



# Low-energy Shock Wave Therapy—A Novel Treatment Option for Erectile Dysfunction in Men With Cardiovascular Disease

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Patients with cardiovascular disease (CVD) are prone to developing erectile dysfunction (ED) owing to the common risk factors and pathogenesis underlying ED and CVD. As a result, ED affects nearly 80% of male patients with CVD. The efficacy of phosphodiesterase type 5 inhibitors, vacuum erection devices, or intracavernosal injection of vasodilating agents is well established in the treatment of ED; however, their use is limited. Low-energy shock wave therapy is a novel modality that may become a causative treatment for ED. This review aims to assess the efficacy and safety of low-energy shock wave therapy in the treatment of ED in men with CVD. *UROLOGY* 109: 19–26, 2017. © 2017 Elsevier Inc.

Erectile dysfunction (ED) is defined as an inability of the male to achieve or maintain erection of the penis sufficient to permit satisfactory sexual intercourse (the symptoms should persist for at least 3 months, unless ED is associated with injury or surgery).<sup>1</sup> ED affects mostly men older than 50 years of age, with the majority of such cases being associated with vascular disorders.<sup>2</sup> Nearly 80% of men with cardiovascular disease (CVD) cope with ED, and more than 80% of them claim good sexual function to be important or very important.<sup>3,4</sup>

As per the guidelines of the European Association of Urology from 2015, phosphodiesterase type 5 inhibitors (PDE5-I) and vacuum erection devices (VED) have an established position in the treatment of ED in men.<sup>5</sup> Generally, the use of PDE5-Is in patients with cardiac disorders is safe and effective but lacks a long-term effect and, hence, it does not allow for a return to fully spontaneous sexual activity.

Treatment with PDE5-Is is associated with a high percentage of treatment withdrawals as observed, especially among younger men.<sup>6,7</sup> Reasons for quitting the therapy include a lack of response to treatment,<sup>8,9</sup> side effects associated with blocking other phosphodiesterase isoenzymes, lower efficacy in patients with diabetes and those following neurovascular bundles sparing prostatectomy,<sup>10</sup>

and risk of symptomatic hypotension in patients with cardiac disorders taking  $\alpha$ -blockers. The use of PDE5-Is is also contraindicated in patients with abnormal blood pressure (<90/50 or >170/100 mm Hg).<sup>5</sup>

VED with a ring placed at the base of the penis provide passive blood retention within the corpora cavernosa and can be used for both rehabilitation and obtaining erection; however, for many patients with CVD, the use of VED is contraindicated (eg, anticoagulant therapy increases the risk of blood extravasation).<sup>11,12</sup>

Second-line therapy is recommended for patients not responding to first-line therapy or those who cannot use oral therapy. It is based on the delivery of vasoactive substances in the form of direct intracavernous injections or intraurethral pharmacotherapy. Systemic side effects result from the penetration of vasoactive substances into the systemic circulation and may lead to transient hypotension or tachycardia.<sup>13</sup>

In light of the presented methods for the treatment of ED, the development of new therapeutic options encompasses mainly those that would improve sexual performance in the long term, be free from adverse effects, and allow patients to conduct spontaneous sexual activity. One of the most promising techniques is the application of low-energy shock wave therapy (LESWT). Despite limited data regarding its long-term efficacy and safety, it was included in the guidelines of the European Association of Urology, however, without clear recommendations.<sup>5,14</sup> Recently, many original articles have been published with new data, which may strengthen recommendations for the use of LESWT in the treatment of erectile disorders, especially for patients with CVD.

The aim of the present paper is to assess current evidence on the efficacy and safety of LESWT and to prepare

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justification for its use in the treatment of ED in men with CVD. We hope that this review will provide information to help physicians make the decision to include LESWT as a therapy option for ED in this group of patients.

### Mechanism of Shock Wave Action

The shock wave is a mechanical wave of a very short duration (10 ms). Initially, the pressure increases from an ambient value to a maximum value of 100 MPa; next, it decreases exponentially, achieving a lower value than at the start; and, finally, it returns to the initial value. In human tissue, mechanical vibrations propagate in the form of longitudinal waves at a speed of about 1540 m/s. The devices used for therapeutic purposes employ a wave that is generated outside of the patient's body (extracorporeal) and transmitted to the target tissues.

Initially, shock wave therapy (lithotripsy) was developed to crush stones formed in the upper urinary tract or gallbladder.<sup>10,15,16</sup> First devices used for this purpose generated a wave of about 900 bars. Reducing the pressure to 100 bars created new possibilities for the treatment of musculoskeletal disorders, Peyronie disease, and vascular diseases, which are rooted in atherosclerosis.<sup>17-20</sup>

Despite obvious clinical effects, the exact mechanism of LESWT remains unknown. Reports show that LESWT activates the release of angiogenic factors, which promote the neovascularization of tissue with subsequent improvement of blood supply. Animal studies report the formation of new blood vessels in full-thickness excised lesions in the skin, upregulation of mRNA expression of potent angiogenesis ligands in the chronic ischemic myocardium, and improvement in myocardial perfusion.<sup>21,22</sup>

The *in vitro* effect of LESWT on tissue obtained from normal and ischemic hearts includes increased proliferation and differentiation of endothelial cells, an increased number of mature endothelial cells and endothelial cells involved in neo-angiogenesis, and increased numbers of primitive cardiomyocytes and smooth muscle cells.<sup>23</sup> Additionally, 2 possible mechanisms of promoting production of nitric oxide during shock wave exposure are described: enzymatic, based on increased expression of endothelial nitric oxide synthase; and nonenzymatic, requiring the presence of L-arginine and hydrogen peroxide molecules.<sup>24,25</sup>

### Studies on Patients Responding to PDE5-I Treatment

Because of therapeutic success in patients with severe angina pectoris or acute and chronic wounds, researchers started to consider the use of LESWT in ED treatment.<sup>26,27</sup>

The first attempt at using LESWT in 20 men with vasculogenic ED who responded to PDE5-Is was made by Vardi et al.<sup>28</sup> At 1 month post treatment, the mean International Index of Erectile Function ED (IIEF-ED) domain significantly increased from  $13.5 \pm 4.1$  to  $20.9 \pm 5.8$  ( $P < .001$ ). The improvements in the erectile function domain and parameters of nocturnal penile tumescence were maintained at 3 and 6 months after the treatment. Vas-

cular endothelial function was assessed using a flow-mediated dilatation technique, which measures the degree of artery dilation following its occlusion. It improved significantly in patients subjected to LESWT. Significant improvement was reported for mean basal blood flow in penile arteries ( $7.3$  vs  $17.8$  mL/min/dL;  $P < .001$ ) and post-ischemic maximal flow measured after a 5-minute occlusion ( $12.0$  vs  $28.9$  mL/min/dL;  $P < .001$ ) after the end of treatment.

The analysis performed by Hisasue et al.<sup>29</sup> included 57 patients. Significant improvement in IIEF-ED and Erection Hardness Score (EHS) was observed at 1, 3, and 6 months after the end of treatment ( $P < .001$ ). Additionally, the mean penile circumference change increased from 13.1 mm at baseline to 20.2 mm after LESWT therapy ( $P < .001$ ).

The study by Ruffo et al.<sup>30</sup> included 31 men with mild to severe ED. At 1 month post treatment, significant improvement was achieved in the mean erectile function domain ( $16.54 \pm 6.35$  vs  $21.13 \pm 6.31$ ;  $P = .0075$ ) and the percentage of positive answers to the second ( $61\%$  vs  $86\%$ ;  $P = .0292$ ) and the third ( $32\%$  vs  $58\%$ ;  $P = .0402$ ) questions of Sexual Encounter Profile questionnaire recorded in patients' log, and it was maintained until the follow-up visit at 3 months after the end of treatment. The mean value of the erectile function domain was  $21 \pm 6.38$  and was significantly greater ( $P = .0096$ ) than before LESWT application.

Pelayo-Nieto et al.<sup>31</sup> conducted their study on a group of 15 men with mild (40%) and moderate (60%) ED. Eighty percent of patients reported significant improvement in erectile function domain ( $14.23$  vs  $19.69$ ;  $P < .013$ ). Additionally, the baseline percentage of positive answers to the third question of Sexual Encounter Profile ( $P = .0013$ ) and mean EHS ( $P < .01$ ) increased significantly after LESWT.

A multicenter open-label prospective study carried out by Reisman et al.<sup>32</sup> included 58 patients both responders and nonresponders to PDE5-I. LESWT was effective in 81.03% of patients. At 6 months post treatment, a significant increase by an average of  $7.5 \pm 4.7$  in the mean erectile function domain was observed, in relation to the baseline value, which was  $14.8 \pm 4.8$ . As a result, 4 patients stopped using PDE5-I because of the restoration of spontaneous erections.

### Studies on Patients Not Responding to PDE5-I Treatment

The challenge facing research on the effectiveness of LESWT is the group of patients with ED who, owing to poor efficacy or complete lack of response to treatment, discontinued the therapy with PDE5-I. Gruenwald et al.<sup>33</sup> conducted an open-label prospective study on 29 patients with a low erection hardness (EHS  $< 2$ ) during PDE5-I therapy. There were 2 follow-up visits after the end of LESWT treatment: the first at 1 month, when patients had not yet been on PDE5-I, and the second at 2 months, when the patients were on PDE5-I. The mean domain of erectile function increased significantly at 1 month ( $8.8$  vs  $12.3$ ;  $P < .035$ )

and at 2 months post treatment (8.8 vs 18.8;  $P < .0001$ ). Vascular endothelial function assessed with flow-mediated dilatation at baseline and at the first follow-up visit showed significant improvement ( $P = .0001$ ). It is worth noting that 7 subjects from the study group had previously used injections of vasoactive substances and 2 were candidates for penile implants. At 1 month post treatment, 34.5% of patients could return to sexual activity without the necessity for pharmacotherapy.

Another study on a group of 20 men was conducted by Bechara et al,<sup>34</sup> who reported a 60% response to LESWT. There was an overall significant increase in erectile function domain from 14.9 at baseline to 18.2 at 1 month and 19.7 at 3 months after the end of LESWT treatment ( $P < .05$ ). The significant increase was also observed in responders to LESWT (14.8, 19.4, 23.8, respectively).

The long-term assessment of efficacy and safety of LESWT conducted by Bechara et al<sup>35</sup> among 40 patients with vasculogenic ED revealed that 60% of them regained erectile function. In the group of 24 responders to the treatment, the mean erectile function domain increased from 14.8 at baseline to 24.1 at 3 months post treatment. Its level remained stable and was 24.3, 23.2, and 23.9 at 6, 9, and 12 months after the end of LESWT therapy. The improvement was greater in patients with more advanced ED, with changes of 13, 10.5, 6.8, and 4.5 points for patients with severe, moderate, mild to moderate, and mild ED, respectively. The authors concluded that in the majority of responders to LESWT, the efficacy of response was maintained for 12 months.

### Randomized Double-blind Placebo-controlled Trials

The efficacy of LESWT was demonstrated in several randomized double-blind controlled trials.

Vardi et al<sup>36</sup> conducted a trial among responders to PDE5-I, randomly allocating them to the treatment group (40 patients) or the sham group (19 patients). Twenty-six (65%) men from the treated group and 4 (20%) men from the sham group achieved a 5-point or greater increase in IIEF-ED questionnaire ( $P = .0001$ ). Out of the 28 men with EHS  $\leq 2$  treated with LESWT, 19 (67.86%) reported an increase in EHS to 3 or greater values. In the treatment group, penile hemodynamics improved significantly in terms of changes in the resting and maximal post-ischemic penile blood flow ( $P = .0001$ ) and showed strong positive correlations with changes in the IIEF-ED scores ( $P = .0001$ ). Both the erectile function domain and the maximal post-ischemic blood flow improved significantly ( $P = .001$ ) in 22 (56%) patients from the treated group and in 1 (5%) patient from the sham group.

Srini et al<sup>37</sup> aimed to assess the efficacy of LESWT in a group of 135 patients; 95 received 12 sessions of LESWT and 40 received a placebo or sham therapy. The erectile function domain, EHS score, and Clinical Global Impression of Change Scale score were assessed at 1, 3, 6, 9, and 12 months post treatment. In the treated group, there was a significant increase in the mean EHS value and mean erectile function domain from the baseline visit to the fifth

follow-up visit. Out of 60 men with EHS  $\leq 2$  who were unable to achieve spontaneous erections hard enough for penetration at baseline, 47 (78%) were able to do so at 1 month post treatment and 43 (71%) at 12 months (EHS  $\geq 3$ ).

Kitrey et al<sup>38</sup> conducted a study in patients with vasculogenic ED who stopped using PDE5-Is because of a lack of efficacy (EHS  $\leq 2$  on PDE5-I). Thirty-seven patients were treated with LESWT, whereas 18 received sham treatment. In the LESWT group, 54.1% of patients achieved erections hard enough for penetration (EHS = 3), whereas in the control group, none achieved erections hard enough for penetration ( $P < .0001$ ). A significant change in the erectile function domain was achieved in 40.5% of men treated with LESWT and none in the control group ( $P = .001$ ). Patients receiving LESWT experienced a significant increase in penile flow in comparison with the control group (152 vs -8 mL/min/dL tissue\* $s$ ;  $P < .0001$ ). Sixteen patients from the control group received LESWT therapy after they completed the study. Because of this additional treatment, 9 (56.3%) of those patients achieved erections hard enough for penetration ( $P < .005$ ).

The analysis of Yee et al<sup>39</sup> included 30 patients treated with LESWT and 28 controls. The mean erectile function domain and mean EHS value was higher in the treatment group than in the control group ( $P = .156$ ,  $P = .163$ , respectively) at 4 weeks post treatment. The analysis based on the division of patients into groups according to the initial domain of erectile function revealed that in the group with severe ED (31% of the treated group and 35.7% in the control group), there was a significant difference in terms of improvement in mean erectile function domain between the LESWT group and the control group ( $10.1 \pm 4.1$  vs  $3.2 \pm 3.3$ ;  $P = .003$ ).

Olsen et al<sup>40</sup> conducted their study on patients with EHS below 2. The analysis encompassed 51 allocated to the group treated with LESWT and 54 allocated to the sham group. The comparison of the mean erectile function domain score changed at the 5-week follow-up between groups, taking into account 3 subgroups depending on the degree of improvement in questionnaire score ( $<5$ ,  $\geq 5$ , and  $\geq 10$  points), revealed no significant differences ( $P = .67$ ). Finally in the LESWT group, 29 (57%) men achieved EHS between 3 and 4, which allowed them to have sexual intercourse, 3 (6%) men achieved EHS between 1 and 2, and 19 (37%) saw no effect of the treatment of ED, whereas in the control group, these values were 5 (9%), 7 (13%), and 42 (78%), respectively. After LESWT treatment, there were significant differences between the study group and the control group in terms of the percentage of patients who achieved EHS between 3 and 4 (57% vs 9%,  $P = .0001$ ) and the percentage of patients with no effect from the treatment (37% vs 78%,  $P = .0001$ ). The authors raised the problem of understanding the questionnaires by patients despite them being instructed by a doctor earlier. Additionally, a narrower probe for LESWT treatment than in an electrohydraulic unit and the therapy was performed in 3 positions (distal, central, and proximal) on either side of the penis, but did not include the crura.

Fojecki et al<sup>41</sup> analyzed a group of 126 men with an erectile function domain score <25 points. The mean erectile function domain score at baseline was 10.9. At 4 weeks after the end of the 5-week treatment cycle, the score was 13.1, whereas at 4 weeks after the end of the next cycle, it was 11.8. In the control group, the mean erectile function domain was 11.5 at baseline and rose to 13.0 after the first treatment cycle of sham therapy. After the next 5-week cycle of LESWT therapy, the mean erectile function domain was 12.6 in the sham group. There was no significant difference in the treatment efficacy between study groups (37.9% vs 38.3%,  $P = .902$ ) in terms of change in erectile function and EHS (3.5% vs 6.7%;  $P = .369$ ). The authors concluded that using a reduced number of impulses did not affect the intensity of ED. Therefore, future studies should focus on determining the number of impulses and the shock wave penetration depth into the erectile tissue that would be most effective in the treatment of vasculogenic ED.

### LESWT Devices for the Treatment of ED

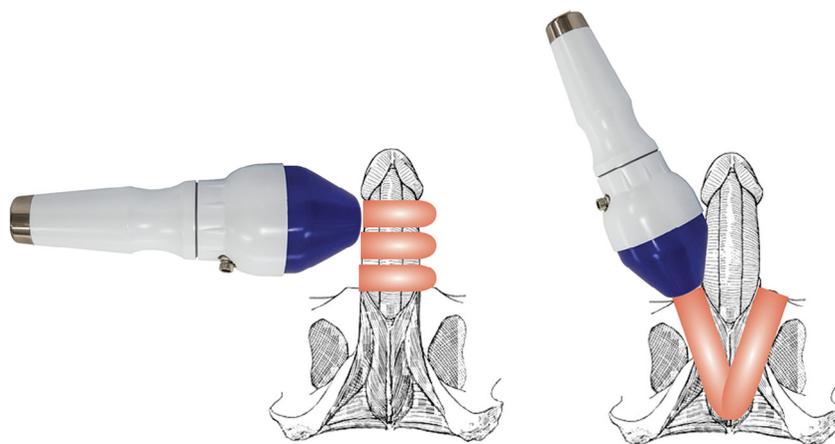
In the treatment of ED, a low-energy shock wave of not more than 0.2 mJ/mm<sup>2</sup> is used. It is characterized by a low frequency range from 1 to 8 Hz, a fast and high increase in pressure in relation to the ambient pressure (usually between 50 and 80 MPa), and a very short wave duration (<10 ns). Devices used in clinical practice employ different mechanisms of shock wave production. In the ED1000 device (Medispec Ltd, Germantown, MD), a shock wave is generated via an electrohydraulic method. The target volume has the shape of a 3-dimensional ellipsoid (diameter: 18 mm; height: 100 mm). During the application of shock waves, the penis is stretched manually (Fig. 1).<sup>28</sup> In other devices, such as Duolith SD1 (Storz, Tägerwil, Switzerland) and Dornier Aries (Dornier MedTech Systems, Munich, Germany), shock waves are applied in a similar way, but they are produced using an electromagnetic method. In such devices, the application transducer is much smaller than in devices using the electrohydraulic

method.<sup>40,42</sup> Devices such as Renova (Direx Group, Wiesbaden, Germany) and FBL10 (Richard-Wolf GmbH, Knittlingen, Germany) have an applicator of a different linear construction. In the first device, waves are generated by the use of the electromagnetic method and delivered to the penis by a transducer, which creates a 70-mm long, 10-mm wide, and 40-mm deep focal volume.<sup>32</sup> The second device is based on a piezoelectric method. It is equipped with gel pads that cover an area of 5 cm in width and allows for 10-mm penetration depth.<sup>41</sup> Table 1 presents basic technical data of the devices used for the treatment with LESWT.

### Impact of CVD and Risk Factors for CVD on the Efficacy of LESWT

The percentage of patients with CVD and risk factors for CVD differed among the studies included in this review (Table 2). The groups with the highest percentage of patients with CVD were analyzed by Gruenwald et al (55.17%) and Kitrey et al (48.65%).<sup>33,38</sup> In both studies, the mean erectile function domain increased significantly after treatment ( $P < .035$  and  $P < .001$ , respectively). The studies performed by Yee et al and Olsen et al included a low percentage of patients with CVD (1.72% and 3.92%, respectively).<sup>39,40</sup> In both analyses, at 1 month post treatment, the change in the mean erectile function domain was insignificant. Therefore, the high percentage of patients with CVD in the treated groups did not negatively affect the efficacy of LESWT in the treatment of ED.

According to some papers, LESWT is more effective in patients with a smaller number of risk factors for CVD (comorbidities), which negatively affect the functioning of vascular endothelium. Hisasue et al demonstrated that significant improvement was achieved only in patients older than 65 years of age and with 2 or fewer risk factors for CVD.<sup>29</sup> Similarly, Reisman et al claimed that the therapy with LESWT was effective in 93.7% of risk-free patients and in 76.3% of patients burdened with at least 1 CVD risk factor.<sup>32</sup> They also emphasized that LESWT was more



**Figure 1.** A diagram of application of shock waves to the corpora cavernosa of the penis (with permission from Medispec Ltd). (Color version available online.)

**Table 1.** Devices for LESWT therapy

Device	Number of Session Per Week/Per Cycle	Number of Application Loci (Corpus + Crura)	Impulses Per Session	Frequency, Energy	Weeks Per Cycle
ED 1000	2/12	5 (3 + 2)	1500	2 Hz	9
Medispec Ltd, Germantown, MD				0.09 mJ/mm <sup>2</sup>	
Renova	1/4	4 (2 + 2)	3600	5 Hz	4
Direx Group, Wiesbaden, Germany				0.09 mJ/mm <sup>2</sup>	
Duolith SD1	1/5	6 (6 + 0)	3000	5 Hz	5
Storz, Tägerwilten, Switzerland				0.15 mJ/mm <sup>2</sup>	
Dornier Aries	1/6	5 (Glans penis, corpus cavernosum, corpus spongiosum, bulbospongiosus muscle, ischiocavernosus muscle)	5000	Frequency n/a	6
Dornier MedTech Systems, Munich, Germany				0.051-0.062 mJ/mm <sup>2</sup>	
FBL10	1/10	3 (1 + 2)	6000	5 Hz	14
Richard-Wolf GmbH, Knittlingen, Germany				0.09 mJ/mm <sup>2</sup>	

LESWT, low-energy shock wave therapy.

effective in patients without diabetes than in patients with diabetes (88.24% vs 70.83%). There was no significant difference in age and duration of ED between diabetic and nondiabetic patients, which suggests a negative impact of diabetes on the efficacy of LESWT.

Pelayo-Nieto et al<sup>31</sup> conducted an analysis of the impact of concomitant smoking, obesity and overweight, and diabetes on the efficacy of LESWT. Smoking and increased body weight significantly reduced treatment efficacy, but diabetes did not (62.5% vs 100%,  $P = .1$ ). Bechara et al<sup>37</sup> reported that the presence of comorbidities such as CVD (41.7% vs 43.8%;  $P = .9999$ ), hypertension (58.3% vs 68.8%;  $P = .7397$ ), dyslipidemia (45.8% vs 56.3%;  $P = .7475$ ), and diabetes (12.5% vs 43.8%;  $P = .0588$ ) had no significant impact on the treatment results. The results of a similar overtone are presented by Bechara et al in their paper from 2015.<sup>34</sup>

In the literature, there is no conclusive data on the impact of CVD and CVD risk factors on the efficacy of LESWT in the treatment of ED. However, the safety of this therapy and the virtual lack of contraindications to its use make LESWT an interesting therapeutic option for this group of patients, despite the possible negative influence of cardiac risk factors on the efficacy of LESWT.

### Perspectives

The efficacy of LESWT in the treatment of ED is admittedly lower than those reported in the studies on the use of PDE5-I,<sup>43,44</sup> but its impact on the vascular endothelium, that is, on the dysfunction in the *primum movens* of vasculogenic ED, can be considered a causative treatment. The improvement of erection also has a specific rehabilitative effect because restoring the flow through the corpora cavernosa prevents the progression of degenerative changes.<sup>28,29</sup> Improvement in spontaneous nocturnal penile tumescence is particularly important because of its role in the prevention of morphological changes in the corpora cavernosa of the penis and the prevention of ED.<sup>45</sup> Apart from the studies analyzed in this review, the first meta-analysis has been published,<sup>46</sup> which along with vasculogenic ED (8 studies) also presented ED occurring in patients who underwent prostatectomy (1 study), patients with chronic pelvic pain (1 study), and patients with Peyronie disease (4 studies). The authors concluded that LESWT may have the potential to be the first-choice noninvasive treatment option for patients with ED.

Treatment safety is an important issue in patients with CVD. To date, no serious side effects have been reported in long-term follow-up in relation to the treatment with shock waves of either low or high intensity.<sup>47,48</sup> Animal studies evaluating functional and structural changes in the erectile tissue after application of a shock wave showed intensification of apoptosis.<sup>49</sup> To solve this problem, further studies on changes in the erectile tissue caused by LESWT are required. One of such studies is the trial NCT02620982, G140216, which evaluates possible fibrosis due to LESWT treatment.<sup>42</sup> Expected completion of this project was scheduled for September 2016.

**Table 2.** Characteristic of the studies on the use of LESWT in patients with erectile dysfunction

Study	Study Type	Patients in Total (Sham) Group* Device	Follow-up After the End of LESWT	Evaluation Tools for ED	P Value for IIEF†	Patients With Comorbidities From the Group Treated With LESWT					
						CVD n (%)	DIA n (%)	SMO n (%)	OB n (%)	HYP n (%)	HL n (%)
Vardi et al 2010 <sup>28</sup>	Cohort study	20 ED1000	1, 3, 6 mo	IIEF, EDITS, SEAR, QEQ, RS, NPT, FMD	$P < .001$	5 (25)	5 (25)			15 (75) M	
Hisasue et al 2016 <sup>29</sup>	Cohort study	56 ED1000	1, 3, 6 mo	IIEF, EHS, MPCC	$P < .001$	5 (9)	10 (18)	33 (59)		21 (38)	13 (23)
Vardi et al 2012 <sup>36</sup>	RCT	40 (20) ED1000	1, 3 mo	IIEF, EHS, FMD	$P = .0322†$	n/a (20)	30%	75% B			
Srini et al 2015 <sup>37</sup>	RCT	95 (40) ED1000	1, 3, 6, 9, 12 mo	IIEF, EHS, CGIC, NPT, penile Doppler	$P < .0001$	3 (3.16)				21 (22)	19 (20)
Gruenwald et al 2012 <sup>33</sup>	Cohort study	29 ED1000	1, 2 mo	IIEF, QEQ, EHS, FMD	$P = .035$	16 (55)	21 (72)	12 (41)	8 (28)	24 (83)	27 (93)
Kitrey et al 2016 <sup>38</sup>	RCT	37 (18) ED1000	1 mo	IIEF, EHS, FMD, CGIC	$P < .001$	18 (49)	21 (57)	31 (83.78) B			
Yee et al 2014 <sup>39</sup>	RCT	30 (28) ED1000	1 mo	IIEF, EHS	$P = .67$	1 (2)	19 (33)	13 (22)		37 (64)	31 (53)
Ruffo et al 2015 <sup>30</sup>	Cohort study	31 Renova	1, 3 mo	IIEF, SEP-Q2, SEP-Q3, GAQ-Q1, GAQ-Q2	$P = .0075$	7 (23)	12 (39)			18 (58)	13 (42)
Bechara et al 2015 <sup>34</sup>	Cohort study	20 Renova	1, 3 mo	IIEF-6, GAQ, SEP-Q2, SEP-Q3	$P < .05$	5 (25)	11 (55)			11 (55)	5 (25)
Pelayo-Nieto et al 2015 <sup>31</sup>	Cohort study	15 Renova	1, 6 mo	IIEF, EHS, SEP-Q2, SEP-Q3, GAQ-Q1, GAQ-Q2	$P < .013$		8 (53)	15 (100)	4 (27)		
Reisman et al 2015 <sup>32</sup>	Cohort study	58 Renova	1, 3, 6 mo	IIEF, SEP-Q2, SEP-Q3, GAQ-Q1, GAQ-Q2	$P < .001§$	25 (43)	24 (41)	36 (62)		23 (40)	27 (47)
Bechara et al 2016 <sup>35</sup>	Cohort study	40 Renova	1, 3, 6, 9, 12 mo	IIEF, EHS, SEP-Q2, SEP-Q3, GAQ-Q1, GAQ-Q2	$P < .0001#$	17 (43)	10 (25)			25 (63)	20 (50)
Olsen et al 2015 <sup>40</sup>	RCT	49 (51) Duolith SD1	5, 12, 24 wk	IIEF, EHS	$P = .067$	2 (4)	9 (18)	5 (10)		17 (33)	
Fojecki et al 2017 <sup>41</sup>	RCT	126 (63) FBL10	9, 19 wk	IIEF, EHS, SQoL-M, EDITS	$P = .902†$	8 (13)	6 (10)	7 (11)		28 (44)	44 (70)

B, (SMO+OB+HYP+HL); CVD, patients with cardiovascular disease; DIA, patients with diabetes; ED, erectile dysfunction; HL, patients with hyperlipidemia; HYP, patients with arterial hypertension; M, (HYP+HL); OB, obese patients, SMO, smokers.

\* Patients who completed the study.

† P values represent the comparison between baseline and follow-up values in the treated groups.

‡ Significance of the test for the difference of mean success rates.

§ Result after 6-month follow-up.

# Result after 12-month follow-up (only for patients who responded to LESWT).

No adverse events were observed in patients with CVD on acetylsalicylic acid, indicating that LESWT is safe in patients undergoing antiplatelet therapy.<sup>41</sup>

An important feature of LESWT is its high tolerance. Patients occasionally experience transient stinging at the sites of LESWT application. These symptoms are well tolerated and resolve without treatment.

There is cause for moderate optimism about the first studies, in which the therapeutic effect has been shown to have been maintained for 12 months. Srini et al reported that out of 60 men who were unable to achieve spontaneous erections hard enough for penetration at baseline, 43 (71%) were still able to do so at 12 months after the end of treatment (EHS  $\geq$  3). Improvement in the erectile function domain was smaller than at 1 month post treatment, but similar to those presented before the second 3-week cycle of LESWT treatment.<sup>37</sup> In the Bechara et al analysis conducted on nonresponders to PDE5-I therapy, the positive effect of shock waves was maintained for 12 months in 91.7% of those who responded to LESWT treatment.<sup>35</sup> There is also a preliminary report conducted by Vardi et al, who observed a reduction in the positive effect of treatment in 50% of patients after 2-year observation. The loss of positive effects was greater in patients with diabetes and severe ED.<sup>50</sup>

Being aware of the progressive nature of atherosclerosis, it would be worth taking into account management strategies aimed at reducing the impact of modifiable risk factors that negatively affect patients subjected to LESWT in future studies on the efficacy of LESWT. The presence of modifiable risk factors may affect the dynamics of reducing the beneficial effect of LESWT over time through unfavorable influence on the vascular endothelium. What is more, it is proven that the awareness of the negative impact of modifiable risk factors on ED is still very low among patients with CVD.<sup>3</sup>

Despite the simplicity and noninvasiveness of the LESWT procedure, the efficacy of this method depends on the proper qualification of patients for treatment. Clinical conditions that were considered as exclusion criteria in the above-cited papers were the following: hormonal disorders including the use of anti-androgens, selected neurological or mental disorders, radical prostatectomy, spinal cord injury, anatomic abnormalities of the penis, clinically significant chronic hematological disease, and radiotherapy in the pelvic region. Thus, proper application of LESWT requires adequate training and gaining expert knowledge about ED. This part of the use of LESWT should not be neglected in any way.

## CONCLUSION

LESWT seems to be a promising method for patients with CVD and ED. Its advantage is its causative effect, proven efficacy in patients with risk factors for CVD and ED, and virtual lack of side effects. Such characteristics allow practitioners to use this therapy in a broad group of pa-

tients with CVD, with a particular focus on patients with contraindications to the use of other treatment methods.

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