED •double-blinded, 1:1 randomised, sham-controlled •$N = 58$ (30 LiESWT, 28 control) •1 month follow-up	•EFD: 0.09 mJ/mm^2 •Electrohydraulic •Focused SW •2 Hz •Omnispec ED1000	•2 /week •3 weeks treatment—3 weeks no treatment—3 weeks treatment •12 × 1500 pulses (18,000) •500 pulses at 5 points	+7.6	66.6%	Low risk of bias
Olsen et al. [26]	•Monocentric RCT •PDE5i-responders •Vasculogenic ED •double-blinded, 1:1 randomised, sham-controlled •$N = 105$ (51 LiESWT, 52 control) •5 weeks follow-up	•EFD: 0.15 mJ/mm^2 •Electromagnetic •Focused SW •5 Hz •Duolith SD1	•1 /week •5 weeks treatment •5 × 3000 pulses (15,000) •500 pulses at 6 points	43,18% MCID	56.8%	Low risk of bias
Srini et al. [27]	•Monocentric RCT •PDE5i-responders •Vasculogenic ED •double-blinded, 3:1 randomised, sham-controlled •$N = 139$ (60 LiESWT, 17 control) •12 months follow-up	•EFD: 0.09 mJ/mm^2 •Electrohydraulic •Focused SW •2 Hz •Omnispec ED1000	•2 /week •3 weeks treatment – 3 weeks no treatment – 3 weeks treatment •12 × 1500 pulses (18,000) •500 pulses at 5 points	+12.5	49.47%	High risk of bias Very high dropout rate
Kitrey et al. [28]	•Monocentric RCT •PDE5i-non-responders •Vasculogenic ED •double-blinded, 2:1 randomised, sham-controlled •$N = 58$ (37 LiESWT, 18 control) •1 month follow-up	•EFD: 0.09 mJ/mm^2 •Electrohydraulic •Focused SW •2 Hz •Omnispec ED1000	•2 /week •3 weeks treatment – 3 weeks no treatment – 3 weeks treatment •12 × 1500 pulses (18,000) •500 pulses at 5 points	+5.25	54%	Low risk of bias
Motil et al. [29]	•Multycentric RCT •PDE5i-responders •Vasculogenic ED •Randomised (?), placebo-controlled	•EFD: 0.16 mJ/mm^2 •Piezoelectric •Linear SW •8 Hz •Piezowave2	•1/week •4 weeks treatment •4 × 4000 pulses (16,000) •2000 pulses at 2 points	81.3% MCID	N/A	High risk of bias

Table 2 (continued)

Study	Study design	Li-ESWT setup	Li-ESWT protocol	IIEF change	Rate EHS ≥ 3	Risk of bias
	•$N = 125$ (75 LiESWT, 50 control) •1 month follow-up					
Fojecki et al. [30]	•Monocentric RCT •Vasculogenic ED •double-blinded, 1:1 randomised, sham-controlled •$N = 126$ (58 LiESWT, 60 control) •1 month follow-up	•EFD: 0.09 mJ/mm^2 •Piezoelectric •Linear SW •5 Hz •FBL10 (Richard-Wolf GmbH)	•1/week •5 weeks treatment •5 × 600 pulses (3,000)	+2.2	3.5%	Low risk of bias
Kalyvianakis and Hatzi [31]	•Monocentric RCT •PDE5i-responders •Vasculogenic ED •Double-blinded, 2:1 randomised, sham-controlled •$N = 46$ (30 LiESWT, 16 control) •12 months follow-up	•EFD: 0.09 mJ/mm^2 •Electrohydraulic •Focused SW •2 Hz •Omnispec ED1000	•2/week •3 weeks treatment—3 weeks no treatment—3 weeks treatment •12 × 1500 pulses (18,000) •500 pulses at 5 points	+5.3 (66% MCID)	N/A	Low risk of bias
Yamacake et al. [32]	•Monocentric RCT •ED in kidney transplant recipients •double-blinded, 1:1 randomised, sham-controlled •$N = 20$ (10 LiESWT, 10 control) •3 months follow-up, 12 months only for the treatment group	•EFD: 0.09 mJ/mm^2 •Electropneumatic •Unfocused SW •Swiss Dolorclast EMS	•2/week •3 weeks treatment •6 × 2000 pulses (12,000) •2000 pulses by continuous movement of the probe	+6,3	50%	Low risk of bias
Zewin et al. [33]	•Monocentric RCT •ED after nerve sparing radical cystectomy with orthotopic neobladder •Double-blinded, 1:1:1 randomised, sham-controlled •$N = 128$ (42 LiESWT, 43 PDE5is, 43 control) •9 months follow-up	•EFD: 0.09 mJ/mm^2 •Electromagnetic •Focused SW •Dornier Aries	•2/week •3 weeks treatment—3 weeks no treatment—3 weeks treatment •12 × 1500 pulses (18,000) •500 pulses at 5 points	+17.3 vs +15.6 (Li-ESWT vs. control)	76.2% vs. 60.5%	Low risk of bias
Fojecki et al. [35]	•Monocentric RCT •Evaluation of different protocol •Vasculogenic ED •double-blinded, 1:1 randomised •$N = 126$ (10 sessions (58) vs. 5 sessions (60)) •12 months follow-up	•EFD: 0.09 mJ/mm^2 •Piezoelectric •Linear SW •5 Hz •FBL10 (Richard-Wolf GmbH)	Protocol A •1 /week •5 weeks treatment—4 weeks no treatment—5 weeks treatment •10 × 600 pulses (6000) Protocol B •1 /week •5 weeks sham-treatment—	(DIIEF-EF score > 5) 54% in group A vs. 47% in group B (ns)	Group A 34% and group B 24% (ns)	Low risk of bias

Table 2 (continued)

Study	Study design	Li-ESWT setup	Li-ESWT protocol	IIEF change	Rate EHS ≥ 3	Risk of bias
			4 weeks no treatment— 5 weeks treatment •5 × 600 pulses (3000)			
Kalyvianakis et al. [36]	•Monocentric RCT •Evaluation different protocols •Vasculogenic ED •double-blinded, 1:1 randomised •$N = 43$ (6 sessions (21) vs. 12 sessions (22)) and (12 sessions (18) vs. 18 sessions (18)) •12 months follow-up	•EFD: 0.05 mJ/mm^2 •Electromagnetic •Semi-Focused SW •8 Hz •Dornier Aries 2 • The treatment application was: 5000 / session, 1000 to the left and right penile shaft, 1000 each to the 2 crura, and 500 each to the left and right penile hilum. All with continuous movement of the probe	Protocol A •1 /week •6 weeks treatment •6 × 5000 pulses (30,000) Protocol B •2 / week •6 weeks treatment •12 × 5000 pulses (60,000) After 6 months +6 sessions on each group. Protocol A + Protocol C •2 / week •3 weeks treatment •+ 6 × 5000 pulses (30,000) •12 sessions in total (60,000 pulses) Protocol B + Protocol D •1/week •6 weeks treatment •+6 × 5000 (30,000) •18 sessions in total (90,000 pulses)	+3.1 (MCID 62%) Protocol A vs +5.1 (MCID 71%) Protocol B Protocol A + C additional + 1.8 vs. Protocol B + D additional +1.7	SEP3: 47.4% Protocol A vs 65.2% Protocol B 61.9% Protocol A + C vs. 68.4% Protocol B + D	Low risk of bias
Katz et al. [37]	•Monocentric RCT •Evaluation of different protocols •double-blinded, 1:1 randomised •$N = 80$ ((40) 5 × 720 in 1-week vs. (40) 6 × 600 in 2 weeks) •6 months follow-up	•EFD: 0.09 mJ/mm^2 •Electromagnetic •Linear SW •MoreNova	Protocol A •1/day •1 week treatment (5 days) •5 × 720 pulses (3,600) Protocol B •1 every other day (3/week) •2 weeks treatment •6 × 600 pulses (3600)	Protocol A no significant difference vs. Protocol B + 4.2	N/A	High risk of bias (Only preliminary results the RCT still recruits)

analysis. Interestingly, 3 RCTs included evaluation of penile hemodynamics using triplex ultrasonography, which allowed us to perform a meta-analysis of this outcome [31–33].

Quality evaluation of RCTs and analysis for risk of bias

All the RCTs reported that the patients were randomised into LI-ESWT or sham-control group, but only 7 of them provide adequate information regarding the randomisation process. Half of the studies did not describe how the physicians were blinded to the study participants. The remaining described in detail how the blinding process was reassured and how the sham-controlled treatment was performed in order to allow the blinding between participants and physicians. All studies (except for one) used sham therapy for the control group using shockwave probes that looked and sounded similar to the active treatment probe. Most of the studies were considered to be of low risk of bias except 2 studies. The study by Motil et al. provided inadequate information regarding the randomisation as well as the blinding process, the outcome measures were only partially described, and the controlled treatment was performed with the device switched off with typical shockwave sound recording playing through external speakers, which could not allow blinding among the physicians [29]. The study by Srini et al. provided also inadequate information regarding the randomisation and blinding process, it had a very high dropout rate which was not adequately explained in the paper, and used statistically different groups at baseline in terms of ED and comorbidities [27]. Both these studies were decided to be included in the final meta-analysis since they both represent the larger RCTs regarding LI-ESWT for ED. Furthermore, although the study of Motil et al. had its limitations, it is the only multicentric RCT until now. On the other hand, studies with very low risk of bias had also their limitations regarding the treatment protocol and/or application of LI-ESWT which could also influence their partially negative results [25, 26, 30, 32]. Finally, in the study by Yamacake et al., although the methodology is adequately described in the paper, there were also used statistically different groups at baseline in terms of the severity of ED [32]. Figure 2 shows the risk of bias in all domains of assessment, showing that more than 50% of RCTs included display low risk of bias in all examined domains.

Evaluation of the effect of LI-ESWT for ED in terms of IIEF-EF and EHS, and penile doppler duplex/ triplex ultrasound

IIEF-EF was used in all 10 RCTs as prevailing assessment tool for erectile dysfunction. Data including the mean value and standard deviation at baseline and at the end of the treatment, as well as the number of participants in treatment and control groups, were available in 8 studies. The other 2 studies reported only the minimal clinically important difference (MCID) of the IIEF-EF score. A meta-analysis was performed for: (a) the mean difference of IIEF-EF score between treatment and control groups at final follow-up visit, (b) the mean difference in pooled change in IIEF-EF score from baseline to follow-up between treatment and control groups, and (c) the number of patients reaching the MCID in IIEF-EF score at follow-up (Fig. 3a–c respectively). The IIEF-EF score at follow-up was significantly higher in the LI-ESWT group compared to sham-control group (MD: 3.71; 95% CI [0.29–7.14]; $p = 0.03$). The LI-ESWT group showed also to have a statistically significant higher IIEF-EF change from baseline in comparison to control group (MD: 3.97; 95% CI [2.09–5.84]; $p < 0.0001$). Furthermore, the percentage of patients reaching MCID in IIEF-EF in LI-ESWT group was significantly higher than in the control group (OR: 8.54; 95% CI [2.64–27.63]; $p = 0.0003$). A subgroup analysis depending on the studied population was performed. In the subgroup of patients with vasculogenic ED that where PDE5i-responders (5 studies), no significant difference between the groups regarding the mean IIEF-EF score at follow-up was observed (MD: 4.33; 95% CI [−0.90 to 9.55]; $p = 0.10$). Conversely, in the same subgroup, a significant difference in IIEF-EF change from baseline was observed (MD: 4.12; 95% CI [1.30–6.95]; $p = 0.004$), as well as a significant difference in the proportion of patients reaching MCID (OR: 7.26; 95% CI [1.44–36.54]; $p = 0.02$), both favouring the LI-ESWT group. This result could be explained by the fact that some of the studies had significant different IIEF-EF scores between the groups at baseline (mostly higher scores in the control group).

The erection hardness score (EHS) was available in 7 of the studies and we performed a meta-analysis regarding the proportion of patients reaching an EHS ≥ 3 at follow-up. The results showed that more patients in LI-ESWT group reached an EHS ≥ 3 at follow-up compared to the control group (OR 4.35; 95% CI [1.82–10.37]; $p = 0.0009$). In the subgroup of patients with vasculogenic ED that were PDE5i-responders (5 studies), LI-ESWT helped more patients reach an EHS ≥ 3 at follow-up compared to sham-control (OR 5.02; 95% CI [1.51–16.73]; $p = 0.009$) (Fig. 4a).

Three of the RCTs contained adequate data regarding penile hemodynamics at baseline and at follow-up. The meta-analysis showed that LI-ESWT significantly increases the PSV from baseline in comparison to control (MD: 4.12; 95% CI [2.30–5.94]; $p \leq 0.00001$) and reaches higher levels at follow-up (MD: 4.48; 95% CI [2.60–6.35]; $p < 0.00001$) (Fig. 4b, c).

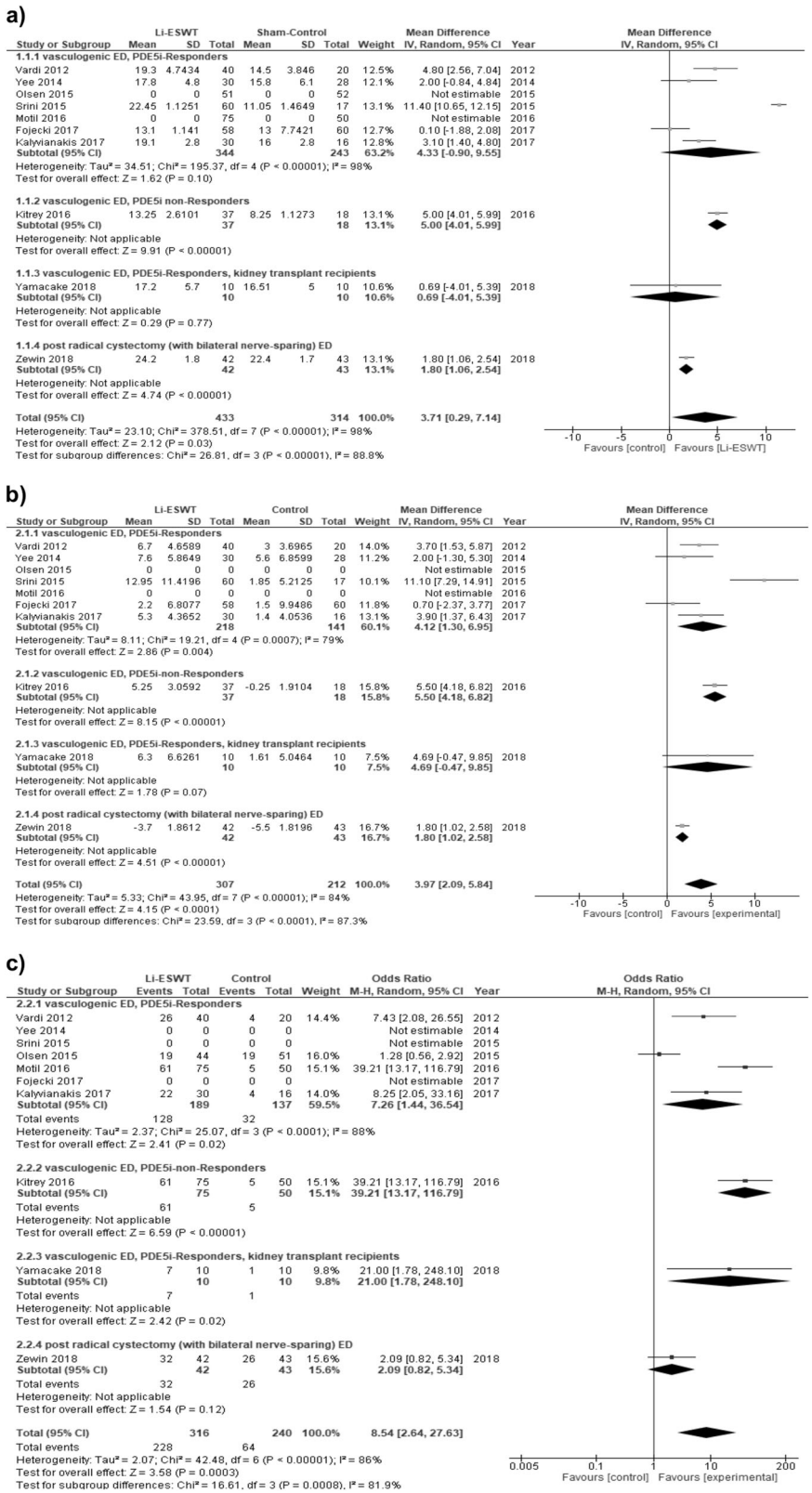

Fig. 3 **a** Forest plot of the mean difference in IIEF-EF score between men with ED undergoing LI-ESWT and sham-control therapy at follow-up. **b** Forest plot of the mean difference in the pooled change in IIEF-EF score from baseline to follow-up between men with ED undergoing LI-ESWT and sham-control therapy. **c** Forest plot of the odds ratio to reach the MCID in IIEF-EF score at follow-up between men with ED undergoing LI-ESWT and sham-control therapy. (With subgroup analysis regarding the targeted population). LI-ESWT, low intensity shockwave treatment; IIEF-EF, international index of erectile function-erectile function domain; ED, erectile dysfunction; MCID, minimal clinical important difference

The majority of the studies does not report the number or percentage of patients who had worsening or non-improving erectile function in the control and treatment groups. However, in the study of Kalyvianakis et al. the authors showed an individual plot of the maximum PSV at baseline and at three months after the treatment in both

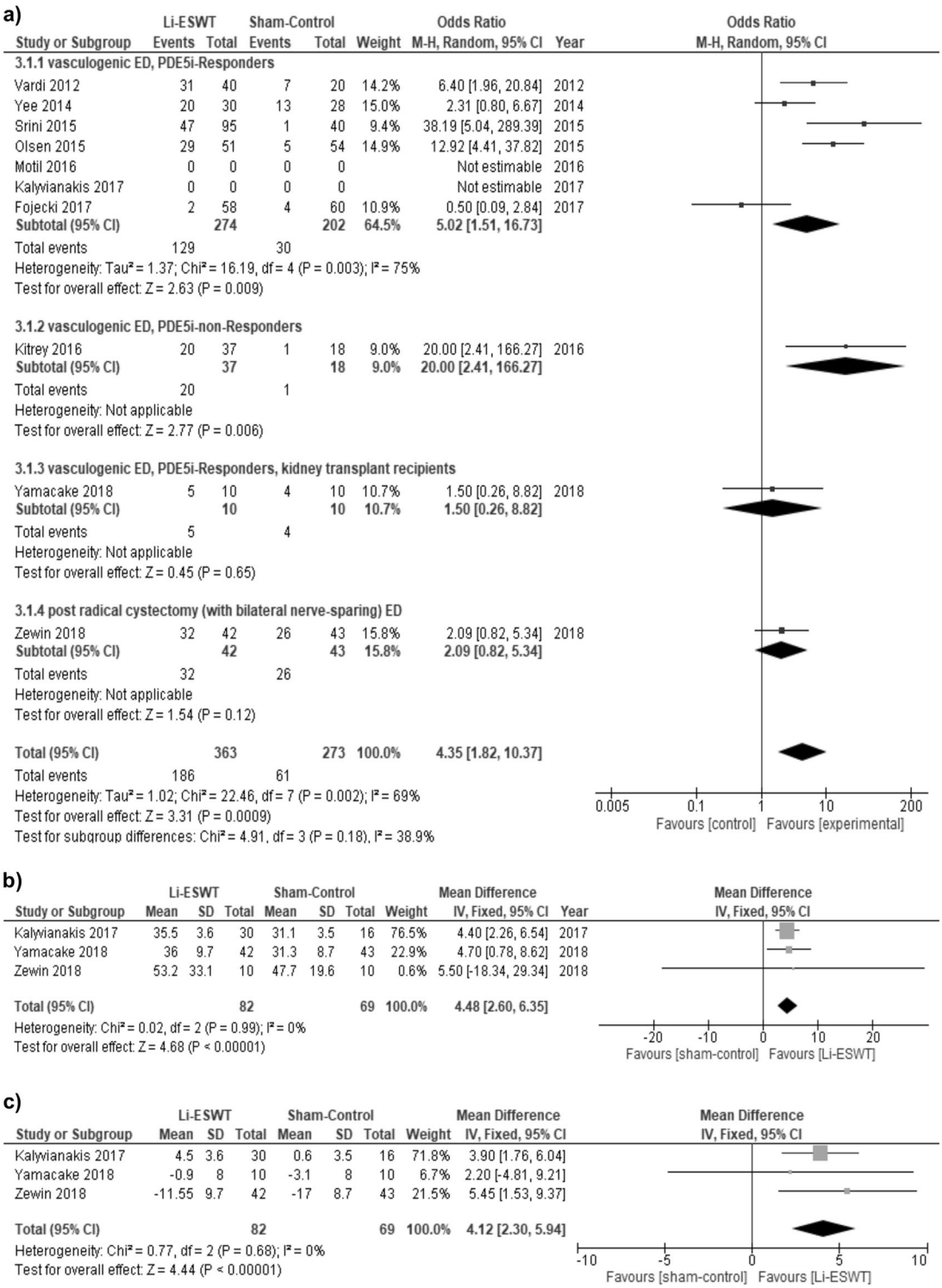

Fig. 4 **a** Forest plot of the odds ratio to reach an EHS ≥ 3 at follow-up between men with ED undergoing LI-ESWT and sham-control therapy (with subgroup analysis regarding the targeted population). **b** Forest plot of the mean difference in PSV between men with ED undergoing LI-ESWT and sham-control therapy at follow-up. **c** Forest plot of the mean difference in the pooled change in PSV from baseline to follow-up between men with ED undergoing LI-ESWT and sham-control therapy. LI-ESWT, low intensity shockwave treatment; EHS, erection hardness score; ED, erectile dysfunction; PSV, peak systolic velocity

groups. While in the sham treatment group the PSV remained unchanged, in the LI-ESWT group an increase in PSV was shown in all but one patient. PSV in this patient remained unchanged [31]. On the other hand, Olsen et al. reported that 37% of the patients in the LI-ESWT group showed no change in erectile function in comparison to 78% of the patients in the sham-treatment group [26]. Overall, in the majority of the studies no patient reported worsening in erectile function after the treatment.

Evaluation of the effect of LI-ESWT for ED regarding the treatment protocol and the duration of follow-up

A subgroup analysis regarding the treatment protocol with the mean IIEF-EF score at follow-up as end point between the groups was performed. Five RCTs had used the same shockwave generator (Omnispec ED1000) with the same protocol (electrohydraulic, focused SW; EFD: 0.09mJ/mm^2; 2 sessions per week for 3 weeks then a 3-weeks treatment-break followed by another 3 weeks of treatment; 1500 shockwave pulses per session delivered at 5 points; with a total of 18,000 SW). Regarding the other RCTs, there was only one RCT available for each treatment protocol. A meta-analysis over the 5 studies with the same protocol (see above) showed a significant difference in the final IIEF-EF scores between the groups, favouring the LI-ESWT group (MD: 5.34; 95% CI [1.36–9.32]; $p = 0.008$) (Fig. 5a).

Three RCTs directly comparing 2 different protocols of LI-ESWT were also available in the literature (Table 2). Katz et al. compared a protocol of 5 daily sessions of 720 shockwave pulses (3600 in total) versus a protocol of 6 sessions every other day of 600 shockwave pulses for 2 weeks (3600). The first protocol did not show any difference in IIEF scores at 6 months follow-up while the second protocol showed a significant increase in IIEF score of 4.2 points, indicating that the intensive daily application failed to produce equal results. The study reported only preliminary results since they are still recruiting and these results should be interpreted with caution [37]. A second study by Fojecki et al. comparing 12-month long-term results of two different protocols (5 weekly sessions of 600 shockwave pulses (3000 in total) vs. 10 weekly sessions of 600 shockwave pulses with a 4-week-break after the first 5 weeks (6000 in total)), showed that 2 cycles of linear LI-ESWT are not superior to 1 cycle at both 6-months and 12-months follow-up [35]. On the contrary, Kalyvianakis et al. showed (mainly using the SEP3 question) that patients with erectile dysfunction can benefit more from 12 sessions twice per week compared with 6 sessions once a week, indicating that the total number of sessions affects the efficacy of the treatment. They also showed that retreating the same patients after 6 months could further improve erectile function without side effects. A limitation of this study is that the above-mentioned results were not statistically significant regarding IIEF-EF score or MCID between the two groups [36].

Subgroup analysis regarding the duration of follow-up using the IIEF-EF scores at 1, 3, 6, and 12 months follow-up showed that the positive effect of LI-ESWT lasts for 12 months, although it could be weaker with time. The corresponding detailed meta-analysis is shown in Fig. 5b.

All studies reported that LI-ESWT for ED was not associated with any pain, discomfort or side-effects such as ecchymoses of haematuria. The initial study of Fojecki et al. reported some local irritation but no adverse effects of the treatment [30]. In the second study with the long-term results, they also reported no adverse effects of the treatment, but they mentioned that one patient of group A (fewer treatment sessions than group B) was diagnosed with Peyronie disease 6 months after the treatment [35].

Discussion

This systematic review and meta-analysis of 10 RCTs including a total of 872 patients with ED, showed a statistically significant improvement in IIEF-EF score (improvement from baseline as well as MCID [8]), EHS (patients with EHS ≥ 3), and penile hemodynamics (PSV) after LI-ESWT in comparison to sham-controlled treatment. These results indicate that LI-ESWT could both, subjectively (validated questionnaires) and objectively (penile hemodynamics) improve erectile function in patients with vasculogenic ED.

Noteworthy, this is not the first meta-analysis in this field. So far, five other meta-analyses have been conducted [38–42], but all of them had certain limitations (Table 3). In the meta-analysis from Lu et al. [38], a very heterogenous population (men with ED, men with Peyronie's disease (PD) ± ED [43], and men with chronic pelvic pain syndrome (CPPS) + ED) was included. Furthermore, a nonrandomized-controlled trial was also included in this meta-analysis. These two limitations result in high risk of bias, and consequently lead to maximum level of evidence 2a in this meta-analysis. The same limitations, as mentioned above, apply also to the more recent meta-analysis of Man and Li [42]. In the meta-analysis of Angulo et al., there was no quality assessment of the included studies. In their meta-analysis, the authors included only three RCTs (one of them with high risk of bias) showing a moderate improvement in IIEF score of 2.54 [39]. The meta-analysis of Zou et al. [41] showed similar limitations as the study by Angulo [39]. Additionally, they did not perform a meta-analysis of the absolute scores but only risk ratio assessment of the proportion of patient's reported to have clinically significant improvements (IIEF and EHS). Finally, the meta-analysis

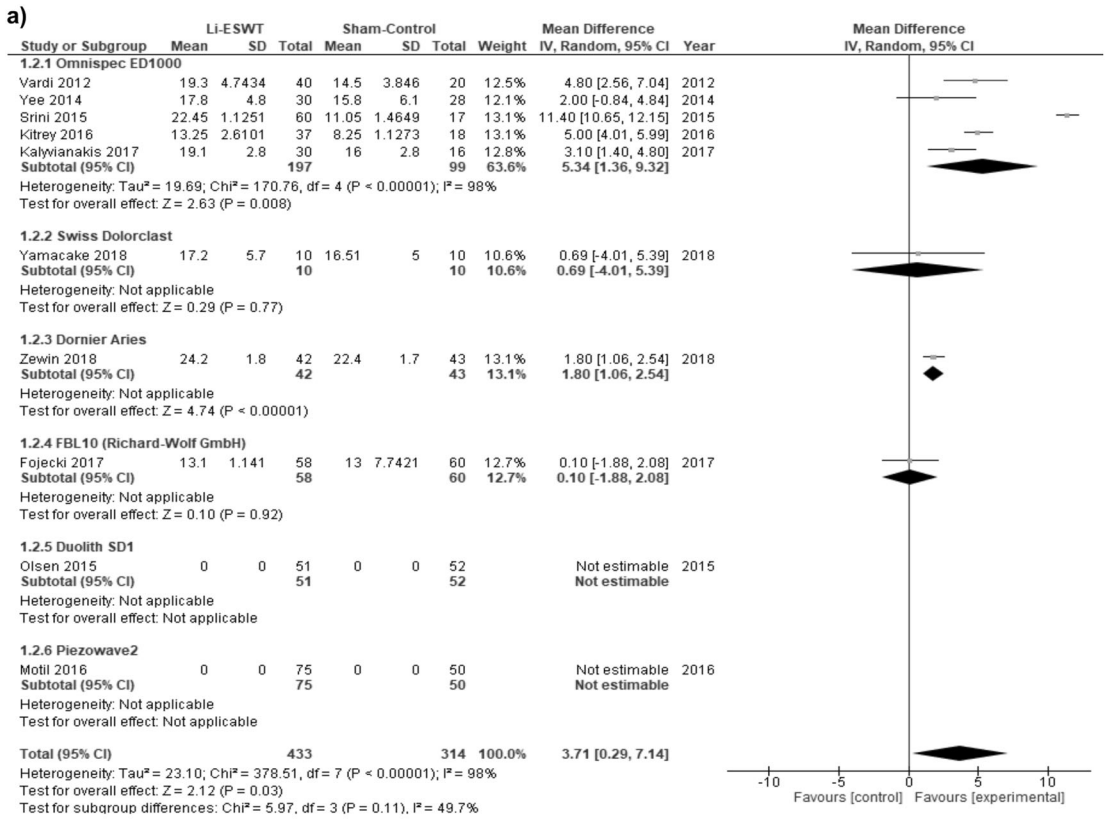

Fig. 5 **a** Forest plot of the mean difference in IIEF-EF score between men with ED undergoing LI-ESWT and sham-control therapy at follow-up with subgroup analysis regarding the treatment protocol. **b** Forest plot of the mean difference in IIEF-EF score between men with ED undergoing LI-ESWT and sham-control therapy at follow-up with subgroup analysis regarding the duration of follow-up

Table 3 Meta-analyses on Li-ESWT for ED

Study	Meta-analysis design	Outcomes	Limitations
Lu et al. [38]	•Systematic review and meta-analysis •6 RCTs, 1 case-control study (nonrandomized) •Population: ED, PD + ED, CPPS + ED •Outcomes: IIEF, EHS •$N = 522$	•IIEF: +2.00; 95% CI [0.99–3.00]; $p < 0.0001$ •EHS: RD: 0.36; 95% CI [0.28–0.43]; $p < 0.00001$ •Both compared with sham-control at final follow-up	•Inclusion of studies with high risk of bias and with ED as a secondary endpoint (primary endpoint PD or CPPS) •Inclusion of a nonrandomized trial in the meta-analysis •Inclusion of trials on Peyronie's disease with LI-ESWT directed at plaque only, and not in the corpora cavernosa
Angulo et al. [39]	•Systematic review and meta-analysis •4 RCTs •Population: ED only •Outcomes: IIEF •$N = 384$	•IIEF: +2.54; 95% CI [2.12–2.95]; $p < 0.0001$ •Compared with sham-control at final follow-up	•No assessment of bias •Only 3 RCTs in the meta-analysis, one of them with high risk of bias
Clavijo et al. [40]	•Systematic review and meta-analysis •7 RCTs (3 of them only abstracts) •Population: ED only •Outcomes: IIEF difference from baseline •$N = 602$	•IIEF: +4.17; 95% CI [−0.5–8.3]; $p < 0.0001$ •Compared difference in pooled change in IIEF-EF score from baseline to follow-up with sham-control	•The 95% CI crosses the midline of 0, implying that it could not be statistically significant •Inclusion of studies (mainly the abstracts) at high risk of by us or with inadequate assessment of bias •Use of unpublished data (it makes quality assessment virtually impossible) •Possible population overlap in the abstract of Feldman et al. with previous trials of the same group, also included in the meta-analysis
Zou et al. [41]	•Systematic review and meta-analysis •4 RCTs •Population: ED only •Outcomes: IIEF •$N = 384$	•IIEF: RR: 2.50; 95% CI [0.74–8.45]; $p = 0.14$ (ns) •EHS: RR: 8.31; 95% CI [3.88–17.78]; $p < 0.00001$ •Compared the difference in the reported effective treatment as measured with both scores with sham-control at final follow-up	•Inclusion of studies with high risk or unclear risk of bias •They did not use the raw data of IIEF score and EHS in the meta-analysis but only the reported significant effective treatment is proportion of patients •Only 3 RCTs in the meta-analysis of IIEF score, 1 of them with high risk of bias
Man and Li [42]	•Systematic review and meta-analysis •8 RCTs, 1 case–control study (nonrandomized) •Population: ED, PD + ED, CPPS + ED •Outcomes: IIEF, EHS •$N = 637$	•IIEF: +2.54; 95% CI [0.83–4.25]; $p = 0.004$ •EHS: RD: 0.38; 95% CI [0.07–0.69]; $p = 0.02$ •Both compared with sham-control at final follow-up	•Inclusion of studies with high risk of bias and with ED as a secondary endpoint (primary endpoint PD or CPPS) •Inclusion of a nonrandomized trial in the meta-analysis •Inclusion of trials on Peyronie's disease with LI-ESWT directed at plaque only, and not in the corpora cavernosa •Used in some cases meta-analysis of fixed-effects model of mean differences, although the data showed high heterogeneity

by Clavijo et al. [40], had also its limitations, despite the fact that this study reported the most adequate methodology so far. Three of the seven RCTs included in this meta-analysis were only conference abstracts, making the quality assessment of these studies virtually impossible. Furthermore, the abstract by Feldman et al. [44] could include population that overlaps with previous trials of the same study group. Finally, the 95% CI over the final measurement crosses the zero midline, indicating that it is not statistically significant. All of the above mentioned meta-analyses included a heterogenous population of ED patients (i.e., PDE5i-responders and nonresponders, etc.) with different treatment protocols. Thus, definitive conclusions and recommendations regarding the ideal population and the ideal treatment protocol cannot be made.

Our meta-analysis is the first that involved RCTs only, with adequate quality assessment, in patients with ED only. Moreover, our study included results regarding both, patient-subjective outcomes (IIEF, EHS) and objective outcomes (penile hemodynamics). Additionally, we tried to identify the ideal population and the ideal treatment protocol for LI-ESWT. The majority of the studies included patients with mild to severe ED (IIEF-EF ≤ 21). Some of them included patients with moderate to severe ED only [26–28]. The available data are not sufficient enough to draw conclusions on the efficacy of LI-ESWT depending on the baseline severity of ED. However, in subgroup analysis, we found that there is adequate amount of data to conclude (with a level of evidence 1a) that LI-ESWT can ameliorate erectile function in patients with vasculogenic ED that are PDE5i-responders with at least the minimally clinical important difference regarding IIEF-EF score (>4). Overall review of the available data suggests that PDE5i non-responders have lower response rates than those observed in the treatment-naive or PDE5I responders, which might be associated with the fact that they more often have moderate or severe ED. Kalyvianakis et al. tried to find possible prognostic factors distinguishing high-responders from non-responders to LI-ESWT. They found that high-responders were likely to be younger and more responsive to PDE5i, but the effectiveness of the treatment was independent from the baseline disease severity [36]. More studies are needed in order to find the response rate of LI-ESWT depending on the baseline severity of ED and the ideal protocol for each category (mild to severe ED).

Although there is much evidence arguing that the treatment protocol introduced by Vardi et al. works, this does not mean that it is the ideal one. Different Li-ESWT protocols, should be investigated in experimental studies as well as well-designed RCTs, in order to identify the ideal EFD, the ideal number of sessions (including interval and frequency of the treatment) and total number of shockwaves applied. We recommend that future research in this field should initially investigate new protocols, compared to the protocol proposed by Vardi et al. [1]. Future research should answer the following: (1) is the 3-week-break period essential? and (2) if increasing or decreasing the number of treatments, or the number of shockwave pulses per session, or the EFD will show better results regarding erectile function. In order to compare different protocols and devices, new comparison indexes that would include all the above-mentioned parameters should emerge, calculating the "biologically effective energy" of each protocol and device. Thus, it could be investigated if there is an upper limit of shockwaves or "energy" which can be applied, and if there is a saturation effect of repeated treatments. Since we currently believe that the effect is energy-depended, perhaps different treatment protocols should be applied depending on the severity or the type/cause of ED [45].

Currently, there are two major categories of LI-ESWT application: linear and focused shockwaves. Although focused shockwaves have shown their effectiveness regarding erectile function, the results of linear shockwave applicators are still conflicting. Larger RCTs for linear LI-ESWT are needed in order to allow for possible conclusions and recommendations. Furthermore, a direct comparison between these two modalities should also be considered in future research.

Today, there is evidence to support that LI-ESWT works for patients with vasculogenic ED that are PDE5i-responders. Although some single-arm cohort studies show that LI-ESWT could turn PDE5i-nonresponders into responders, there is only one RCT available, showing that LI-ESWT can improve erectile function in PDE5i-nonresponders [28]. Larger multicentric RCTs regarding PDE5i-nonresponders (as well as other ED populations, such as post radical prostatectomy ED) are needed. Furthermore, RCTs comparing LI-ESWT alone or in combination with PDE5i for ED are also needed [46].

Although several studies tried to explain the mechanism of action of LI-ESWT, it is not completely understood. LI-ESWT seems to improve erectile function in a variety of animal models of erectile dysfunction possibly through stimulation of mechanosensors, inducing the activation of neoangiogenesis processes, recruitment and activation of progenitor cells, improvement of microcirculation, nerve regeneration, remodelling of erectile tissue with increase in muscle/collagen ratio, and reducing inflammatory and cellular stress responses [3]. A recent study showed that LI-ESWT could additionally lower sympathetic nervous system activity [47]. Most of these studies demonstrate preliminary results, but no definitive answers regarding the actual mechanism of action of LI-ESWT.

Our study has several important limitations that need to be addressed. Most included trials had small samples, with the largest study including only 139 patients. The follow-up

was limited to approximately 1 year, which does not allow drawing any conclusions for a longer period of time. An increased heterogeneity was also observed among the studies, which can be attributed mainly to two studies (Fojecki et al. [30] and Srini et al. [27]). Possible causes for this heterogeneity could be the treatment protocol and patient selection, respectively.

In conclusion, the present meta-analysis showed that LI-ESWT significantly improves erectile function in patients with vasculogenic ED. Larger multicentric RCTs with longer than 1-year follow-up are needed, before considering this new treatment as the new standard for the treatment of ED. However, LI-ESWT could be offered to patients with vasculogenic ED (especially to PDE5i-responders) as an alternative first-line treatment, especially in younger patients searching for a non-pharmacological treatment.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Publisher's note: Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

References

1. Vardi Y, Appel B, Jacob G, Massarwi O, Gruenwald I. Can low-intensity extracorporeal shockwave therapy improve erectile function? A 6-month follow-up pilot study in patients with organic erectile dysfunction. Eur Urol. 2010;58:243–8.
2. Fode M, Lowenstein L, Reisman Y. Low-intensity extracorporeal shockwave therapy in sexual medicine: a questionnaire-based assessment of knowledge, clinical practice patterns, and attitudes in sexual medicine practitioners. Sex Med. 2017;5:e94–8.
3. Fode M, Hatzichristodoulou G, Serefoglu EC, Verze P, Albersen M. Low-intensity shockwave therapy for erectile dysfunction: is the evidence strong enough? Nat Rev Urol. 2017;14:593.
4. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Ann Intern Med. 2009;151:264–9.
5. Higgins JPT, Green S. Cochrane handbook for systematic reviews of interventions version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. http://handbook.cochrane.org.
6. Chitale S, Morsey M, Swift L, Sethia K. Limited shock wave therapy vs sham treatment in men with Peyronie's disease: results of a prospective randomized controlled double-blind trial. BJU Int. 2010;106:1352–6.
7. Hatzichristodoulou G, Meisner C, Gschwend JE, Stenzl A, Lahme S. Extracorporeal shock wave therapy in Peyronie's disease: results of a placebo-controlled, prospective, randomized, single-blind study. J Sex Med. 2013;10:2815–21.
8. Rosen RC, Allen KR, Ni X, Araujo AB. Minimal clinically important differences in the erectile function domain of the International Index of Erectile Function scale. Eur Urol. 2011;60:1010–6.
9. Souper R, Hartmann J, Alvarez M, Fuentes I, Astroza G, Marconi M. Correlation between peak systolic velocity and diameter of cavernosal arteries in flaccid versus dynamic state for the evaluation of erectile dysfunction. Int J Impot Res. 2017;29:132.
10. Higgins JP, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ. 2011;343:d5928.
11. Gruenwald I, Appel B, Vardi Y. Low-intensity extracorporeal shock wave therapy—A novel effective treatment for erectile dysfunction in severe ED patients who respond poorly to PDE5 inhibitor therapy. J Sex Med. 2012;9:259–64.
12. Bechara A, Casabé A, De Bonis W, Nazar J. Effectiveness of low-intensity extracorporeal shock wave therapy on patients with erectile dysfunction (ED) who have failed to respond to PDE5i therapy. A pilot study. Arch Esp Urol. 2015;68:152–60.
13. Chung E, Cartmill R. Evaluation of clinical efficacy, safety and patient satisfaction rate after low-intensity extracorporeal shockwave therapy for the treatment of male erectile dysfunction: an Australian first open-label single-arm prospective clinical trial. BJU Int. 2015;115:46–9.
14. Pelayo-Nieto M, Linden-Castro E, Alias-Melgar A, Grovas DE, Carreño-de la Rosa F, Bertrand-Noriega F, et al. Linear shock wave therapy in the treatment of erectile dysfunction. Actas Urol Esp. 2015;39:456–9.
15. Reisman Y, Hind A, Varaneckas A, Motil I. Initial experience with linear focused shockwave treatment for erectile dysfunction: a 6-month follow-up pilot study. Int J Impot Res. 2015;27:108.
16. Ruffo A, Capece M, Prezioso D, Romeo G, Illiano E, Romis L, et al. Safety and efficacy of low intensity shockwave (LISW) treatment in patients with erectile dysfunction. Int Braz J Urol. 2015;41:967–74.
17. Bechara A, Casabé A, De Bonis W, Ciciclia PG. Twelve-month efficacy and safety of low-intensity shockwave therapy for erectile dysfunction in patients who do not respond to phosphodiesterase type 5 inhibitors. Sex Med. 2016;4:e225–32.
18. Frey A, Sønksen J, Fode M. Low-intensity extracorporeal shockwave therapy in the treatment of postprostatectomy erectile dysfunction: a pilot study. Scand J Urol. 2016;50:123–7.
19. Hisasue SI, China T, Horiuchi A, Kimura M, Saito K, Isotani S, et al. Impact of aging and comorbidity on the efficacy of low-intensity shock wave therapy for erectile dysfunction. Int J Urol. 2016;23:80–4.
20. Ayala HA, Cuartas JP, Cleves DC. Impact on the quality of erections after completing a low-intensity extracorporeal shock wave treatment cycle on a group of 710 patients. Adv Urol. 2017:1843687. https://doi.org/10.1155/2017/1843687.
21. Tsai CC, Wang CJ, Lee YC, Kuo YT, Lin HH, Li CC, et al. Low-intensity extracorporeal shockwave therapy can improve erectile function in patients who failed to respond to phosphodiesterase type 5 inhibitors. Am J Mens Health. 2017;11:1781–90.
22. Chen X, Huang HW, Zhu XB, Chen GX, Li PC, Song F, et al. Focused low-intensity extracorporeal shock wave therapy for erectile dysfunction: preliminary observation of 32 cases. Natl J Androl. 2018;24:529–32.
23. Kitrey ND, Vardi Y, Appel B, Shechter A, Massarwi O, Abu-Ghanem Y, et al. Low intensity shock wave treatment for erectile dysfunction—how long does the effect last? J Urol. 2018;200:167–170.
24. Vardi Y, Appel B, Kilchevsky A, Gruenwald I. Does low intensity extracorporeal shock wave therapy have a physiological effect on erectile function? Short-term results of a randomized, double-blind, sham controlled study. J Urol. 2012;187:1769–75.
25. Yee CH, Chan ES, Hou SS, Ng CF. Extracorporeal shockwave therapy in the treatment of erectile dysfunction: a prospective, randomized, double-blinded, placebo controlled study. Int J Urol. 2014;21:1041–5.
26. Olsen AB, Persiani M, Boie S, Hanna M, Lund L. Can low-intensity extracorporeal shockwave therapy improve erectile

dysfunction? A prospective, randomized, double-blind, placebo-controlled study. Scand J Urol. 2015;49:329–33.
27. Srini VS, Reddy RK, Shultz T, Denes B. Low intensity extracorporeal shockwave therapy for erectile dysfunction: a study in an Indian population. Can J Urol. 2015;22:7614–22.
28. Kitrey ND, Gruenwald I, Appel B, Shechter A, Massarwa O, Vardi Y. Penile low intensity shock wave treatment is able to shift PDE5i nonresponders to responders: a double-blind, sham controlled study. J Urol. 2016;195:1550–5.
29. Motil I, Kubis I, Sramkova T. Treatment of vasculogenic erectile dysfunction with Piezowave2 device. Application of low intensity shockwaves using novel linear shockwave tissue coverage (LSTC-ED®) technique. A prospective, multicentric, placebo-controlled study. Adv Sex Med. 2016;6:15.
30. Fojecki GL, Tiessen S, Osther PJ. Effect of low-energy linear shockwave therapy on erectile dysfunction—a double-blinded, sham-controlled, randomized clinical trial. J Sex Med. 2017;14:106–12.
31. Kalyvianakis D, Hatzichristou D. Low-intensity shockwave therapy improves hemodynamic parameters in patients with vasculogenic erectile dysfunction: a triplex ultrasonography-based sham-controlled trial. J Sex Med. 2017;14:891–7.
32. Yamaçake KG, Carneiro F, Cury J, Lourenço R, Françolin PC, Piovesan AC, et al. Low-intensity shockwave therapy for erectile dysfunction in kidney transplant recipients. A prospective, randomized, double blinded, sham-controlled study with evaluation by penile Doppler ultrasonography. Int J Impot Res. 2018;14:1.
33. Zewin TS, El-Assmy A, Harraz AM, Bazeed M, Shokeir AA, Sheir K, et al. Efficacy and safety of low-intensity shock wave therapy in penile rehabilitation post nerve-sparing radical cystoprostatectomy: a randomized controlled trial. Int Urol Nephrol. 2018;19:1–8.
34. Qi T, Ye L, Wang B, Zhang B, Chen J. Comparison of the effects of extracorporeal shock wave therapy and a vacuum erectile device on penile erectile dysfunction: a randomized clinical trial. Medicine. 2017;96:e8414.
35. Fojecki GL, Tiessen S, Osther PJ. Effect of linear low-intensity extracorporeal shockwave therapy for erectile dysfunction—12-Month follow-up of a randomized, double-blinded, sham-controlled study. Sex Med. 2018;6:1–7.
36. Kalyvianakis D, Memmos E, Mykoniatis I, Kapoteli P, Memmos D, Hatzichristou D. Low-intensity shockwave therapy for erectile dysfunction: a randomized clinical trial comparing 2 treatment protocols and the impact of repeating treatment. J Sex Med. 2018;15:334–45.
37. Katz JE, Molina ML, Clavijo R, Prakash NS, Ramasamy R. A phase 2 randomized trial to evaluate different dose regimens of low-intensity extracorporeal shockwave therapy for erectile dysfunction: clinical trial update. Eur Urol Focus. 2018. https://doi.org/10.1016/j.euf.2018.07.011.
38. Lu Z, Lin G, Reed-Maldonado A, Wang C, Lee YC, Lue TF. Low-intensity extracorporeal shock wave treatment improves erectile function: a systematic review and meta-analysis. Eur Urol. 2017;71:223–33.
39. Angulo JC, Arance I, de Las Heras MM, Meilán E, Esquinas C, Andrés EM. Efficacy of low-intensity shock wave therapy for erectile dysfunction: a systematic review and meta-analysis. Actas Urol Esp. 2017;41:479–90.
40. Clavijo RI, Kohn TP, Kohn JR, Ramasamy R. Effects of low-intensity extracorporeal shockwave therapy on erectile dysfunction: a systematic review and meta-analysis. J Sex Med. 2017;14:27–35.
41. Zou ZJ, Tang LY, Liu ZH, Liang JY, Zhang RC, Wang YJ, et al. Short-term efficacy and safety of low-intensity extracorporeal shock wave therapy in erectile dysfunction: a systematic review and meta-analysis. Int Braz J Urol. 2017;43:805–21.
42. Man L, Li G. Low-intensity extracorporeal shock wave therapy for erectile dysfunction: a systematic review and meta-analysis. Urology. 2018;119:97–103.
43. Gao L, Qian S, Tang Z, Li J, Yuan J. A meta-analysis of extracorporeal shock wave therapy for Peyronie's disease. Int J Impot Res. 2016;28:161.
44. Feldman R, Denes B, Appel B, et al. The safety and efficacy of Li-ESWT in 604 patients for erectile dysfunction: summary of current and evolving evidence. J Urol. 2015;193:e905–6.
45. Hatzichristou D. Low-intensity extracorporeal shock waves therapy (LI-ESWT) for the treatment of erectile dysfunction: Where do we stand? Eur Urol. 2017;71:234–6.
46. Fode M, Albersen M, Østergren PB. Is low-intensity shockwave therapy for erectile dysfunction ready for clinical practice? Int J Impot Res. 2018. https://doi.org/10.1038/s41443-018-0081-z.
47. Sokolakis I, Dimitriadis F, Psalla D, Karaliulakis G, Kalyvianakis D, Hatzichristou D. Effects of low-intensity shock wave therapy (LiST) on the erectile tissue of naturally aged rats. Int J Impot Res. 2018. https://doi.org/10.1038/s41443-018-0064-0.