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European Association of Urology

Platinum Priority – Review – Andrology

Editorial by Dimitris ?atzichristou on pp. 234–236 of this issue

Low-intensity Extracorporeal Shock Wave Treatment Improves Erectile Function: A Systematic Review and Meta-analysis

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Article info

Article history:
Accepted May 31, 2016

Associate Editor:
Christian Gratzke

Keywords:
Erectile dysfunction (ED)
Low-intensity extracorporeal shock wave therapy (LI-ESWT)
Meta-analysis
Clinical outcome
International Index of Erectile Function (IIEF)

Abstract

Context: As a novel therapeutic method for erectile dysfunction (ED), low-intensity extracorporeal shock wave treatment (LI-ESWT) has been applied recently in the clinical setting. We feel that a summary of the current literature and a systematic review to evaluate the therapeutic efficacy of LI-ESWT for ED would be helpful for physicians who are interested in using this modality to treat patients with ED.
Objective: A systematic review of the evidence regarding LI-ESWT for patients with ED was undertaken with a meta-analysis to identify the efficacy of the treatment modality.
Evidence acquisition: A comprehensive search of the PubMed and Embase databases to November 2015 was performed. Studies reporting on patients with ED treated with LI-ESWT were included. The International Index of Erectile Function (IIEF) and the Erection Hardness Score (EHS) were the most commonly used tools to evaluate the therapeutic efficacy of LI-ESWT.
Evidence synthesis: There were 14 studies including 833 patients from 2005 to 2015. Seven studies were randomized controlled trials (RCTs); however, in these studies, the setup parameters of LI-ESWT and the protocols of treatment were variable. The meta-analysis revealed that LI-ESWT could significantly improve IIEF (mean difference: 2.00; 95% confidence interval [CI], 0.99–3.00; $p < 0.0001$) and EHS (risk difference: 0.16; 95% CI, 0.04–0.29; $p = 0.01$). Therapeutic efficacy could last at least 3 mo. The patients with mild-moderate ED had better therapeutic efficacy after treatment than patients with more severe ED or comorbidities. Energy flux density, number of shock waves per treatment, and duration of LI-ESWT treatment were closely related to clinical outcome, especially regarding IIEF improvement.
Conclusions: The number of studies of LI-ESWT for ED have increased dramatically in recent years. Most of these studies presented encouraging results, regardless of variation in LI-ESWT setup parameters or treatment protocols. These studies suggest that LI-ESWT could significantly improve the IIEF and EHS of ED patients. The publication of robust evidence from additional RCTs and longer-term follow-up would provide more confidence regarding use of LI-ESWT for ED patients.
Patient summary: We reviewed 14 studies of men who received low-intensity extracorporeal shock wave treatment (LI-ESWT) for erectile dysfunction (ED). There was evidence that these men experienced improvements in their ED following LI-ESWT.

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http://dx.doi.org/10.1016/j.eururo.2016.05.050
0302-2838/

1. Introduction

Phosphodiesterase type 5 inhibitors (PDE5-Is) are currently the most widely used treatments for male erectile dysfunction (ED); however, these medications merely treat ED symptoms. They do not correct the underlying penile pathophysiology, such as vascular lesions secondary to diabetes mellitus, structural lesions secondary to trauma, or neurologic injury secondary to prostatectomy, that is responsible for the ED [1]. A novel method to prevent the deterioration of erectile function due to these pathophysiologic processes is desperately needed. Based on studies generated from other clinical fields, low-intensity extracorporeal shock wave treatment (LI-ESWT) has been used to treat ED for almost 10 yr, and encouraging results have been reported.

Since the 1980s, when it was first introduced for renal lithotripsy, shock wave therapy has been rapidly adopted all over the world for different disease processes, producing either destructive effects or promoting regenerative effects. The shock wave is a kind of acoustic wave that carries energy and that, when propagating through a medium, can be targeted and focused noninvasively to affect a distant selected anatomic region. When LI-ESWT is applied to an organ, the shock waves interact with the targeted tissues and induce a cascade of biological reactions. This results in the release of growth factors, which in turn triggers neovascularization of the tissue with subsequent improvement of the blood supply [2]. LI-ESWT has been used to treat musculoskeletal disorders [3], myocardial infarction [4], nonhealing wounds [5], and ED [6].

Improvements in both International Index of Erectile Function (IIEF) and Erection Hardness Score (EHS) have been reported after using LI-ESWT for patients with ED. At the beginning of research into LI-ESWT, most studies were retrospective and included few patients. In the past 2 yr, well-designed prospective studies have been conducted and concluded that LI-ESWT is a feasible noninvasive method for improving male ED.

We performed a systematic review of the current body of literature investigating the application of LI-ESWT for ED. Our goal was to analyze the available data to determine the efficacy of LI-ESWT for ED.

2. Evidence acquisition

2.1. Search strategy

We performed a systematic search of PubMed and Embase databases for studies on LI-ESWT and ED. The search terms were *shock wave AND (erectile dysfunction OR IIEF OR EHS)*. We investigated the current studies of LI-ESWT for patients with ED, the therapeutic efficacy of LI-ESWT for patients with ED, and the relationship of therapeutic efficacy and different setup parameters and protocols.

2.2. Inclusion and exclusion criteria

All clinical studies that investigated the efficacy of LI-ESWT for ED were included regardless of study design. Both randomized controlled trials (RCTs) and cohort studies were included. No limitation was placed on PDE5-I consumption during the LI-ESWT treatment period or on the severity of ED. The follow-up data were abstracted from these studies. If more than one study was published by a medical center, only the last report was included in our review. All literature reviews, editorial comments, background, animal models, and case reports were excluded.

2.3. Data extraction and synthesis

The abstracts were independently reviewed by three authors (Z.L., G.L., T.F.L.) to determine eligibility for inclusion. The basic details of the study, setup parameters of the LI-ESWT machine, treatment protocols, assessment tools, and *p* values were abstracted manually from each of the studies (G.L., Z.L.), and the data were verified (T.F.L.).

2.4. Study outcomes

Fourteen studies were included in our review. Seven studies were RCTs and were included for meta-analysis. The patients were distributed in different areas of the world, and there were no overlaps of populations among the studies. Details are shown in Table 1 and Supplementary table.

2.5. Meta-analysis

The abstracted data were analyzed with RevMan 5.3 software (Cochrane Collaboration, London, UK). The risk of bias in the included studies was assessed by the Cochrane Collaboration's tool. The proper effect sizes and statistical analysis methods were chosen according to different data types and evaluation purposes. For continuous variables, weighted mean difference (MD) and a 95% confidence interval [CI] were used. For discontinuous variables, risk difference (RD) and a 95% CI were used. For the heterogeneity test between studies, the I^2 test was used. The data without significant heterogeneity ($p > 0.05$, $I^2 \leq 50\%$) were analyzed by the fixed-effects model. The data with heterogeneity that could not be explained were analyzed by the random-effects model. The data that could not be analyzed were described. The results of the meta-analysis are presented in forest plots. Publication bias is presented in funnel plots.

3. Evidence synthesis

A Preferred Reporting Items of Systematic Reviews and Meta-analyses (PRISMA) flow chart of screening and selection results is shown as Figure 1.

3.1. The current studies of low-intensity extracorporeal shock wave treatment for erectile dysfunction

A total of 14 studies involving 833 patients were included in this review. All of the studies were published between 2005 and 2015. These studies were performed by different medical centers in different countries. Most of these ED patients had an organic etiology, such as a vascular lesion [7,8], a nerve injury [9], or a lesion of the cavernous body of

Table 1 – Current studies of low-intensity extracorporeal shock wave treatment for erectile dysfunction patients

Study	Year of publication	Country	Disease	Setup of LESW		Protocol of LESW treatment			Follow-up, mo	Evaluation tools for ED	*p* value of IIEF after LI-ESWT	Study design
				Energy density, mJ/mm^2	No. of pulses each treatment	No. of treatments each week	No. of sites of treatment	Total treatment courses, wk				
Olsen et al [19]	2015	Denmark	ED	0.15	3000	1	6	5	1, 3, 6	IIEF-5, EHS	0.67	RCT
Frey A	2015	Denmark	ED after RP	NA	3000	2	3	6	1, 12	IIEF-5	0.0049	Cohort study
Bechara et al [15]	2015	Argentina	ED	0.09	5000	1	4	4	3	IIEF-6, SEP2, SEP3, GAQ	NA	Cohort study
Chung and Cartmill [7]	2015	Australia	ED	0.25	3000	2	4	6	1, 4	IIEF-5, EDITS, overall satisfaction score	<0.05	Cohort study
Pelayo-Nieto et al [8]	2015	Mexico	ED	0.09	5000	1	4	4	1, 6	IIEF, SEP, GAQ	0.013	Cohort study
Hisasue	2015	Japan	ED	0.09	1500	2	5	9	1, 3, 6	IIEF, EHS, MPCC	<0.05	Cohort study
Srini et al [16]	2015	Indian	ED	NA	NA	NA	NA	NA	1, 3, 6, 9, 12	IIEF-EF, EHS, CGIC	0.0001	RCT
Yee et al [18]	2014	Hong Kong	ED	0.09	1500	2	5	9	1	IIEF-ED, EHS,	0.001	RCT
Palmieri et al [10]	2012	Italy	ED + PD	0.25	2000	1	NA	4	3, 6	IIEF, quality of life	<0.05	Cohort study
Vardi et al [17]	2012	Israel	ED	0.09	1500	2	5	9	1	IIEF, EHS, penile blood flow	0.0322	RCT
Zimmermann et al [14]	2009	Austria	ED + chronic pelvic pain	0.25	3000	1	NA	4	1, 3	IIEF	0.034	RCT
Chitale et al [11]	2010	UK	ED + PD	NA	3000	1	NA	6	3, 6	IIEF	0.249	RCT
Poulakis et al [12]	2006	Germany	ED + PD	0.17	2000	1	NA	5	1, 3, 6	IIEF-5	0.205	RCT
Skolarikos et al [13]	2005	Greece	ED + PD	NA	3000	NA	NA	6	3, 12	IIEF-5	0.06	Cohort study

CGIC = Clinical Global Impression of Change; ED = erectile dysfunction; EDITS = Erectile Dysfunction Inventory of Treatment Satisfaction; EHS = Erectile Hardness Score; GAQ = Global Assessment Questionnaire; IIEF = International Index of Erectile Function; LI-ESWT = low-intensity extracorporeal shock wave treatment; MPCC = maximal penile circumferential change; NA = not available; PD = Peyronie's disease; RCT = randomized controlled trial; RP = radical prostatectomy; SEP = Sexual Encounter Profile.

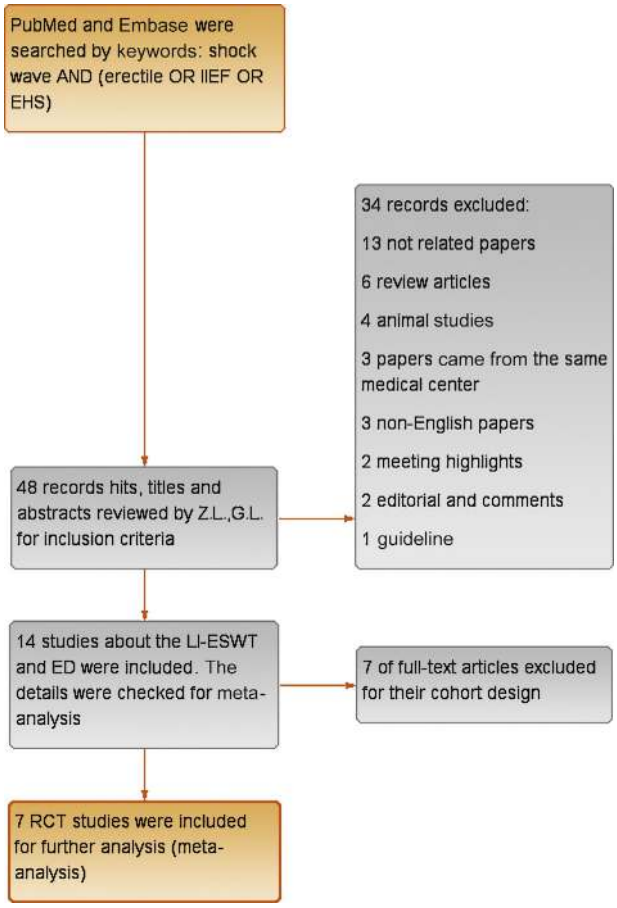

Fig. 1 – The search terms were *shock wave AND (erectile OR IIEF OR EHS)*. Forty-eight records were enrolled. After review, 14 studies about low-intensity extracorporeal shock wave treatment and erectile dysfunction were included. Seven were randomized controlled trials and were included in the meta-analysis.
ED = erectile dysfunction; EHS = Erection Hardness Score; IIEF = International Index of Erectile Function; LI-ESWT = low-intensity extracorporeal shock wave treatment; RCT = randomized controlled trial.

the penis (Peyronie's disease [PD]) [10–13]. One study focused on ED patients with chronic pelvic pain [14]. Most of the studies prohibited the usage of PDE5-Is during the treatment course. Some RCTs even set a washout period for patients who had taken PDE5-I before they started LI-ESWT. Only three studies did not limit the use of PDE5-Is during the treatment [10,11,15]. One of these studies was included for meta-analysis because of its RCT design.

Of the 14 included studies, 7 were RCTs, and the remaining 7 were cohort studies (Table 1). According to the conventions of evidence-based medicine, RCTs provide level 1 evidence, the highest level of evidence. Consequently, the seven RCTs were included for meta-analysis.

The setup parameters of LI-ESWT were different among studies. The energy flux density (EFD) varied from 0.09 to 0.25 mJ/mm^2, and the number of shock wave pulses of each treatment was between 1500 and 5000. In most of the studies, LI-ESWT directed treatment at multiple sites on the penis during each treatment. The treatment course of most studies was not longer than 6 wk, and only three studies had a longer treatment course of 9 wk.

The IIEF was the prevailing assessment tool for ED patients, and all studies in our analysis provided the IIEF before and after LI-ESWT. This made it possible to perform further meta-analysis. Another frequently used assessment tool was the EHS, which was provided by five studies. Other tools, such as the Sexual Encounter Profile, the Global Assessment Questionnaire, maximal penile circumferential change, and the Clinical Global Impression of Change, were not used consistently throughout multiple studies and so were not used for further meta-analysis.

3.2. The quality evaluation of the studies and analysis for the risk of bias

The Cochrane Collaboration's tool was used for assessing the quality of the study and the risk of bias. The RCTs reported that the patients were assigned randomly into LI-ESWT or control groups without describing the process of randomization [16,17]. Most studies did not describe how the physicians were blinded to the study participants. When the patients in the control group received the sham treatment, the LI-ESWT output energy would need to be reduced to zero, thus it would be difficult to keep the physician blinded to this change. Only the study by Yee et al [18] reported the details of how the double blinding was

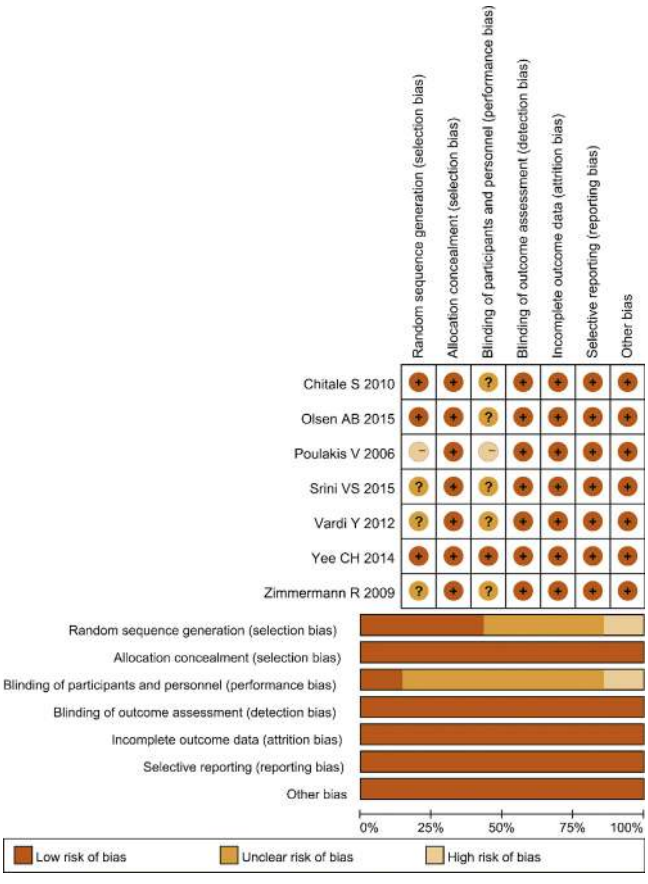

Fig. 2 – There were seven randomized controlled studies included in our meta-analysis. The quality of studies was assessed with the Cochrane Collaboration's tool. This revealed that 57.1% of the studies had an unclear risk of bias in randomization, and only 16.7% of studies had good blinding for both patients and doctors.

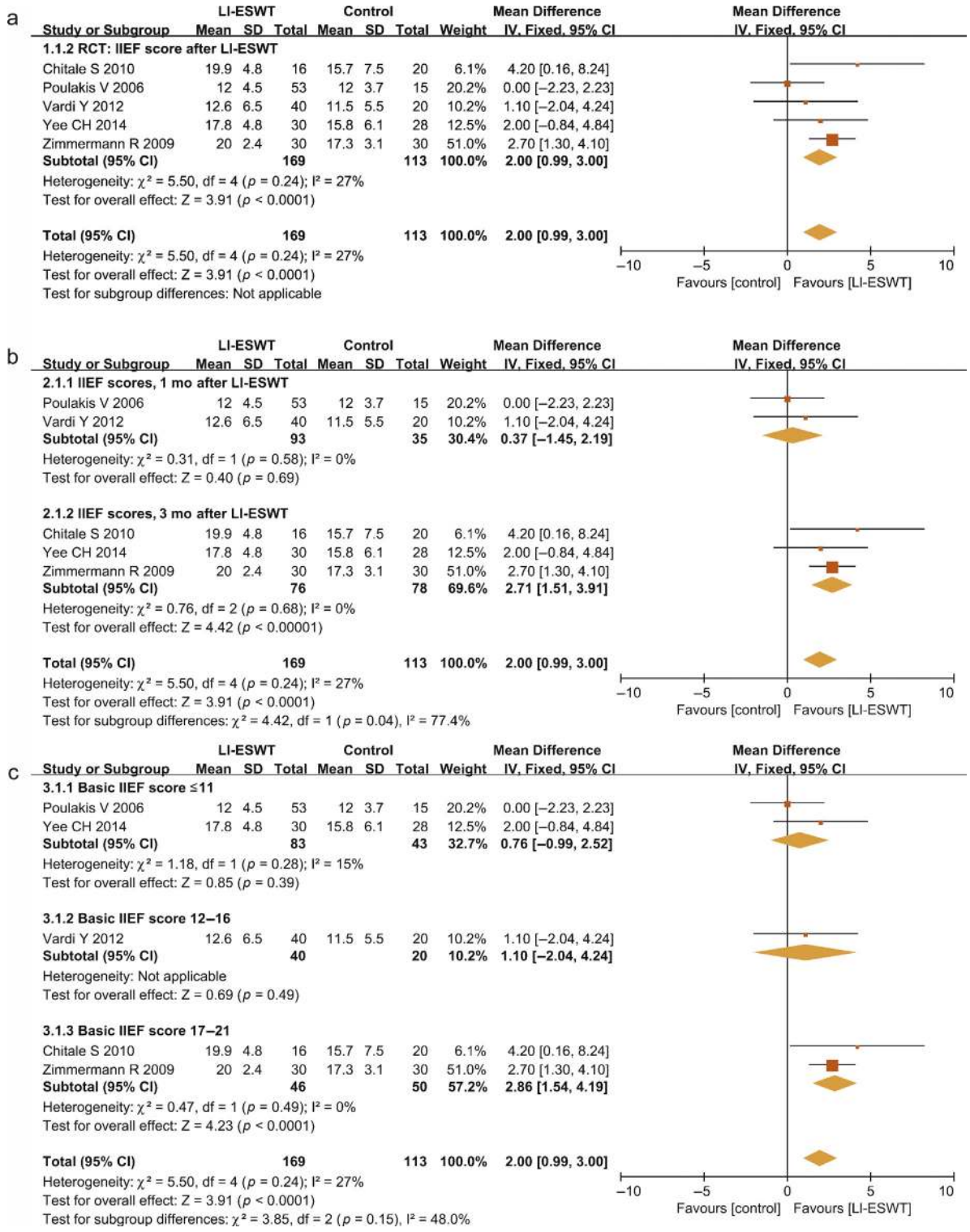

Fig. 3 – Clinical outcomes. (a) Although some studies did not prove that low-intensity extracorporeal shock wave treatment (LI-ESWT) could increase International Index of Erectile Function (IIEF), the meta-analysis results showed that LI-ESWT could improve IIEF significantly (mean difference [MD]: 2.00; 95% confidence interval [CI], 0.99–3.00; $p < 0.0001$). (b) Subgroup analysis: The studies that assessed the IIEF at 1 mo did not reveal a significant improvement (MD: 0.37; 95% CI, −1.45 to 2.19; $p = 0.69$). However, the studies assessing IIEF at 3 mo showed significant improvement (MD: 2.71; 95% CI, 1.51–3.91; $p < 0.0001$). (c) The IIEF in the group with mild erectile dysfunction (ED) increased significantly (MD: 2.86; 95% CI, 1.54–4.19; $p < 0.0001$), but in the severe and moderate groups, it did not ($p = 0.39$ and $p = 0.49$, respectively). (d) The studies of ED patients without any comorbidities revealed a significant increase of IIEF (MD: 2.36; 95% CI, 1.19–3.53; $p < 0.0001$) compared with the studies recruiting ED patients with Peyronie's disease. (e) The IIEF of patients in the group with LI-ESWT plus phosphodiesterase type 5 inhibitors improved more significantly (MD: 4.20; 95% CI, 0.16–8.24; $p = 0.04$).

CI = confidence interval; ED = erectile dysfunction; IIEF = International Index of Erectile Function; IV = inverse variance; LI-ESWT = low-intensity extracorporeal shock wave treatment; PD = Peyronie's disease; PDE5-I = phosphodiesterase type 5 inhibitor; RCT = randomized controlled trial; SD, standard deviation.

ensured. Figure 2 shows that 57.1% studies had an unclear risk of bias in randomization and that only 16.7% of studies had good blinding for both patients and doctors.

3.3. The evaluation of the therapeutic efficacy of low-intensity extracorporeal shock wave treatment for patients with erectile dysfunction

The IIEF, the prevailing assessment tool for ED patients, was available for abstraction from five RCTs. The data included mean value and standard deviation of the IIEF and the number of patients in the treatment and control groups. The studies by both Yee et al [18] and Poulakis et al [12] concluded that the IIEF did not increase significantly in the treatment group compared with the control group; the p values were 0.156 and 0.205, respectively. The remaining three RCTs reported that the IIEF increased significantly in the LI-ESWT group compared with the control group [11,14,17]; the p value was <0.05. The overall meta-analysis of the data revealed that LI-ESWT improved the IIEF significantly overall in the treatment groups (MD: 2.00; 95% CI, 0.99–3.00; $p < 0.0001$) (Fig. 3a).

Subgroup analysis was performed. Figure 3b shows that Poulakis et al [12] and Vardi et al [17] assessed IIEF at 1 mo after LI-ESWT and that the IIEF did not increase significantly (MD: 0.37; 95%CI, −1.45 to 2.19; $p = 0.69$). Three other studies, however, assessed IIEF at 3 mo after treatment and found that the IIEF increased significantly (MD: 2.71; 95% CI, 1.51–3.91; $p < 0.0001$). In Figure 3c, the studies were divided into three groups by the IIEF before LI-ESWT—≤11, 12–16, and 17–21—corresponding to severe, moderate, and mild ED, respectively. The meta-analysis showed that the IIEF of patients in the mild ED group increased significantly after LI-ESWT (MD: 2.86; 95% CI, 1.54–4.19; $p < 0.0001$). The patients in the severe and moderate groups did not show a significant increase in IIEF ($p = 0.30$ and $p = 0.49$). In Figure 3d, the studies were divided into two groups: the ED group and the ED with PD group. The subgroup analysis showed that the patients in the ED group improved significantly in IIEF (MD: 2.36; 95% CI, 1.19–3.53; $p < 0.0001$). The patients in the ED with PD group had no significant improvement in IIEF ($p = 0.33$). Finally, the studies were divided into two groups by usage of PDE5-Is. Figure 3e shows that the IIEF increased in both groups but

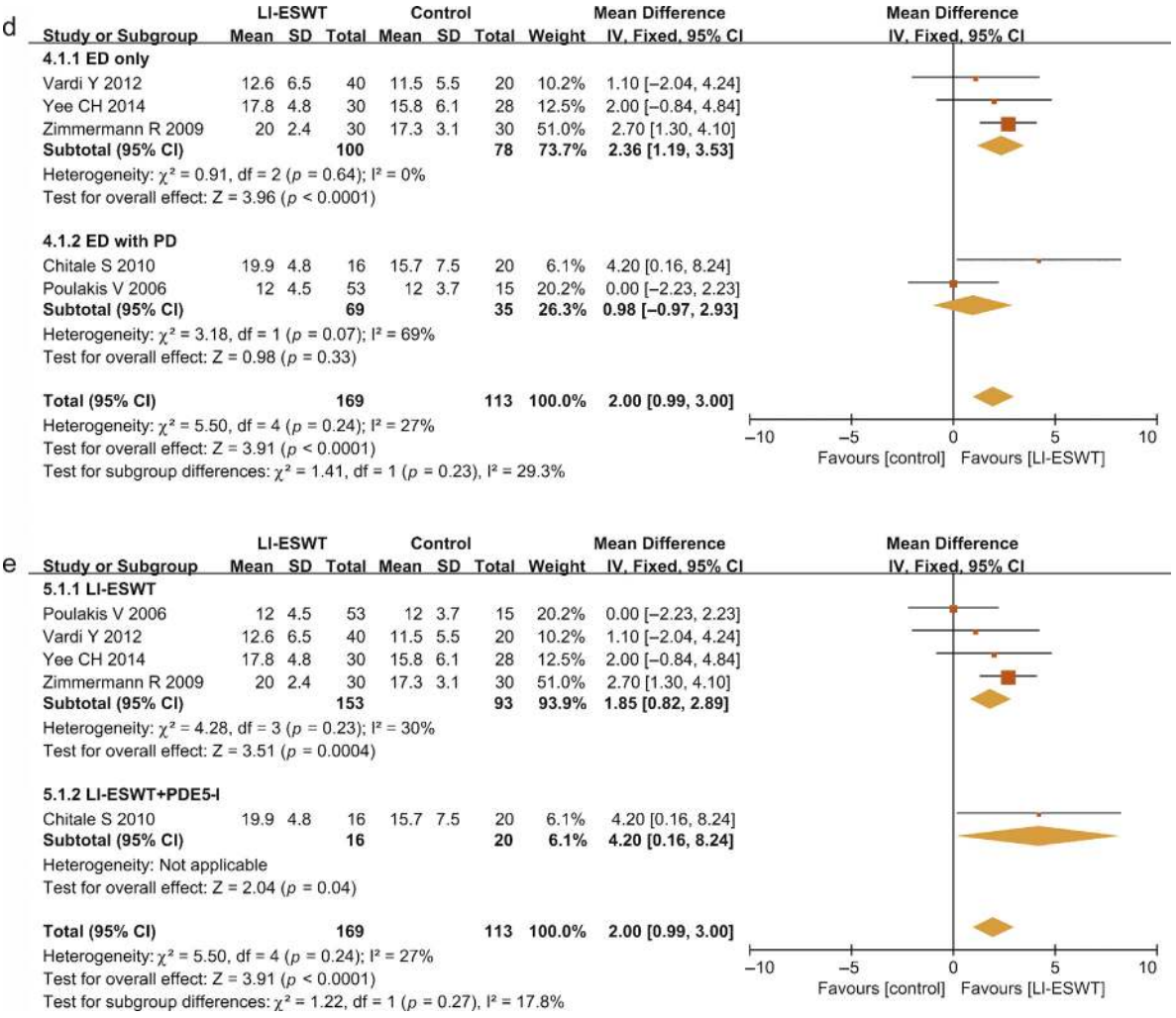

Fig. 3. (*Continued*).

increased more significantly in the group with LI-ESWT combined with PDE5-I use (MD: 4.20; 95% CI, 0.16–8.24; $p = 0.04$).

These results indicate that LI-ESWT increased the IIEF and improved the erectile function of ED patients. According to the results of the current studies, the patients treated by LI-ESWT developed a good therapeutic effect by 3 mo. The patients who had mild or moderate ED and the ED patients who had no comorbidities benefited more from LI-ESWT than the patients with severe ED or with comorbidities.

Different LI-ESWT setup parameters, such as EFD and number of pulses, and different treatment protocols, including treatment frequency and length of course, resulted in differences in reported efficacy. The studies were divided into three groups according to EFD. The results (Fig. 4a) showed that the studies using the highest EFD (>0.2 mJ/mm^2) reported significantly increased IIEFs (MD: 2.86; 95% CI, 1.54–4.19; $p < 0.0001$). The improvement of IIEF in this ED and PD subgroup was partially due to the improvement of PD. After excluding this subgroup, we found that the improvement in IIEF was better in the group with EFD 0.09 mJ/mm^2 compared with EFD 0.1–0.2 mJ/mm^2, although neither group reached statistical significance. Next, the studies were divided into two groups based on the number of shock waves delivered during each treatment. The results (Fig. 4b) showed that the studies administering more shock waves reported a significant increase in IIEF (MD: 2.86; 95% CI, 1.54–4.19' $p < 0.0001$) compared with the studies delivering fewer shock waves. To compare different durations of treatment, the studies were divided into two groups according to duration of treatment of LI-ESWT. Figure 4c shows that the studies with a treatment course of <6 wk reported a significant increase in the IIEF (MD: 2.11; 95% CI, 0.98–3.25; $p = 0.0003$).

These results suggest that different setup parameters and different treatment protocols of LI-ESWT have substantial influence on therapeutic efficacy. In summary, within the scope of this review, lower energy density, increased number of pulses, and shorter treatment courses of <6 wk resulted in better therapeutic efficacy.

The EHS data were available for abstraction from four RCTs. In the studies by Yee et al [18] and Olsen et al [19], EHS was reported at 3 mo after LI-ESWT. In the study by Yee et al, the EHS did not increase significantly. In subgroup analysis (Fig. 5), at 1 mo after LI-ESWT, the EHS increased significantly in three studies (RD: 0.47; 95% CI, 0.38–0.56; $p < 0.00001$). EHS did not improve as significantly after 3 mo as it did after 1 mo, but it still increased with statistical significance (RD: 0.16; 95% CI, 0.04–0.29; $p = 0.01$). These results indicate that LI-ESWT improves the erectile hardness of the penis for ED patients, especially at 1 mo after treatment, and that this improvement lasts for at least 3 mo.

3.4. Discussion

LI-ESWT has been used as a novel therapy for ED patients for the past 10 yr. Clinical studies and reports focused on this topic have increased dramatically in past 5 yr, especially in 2015. This implies that LI-ESWT as a therapeutic method for patients with ED has been increasingly adopted by both physicians and patients.

The IIEF is a patient-reported assessment that is purely subjective. In this review, we found that in some studies, patients in the control group also reported improvement of the IIEF [12,17,18]; however, patients in the LI-ESWT group improved more significantly than those in the control group. The range of improvement in the IIEF was from 5.3 to 7.6 points for the LI-ESWT group in our analysis [14,18]. It is undeniable that some studies revealed improvement with statistical significance; however, this improvement may have no significant clinical value. The minimal clinically important difference (MCID) of IIEF better assesses the true clinical efficacy of LI-ESWT. We recommend that, in the future, investigators use the MCID of IIEF as a more accurate and meaningful tool for evaluating the effect of LI-ESWT in the treatment of patients with ED [20].

The clinical outcome of LI-ESWT is closely related to the energy delivered to the target unit area, or EFD. The EFD used varied from 0.09 to 0.25 mJ/mm^2 among the studies included in our analysis. Based on this review, we could not determine the best EFD for ED therapy. Studies investigating the use of LI-ESWT for various regenerative purposes have used varying energy densities. An investigation by Goertz et al showed that an energy density of 0.04 mJ/mm^2 could accelerate angiogenesis for skin burns [21]. The study by Abe et al revealed that an energy density of 0.1 mJ/mm^2 for a rat model of acute myocardial infarction suppressed ventricular remodeling and had a good anti-inflammatory effect [22]. The study by Tara et al found that an energy density of 0.11–0.21 mJ/mm^2 could encourage therapeutic angiogenesis for human ischemic tissues [23]. Ioppolo et al reported that for some musculoskeletal disorders, energy density could be increased to 0.3 mJ/mm^2 [24]. In the current review, most of the included studies used an energy density of 0.09 mJ/mm^2, which Vardi et al first reported in 2010 [17]. Most subsequent studies adopted this EFD and presented encouraging results. Additional studies and a longer duration of treatment are needed to establish whether therapeutic efficacy is positively correlated with energy density.

Some studies included in our review concluded that the biological efficacy of LI-ESWT was dosage dependent [25]. It seemed that more pulses would bring better biological efficacy. With this hypothesis in mind, some studies adopted multiple treatment sites, more frequent treatments, and longer courses of treatment. Meta-analysis showed that 3000 pulses per treatment brought more improvement than 1500 or 2000 pulses per treatment; however, more frequent treatment and longer treatment course did not improve erectile function significantly. The optimal treatment protocol remains to be defined. Whether there may be a plateau stage of treatment remains uncertain and requires further investigation. In addition, based on the premise that more treatment sites would produce better results, shock waves were delivered to multiple sites, such as the dorsal surface, both sides, and both crus of the penis. It seemed that more sites treated

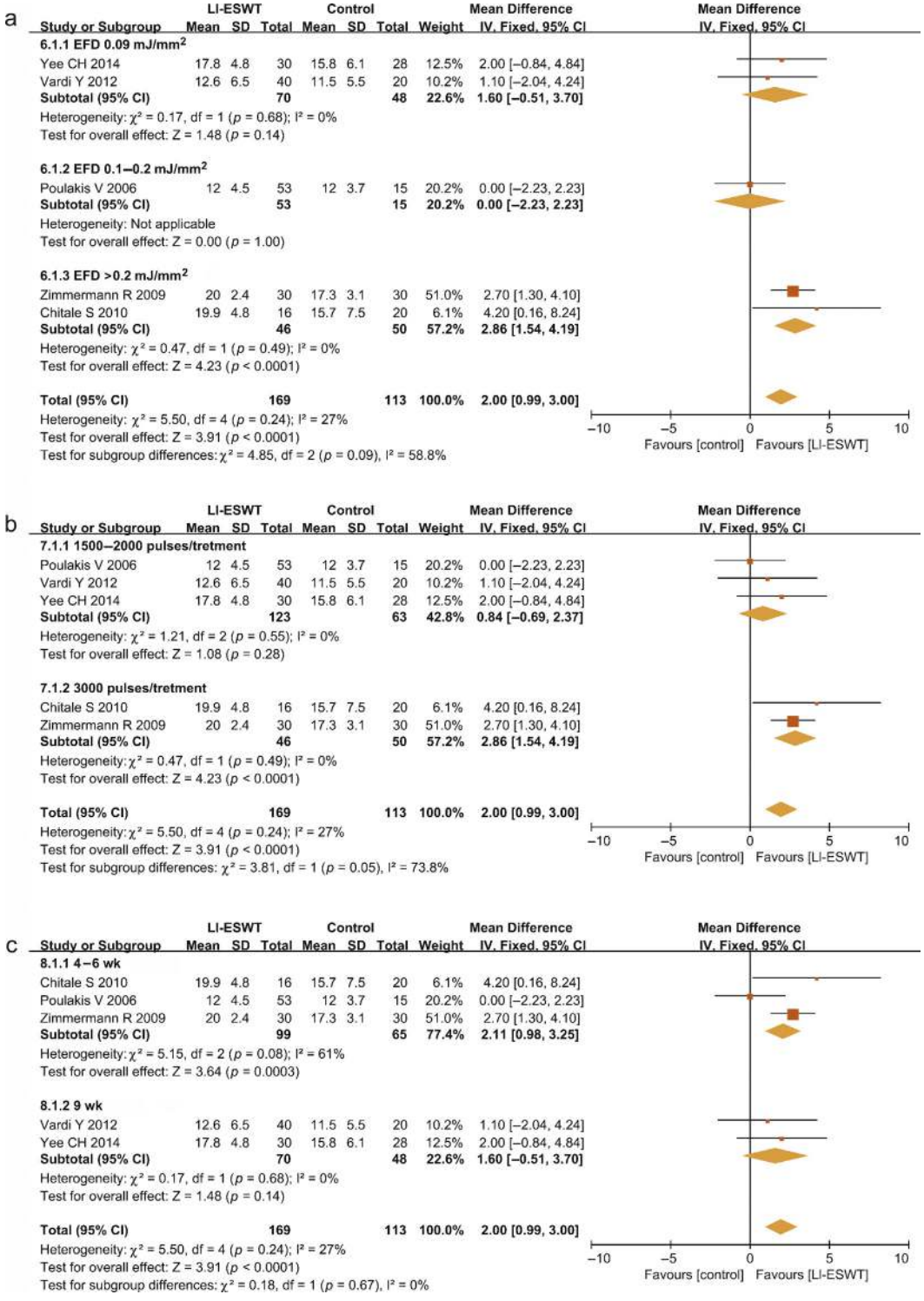

Fig. 4 – Relationship of energy dosage and treatment procedures. (a) The studies using higher energy flux density (EFD; >0.2 mJ/mm^2) resulted in significantly increased International Index of Erectile Function (IIEF; mean difference [MD]: 2.86; 95% confidence interval [CI], 1.54–4.19; $p < 0.0001$) in the erectile dysfunction (ED) and Payronie's disease groups. In ED-only groups, the improvement of IIEF was better for the group with EFD 0.09 mJ/mm^2 compared with EFD 0.1–0.2 mJ/mm^2, although it did not reach statistical significance. (b) The studies delivering more shock waves per treatment resulted in an increased IIEF (MD: 2.86; 95% CI, 1.54–4.19; $p < 0.0001$). (c) The studies with total course of treatment <6 wk revealed significant IIEF increase (MD: 2.11; 95% CI, 0.98–3.25; $p = 0.0003$) versus studies with longer courses of treatment (9 wk).
CI = confidence interval; EFD = energy flux density; IV = inverse variance; LI-ESWT = low-intensity extracorporeal shock wave treatment; SD, standard deviation.

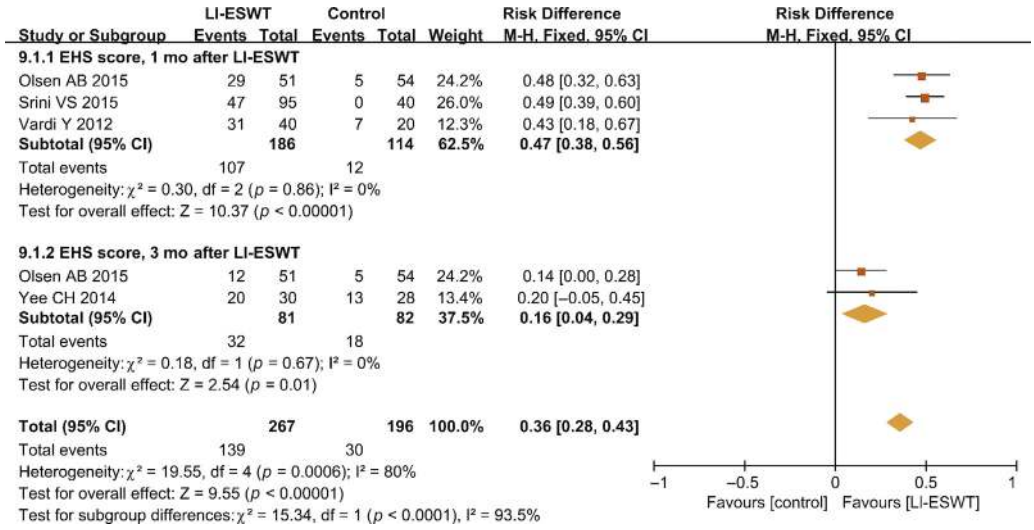

Fig. 5 – The Erection Hardness Score (EHS) increased significantly (risk difference [RD]: 0.47; 95% confidence interval [CI], 0.38–0.56; $p < 0.00001$) at 1 mo after treatment. Three months later, EHS slightly decreased but still improved with statistical significance (RD: 0.16; 95% CI, 0.04–0.29; $p = 0.01$). CI = confidence interval; EHS = Erection Hardness Score; LI-ESWT = low-intensity extracorporeal shock wave treatment; M-H = Mantel-Haenszel.

might produce better results. It is well known that shock waves can propagate 3–5 cm in human tissue [26]. It remains to be determined if it is necessary or beneficial to deliver treatment to multiple sites. This is also an area of potential future investigation.

The underlying mechanism of action of LI-ESWT is currently under investigation. According to recent reports, the effect is primarily related to the stimulation of cell proliferation, tissue regeneration, and angiogenesis [27,28]. In 2013, Qiu et al explored the therapeutic effect of LI-ESWT on a diabetic animal model and demonstrated that LI-ESWT can partially resolve diabetes mellitus–associated ED by promoting regeneration of neuronal nitric oxide synthase (nNOS)–positive nerves, endothelium, and smooth muscle in the penis [28]. Meanwhile, Liu and colleagues reported their results after treatment of a rat model of ED with LI-ESWT. The expression of some proteins, such as α-smooth muscle actin, von Willebrand factor, nNOS, and vascular endothelial growth factor, was upregulated [29]. In 2013, Siegfried and colleagues reported that LI-ESWT could stimulate the regeneration of injured nerve fibers. They believed that the potential mechanism of LI-ESWT was enhanced by neovascularization in the regenerating nerve and that VEGF and transforming growth factor β were associated with the process [30]. Very recently, it was reported that LI-ESWT improved erectile function in a rat model of pelvic neurovascular injury. Penile tissue components, especially vascular and neuronal tissue, demonstrated improved recovery after LI-ESWT therapy [27].

Several weaknesses contributed to the quality of the data provided. As shown in Table 1, five of seven studies published in 2015 were cohort studies. It is undeniable that these cohort studies have good study designs and robust data collection; each has an appropriate sample size and clear comparison. In evidence-based medicine, however, the evidence level of cohort studies is level 2, and thus they have lower power than RCTs, which provide level 1 evidence. To evaluate the efficacy of LI-ESWT more accurately, more RCTs with good study designs are needed. In addition, even in the RCTs that were included in this review, there were still some deficiencies. The details of randomization, the implementation of double blinding, the details of the treatment protocol, and the data from long-term follow-up are fundamental factors for assessing the quality of a study. As shown in Figure 2a and 2b, we found that most of the included RCTs did not describe the details of randomization or blinding, and the potential biases involved are unclear. If bias existed, it would have a great impact on the interpretation of the meta-analysis.

Most of the studies focused on the improvement of erectile function after LI-ESWT. Nevertheless, the potential impact of factors related to ED, such as age, hypertension, diabetes, hyperlipidemia, and coronary artery disease, are not discussed. Only four RCTs in our analysis provided the age data comparing the patients in the treatment and control groups [12,17–19]. No further investigation was performed to determine the influence of age on the efficacy of LI-ESWT. Three RCTs provided the profile of patient comorbidities, such as hypertension, diabetes, hyperlipidemia, and coronary artery disease, but no further information was provided about the relationship between the clinical outcome of LI-ESWT and those comorbidities [17–19]. In the future, more RCTs with stratification of age and comorbidities will help determine the influence of these factors on the efficacy of LI-ESWT for patients with ED.

With the aim of determining the efficacy of LI-ESWT alone and to avoid confusion, most of the included studies prohibited the usage of PDE5-Is during shock wave treatment. Nevertheless, because the goal of treatment is to maximize improvement of erectile function, a combination of LI-ESWT and PDE5-Is may be the best choice. Gruenwald et al found that LI-ESWT effectively converted PDE5-I nonresponders to responders [31], and our results (Fig. 3e) support the use of LI-ESWT and PDE5-Is in

combination. Additional clinical trials are needed to further investigate this clinical question.

4. Conclusions

In recent years, LI-ESWT as a therapy for ED has attracted extensive attention. Studies of this topic have increased sharply, and most of these studies reveal encouraging results, such as improved IIEF and EHS and an effect that lasts up to 3 mo. The setup parameters and the treatment protocols are important for the therapeutic effects of LI-ESWT for patients with ED. The mechanism of LI-ESWT is to improve or even reverse the pathologic damage of tissue that causes ED. Additional studies are needed to explore the influences of age and comorbidities on response to LI-ESWT and to define the effects of LI-ESWT in combination with PDE5-Is. From our review, it is clear that LI-ESWT may have the potential to be the first-choice noninvasive treatment for patients with ED.

Author contributions: Tom F. Lue had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Lue, Lin.
Acquisition of data: Lin, Lu, Lee, Wang.
Analysis and interpretation of data: Lu, Lee, Lin.
Drafting of the manuscript: Lu, Lin, Reed-Maldonado.
Critical revision of the manuscript for important intellectual content: Lin, Reed-Maldonado, Lue.
Statistical analysis: Lu, Lin.
Obtaining funding: Lue, Lin.
Administrative, technical, or material support: Wang, Lu.
Supervision: Lue.
Other (specify): None.

Financial disclosures: Tom F. Lue certifies that all conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the manuscript (eg, employment/ affiliation, grants or funding, consultancies, honoraria, stock ownership or options, expert testimony, royalties, or patents filed, received, or pending), are the following: Tom F. Lue is a consultant for Pfizer, Eli Lilly, and Boston Scientific and chief medical officer and stock holder for AWCT, Inc.

Funding/Support and role of the sponsor: This work was supported by the US Army, Navy, Air Force, Department of Veterans Affairs and Office of Health Affairs to support the AFIRM II effort under award W81XWH-13-2-0052. The US Army Medical Research Acquisition Activity (820 Chandler Street, Fort Detrick, MD 21702-5014, USA) is the awarding and administering acquisition office. Opinions, interpretations, conclusions and recommendations are those of the authors and are not necessarily endorsed by the US Department of Defense.

Acknowledgments: We thank Dr. Chi-Fai Ng for providing us with the data details of their study. Dr. Chi-Fai Ng is from Division of Urology, Department of Surgery, Prince of Wales Hospital, the Chinese University of Hong Kong, Hong Kong, China.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.eururo.2016.05.050.

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