VILNIUS UNIVERSITY

Greta
BURNEIKAITĖ

EFFICACY OF EXTRACORPOREAL SHOCKWAVE MYOCARDIAL REVASCULARIZATION THERAPY IN PATIENTS WITH STABLE ANGINA PECTORIS: THE RANDOMIZED, TRIPLE-BLIND, SHAM PROCEDURE CONTROLLED STUDY

DOCTORAL DISSERTATION

Biomedical science, Medicine (06 B)

Vilnius, 2017

The doctoral dissertation was prepared during the period of 2012–2016 at the Clinic of Heart and Vascular Diseases of Vilnius University, Lithuania.

Scientific supervisor – Prof., Dr. Jelena Čelutkienė (Vilnius University, Biomedical sciences, Medicine – 06 B).

Scientific consultant – Prof., Dr. Habil. Aleksandras Laucevičius (Vilnius University, Biomedical sciences, Medicine – 06 B).

ACKNOWLEDGEMENT

I have been immensely fortunate to conduct research work under the guidance of prof. Aleksandras Laucevičius who is highly interested in the science novelties and its practical implementation. This work would not have been completed without close mentorship, support and confidence of Prof. Aleksandras Laucevičius.

I would like to thank to Prof. Jelena Čelutkienė, my main supervisor, for inspiring me with her enthusiasm for scientific discovery in cardiology research. The route we travelled together was not the easiest, but this way I saw and learned a lot. Thank you for your support and hard work in each step of study conduction, rapid and stringent feedback regardless of daytime or weekday, and for all the time spent on raising me in science.

I would like to thank to my thesis reviewers: Prof. Jolanta Dadonienė, Prof. Aleksandras Kibarskis, and Dr. Jolita Badarienė, for their insightful and very useful comments and encouragement.

I would like to thank to all research partners and co-authors, especially for Prof. Evgeny Shkolnik and Prof. Amir Lerman for expert advices, friendly and supportive cooperation.

Many thanks to other trial investigators: Prof. Nomeda Valevičienė, Dr. Donatas Vajauskas, Assoc. prof. Sigita Glaveckaitė, Darius Palionis, Eglė Čiburienė, Renata Komiagienė, Kamilė Čerlinskaitė for stress tests assessments, to Dr. Irena Butkuvienė for help in patient recruitment, Roma Puronaitė and Audrius Indriulionis for help in statistical analysis, and to co-investigators in Moscow site.

I wish to express my sincere gratitude to all colleagues at the Departments of Centre of Cardiology and Angiology, Centre of Radiology and nuclear medicine at Vilnius University hospital Santaros klinikos who have helped and supported me during the work on this thesis, and especially my senior consultant Assoc. prof. Birutė Petrauskienė, for positive support.

A distinct gratitude goes to Medispec and Spectramed for providing applicators for this study, to Lithuanian Hypertension society for helping and providing the funding for the work.

I give very special thanks to all patients who took part in the study.

Lastly, I would like to thank my family for all their love and encouragement, to all of my friends who supported me in writing, and stimulated me to strive towards my goal.

TABLE OF CONTENTS

ABBREVATIONS

ACE – angiotensin-converting enzyme
ARB – angiotensin receptor blocker
BMS – bare metal stent
BP – blood pressure
CABG – coronary artery bypass grafting
CAD – coronary artery disease
CCS – Canadian Cardiovascular Society
CI – confidence interval
CRP – C-reactive protein
CSWT – cardiac shockwave therapy
CV – cardiovascular
DES – drug-eluting stent
DSE – dobutamine stress echocardiography
ECG – electrocardiogram
EECP – Enhanced external counterpulsation
EF – ejection fraction
EPC – endothelial progenitor cells
eNOS – endothelial nitric oxide synthase
ESC – European Society of Cardiology
FFR – fractional flow reserve
FGF – fibroblast growth factor
HR – heart rate
IQR – interquartile range
LDL – low density lipoprotein
LV – left ventricle
MACE – major adverse cardiac events
MI – myocardial infarction
MRI – magnetic resonance imaging
NO – nitric oxide
OMT – optimal medical treatment
PCI – percutaneous coronary intervention
PCNA – proliferating cell antinuclear antigen

PDGF – platelet-derived growth factor
PlGF – placental growth factor
RA – refractory angina
RCT - randomized clinical trials
ROS – reactive oxygen species (NO)
SAQ – Seattle angina questionnaire
SCAD – Stable coronary artery disease
SCS – Spinal cord stimulation
SD – standard deviation
SDS – summed difference score
SMD – standardized mean difference
SPECT – single photon emission computed tomography
SRS – summed rest score
SSS – summed stress scores
STEMI – ST-segment elevation myocardial infarction
SW – shock waves
VEGF – vascular endothelial growth factor
WMS – wall motion score
WMSI – wall motion score index
VUH SK – Vilnius University Hospital Santaros klinikos

1. INTRODUCTION

1.1 Background

During the last two decades a reduction of about 20% of the deaths due to cardiovascular diseases has been recorded in the United States [1] and many European countries [2]. Major advances in medical therapy as well as improved revascularization techniques with coronary artery bypass surgery or percutaneous intervention have markedly improved life expectancy and quality of life in patients with coronary artery disease (CAD). Despite the progress in the fields of interventional cardiology, cardiothoracic surgery and optimal medical treatment (OMT), up to 14% of patients still face considerable CAD burden with myocardial ischemia and intractable angina, which is not amenable to further traditional revascularization options [3-4]. Many of these patients have diffuse and distal atherosclerosis, which makes percutaneous coronary intervention (PCI) difficult and bypass surgery unlikely to help, as the recipient vessel is of small calibre and poor quality. These patients often have had one or more prior percutaneous interventions or/and prior bypass operation, after which vein grafts have degenerated but the arterial graft remains open. A second bypass procedure has a higher procedural risk than the first one, especially with older age and concomitant disease such as renal dysfunction and diabetes. There is also a risk of damage to the functioning arterial graft. In a Task force report from the European Society of Cardiology (ESC) [5] *refractory angina* (RA) is defined as a chronic condition characterized by the presence of angina pectoris (duration of more than 3 months), caused by coronary insufficiency in the presence of CAD in patients on optimal medical therapy, for whom revascularization is not feasible. Treatment of these patients is a major challenge to cardiologists because corrective options are limited.

Thus, it is crucial to develop alternative therapeutic strategies for severe ischemic heart disease. New medical treatment options such as ranolazine [6], ivabradine [7] have been suggested for patients with RA. Despite these new therapies, patients may continue to be limited with angina, which markedly affects their quality of life. Further techniques to enhance myocardial perfusion and reduce symptoms in patients with refractory angina have included enhanced external counterpulsation (EECP) [8], and spinal cord stimulation (SCS) [9]. These treatment modalities are time consuming,

contraindicated in many cases, and recent data derived from randomized studies failed to show compelling beneficial effect [10-11]. Another treatments concepts dedicated to induce neoangiogenesis incorporate such sophisticated modalities as transmyocardial laser revascularization [12], myocardial or intracoronary application of proteins [13] or genetic vectors encoding proteins with angiogenesis potential [14], and stem cell based therapies [15-16]. Transmyocardial laser revascularization has been studied widely during past decade but has never been introduced in daily practice. Furthermore, these therapies are invasive, expensive and have not yet been proven as clinically efficacious and feasible for patients.

A cardiac shockwave therapy (CSWT) has been newly developed method originating from lithotripsy; it utilises non-invasive application of low-intensity shock waves to stimulate angiogenesis. Several experimental studies demonstrated that the application of low intensity shockwaves (SW) might induce the release of angiogenic factors such as endothelial nitric oxide synthase (eNOS), vascular endothelial growth factor (VEGF), and proliferating cell antinuclear antigen (PCNA) [17-19]. Furthermore, number of published clinical studies showed the efficacy and safety CSWT in patients with refractory angina [20-23]. Patients notice marked improvement of symptoms, for example, the decrease in nitroglycerine uptake, enhance of exercise tolerance after the treatment. Moreover, CSWT improves myocardial perfusion evaluated with the help of single photon emission computed tomography (SPECT), reduction of Canadian Cardiac Society (CCS) angina class, and increase in Seattle angina questionnaire (SAQ) score (consistent with symptomatic improvement).

Clinical research in intriguing CSWT field continues since 1999, and several new trials are being published every year. First review by Ruiz Garcia was published in 2011 [24]. Overall, cardiac shock waves therapy is a potentially effective non-invasive option for patients with CAD, but evidence is limited to small in size, single arm, low to moderate quality single-center studies. This underlines the need for comprehensive systematic review and meta-analysis as well as an adequately powered randomized, placebo controlled trial for further evaluation of efficacy in CSWT. Thus, we started from systematic review and meta-analysis, and subsequently initiated to run a prospective, randomized, triple blind, sham-procedure controlled, multicentre trial to assess efficacy of CSWT in patients with stable angina.

The goal of this work is to study the impact of cardiac shock wave therapy on exercise tolerance, angina symptoms, myocardial perfusion and contraction during stress in patients with coronary artery disease and objective evidence of myocardial ischemia, who are not candidates for traditional revascularization and experience angina despite optimal medical therapy, by means of systematic review, meta-analysis and randomized multicentre trial with sham procedure.

1.2 The hypothesis of the study

Cardiac shock wave therapy relieves angina symptoms, improves exercise tolerance and reduces stress-induced myocardial ischemia detected by perfusion and contraction imaging tests on top of the optimal medical treatment in patients with stable angina.

1.3 The objectives of the study:

1) To evaluate the level of evidence of beneficial effects of CSWT from currently published human studies:
   a) to perform a systematic review, including bias risk analysis;
   b) to perform meta-analysis of impact of CSWT on exercise capacity;
2) To conduct a randomized, triple blind, sham procedure controlled study of the effect of CSWT with primary and secondary outcomes:
   a) Primary outcome is the exercise tolerance of patients with stable angina undergoing CSWT on top of the optimal medical therapy;
   b) Secondary outcomes are:
      - the effect of CSWT on stress-induced impairment of global and regional myocardial contractility;
      - the effect of CSWT on stress-induced myocardial perfusion defects;
      - the effect of CSWT on quality of life and level of angina.

1.4 The novelty of the research

Extracorporeal shock wave therapy has chiefly been studied in stable coronary artery disease and heart failure. Despite the encouraging results, the evidence supporting the use of CSWT mostly comes from small uncontrolled, single center observational studies. Furthermore, data derived from systematic review or meta-

analyses are scarce. Thus, owing to the lack of appropriate evidence, no practice recommendations yet can be formulated about cardiac shock wave in daily clinical use. Therefore we performed systematic review and meta-analysis of maximum available studies, as well as new randomized, placebo controlled study. The data received from this research could potentially fill the gap of pragmatic recommendations of CSWT use in clinical practice.

First step was to analyse the prior studies evaluating efficacy of CSWT in patients with stable CAD. The aim of current systematic review is to summarize the results and also to evaluate the quality and strength of currently accumulated evidence of the anti-anginal efficacy of CSWT. Previously published reviews by Ruiz Garcia in 2011 [24] and Wang et al. in 2015 [25] covered published studies until 2014. The present systematic review is more comprehensive and sought to combine the maximum number of available studies in English published from 1999 to April 2016. The characteristics of this analysis are a well-ordered character of review, an inclusion in meta-analysis studies with single clinical indication and a uniform treatment protocol, as well as assessment of methodological aspects and risk of bias in the randomised trials.

The results of the review grounded the rationale for a new randomized, placebo-controlled study. Present study is designed in accordance to consolidated standards of reporting trials (CONSORT) 2010 statement [26], prospective, sham-procedure controlled, randomized, triple blind and was conducted in two study centres. The multicentre design of present study reduces bias that may be inevitable in single center studies. For the first time, effect of CSWT on stress-induced changes in perfusion, wall motion and myocardial deformation parameters were studied in randomized controlled trial (RCT) using multimodality imaging methods. Moreover, the specific sham applicator with external appearance and the same behaviour simulating an active applicator was used in this study. Furthermore, the new treatment protocol is produced in order to provide standardized treatment to all segments of left ventricle; if in previously published studies, SW were applied only to ischemic segments identified by imaging tests, in our trial SW application covered the whole LV (during the first week SWs are applied to basal, during fifth week – to middle, during ninth week – to apical segments of LV) regardless of the results of imaging tests or coronary angiography. This was done aiming to shape a prerequisite for potentially wider use of CSWT, which would be independent of availability of imaging stress tests.

1.5 **Defence statements**

1.5.1 CSWT reduces stress-induced myocardial ischemia detected by non-invasive tests in stable angina patients.

1.5.2 CSWT provides significant clinical improvement of patients' symptoms and quality of life in stable angina patients.

1.5.3 CSWT markedly improves exercise tolerance of stable angina patients.

1.5.4 CSWT provides major clinical benefit compared to placebo.

2. LITERATURE REVIEW

2.1 Stable coronary artery disease and current anti-anginal management

Stable coronary artery disease (SCAD) is generally characterized by episodes of reversible myocardial demand/supply mismatch, related to ischemia or hypoxia, which are usually inducible by exercise, emotion or other stress, are reproducible, and may also occur spontaneously. Such episodes of ischemia/hypoxia are commonly associated with transient chest discomfort (angina pectoris), though in substantial proportion of patients silent ischemia may take place. The traditional understanding of SCAD is that chest symptoms are caused by narrowings of ≥50% in the left main coronary artery and ≥70% in one or several of the major coronary arteries [27]. This understanding is derived from experimental observations that coronary artery narrowing limits resting and hyperaemic coronary blood flow [28]. Thus, for many years the clinical management of CAD is mainly focused on the identification and removal of the stenosis.

However, plaque is only one element in a complex multifactorial pathophysiological process of atherosclerosis, including spontaneous thrombosis, coronary vasospasm, endothelial dysfunction, inflammation, microvascular dysfunction and angiogenesis. Endothelial dysfunction is characterized by increased oxidative stress and production of reactive oxygen species (ROS) with gradual loss of endothelial nitric oxide (NO) availability and/or increased production of vasoconstrictors. Endothelial dysfunction also involves an activated state promoting inflammatory responses, chemokine and adhesion molecule expression and consecutive interaction with platelets and leukocytes [29-30]. Monocyte-derived macrophages and T lymphocytes produce and secrete mediator molecules, such as cytokines, chemokines, growth factors, enzymes, and disintegrins, which activate endothelial cells, increase vasoreactivity, and cause proliferation of smooth muscle cells and progression of lesion [31]. The new concept of ischemic heart disease focuses on myocardial ischemia more than on coronary artery atherosclerotic plaques.

According to one historical study (included 5183 patients), patients with SCAD and moderate to severe myocardial ischemia proven by stress myocardial perfusion scintigraphy had increased risk of death and myocardial infarction (MI) compared with those with no or mild ischemia [32]. The modern drug therapies, including statins [33], angiotensin-converting enzyme inhibitors [34] and antiplatelets [35] have emerged during past 30 years, and in association with strict risk factor control and lifestyle modification [36-37] have been shown to markedly reduce risk and improve outcomes

of patients with CAD. Traditional antianginal drugs such as β-blockers, calcium channel blockers and nitrates play a key role in pharmacotherapy of SCAD (first line treatment) [27]. These agents decrease oxygen consumption or augment oxygen supply by reducing heart rate, blood pressure, myocardial contractility and enhancing myocardial blood flow; although their ability to reduce angina symptoms is limited. Approximately 5-15% of patients appear to be symptomatic despite "triple therapy" [3, 38]. Improved understanding of myocardial ischemia has led to new therapeutic options such as metabolic modulation, oxygen sparing and coronary flow redistribution. The addition of novel pharmacological agents such as ivabradine, nicorandil or trimetazidine should be considered as second line treatment [27]. The novel antianginal drugs have been studied in patients with CAD, and the recommendations from ESC [27] and the American College of Cardiology Foundation (ACCF)/ American Heart Association (AHA) guidelines [39] for the medical treatment are summarized in Table 1.

TABLE 1. **Second line antianginal medication for stable coronary artery disease**

Medication	Mechanism of action	Effects	Guidelines / level of recommendation	Reference
Ivabradine	I_f current inhibition	• Reduce automaticity of spontaneous depolarization in the sinoatrial node cells • Possible vasodilatation	• ESC 2013: IIa, B	[40-41]
Nicorandil	Mitochondrial K_{ATP} channel opener	• Vasodilatation of conductance and resistance vessels	• ESC 2013: IIa, B	[42-43]
Ranolazine	Late I_{Na} current inhibition	• Reduce Ca^{2+} overload, LV wall tension • Improves myocardial perfusion • Partially inhibits fatty-acid oxidation	• ESC 2013: IIa, B • ACC/AHA 2012: IIa, B^a/A^b	[6, 44-45]
Trimetazidine	Reversibly inhibits mitochondrial 3-ketoacyl-XoA thiolase	• Reduce fatty-acid oxidation	• ESC 2013: IIb, B	[46-47]
Perhexilline	Inhibits carnitine O-palmitoyl-transferase 1 and 2	• Reduce free fatty acid oxidation and transport into mitochondria	• Limited clinical evidence	[48]
Allopurinol	Inhibits Xantine oxidase	• Reduce oxygen wasting, endothelial dysfunction, substrate depletion	• Limited clinical evidence	[49-50]

ESC – European Society of Cardiology, ACC/AHA - American College of Cardiology / American Heart Association, a- ranolazine prescription as a substitute for beta-blockers for relief of symptoms in patients with CAD, b- ranolazine prescription in combination with beta-blockers for relief of symptoms in patients with CAD.

The stable coronary artery disease guidelines recommend revascularization by PCI or coronary artery bypass grafting (CABG) depending on the presence of angina symptoms not controlled with OMT, significant obstructive coronary artery stenosis, the amount of related ischemia and the expected benefit to prognosis and/or symptoms [27, 51].

A number of studies have found that considerable proportion of patients present with persistent symptoms despite coronary revascularization procedures and medical treatment [52-54]. The Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation study (COURAGE) compared treatment strategies of medical therapy alone with medical therapy plus percutaneous coronary intervention (PCI) in patients with SCAD. At the one-year follow up, 34% of patients still complained with angina after PCI compared to 42% of those in the medical therapy group [53]. The benefit of routine early PCI was a modest, but significant reduction in angina symptoms; however, the difference did not remain significant after 3 years (28% of patients in PCI group versus 33% of patients in OMT group) [55].

The pathophysiological relevance of obstructive lesions was investigated in the Fractional Flow reserve versus Angiography for Multivessel Evaluation (FAME) trial. This study included patients with multivessel CAD and they were randomized to undergo routine PCI or guided fractional flow reserve (FFR) measurements PCI [56]. At one year follow up, 22% of patients in routine PCI group still limited with angina, compared with 19% of patients in the FFR-guided PCI group (p=0.20) [56].

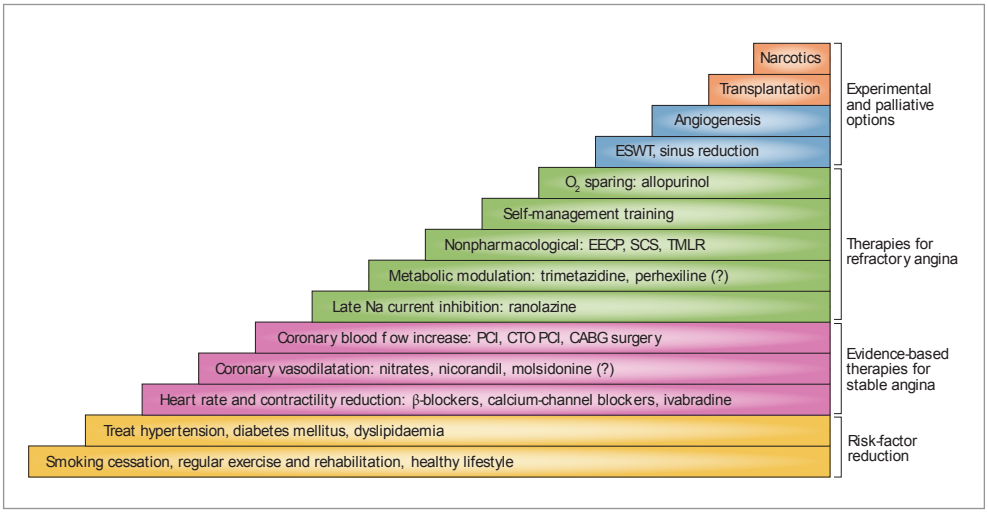
The Bypass Angioplasty Revascularization Investigation (BARI) study compared revascularization strategy of initial PCI versus CABG for management of patients with multivessel disease. Patients were randomly assigned to PCI or CABG. At five years follow up 28% of the 202 patients initially treated with PCI had angina compared with 18% of the 200 surgery-treated patients (p=0.03) [57].

The insufficient control of symptoms after revascularization has been interpreted as a result of incomplete revascularization or in-stent restenosis. However, in the prospective study investigating the incidence of persistent angina and inducible ischemia in patients with CAD after successful PCI, there were one third of patients still experiencing angina and 52% of them presented with a positive stress test at 1 month after the PCI procedure [58]. This finding suggests that the lack of symptomatic improvement involves mechanisms beyond the elimination of epicardial stenosis.

2.2 Refractory angina

An increasing number of patients have advanced CAD with severe symptoms of angina despite optimal medical therapy and revascularization. These patients described as having "refractory angina". The ESC joint group on the Treatment of Refractory angina defined this status "as a chronic condition (≥3 months) characterized by the presence of angina, caused by coronary insufficiency in the presence of CAD, which cannot be adequately controlled by a combination of optimal medical treatment and revascularization" [5]. Revascularization for many of these patients is not available for many reasons, including unsuitable anatomy (diffuse and distal atherosclerosis, lack of graft conduits, recipient vessel of small calibre and poor quality), the presence of leading comorbidities (severe LV dysfunction, peripheral artery disease, advanced kidney disease). Moreover, microvascular dysfunction, vasospastic angina, neurogenic, psychogenic and mitochondrial dysfunction in addition to tissue ischemia are responsible for a persistent pain syndrome [59]. A growing number of novel treatment options have been investigated that target dysfunctions maintaining persistence of angina (Figure 1) [60].

FIGURE 1. **Treatment options for angina**



The treatment of angina starts with the management of risk factors (yellow steps) and the implementation of evidence based therapy for stable angina (pink steps). Alternative options for refractory angina include medical treatment and non-pharmacological treatment (green steps). The blue and orange steps display experimental and palliative options, which should be considered after earlier options have been attempted.

CTO – chronic total occlusion, EECP – enhanced external counterpulsation, ESWT – extracorporeal shock wave therapy (cardiac shock wave therapy is used elsewhere in the text), PCI – percutaneous coronary intervention, SCS – spinal cord stimulation, TMLR – transmyocardial laser revascularization.

Reprinted by permission from Macmillan Publishers Ltd: on behalf of Cancer Research UK: Nature Reviews Cardiology. Henry TD, Datran D, Jolicoeur EM. Treatment of refractory angina in patients not suitable for revascularization. Nature Reviews Cardiolology 2014;11:78-95.

2.2.1 Non-pharmacological therapeutic options

Specific recommendations for emerging invasive and non-invasive methods from European Society of Cardiology [27], Canadian Cardiovascular Society / Canadian Pain Society (CPS) joint guidelines [61] and the American College of Cardiology Foundation (ACCF)/ American Heart Association (AHA) guidelines [39, 62] for the treatment of patients suffering from RA are summarized in Table 2.

Percutaneous coronary intervention (PCI) of chronic total occlusion (CTO)

Retrograde percutaneous recanalization of chronic total occlusion of the coronary arteries is successful in up to 90% of appropriately selected patients in dedicated centres and performed by experienced operators [64]. Advances in CTO PCI, including CTO specific equipment and retrograde approaches, have increased procedural success. Moreover, recently published meta-analysis (included 24486 patients of 25 non-randomized studies) demonstrated 62% lower risk of residual angina in 9 studies (p=0.0001) [65]. Only few studies have reported the effect on symptoms relief [66]. The DECISION-CTO (Optimal medical therapy with or without stenting for coronary chronic total occlusion) randomized trial compared OMT with or without stenting for coronary CTO PCI and included 834 patients. The results of this trial indicate that CTO PCI + OMT is not superior to OMT alone in terms of MACE (primary endpoint), angina symptoms and quality of life measures were similar (secondary outcomes) [67].

Spinal cord stimulation (SCS)

Spinal cord stimulator is a device, implanted by minimally invasive procedure. A multipolar electrode is surgically positioned in the epidural space to deliver an electrical current to the dorsal columns between C7 and T4 vertebrae. The SCS therapy is self-administered and usually requires stimulation for 1 h, three times per day, or when angina occurs. The mechanism of SCS action is an anti-nociceptive activation of spinal afferent neurons and inhibition of sympathetic efferents, attenuating vasoconstriction and reducing ischaemia [68].

The efficacy of SCS has been compared with various control treatments (such as CABG surgery and percutaneous myocardial laser revascularization) in seven randomized trials. The data from these small size studies have been aggregated in a meta-analysis, showing a significant improvement for patients allocated to SCS in terms of exercise capacity and quality of life with low complication rates (e.g. infection,

TABLE 2. **Invasive and non-invasive methods for refractory angina treatment [27, 39, 61-62]**

Method	Type	Efficacy	Guidelines / level of recommendation a	Comments	Reference
PCI of chronic total occlusion	Invasive	↑ Survival ↓ MACE ↓ Angina	ESC 2013: IIb, B for proven myocardial ischemia in corresponding territory	Recent RCT showed negative results in terms of MACE, angina frequency and SAQ scores	[64-65, 67]
Spinal cord stimulation	Invasive	↑ Exercise capacity ↑ QOL ↓ Angina ↓ Nitrates use	May be considered: ACC/AHA: 2012/2014:IIb, C CCS 2012: WR, MQE ESC 2013: IIb, B	Two positive meta-analyses, two recent placebo controlled trials – negative	[9-10, 69-71]
Enhanced external counterpulsation	Non-invasive	↓ Angina ↓ Nitrates use ↑ Exercise tolerance ↑ Endothelial-derived vasoactive agents	May be considered: ACC/AHA 2012/2014:IIb, B CCS 2012: WR, LQE ESC 2013: IIa, B	Positive results from registries, II phase trials and meta-analysis	[8, 11, 73-77]
Transmyocardial laser revascularization	Invasive	↓ Angina ↑ 30 days mortality	ACC/AHA 2012/2014:IIb, B Not recommended: CCS 2012: SR, HQE ESC 2013: III, A	Harmful study No further studies planned	[81-82]
Coronary sinus reduction	Invasive	↓ Angina ↑ QOL ↓ Perfusion defect	-	Positive COSIRA study (II phase, placebo controlled); COSIRA III phase study is initiated	[85]
Cardiac shock wave therapy	Non-invasive	↓ Angina ↑ QOL ↑ LVEF ↓Nitrates use ↑ Exercise tolerance ↓ Perfusion defect	-	Positive results derived from small size observational, randomized studies and meta-analyses	[20-25, 63]
Cell based therapies	Invasive	↓ Angina ↑ Exercise tolerance ↓ Perfusion defect ↓ MACE	-	Positive results derived from II phase trials and meta-analyses; III phase studies were stopped prematurely for financial reasons. Further data from randomized studies needed	[16, 87-89]
Protein and gene therapies	Invasive	↓ Angina ↑ Exercise tolerance	-	Positive results from II phase trials; Further data from randomized studies needed	[13-14, 92-94]

ACC/AHA - American College of Cardiology / American Heart Association, CAD – coronary artery disease, CCS – Canadian Cardiovascular Society, ESC – European Society of Cardiology, HQE – high-quality evidence, LVEF – left ventricular ejection fraction, LQE – low-quality evidence, MACE – major adverse cardiac events, MQE – moderate-quality evidence, PCI – percutaneous coronary intervention, RCT – randomized controlled trial, SR – strong recommendation, QOL – quality of life, WR – weak recommendation.

lead displacement, etc.) [69]. A registry of 235 patients demonstrated reduction in angina frequency, CCS class, sublingual nitrates use and improved quality of life up to 1-year of follow-up [70]. Despite promising results from meta-analyses, two recent RCT did not show any beneficial effect of SCS. The largest blinded trial STARTSTIM (Stimulation Therapy for Angina RefracTory to Standard Treatments, Interventions, and Medications) had difficulty to reach enrolment targets (included 68 patients) and showed no difference in terms of angina frequency or exercise time between active-treatment and control groups, both of which showed improvement consistent with a placebo effect [10]. Similarly, a pilot RASCAL (Effectiveness and Cost-Effectiveness of Spinal Cord Stimulation for Refractory Angina) trial sought to randomize patients to SCS versus usual care but failed to meet enrollment targets (included 29 patients). There was a trend toward larger improvements in angina frequency and the 6-minute walk test in the SCS group [71].

Enhanced external counterpulsation (EECP)

During treatment session, external compressive cuffs are placed on the calves, lower and upper thighs that are sequentially inflated during diastole, which induces diastolic pressure augmentation, therefore increasing coronary perfusion pressure and preload in a similar manner to invasive aortic balloon pumping [72]. Treatment includes a series of 1-hour sessions over 7 weeks (in total 35 hours). Symptom relief has been documented in registry studies for over 2 years after therapy [73]. The MUST-EECP (MUlticenter STudy of Enhanced External Counterpulsation) randomized study enrolled 139 patients with refractory angina to 35 hours of active versus inactive counterpulsation [8]. No difference was reported in total exercise duration between study groups, only time to exercise induced ST-depression on the treadmill test increased significantly ($p=0.01$), while nitroglycerine use and angina frequency showed trends to improvement [8]. Further placebo controlled studies showed that EECP improved flow-mediated dilation of the brachial and femoral arteries and increased plasma levels of the endothelial-derived vasoactive agents (nitric oxide and 6-keto-prostaglandin), decreased concentration of inflammatory markers (tumor necrosis factor and high-sensitivity C-reactive protein, among patients assigned to EECP group [74]. Furthermore, EECP showed improvement in myocardial perfusion [75], in invasive hemodynamic measures of collateral function [11, 76].

The suggested mechanisms of action include recruitment of myocardial collaterals through activation of growth factors, improvement of endothelial function, the

release of pro-angiogenic cytokines, and a peripheral training effect similar to those observed with regular physical exercise (promotes decrease in peripheral vascular resistance) [73-74, 77-78].

EECP is contraindicated in patients with decompensated HF, severe peripheral artery disease, uncontrolled hypertension, abdominal aorta aneurysm and aortic insufficiency [72-73]. EECP has been approved by the United States Food and Drug Administration (FDA) and recommended for the management of CCS class III and IV refractory angina.

Transmyocardial laser revascularization (TMLR)

During this procedure, which may be performed via a percutaneous catheter system or thoracotomy, a number of transmyocardial channels are created with a laser; these channels were supposed to carry blood from the ventricular cavity directly to myocardium. A series of trials were conducted in many centres in the nineties but has now largely been abandoned after results were published [11, 79-80]. A blinded, randomized, placebo-controlled DIRECT trial of percutaneous laser myocardial revascularization to improve angina symptoms in patients with severe coronary disease showed no difference in exercise duration and clinical symptoms between study groups, which showed improvement consistent with a placebo effect [81]. Regarding safety, the 30-day incidence of MI was higher in patients treated with TMLR. Briones et al. in a Cochrane review (included 1137 patients of 7 RCT) has demonstrated superiority of TMLR in reducing angina, while risks associated with transmyocardial laser revascularization outweigh the potential clinical benefits and that the procedure may cause unacceptable risks [82].

Coronary sinus reduction

Percutaneous sinus reducer implantation is a developing modality for refractory angina treatment. The reducer is an hourglass shaped device that is implanted in coronary sinus. Controlled narrowing of the coronary sinus creates an upstream pressure gradient that results in the redistribution of blood from the less ischemic epicardium to the ischemic endocardium thus reducing myocardial ischemia [83]. Under physiological conditions, the sub-epicardial arteries constrict in response to stress, and redirect blood flow into the sub-endocardium — a compensatory mechanism that might be dysfunctional in patients with advanced CAD [84]. Recently published COSIRA (COronary SInus Reducer for treatment of refractory

Angina) is a double blind, placebo controlled, randomized II phase trial, which enrolled 104 patients with CCS class III or IV refractory angina. At 6-month follow-up, improvement by 2 and 1 CCS angina classes was achieved in 35% and 71% of patients assigned to treatment group compared to 15% and 42% of patients assigned to placebo group, respectively (p=0.020). Furthermore, significant improvements in myocardial perfusion and SAQ scores were also reported [85]. Further investigations are continued and a multicenter, randomized III phase trial is initiated in the United States in 2017.

Cell based therapies

Experimental evidence suggests that cell therapy can promote neovascularization and consequently improve myocardial perfusion and contractile function [86]. Recently published meta-analysis of six RCTs showed improvements in angina frequency, use of nitrates, CCS angina class, exercise tolerance, myocardial perfusion and MACE in cell-treated patients [87]. The largest double blind, placebo controlled trial ACT-34 (included 167 patients) compared autologous $CD34^+$ cells delivered into myocardium versus placebo. This study revealed significant reduction in angina and improvement in exercise time in patients assigned to treatment group [16, 88]. The III phase RENEW (Efficacy and Safety of Intramyocardial Autologous $CD34^+$ Cell Administration in Patients With Refractory Angina) trial, which aimed to compare $CD34^+$-cell injection to no intervention, or placebo injection was terminated early, due to financial aspects. However, it confirmed previous findings, seen in I phase and II phase trials, of the improvements in exercise time and angina frequency [89].

Overall, cell based therapy demonstrates early encouraging results; still the most effective cell type, preparation, dose and method of delivery should be clarified in further investigations.

Protein and gene therapies

Experimental studies data showed that angiogenic response to myocardial ischemia could be augmented with the use of protein growth factors or gene therapy [90-91]. Two large, randomized, placebo-controlled trials encompassing intracoronary VEGF and fibroblast growth factor (FGF) did not show improvement in exercise time (primary end point), but it revealed improvements in terms of secondary endpoints, such as angina frequency and quality of life in patients with angina [13, 92]. These findings were in line with other double blind, placebo controlled, randomized Angiogenic gene therapy III phase trials (AGENT-3 and AGENT-4) involving

intracoronary delivery of an adenovirus encoding FGF5 (Ad5FGF). These two studies failed to show difference in terms of change in exercise treadmill time from baseline to 12 weeks [93]. The RCTs evaluating effect of intramyocardial delivery of the gene encoding VEGF did not demonstrate improvements in ischemia amount assessed by single-photon emission computed tomography (primary endpoint), although reduction of angina was noted [14, 94].

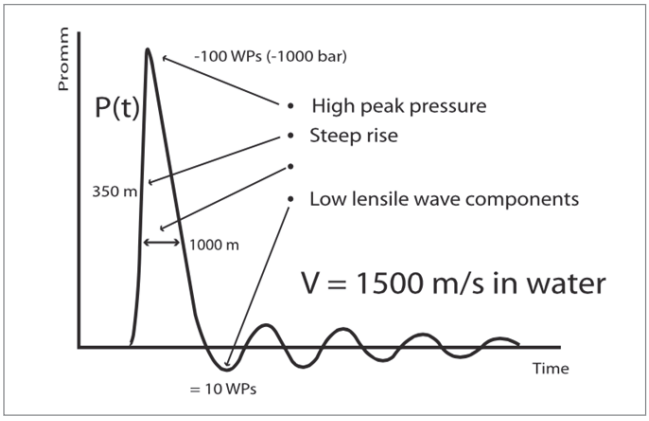
2.3 Cardiac shock wave therapy

Ultrasound-guided cardiac shock wave therapy is a non-invasive modality in patients with stable CAD.

2.3.1 Basic concepts

SWs belong to acoustic waves that can be transmitted through a liquid medium and focused with precision of several millimetres to any intended treatment area inside the body. In contrast to ultrasound, SW is a single pressure pulse with a short needle-like positive spike <1 Ws in duration and up to 100 MPa an amplitude, followed by a tensile part of several microseconds with lower amplitude (Figure 2).

FIGURE 2. **Characteristics of shockwave**



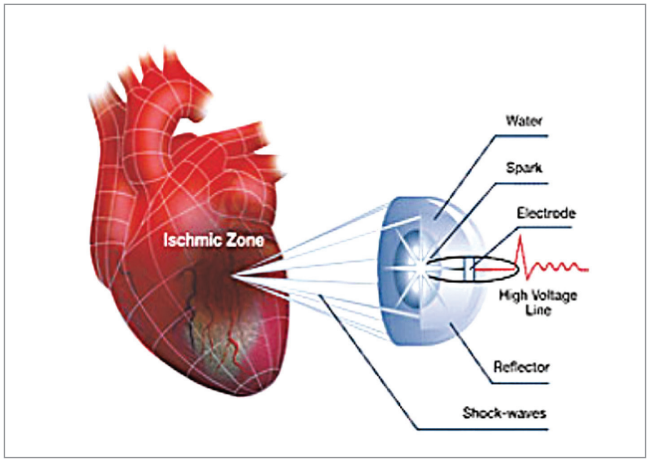
Reprinted by permission from Medispec Ltd [95].

SWs are generated by electrohydraulic effect: high voltage creates electric spark discharge. The water vaporizes and creates an explosion, generating high-energy shock waves. SWs are delivered non-invasively to the affected ischemic area, focused by a special ellipsoid reflector. The reflector is coupled to the patient's skin with a

water cushion (Figure 3). Echocardiography is used to locate the area of interest, and to map the exact position and extent of ischemic zone. Shockwaves are delivered via the anatomical acoustic window to the treatment area under ECG-R wave gating to avoid ventricular arrhythmias. Several treatment sessions are required.

Currently, there are no standardized guidelines for the use of shockwaves in cardiovascular conditions. A range of regimes with respect to the choice of machine, positioning of the patient, doses and treatment frequencies has been employed.

FIGURE 3. **Generation of shockwaves by electrohydraulic effect**



Reprinted by permission from Medispec Ltd [95].

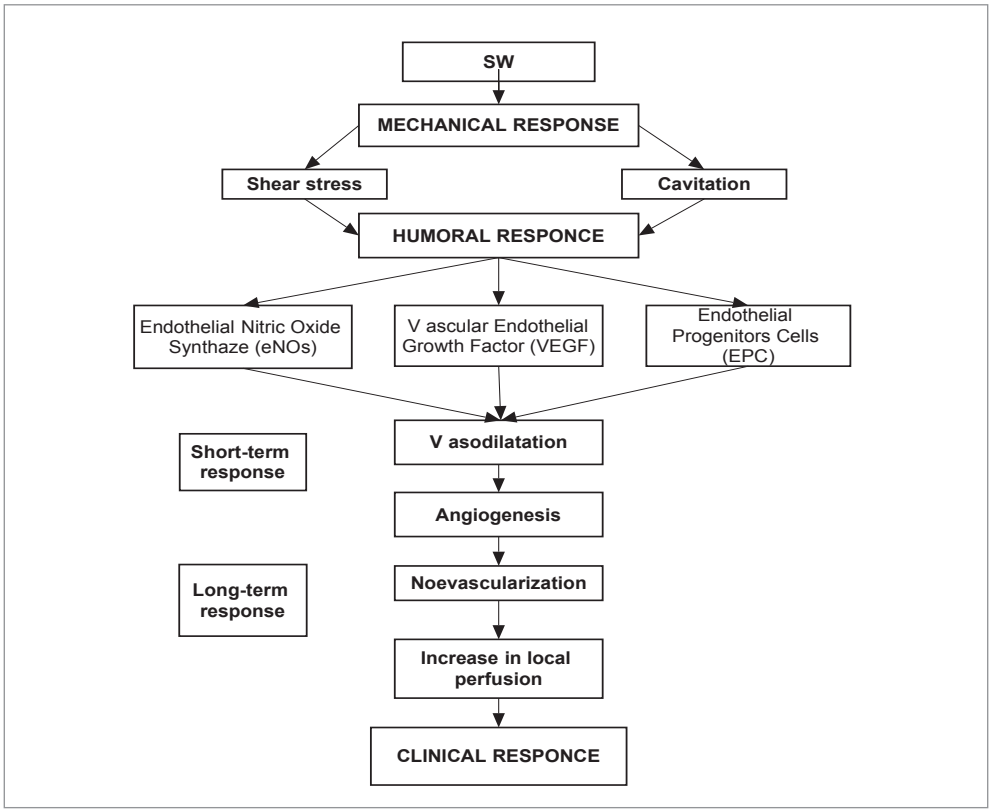
2.3.2 Mechanism of cardiac shock wave therapy

Experimental studies showed that SW might induce shear stress to endothelial cells and produce complex cascade of short- and long-term reactions leading to arteriogenesis (Figure 4).

When a SW hits tissue, cavitation (a micrometre-sized violent collapse of bubbles) is induced by the first compression of the positive pressure part and the expansion with tensile part of SW [96]. Because the physical forces generated by cavitation are highly localized, SW could induce localized stress on cell membranes, as altered shear stress affects endothelial cells [97]. The other reports have demonstrated the humoral effects of SW, including hyperpolarization and Ras activation [98], an increase in nitric oxide synthesis [17, 99], an up regulation of vascular endothelial growth factor (VEGF), its receptor Flt-1 and placental growth factor (PGF) [100-102], in addition

to an enhanced expression of stromal-derived factor-1 [103]. There are some data that CSWT causes recruitment of progenitor cells to the ischemic zones [104-105]. Fu et al. [19] reported that CSWT enhanced angiogenesis and remarkably improved heart function in mini-pigs.

FIGURE 4. **The proposed mechanisms of cardiac shock wave therapy for arteriogenesis**



SW – shock waves.

2.4 Mechanisms of angiogenesis and arteriogenesis

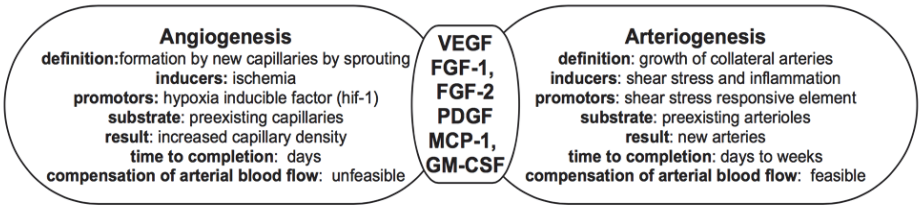
The formation of a functional, integrated vascular network is a fundamental process in the growth and maintenance of tissue. Vascularization occurs by three distinct processes: vasculogenesis, angiogenesis, and arteriogenesis. After birth, new blood vessels formation proceeds via angiogenesis and arteriogenesis.

Angiogenesis is a process by which new capillary blood vessels sprout from a pre-existing blood vessel [106]. This process is important for wound healing in granulation tissue.

Arteriogenesis is the rapid proliferation of pre-existing collateral arteries. These vessels are small diameter, thin-walled conduits that are composed of an endothelial lining, an internal elastic lamina, and one or two layers of smooth muscle cells [107]. Importantly, these vessels have the ability to dramatically increase the lumen by growth so as to provide enhanced perfusion to the jeopardized ischemic regions.

The mechanisms of arteriogenesis and angiogenesis are different; although many stimuli elicit both responses [108-109], see Figure 5. An increased number of capillaries, induced by hypoxia, may increase the flow to the myocardium by lowering the resistance. This increase in flow induces enlargement of the supplying collateral artery by increased fluid shear stress. Thus, angiogenesis and arteriogenesis are dependent on each other, as higher collateral flow requires an adequate capillary network in the myocardium, and newly grown capillaries depend on increased blood flow in the supplying artery. In coronary artery disease, collateral growth is needed upstream and adjacent to the ischemic region, while capillary growth within the ischemic region increases the nourishing of the ischemic or hibernating myocardium [109].

FIGURE 5. **Characteristics of angiogenesis and arteriogenesis**



VEGF - vascular endothelial growth factor, FGF – fibroblast growth factor, PDGF - platelet-derived growth factor, MCP – monocyte chemo-attractant protein, GM-CSF - granulocyte macrophage colony-stimulating factor.

Modified from Buschmann et al [109] by permission from The American Physiological Society.

Arteriogenesis is stimulated by increased flow shear stress but only to a limited degree by ischemia [110]. The translation of the mechanical force to the cellular level is not completely understood. Adhesion molecules such as VCAM, ICAM and the monocyte chemo-attractant protein MCP-1 are important, as well as monocytes and endothelial progenitor cells. Growth factors such as vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF), placental growth factor (PlGF),

transforming growth factor beta (TGFß) and also the stem-cell releasing factors granulocyte colony-stimulating factor (G-CSF) and granulocyte macrophage colony-stimulating factor (GM-CSF) have been shown to augment arteriogenesis and angiogenesis. The growth and maintenance of the artery size does not only involve endothelial cells but also supporting smooth muscle cells and pericytes, which are influenced by platelet-derived growth factor (PDGF). The surrounding extracellular matrix is also remodelled to accommodate the growing artery. This remodelling is accomplished by proteinases such as plasminogen activators (PAI-1) and matrix metalloproteinases [111-112]. Both angiogenic activators (VEGF, TGFß) and inhibitors (trombospondin, endostatin) are liberated from their matrix-bound state during the remodelling process.

Angiogenesis is regulated by tissue hypoxia and ischemia. Hypoxia directly inhibits the hydroxylation of the transcription factor HIF-1, dramatically increasing its cellular levels within minutes. HIF induces the transcription of VEGF, VEGF receptors 1 and 2, nitric oxide synthases and PAI-1 [113]. Indirectly, FGFs, Angiopoetin-2, Tie-2, MCP-1 and PDGF are induced.

Although the importance of coronary collaterals in diminishing myocardial ischemia has been appreciated for a long time, it is a new finding that a considerable collateral circulation exists also in humans without coronary stenosis [114]. The extent of collateral flow is highly variable between individuals, both with and without coronary stenosis. There is a moderate correlation between stenosis severity and collateral flow [115].

In humans, exercise training and/or the presence of a significant stenosis may increase shear stress. It has been suggested that the severity of the stenosis is the only independent variable that is related to collateral growth in patients who have CAD [115]. The increase in the grade of a stenosis leads to an increased pressure gradient to the interconnecting collateral channels. This translates to an elevated blood flow and shear stress resulting in arteriogenesis [109].

2.5 Cardiac shock wave therapy studies

In the medical field high-energy extracorporeal shock wave therapy (ESWT) was introduced more than 30 years ago as a treatment option for urinary tract stones [116]. ESWT has changed the treatment of urinary calculi, and even today it remains the primary treatment in most non-complicated cases [117]. ESWT has also been applied in biliary tract [118], pancreatic [119] and salivary stones treatment [120].

Experimental data showed that low energy ESWT has regenerative features and has been developed as a treatment standard for a variety of orthopedic and soft tissue diseases [121], including wound healing in diabetic patients [122].

In animal models Wang *et al.* observed the capacity for shock wave therapy to cause neovascularization in joints; the registered early release of angiogenesis-mediating growth and proliferation factors including eNOS, VEGF and PCNA resulted in improved blood supply and tissue regeneration [123]. Other in vitro studies demonstrated that low energy shock waves increases eNOS activity and intracellular NO production with effect observed for up to 4 weeks after treatment [17, 99].

These reports led to the use of shock wave therapy in animal models of regional ischemia. Oi *et al.* demonstrated in a model of hind limb ischemia in rabbits that SWs induced the development of collateral arteries and increased the capillary density in the treated areas [124]. Aicher *et al.* showed that shock wave therapy facilitated recruitment of endothelial progenitor cells and improved blood flow recovery as assessed by laser Doppler imaging in a similar model [125]. De Sanctis et al. and Belcaro et al. used this technology clinically to treat critical limb ischemia and succeeded in showing that low energy shockwaves increase local perfusion [126-127].

Shimokawa group in vitro study found that a low-energy SW (0.09 mJ/mm^2, about 10% of the energy density used for urolithiasis) effectively increased the expression of vascular endothelial growth factor (VEGF) in cultured human umbilical endothelial cells (HUVEC) [128]. Based on this in vitro study, they examined the effects of shock wave therapy in a porcine model of chronic myocardial ischemia, and demonstrated improvement of left ventricular systolic function, wall thickening fraction and regional myocardial blood flow. In addition, they also found a significant increase of markers of neovascularization such as VEGF, the VEGF receptor Flt-1, as well as significant growth of capillaries in the ischemic myocardium of the treatment group when compared to the non-treated group [128]. In porcine model for acute myocardial infarction, the same group demonstrated that early application of SW could improve left ventricular remodeling and increase the capillary density in the border zone of the ischemic area [129]. Fu *et al.* demonstrated that CSWT markedly increased endothelial progenitor cells (EPC) and EPC homing-related chemokines in LV ischemic area, enhanced angiogenesis, reduced inflammatory response, oxidative stress, cellular apoptosis and fibrotic changes in LV myocardium [19]. These effects may contribute to the improvement in LV function and reverse remodeling.

The observed immediate increase in blood flow due to local vasodilatation, and the formation of new capillaries in the treated tissue has led to one of its promising application in cardiovascular medicine as a possible treatment for patients with stable angina. Since 1999 [130], cardiac shock-wave therapy (CSWT) as a tool for the management of RA has been investigated in a considerable number of clinical studies. However, it is unclear what amount and level of evidence is accumulated up to date. Therefore systematic review and meta-analysis were conducted to evaluate the effect of CSWT.

3. METHODS

3.1 Systematic review and meta-analysis

3.1.1 Data sources

A comprehensive research was performed using medical bibliographic databases: Cochrane Controlled Trials Register, Medline, Medscape, Research Gate, Science Direct, Web of Science (from 1999 to April of 2016), and Google Web. Also, references were reviewed in selected articles. Data sources evaluating the efficacy of CSWT in CAD patients were selected. Publications were selected by pre-defined criteria and independently reviewed by two observers following preferred reporting items for systematic reviews and meta-analyses (PRISMA) statement [131]. Disagreements were closely reviewed and resolved by consensus. The keyword used to identify relevant studies included: *coronary artery disease*, *ischemic heart disease, refractory angina treatment, stable angina treatment* combined with *extracorporeal cardiac shock wave therapy, myocardial shock wave therapy, extracorporeal myocardial revascularisation*.

3.1.2 Selection criteria

In order to be included, trials had to assess the treatment with CSWT of CAD patients, written in English. Selected studies included patients with stable CAD proven by coronary angiography or computed tomography angiography, not amenable to revascularization, angina class II-IV (Canadian Cardiology Society, CCS) despite medical treatment, and documented stress induced myocardial ischemia. Trials investigating combination of CSWT with stem cell therapy were not included.

3.1.3 Definition of endpoints

The primary endpoint of this meta-analysis was the effect of cardiac shock waves on exercise capacity.

The second purpose of this systematic review was to examine the effect of cardiac shock wave therapy on clinical parameters, such as Canadian Cardiovascular Society (CCS) angina class, nitroglycerine consumption, New York Heart Association (NYHA) class, quality of life, and parameters of left ventricular function and myocardial perfusion.

3.1.4 Data extraction

Information on 1) study design (including study type, method of randomization and blinding of patients, study personnel and outcome assessors), 2) sample size and patients characteristics (including age, sex), 3) intervention strategies (including treatments schedule, follow up duration), 4) outcome measures (including (short-acting nitrates consumption per week, CCS angina class and NYHA functional class, Seattle Angina Questionnaire [SAQ] scores, and parameters of the functional tests such as exercise duration, workload, global and regional left ventricular function, myocardial perfusion) were extracted into Microsoft Excel (Microsoft, Seattle, Wash., USA) spread sheets.

3.1.5 Statistical analysis

Variables were presented as mean value ± standard deviation (SD) for continuous data with normal distribution and as median with interquartile range (IQR: Q1, Q3) for data not normally distributed, whereas categorical variables were expressed as number (%).

Assessment of risk bias of randomized trials was performed in accordance with the Cochrane Collaboration tool [132] and was based on information on concealment of allocation and random sequence generation, blinding of participants and personnel, completeness of outcome data and selectivity of reporting. Two observers independently assessed the risk of bias for each study according to the low/ unclear/ high scale, and disagreement was resolved by discussion and consensus.

The average of absolute change was calculated in the included studies measures of exercise capacity from baseline to follow up (including standard deviation) in the intervention and control groups. The effect sizes used in each study are presented as standardized mean difference (SMD) with 95% confidence interval (CI) to allow for combination of different measurements of exercise capacity. In line with Cohen's classification [133], effect sizes were divided into trivial (Cohen's d ≤0.2), small (<0.5), moderate (<0.8), and large (>0.8).

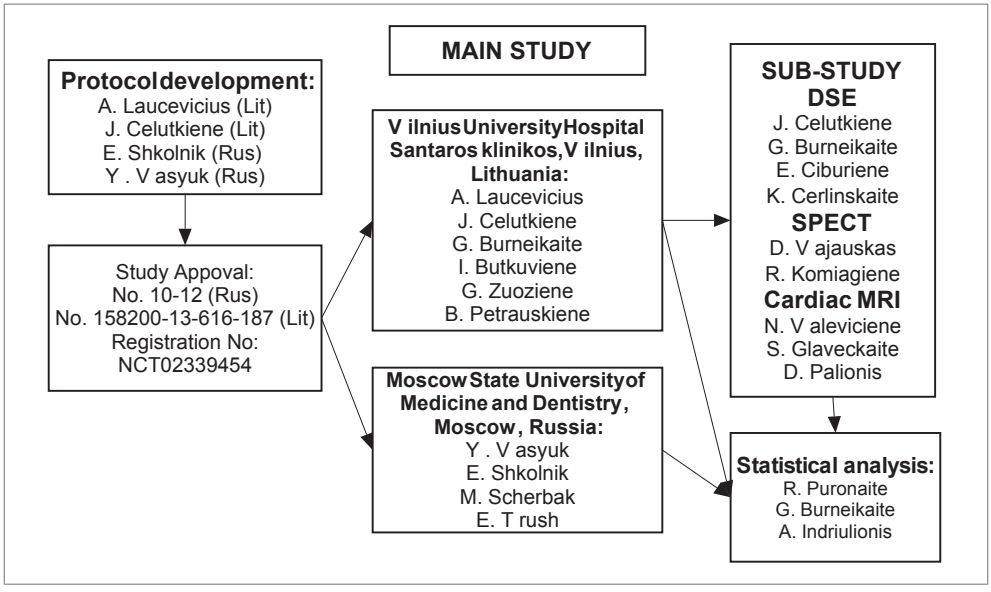
Heterogeneity was assessed by using the chi-square test for heterogeneity and the I^2 statistic to determine the proportion of variation attributable to heterogeneity among studies. Values of I^2 were considered as low (<25%), moderate (25–50%) and high (>50%) heterogeneity. Meta-analysis results are presented as forest plots. Random effects model according to Der Simonian-Laird was used to verify the significant evidence of heterogeneity between the results of studies. Publication bias

was estimated by drawing funnel plot. The analysis was performed using RevMan 5.3 software (Copenhagen, The Nordic Cochrane Centre) [134].

3.2 Study design

A prospective, randomized, triple blind, sham-procedure controlled study was designed to assess the antianginal efficacy of CSWT, on top of standard medical therapy in patients with stable angina. Study protocol was created according to CONSORT statement recommendations for parallel group randomized trials [26]. The study was conducted at two centres Vilnius University Hospital Santaros klinikos (Vilnius, Lithuania) and Moscow State University of Medicine and Dentistry (Moscow, Russia) in accordance with Good Clinical Practice, Declaration of Helsinki 2013. This study was validated by the ethical committee (Vilnius Regional Ethics Committee, Approval No. 158200-13-616-187, and Moscow State University of Medicine and Dentistry Local Ethics Committee, Approval No. 10-12) and was registered on clinicaltrial.gov (NCT02339454). Investigators included in study teams at both centres are shown in Figure 6.

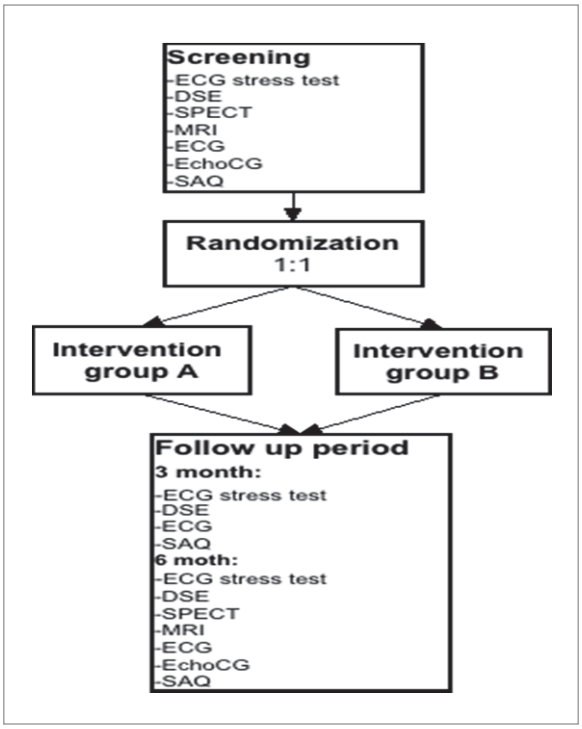
FIGURE 6. **Investigator teams of the study**



DSE – dobutamine stress echocardiography, SPECT – single photon emission computed tomography, MRI – magnetic resonance imaging.

This study consists of four phases: screening for the eligibility criteria, randomization, treatment and follow up, see Figure 7.

FIGURE 7. **Flow chart of the study**



ECG = Electrocardiogram; DSE = Dobutamine stress echocardiography; SAQ = Seattle Angina Questionnaire; SPECT = Single photon emission computed tomography; MRI = Magnetic resonance imaging; EchoCG = Echocardiography.

After providing written consent, subjects who met the inclusion/exclusion criteria entered screening phase. Screening phase consisted of two parts such as optimization of medical treatment and testing. First part of screening phase included evaluation of symptoms, demographic characteristics, medical history and lipid profile, physical examination and vital signs; based on these parameters, the medications were adapted according to the guidelines [27]. Four-week period was kept to ensure clinical stability and stable doses of medication. During second part of the screening patients underwent stress tests for detection of exercise-induced ischemia (Table 3).

TABLE 3. **Schedule of the study procedures**

	Screening		**Rando-mization**	**Treatment period**			**Follow up period**	
	-56 to -29 day	-28 to -1 day	0	1 week	5 week	9 week	3 month	6 month
Informed consent	X							
Inclusion / Exclusion criteria	X	X						
Cardiovascular medical history and risk factors	X							
Other medical history and current conditions	X							
CCS	X	X		X	X	X	X	X
Physical examination	X			X	X	X	X	X
Assignment to study group			X					
SAQ		X					X	X
Echocardiography		X						X
ECG		X						
ECG Treadmill stress test		X						X
Dobutamine stress echocardiography*		X					X	X
Myocardial perfusion imaging SPECT*		X						X
Cardiac MRI*		X						X
Medication review (including nitroglycerin consumption)	X	X		X	X	X	X	X
CSWT / placebo procedure				X	X	X		
AE recording		X		X	X	X	X	X

AE - Adverse event; CCS - Canadian Cardiovascular Society; CSWT - Cardiac shock wave therapy; ECG - Electrocardiogram; DSE - Dobutamine stress echocardiography; MRI - Magnetic resonance imaging; SAQ - Seattle Angina Questionnaire; SPECT - Single photon emission computed tomography.

* - Test was performed only at Vilnius site.

After the baseline evaluation, subjects were randomly assigned to a study group (A or B) according to allocation table (Phase II). Phase III involved CSWT/placebo treatment. Detailed methodology and protocol are described in section 3.2.3.1. During phase IV follow-up visits were performed and outcome measures were assessed at 3 and 6 month after randomization (Table 3).

3.2.1 Randomization and blinding

For this trial, professional statistician generated separate random allocation sequences for two centres. Access to the random allocation lists was granted to only one principal investigator (JC) of the two centres following "centralized" randomization and protected by password. Principle investigator blinded to clinical and instrumental data of enrolled patient performed allocation procedure. The study investigators who performed patients' screening were blind to allocation sequence. Consecutive patients, who met the inclusion criteria and underwent baseline evaluation were randomized by assigning to the application groups A or B in a 1:1 ratio.

As patients, all investigators (clinicians, data assessors) and statistician were blinded to treatment allocation, the design fitted to triple blind study. The randomization code has been disclosed after the last visit of the last patient during the primary statistical analysis. Patients of group B were treated with standard medical therapy and cardiac shock wave applicator (OMT + CSWT) and patient of group A - standard medical therapy and placebo applicator (OMT + placebo).

3.2.2 Study population

The study cohort consisted of 72 randomized patients with coronary artery disease and exercise-induced angina not controlled by the standard optimal medical therapy, who had complied with inclusion/exclusion criteria and had provided informed consent for participation in the study. Patients were found eligible if there was no technical possibility for further percutaneous coronary intervention or surgical revascularization. Inclusion and exclusion criteria are presented in Table 4. Recruitment has commenced in May 2013 and finished in December 2015.

TABLE 4. **Inculsion and exclusion criteria**

Inclusion criteria for main study	• Males and females patients (females of childbearing potential must be using adequate contraceptive precautions such as implants, injectable, combined oral contraceptives, intrauterine devices); • Patients aged ≥ 18 years; • Patients with coronary artery disease confirmed by angiography, prior MI, prior revascularization (PCI, CABG) and with exercise angina not controlled by the optimal medical therapy; • Patient should be on a stable dosage of medications used to treat CAD for at least 4 weeks prior to randomization; • ST-segment depression ≥ 1mm during treadmill exercise test (modified Bruce protocol); • Exercise duration during treadmill test ≥ 2 minutes; • Able and willing to sign informed consent and to comply with study procedures;
Exclusion criteria	• Angina at rest; • ECG abnormalities at rest: left bundle-branch block, ST-segment depression ≥ 1mm at rest, digoxin therapy, WPW-syndrome; • Planned coronary revascularization procedure (PCI or CABG) within 6 months; • Heart failure (class III or IV NYHA); • Left ventricular thrombus; • Uncontrolled hypertension (systolic BP >160 mmHg and/or diastolic BP>100 mmHg); • Hypotension (systolic BP <100 mmHg); • Acute coronary syndrome or coronary revascularization procedure within the prior 3 months before enrolment; • Pregnant or nursing women; • Severe concurrent pathology, including terminal illness (cancer); • Contraindications for exercise testing (e.g., acute myocarditis, pericarditis, deep venous thrombosis, severe aortic stenosis); • Patient is simultaneously participating in another device or drug study.

BP – blood pressure, CABG – coronary artery by-pass grafting, ECG – electrocardiogram, LV – left ventricular, MI – myocardial infarction, NUL - normal upper limit, NYHA – New York Heart Association, PCI – percutaneous coronary intervention, WPW – Wolf-Parkinson-White syndrome.

3.2.3 Study treatment

3.2.3.1 Medical treatment

All patients were maintained on stable doses of optimal medical therapy [27] for 4 weeks before treatment and during all study periods. All patients received antiplatelet therapy with aspirin at a dose of 75 to 150 mg per day or 75 mg of clopidogrel per day, if aspirin intolerance was present. Few patients received dual antiaggregant therapy. All patients received therapy for lowering cholesterol (atorvastatin in most cases) with a target level of low-density lipoprotein (LDL) < 1.8 mmol/L. Medical anti-ischemic therapy included long-acting beta-blockers, calcium channel blockers

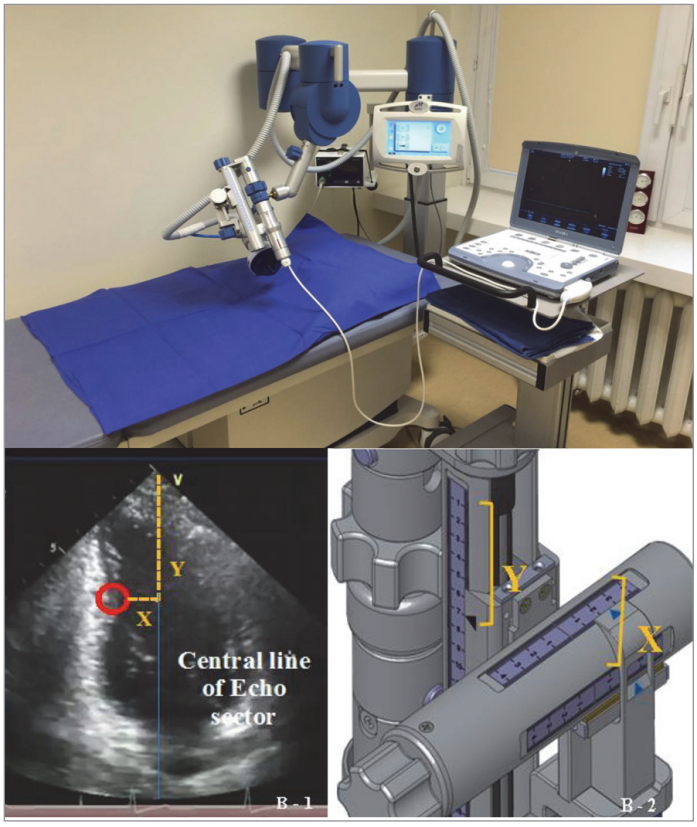
and prolonged nitrates as first line treatment, trimetazidine, ivabradine or ranolazine as second line treatment, along with either angiotensin converting enzyme (ACE) inhibitors as standard secondary prevention.

Regular physical activity, diet (low in saturated fat, cholesterol, and trans-fat; high in fresh fruits, whole grains, and vegetables; and with reduced sodium intake), smoking cessation and weight loss were recommended to all patients [27].

3.2.3.2 Cardiac shock wave therapy

CSWT was performed using a Cardiospec^{TM} device (Medispec Ltd, Germantown, USA) coupled with a cardiac ultrasound imaging system (Vivid i, GE Healthcare, Horten, Norway) to target the treatment area (Figure 8 A). Low intensity shockwaves (100 impulses/spot, energy flux 0.09 mJ/mm^2) were delivered via a special applicator through the anatomical acoustic window to the treatment area under electrocardiographic R-wave gating.

FIGURE 8. **The methodology of cardiac shock wave therapy**



A. Shock wave (SW) generator system (Medispec, Germantown, MD, USA) and cardiac imaging system (Vivid i, GE Healthcare, Horten, Norway).

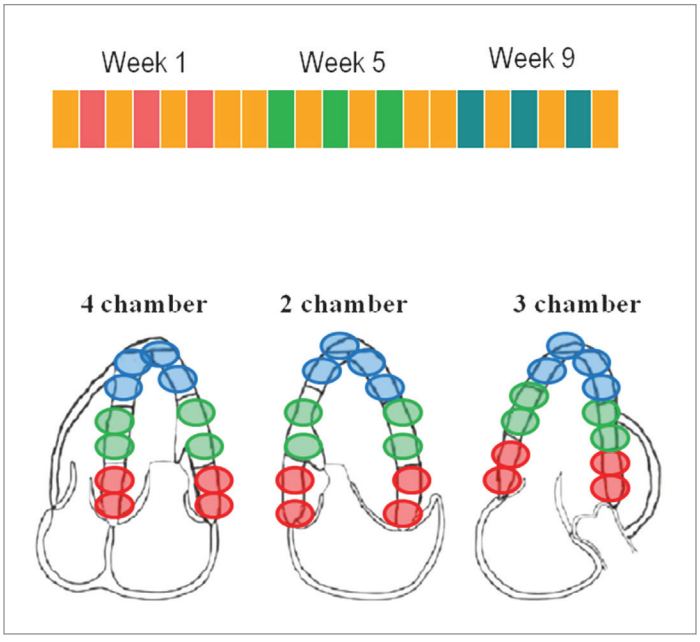
B. SW focal zone alignment: Position of the sub-segment on the 2-dimensional image determined by X and Y coordinates (1). The SW applicator position is identically adjusted along X- and Y-axes corresponding to the X and Y coordinates of the ultrasound image (2).

The patient was positioned on device table and connected with the ECG monitor. The ultrasound probe was used to identify the target area. The shock wave applicator was connected with ultrasound transducer and placed with the membrane in contact with the skin at the target treatment zone, which was visualised in the ultrasound screen (Figure 8 B). For optimal therapy, the treatment area was divided into target zones corresponding to the size of the focal zone of the SW applicator (1 cm diameter circle) (Figure 8 B). The distance to these target zones was measured and marked on the ultrasound screen enabling the operator to see the treated zone in real time. The SW applicator was fixed at the measured distance. An inflatable silicon cushion was filled and ultrasound gel was used for optimal delivery of the shockwaves into the body.

SW application protocol

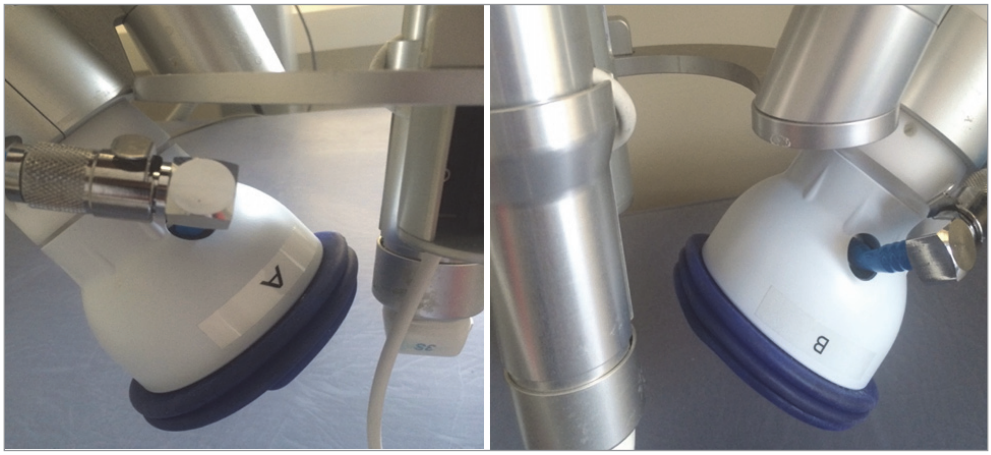
Cardiac shock waves treatment consisted of 9 sessions with 3 sessions per week and was performed on 1st, 5th and 9th study week. Treatment intensity was 100 impulses applied to one spot with up to 1200 impulses to the patient per session or corresponding duration of placebo application (Figure 9). A manufacturer produced the sham applicator by placing an internal shield. Real shockwaves are generated and heard by the patient and treating physician but they were blocked inside the placebo applicator. Treatment and placebo applicators have the same external appearance and behaviour (Figure 10).

FIGURE 9. **Schedule of the study treatment**



During the first treatment week, SWs were delivered to the basal segments of the left ventricle (2 zones in each wall in apical 4-, 2-, 3-chamber positions) every second day (Monday, Wednesday and Friday). A three-week treatment free interval was kept after the treatment week. During the fifth week, SWs were delivered to the middle segments of the left ventricle (2 zones in each wall in apical 4-, 2-, 3-chamber positions) every second day, after that a three-week treatment free interval was kept again. During the ninth week, SWs were delivered to the apical segments of the left ventricle (2 zones in each wall in apical 4-, 2-, 3-chamber positions) every second day (Figure 9). A total of up to 10800 impulses were applied to patient during 9 sessions. Each session lasted about 40 minutes.

FIGURE 10. **Treatment and placebo applicators**



3.2.4 Efficacy assessment

3.2.4.1 ECG Treadmill stress test

All study patients underwent an ECG treadmill stress test using the modified Bruce protocol at baseline, at 3- and 6- months after treatment initiation. Beta-blocking medication was withheld for 48 hours, nitrates and other antianginal medication – 24 hours prior to the ECG stress test in all patients. The exercise stress test was performed at least 3 hours after a light meal. Caffeine and smoking were avoided on the day of test. LE200ce treadmill exercise analysis system (LE200ce, Cardiosoft, General Electric, USA) was used for testing. During the test, twelve ECG leads were monitored continuously, and blood pressure was measured at 2-minute intervals. Peak heart rate, exercise duration, maximum cardiac workload

(which is expressed by metabolic equivalent, METs) and ST-segment depression were recorded.

Criteria to stop the stress testing included ECG changes (2 mm ST-segment depression, complex or sustained arrhythmias), severe angina, fatigue and abnormal blood pressure responses. ST-segment deviation was measured 60 ms after J point compared with the resting value during peak exercise. The ST-segment deviation was considered significant if there was ≥ 1 mm horizontal or down-sloping ST-segment depression in computer-averaged complexes [135]. The following parameters were measured: heart rate and blood pressure at rest and at peak exercise, total exercise time in seconds, major ST-segment deviation at exercise.

METs are calculated automatically by treadmill analysis system by the formula incorporating age, weight, speed, fraction of the elevation and distance.

3.2.4.2 Functional status and quality of life evaluation

All patients were classified according to their symptoms using the Canadian Cardiovascular Society (CCS) grading of stable angina. The CCS angina classification ranges from class I, which indicates no symptoms by ordinary physical activity, to class IV, which indicates angina at any level of physical exertion [136]. During follow up visits patients were asked about number of angina episodes and number of sublingual nitroglycerine doses taken in the past week.

Disease-specific health status was assessed with the Seattle Angina Questionnaire (SAQ) at baseline and at 3- and 6- months follow up. The SAQ is a 19-item questionnaire that measures 5 clinically important dimensions of health affected by angina in patients with CAD: physical limitation, any recent change in the severity of angina, frequency of angina, satisfaction with treatment, and quality of life [137]. Each domain has a score ranging from 0 to 100, with higher scores indicating less disease burden, and has a recall of 4 weeks.

3.2.4.3 Echocardiography

Standard echocardiographic studies were performed with a commercially available ultrasound machine (System Vivid 7, GE Healthcare, Horten, Norway) with a 1,5 – 4,6 MHz transducer according to the standardized protocol in all patients at baseline and at 6 month follow up. LV chamber dimensions and wall thickness were measured in accordance with the guidelines of the American Society of Echocardiography (ASE) and the European Association of Cardiovascular Imaging (EACVI) [138] and

LV mass was calculated using a validated formula [139]. LV end-diastolic and end-systolic volumes and stroke volume were measured by the biplane method of discs from 2D apical 4 chamber and 2 chamber views and used to calculate LVEF. Tricuspid annular plane systolic excursion (TAPSE) by M-mode was used to assess the global right ventricular systolic function. Spectral mitral and tricuspid velocity recordings were obtained at a sweep speed of 50 mm/s at end-expiration. PW tissue Doppler imaging (TDI) was applied in the apical views to acquire mitral and tricuspid annular velocities. The sample volume was positioned within the septal and lateral insertion sites of the mitral leaflets and 1 cm within the lateral insertion site of the tricuspid leaflet. Spectral velocities and TDI measurements obtained at 3 consecutive cardiac cycles were averaged [140]. The following spectral Doppler mitral parameters were taken into analysis of LV function: peak early filling (E-wave) velocity, late diastolic filling (A-wave) velocity, the E/A ratio, deceleration time (DT), early diastolic annular velocity (e'), the E/e' ratio. Left ventricular (LV) diastolic dysfunction was graded as following: mild (grade 1) if the mitral E/A ratio was 0.8, DT > 200 ms and average E/e' ratio was < 8; moderate (grade 2) in case of mitral E/A ratio 0.8-1.5, DT 160–200 ms, average E/e' ratio 9-12; and severe if mitral E/A ratio was ≥ 2, DT < 160 ms, average E/e' > 13 [139].

3.2.5 Adverse events

Incidence of cardiovascular events and serious adverse events during all study were collected and recorded in database, including acute myocardial infarction, unstable angina, coronary revascularization, and cerebrovascular event.

3.2.6 Sub-study of imaging stress tests

The sub-study assessed the potential of CSWT to reduce myocardial ischemia determined by dobutamine stress echocardiography (DSE), cardiac single photon emission computed tomography (SPECT) and magnetic resonance imaging (MRI).

Each sub-study patient underwent DSE, cardiac SPECT and MRI before CSWT treatment and at 6 months follow-up, with DSE performed additionally at 3-month time-point. Beta-blocking medications were discontinued 48 hours, nitrates and other antianginal medications – 24 hours prior to stress tests in all patients. Patients were instructed to refrain from ingesting caffeine-containing beverages for at least 12 hours, before the myocardial perfusion imaging (MPI).

The analysis of each DSE, SPECT and cardiac MRI study images were performed by two blinded to study data independent observers. Discordant assessments were jointly reviewed**,** and concordant interpretation was assessed. Myocardial perfusion, regional wall motion, early and late contrast-enhanced images were performed using the LV 17-segment model [141-142].

During SPECT and MRI tests pharmacologic stress was induced by infusion of adenosine at a standard rate of 140 μg/kg/min (maximal total infusion duration of 6 minutes) [142]. All stress tests were performed under continuous monitoring of heart rate and blood pressure.

Segmental wall motion was semi-quantitatively graded as follows: normal=1; hypokinetic, meaning marked reduction of endocardial motion and thickening=2; akinetic defined as virtual absence of inward motion and thickening=3; and dyskinetic, corresponding to paradoxic wall motion away from the centre of the left ventricle in systole=4. The sum of all segment scores made wall motion score (WMS), divided by the number of interpretable segments made WMSI.

3.2.6.1 Dobutamine stress echocardiography

Electrocardiogram and echocardiogram were performed at rest and intravenous access was secured. Dobutamine was infused at 5, 10, 20, 30, and 40 μg/kg/min. When no end point was reached, atropine (in 4 divided doses of 0.25 mg up to a maximum of 1 mg) was added to the continuing 40 μg/kg/min dobutamine infusion. Non-echocardiographic criteria for test termination were the following: peak atropine dose; 85% of target heart rate; achievement of conventional signs of myocardial ischemia (severe chest pain and/or remarkable ST segment changes). The test also could be stopped for one of the following reasons: intolerable symptoms; limiting asymptomatic side effects consisting of: a) hypertension (systolic blood pressure >220 mmHg; diastolic blood pressure >120 mmHg); b) hypotension (relative or absolute): >30 mmHg fall of blood pressure; c) supraventricular tachycardia or atrial fibrillation; d) ventricular tachycardia or frequent, polymorphous premature ventricular beats.

Transthoracic stress echocardiographic studies were performed with a commercially available ultrasound machine (System Vivid 7 and 9, GE Healthcare, Horten, Norway) with a 1.5 – 4.6 MHz transducer. The images were stored digitally and analysed off-line using customised software (Echopac PCBT08, GE Healthcare). From the parasternal window the long and short axis of the LV and from the apical window 4-, 3- and 2-chamber views were acquired for comparison in four stages of stress test.

Test positivity was defined as the occurrence of at least one of the following conditions: 1) new dyssynergy in a region with normal resting function (i.e., normokinesis becoming hypo-, aki- or dyskinetic), 2) worsening of a resting dyssynergy (i.e., a hypokinesia becoming aki- or dyskinesia). For dobutamine stress echocardiography evaluation, moderate ischemia was defined as ≥3 segments with stress induced severe hypokinesis or akinesis [143].

Speckle tracking images (STI) were recorded at baseline and peak dobutamine levels with breath holding. The frame rate of stored apical 2-, 3- and 4-chamber cine-loops for speckle tracking analysis was in the range of 70–90 frames/sec. After manual tracing of endocardium borders in the end-systolic frame of the 2-D images, the software automatically tracked myocardial motion, creating 6 regions of interest in each apical image, with tracking quality labelled as verified or unacceptable. In segments with unacceptable tracking, the observer readjusted the endocardium trace line until a verified tracking was achieved. If this was not attainable, that segment was excluded from analysis. Graphical displays of deformation parameters (reflecting the average value of all of displacement markers in each segment) were then automatically generated for 6 segments in each view. Peak longitudinal systolic strain at rest and during stress was measured using automated vendor-suggested software.

DSE analysis includes wall motion score (WMS), global myocardial strain analysis, LV ejection fraction with Simpson's biplane method.

3.2.6.2 Myocardial perfusion imaging single-photon emission computed tomography

Imaging protocol. A 1-day ECG gated stress and rest myocardial perfusion single photon emission computed tomography. After 3 minutes of adenosine infusion patients were injected intravenously with a body mass index adjusted dose (250-350 MBq) of technetium 99m (^{99m}Tc)-sestamibi (MIBI). Rest MPI was performed at the same day, 4 hours after the stress MPI, with identical acquisition protocol. Gated SPECT studies were performed 60 minutes after ^{99m}Tc-MIBI injection, with a dual-head INFINIA GP3 (GE Medical Systems, USA) gamma camera, using a low-energy, high-resolution collimator, a 20% symmetrical window at 140 kiloelectron volts (keV), a 64 × 64 matrix, an orbit with 120 projections, with step-and-shoot acquisition at 3-degree intervals and a 25-sec time per stop, patients positioned in supine position with the arms held above the head.

Image analysis. Gated and non-gated SPECT MPI image sets were reconstructed using OSEM iterative reconstruction, with the dedicated Xeleris 2.1 workstation,

using Cedars-Sinai QGS/QPS software package. Images of the left ventricle were displayed in short, vertical long, and horizontal long-axis, and in polar maps.

Perfusion defects were scored using 5-point scoring system as follows: 0 = normal perfusion, 1 = minimal perfusion defect, 2 = moderate perfusion defect, 3 = severe perfusion defect, 4 = no perfusion/perfusion defect. A summed rest score (SRS) and summed stress scores (SSS) were obtained by summing the scores of the 17- segment of the rest and stress ^{99m}Tc-MIBI SPECT images, respectively. Summed difference scores (SDS) were calculating subtracting SSS from SRS. SSS represents the amount of ischemia. Each of these variables composes the extent and severity of perfusion defects. These scores were converted to percent of the total myocardium by dividing the summed scores by 68, the maximum potential score (4x17), and multiplying by 100 [32, 144-145]. These variables were named as total perfusion defect (TPD) at stress, rest and difference. Reversible perfusion defects were considered to represent myocardial ischemia. Fixed/non reversible perfusion defects were considered to be myocardial scars. Summed difference score 0 was considered as normal, between 1 to 4 as mild ischemia, between 4 to7 as moderate ischemia, and more than 7 as severe ischemia of myocardium [146].

Due to image quality not amenable to interpretation in one patient his perfusion images were excluded from the analysis.

An improvement in SDS at follow up by at least 3 points was considered to be significant.

3.2.6.3 Cardiac magnetic resonance imaging

Imaging protocol. Cardiac magnetic resonance imaging was performed with the patient in the supine position using a 1.5 T MR scanner (Avanto, Siemens Medical Solutions, Erlangen, Germany). A cardiac synergy coil was used for signal reception and cardiac synchronization was performed with a vector-ECG. All acquisitions were performed during end-expiratory breath-holds. After acquisition of standard cine scans for the assessment of left ventricular function, a turbo gradient echo pulse sequence (Turbo FLASH) was acquired for perfusion imaging. Then, after at least 3 minutes of adenosine infusion, Turbo FLASH sequence was repeated for stress first-pass perfusion imaging (intravenous bolus application of 0.15 mmol/kg of gadolinium based contrast agent (Magnevist). After 10 minutes waiting period, late gadolinium enhancment (LGE) imaging was done in the identical short axis geometry with the coverage of full left ventricle.

Cine imaging. Three short axis (apical, mid and basal short axis views) and three long axis geometries (4-, 2-, and 3- chamber view) were acquired using an electrocardiogram-trigered balanced steady state free precession sequence (echo time 1.22 ms, repetition time 63 ms, flip angle 65 degrees, field of view (FOV) 250 mm, voxel size 1.9 × 1.3 × 8 mm, matrix size 109 × 192).

Perfusion imaging. The perfusion imaging protocol consisted of a TrueFISP (fast imaging with steady state precession) sequence (echo time 177 ms, repetition time 0.99 ms, flip angle 50 degrees, spatial resolution 2.6 x 2.1 x 8.0 mm).

Late Gadolinium Enhancement imaging. Ten to fifteen minutes after infusing 0.15 mmol/kg of the commercially available gadolinium-based contrast agent (gadopentetate dimeglumine or gadodiamide), an inversion recovery gradient-echo sequence (echo time 3.2 ms, repetition time 700 ms, flip angle 25 degrees, FOV 400 mm, matrix size 156 × 256) was performed in the same planes as the cine images with an inversion time (240 to 330 ms) chosen to reduce the signal from normal myocardium. The typical voxel size was 2.1 × 1.6 × 8 mm. Angulation was kept constant for a short-axis and LGE imaging to enable a match between the LGE and wall motion images.

Image analysis. CMR examinations were analyzed with Argus software (Siemens). Short-axis endocardial contours were manually traced in end-diastole (start of R-wave) and in end-systole (smallest cavity area). Papillary muscles and trabeculations were included in the LV cavity (according to the ASE criteria). EDV and ESV were automatically computed in milliliters using the modified Simpson's rule by summing the cross-sectional areas contained by the endocardial borders of all short-axis slices included in the analysis.

For visual assessment of inducible perfusion deficits, rest and adenosine stress perfusion scans were magnified and displayed simultaneously. Segmental perfusion was interpreted as normal or abnormal. LGE was assessed on a 5-grade scale as follows: 0 = no hypernehancement, 1 = hyperenhancement of 1 to 25% of the tissue in each segment, 2 = hyperenhancement of 26 to 50% of the tissue, 3 = hyperenhancement of 51 to 75% of the tissue, 4 = hyperenhancement of 76 to 100% of the tissue. The LGE-score was obtained by summing the scores of the 17- segments of the LGE images.

3.2.7 Statistical analysis

Baseline patient characteristics were descriptively summarized: continuous variables were expressed as mean value ± standard deviation (SD), whereas categorical variables were expressed as absolute number (percentage). In the first step, the paired parameters were tested for normal distribution with the Shapiro-Wilk test. Chi-square tests or Fisher exact test were used to compare categorical variables. Variables with normal distribution were analyzed by using parametric test (t-test); while not normally distributed variables were analysed by using non-parametric tests (Mann-Whitney). A Wilcoxon rank sum test was used to compare data across independent groups, and a Wilcoxon signed rank test was used to compare paired data between baseline and follow up.

P values <0.05 (two sided) are considered statistically significant. The overall effect of the CSWT was evaluated by comparing the average change of variable in the treatment group with the average change of variable in the placebo group. Statistical analyses were performed with SPSS 20.0 (SPSS, Chicago, IL, USA).

Sample size calculation

For the sample size estimation, a power of 90% and a two-sided type I error of 5% were chosen. The sample size was calculated for each endpoint.

For main study: on the basis of published data [147] we have assumed a standard deviation of 110 s for total exercise duration, this produced 33 patients per group are necessary to detect a ≥90 s difference. Estimating withdrawal of 10% of patients after randomization, approximately 73 patients would have to be included in the study.

For imaging stress tests sub-study: on the basis of study results [148] we have assumed a standard deviation of 6.4 for wall motion score, 22 patients per group are necessary to detect a ≥ 3 points difference. Estimating withdrawal of 10% of patients after randomization, approximately 50 patients would have to be included in the study. On the basis of study results [148] we have assumed a standard deviation of 3.8 for summed difference score, 18 patients per group are necessary to detect a ≥ 3 points difference. Estimating withdrawal of 10% of patients after randomization, approximately 40 patients would have to be included in the study.

The largest sample size was chosen.

Inter-observer agreement

Inter-observer agreement of DSE and SPECT evaluations is determined by having two independent investigators measure representative parameters of stress tests in 15 and 30 randomly selected patients, respectively.

Reproducibility is expressed as the mean difference and the standard deviation of the differences (SD) between values of observer 1 and observer 2 [149].

As measure of reliability intraclass correlation coefficients (ICC) and their confidence intervals based on consistency 2-way mixed effects model were calculated for each parameter [150]. ICC values less than 0.5 indicate poor reliability, values between 0.5 and 0.75 indicate moderate reliability, values between 0.75 and 0.9 indicate good reliability, and values greater than 0.9 indicate excellent reliability [151]. ICC estimates and their 95% confident intervals were calculated using the icc{irr} function of R package (version 3.4.1) [152].

The mean differences of inter-observer measurements of representative parameters of DSE, SPECT and MRI tests are summarized in Table 5, Table 6 and Table 7, respectively.

TABLE 5. **Reproducibility and reliability of dobutamine stress echocardiography**

	Reproducibility	**Reliability**	
	Mean difference ± SD	Intraclass correlation coefficient	95% CI
Wall motion score at rest	-0.2 ± 4.1	0.861	(0.64, 0.95)
Wall motion score at stress	-1.7 ± 4.6	0.816	(0.54, 0.93)
LV ejection fraction at rest, %	1.3 ± 4.6	0.932	(0.81, 0.98)
LV ejection fraction at stress, %	3.8 ± 8.3	0.774	(0.45, 0.92)
LV end-diastolic volume, ml	-3.1 ± 11.9	0.878	(0.68, 0.96)
LV end-systolic volume, ml	-0.2 ± 10.0	0.838	(0.58, 0.94)
Global PSS rest, %	-1.02 ± 1.8	0.625	(0.14, 0.87)
Global PSS stress, %	-2.0 ± 2.6	0.602	(0.13, 0.85)

CI – confidence interval, LV – left ventricular, PSS – peak systolic strain, SD – standard deviation; 4-, 3- and 2CH- 4-, 3- and 2-chamber view.

TABLE 6. **Reproducibility and reliability of single photon emission computed tomography**

	Reproducibility	**Reliability**	
	Mean difference ± SD	Intraclass correlation coefficient	95% CI
Summed stress score	0.01 ± 3.1	0.950	(0.92, 0.97)
Summed rest score	-0.57 ± 2.9	0.942	(0.91, 0.96)
Summed difference score	0.73 ± 3.4	0.757	(0.64, 0.84)

CI – confidence interval, SD – standard deviation.

TABLE 7. **Reproducibility and reliability of cardiac magnetic resonance**

	Reproducibility	**Reliability**	
	Mean difference ± SD	Intraclass correlation coefficient	95% CI
LV ejection fraction, %	- 0.26 ± 3.5	0.935	(0.84, 0.98)
End diastolic volume, ml	6.8 ± 10.5	0.972	(0.93, 0.99)
End systolic volume, ml	-4.17 ± 22	0.705	(0.37, 0.88)

LV – left ventricle, CI – confidence interval, SD – standard deviation.

Number need to treat calculation (NNT)

Study outcome was expressed as an event rate, and then NNT was calculated as the inverse of the absolute risk reduction (ARR) expressed as decimal [153-154].

ARR = (Control event rate) – (Experimental event rate)

NNT = 1/ARR

4. RESULTS

4.1 Results of systematic review and meta-analysis

4.1.1 Study characteristics and patient population

From 590 identified publications after exclusion of irrelevant, experimental, animal and non-English studies 39 studies were selected for review following the PRISMA statement [131], see in Figure 11; their common characteristics are summarized in

FIGURE 11. **Study flow diagram**

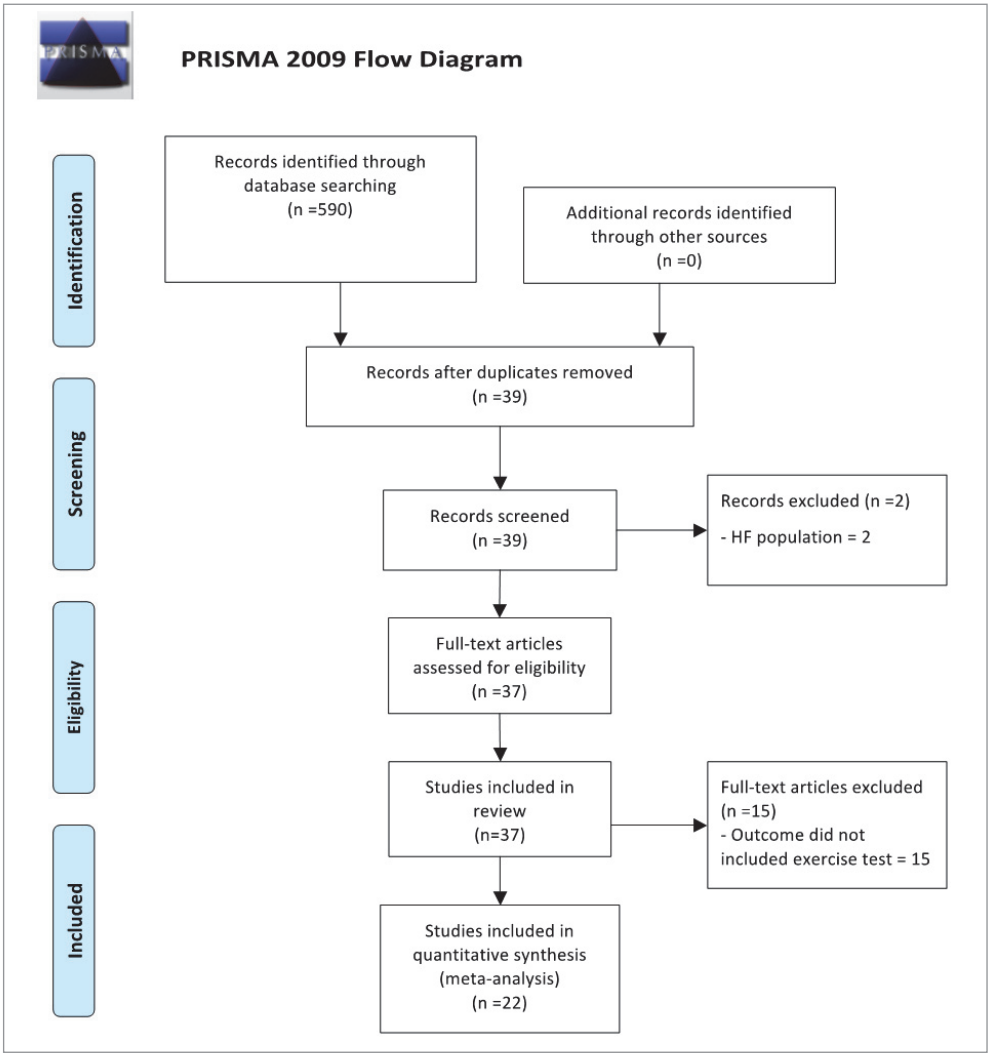


Table 8. Among them 8 randomized controlled trials, 4 non-randomized controlled trails and 27 single arm trials were identified. Study sample size was in the range from 8 to 111 patients; median duration of follow-up lasted 4 months (IQR 2.5, 6) after the end of treatment.

TABLE 8. **Common characteristics of selected 39 human studies of cardiac shock wave therapy**

Author (year)	Study population	Stress test, used to detect myocardial ischemia	Patient Total/ control (n)	Age (years)	Sex, male , n (%)	FU, mon-ths
Non-controlled studies						
Caspari G. H. et al. (1999) [130]	Stable angina	SPECT	9/ -	65±7	nd	6[a]
Gutersohn A. et al. (2003) [155]	Stable angina	SPECT, ET	25/ -	66±7.3	nd	6[a]
Gutersohn A. et al. (2005) [156]	Stable angina	SPECT	14/ -	66	nd	12[b]
Gutersohn A. et al. (2006) [157]	Stable angina	SPECT	23/ -	66	nd	60[a]
Fukumoto Y.et al. (2006) [158]	Stable angina	ET, SPECT	9/ -	67.8	5 (55.5)	12[a]
Lyadov K. et al. (2006) [159]	Stable angina	DSE, CPET	13/ -	59.6±6.9	11 (85)	1[a]
Naber C. et al. (2007) [160]	Stable angina	SPECT	25/ -	63.8±8.2	nd	3[a]
Khattab A.A. et al. (2007) [161]	Stable angina	SPECT	10/ -	nd	nd	1[a]
Naber C. et al. (2008) [162]	Stable angina	SPECT	24/ -	63.8±8.2	18 (75)	3[a]
Takayama T. et al. (2008) [163]	Stable angina	SPECT	17/ -	67.5	17 (100)	6[a]
Wang Y. et al. (2010) [164]	Stable angina	DSE, SPECT	9/ -	63.7±5.7	9 (100)	1[a]
Faber L. et al. (2010) [165]	Stable angina	PET, CPET	16/ -	66±10	nd	1[a]
Vainer J. et al. (2010) [166]	Stable angina	ET, SPECT	22/ -	69±7	18 (81.8)	4[a]
Vasyuk Y.A. et al. (2010) [167]	Ischemic HF	DSE, SPECT	24/ -	63.3±6.1	20 (83.3)	6[a]
Alunni G. et al. (2011) [168]	Stable angina	SPECT	16/ -	71±5.6	12 (80)	12
Vainer J. et al. (2012) [169]	Stable angina	SPECT	50/ -	68±9	40 (80)	4[a]
Alunni G. et al. (2013) [170]	Stable angina	SPECT	25/ -	nd	nd	6[a]
Gabrusenko S.A. et al. (2013) [171]	Stable angina	SPECT	17/ -	67.4±8.6	14 (82.4)	1[b]
Zuoziene G. et al. (2013) [148]	Stable angina	DSE, SPECT	40/ -	67.7±7	30 (75)	3[a]
Prinz C. et al. (2013) [172]	Stable angina	ET, PET	43/ -	67±10	nd	1[a]
Cassar A. et al. (2014) [173]	Stable angina	ET, SPECT	15/ -	65.0±12.1	13 (86.7)	4[a]
Faber L. et al. (2014) [174]	Stable angina	PET	47/ -	67±10	nd	1,5[a]
Prasad M. et al. (2015) [23]	Stable angina	SPECT, ET	111/ -	62.9±10.9	98 (83.7)	3-6[b]
Kaller M. et al. (2015) [175]	Stable angina	PET, ET	21/ -	65±10	13 (61.9)	1.5-2[a]
Cai HY. et al. (2015) [176]	Stable angina	ET	26/ -	63±10	23 (88.5)	4[a]
Liu BY et al. (2015) [177]	Stable angina	SPECT	11/ -	nd	nd	12[a]
Vainer J. et al. (2016) [178]	Stable angina	ET, SPECT	33/ -	69.7±8	27 (82)	4[a]
Non-randomized, controlled studies						
Kikuchi Y. et al. (2010)[c] [179]	Stable angina	CPET	8/ 8	70±3	5 (62.5)	3[a]
Kazmi W.H. et al. (2012) [180]	Stable angina	SPECT	86/ 43	57.7±10.5	73 (84.5)	6[a]
Alunni G. et al. (2015) [20]	Stable angina	SPECT	72/ 29	70±5.3	60 (83.3)	6[a]
Nirala S. et al. (2016) [181]	Stable angina	ET, DSE	52/ 11	63.4±10.8	43 (82.7)	72[a]

TABLE 8 (Continuation)

Author (year)	Study population	Stress test, used to detect myocardial ischemia	Patient Total/ control (n)	Age (years)	Sex, male , n (%)	FU, mon-ths
Randomized, controlled studies						
Peng Y.Z. et al. (2012) [182]	Ischemic HF	SPECT	50/ nd	nd	nd	1[a]
Wang Y. et al. (2012)[d] [183]	Stable angina	DSE, SPECT	55/ 14	64.1±9.8	47 (85)	12[b]
Zhao L. et al. (2015)[e] [184]	Stable angina	SPECT, ET	87/ 27	66.8±8.4	68 (78%)	12[b]
Randomized, placebo controlled studies						
Schmid J.P. et al. (2006) [185]	Stable angina	SPECT	15/ 8	68±8	14 (60%)	3[a]
Yang P. et al. (2012)[d] [186]	Stable angina	SPECT	45/ 20	67±8.3	36 (80%)	3[b]
Leibowitz D. et al. (2012)[d] [147]	Stable angina	ET	28/ 10	63.3±9.2	24 (85.7)	3[a]
Schmid J.P. et al. (2013) [22]	Stable angina	CPET	21/ 10	68.2±8.3	19 (90.5)	3[a]
Yang P. et al. (2013)[d] [187]	Stable angina	SPECT	25/ 11	65.1±8.5	18 (72%)	6[a]

ET - ECG Exercise test, FU – follow up, CPET - cardiopulmonary exercise test, DSE - dobutamine stress echocardiography, PET - positron emission tomography, SPECT - single photon emission computed tomography, nd - no data, a - time after the end of treatment (treatment ends at 9th treatment week), b - time from the treatment initiation, c - double blind, placebo controlled, crossover design; d - double blind, e - single blind.

In total, 1189 patients were included in 39 studies with 1006 patients treated with CSWT (483 patients underwent CSWT in controlled studies), 183 patients entered control groups. The mean age of patients was 66±6.7 years, 80.8% were men. Studies did not include patients with a history of acute coronary syndromes less than 3 months before enrolment, recent revascularization and thrombus in the left ventricle. Medical treatment provided in selected studies' reports is summarized in Table 9.

In most studies the treatment protocol consisted of 9 sessions conducted over a 9-week period with three treatment series performed within the 1st, 5th and 9th week. Shock waves were applied to targeted area of myocardial ischemia detected by imaging stress tests. Wang showed that a modified regimen of 9 treatment sessions within 1 month had similar therapeutic effect, as compared to the standard treatment protocol [183]; only a standard treatment group from this study was included in meta-analysis in order to reduce possible heterogeneity.

No procedure related serious adverse events and good treatment tolerance were reported. In 300 patients, included in 12 studies, cardiac enzymes were studied for safety with no elevation observed after CSWT treatment except one mild case [161]. Some patients noted transient dizziness [178], few patients reported mild chest pain during first procedure, without elevation of troponin, and by decreasing of SW energy further procedures were completed [22, 164, 176, 181, 183, 187].

TABLE 9. **Medical treatment provided in selected studies of cardiac shock wave therapy**

	Patients	Medical treatment						
		β-blocker	Nitrates	CCB	ACEI / ARB	Statins	Anti-platelet	Other anti-anginal
Non-controlled studies								
Naber C. (2008) [160]	Test group (n=24)	24 (100)	18 (75)	11 (45.8)	17 (70.8)	24 (100)	24 (100)	nd
Cassar A. (2014) [173]	Test group (n=15)	12 (78.6)	12 (78.6)	7 (42.9)	8 (50)	15 (100)	15 (100)	6 (35.7)
Prasad M. (2015) [23]	Test group (n=111)	102 (91.9)	98 (88.6)	68 (60.8)	74 (66.7)	nd	107 (96)	nd
Kaller M. (2015) [175]	Test group (n=21)	21 (100)	21 (100)	4 (19)	19 (90.5)	19 (90.5)	14 (66.7)	4 (19)
Vainer J. (2016) [178]	Test group (n=33)	28 (85)	30 (91)	26 (79)	19 (57)	nd	31 (94)	nd
Non-randomized, controlled studies								
Alunni G. (2015) [20]	Test group (n=43)	39 (90)	31 (72)	nd	nd	39 (90)	40 (93)	11 (25.8)
	Control group (n=29)	26 (89)	20 (69)	nd	nd	27 (93)	28 (96)	8 (27)
Randomized, controlled studies								
Wang Y.[a] (2012) [183]	Test group (n=20)	18 (90)	8 (40)	6 (30)	11 (57.1)	18 (90)	20 (100)	nd
	Test group (n=21)	18 (85.7)	9 (42.9)	11 (52.4)	12 (57.1)	17 (81)	21 (100)	nd
	Control group (n=14)	13 (92.9)	4 (38.6)	4 (28.6)	8 (75)	13 (92.9)	14 (100)	nd
Zhao L.[a] (2015) [184]	Test group (n=32)	23 (71.9)	24 (75)	17 (53.1)	20 (62.5)	22 (68.8)	32(100)	nd
	Test group (n=30)	24 (80)	22 (73.3)	14 (46.7)	22 (73.3)	19 (63.3)	30 (100)	nd
	Control group (n=25)	17 (68)	19 (76)	14 (56)	17 (69)	17 (68)	25 (100)	nd
Randomized, placebo controlled studies								
Leibowitz D. (2012) [147]	Test group (n=18)	15 (83)	11 (61)	12 (67)	nd	18 (100)	17 (95)	nd
	Control group (n=10)	7 (70)	6 (60)	5 (50)	nd	8 (80)	8 (80)	nd
Schmid J.P. (2013) [22]	Test group (n=11)	8 (73)	4 (36)	2 (18)	10 (91)	10 (91)	11 (100)	7 (64)
	Control group (n=10)	7 (70)	6 (60)	5 (50)	7 (70)	9 (90)	10 (100)	5 (50)
Yang P. (2013) [187]	Test group (n=14)	9 (64.3)	9 (64.3)	7 (63.3)	9 (64.3)	9 (64.3)	10 (71.4)	nd
	Control group (n=11)	7 (63.6)	6 (54.5	5 (45.5)	8 (72.7)	9 (81.8)	7 (63.6)	nd

ACEI - Angiotensin converting enzyme inhibitor, ARB - Angiotensin II receptor blocker, C - control or placebo group, CCB - calcium channel blocker, T - test group, nd - no data.

4.1.2 Cardiac shock wave therapy effect on clinical variables

All selected studies demonstrated positive effect of CSWT on at least 2 of selected clinical variables (results of 7 controlled studies are shown in Table 10).

TABLE 10. **Effect of cardiac shock wave therapy in 7 controlled studies: clinical and quality of life parameters.**

		Period	CCS class	Nitroglycerine consumption	NYHA class	Seattle angina questionnaire
Yang P. 2013[a] [187]	Test group (n=14)	Baseline	2.0 (1.0, 3.0)	2.0 (0.0, 3.0)	2.0 (1.0, 2.0)	73.5 (60.5, 81.0)
		Follow up	1.0 (1.0, 2.0)[d]	1.0 (0.0, 2.0)[d]	1.0 (1.0, 1.0)[d]	82.0 (74.5, 88.0)[d]
	Placebo group (n=11)	Baseline	2.0 (1.0, 3.0)	2.0 (1.0, 3.0)	1.0 (1.0, 2.0)	73.0 (63.0, 80.0)
		Follow up	2.0 (1.0, 2.0)	2.0 (0.0, 2.0)	2.0 (1.0, 2.0)	78.0 (69.0, 85.0)
Wang Y. 2012[a] [183]	I group[e] () (n=20)	Baseline	2 (1, 2)	1 (0, 2)	1.5 (1, 3)	64.9±11.72
		Follow up	1 (1, 1)[c,d]	0 (0, 1)	1 (1, 1)[c]	75.0±10.45[c,d]
	II group[f] (n=21)	Baseline	3 (2, 3)	2 (0, 3)	2 (1, 2.5)	67.9±13.0
		Follow up	2 (1, 2)	0 (0, 1)	1 (1, 1)	76.14±12.28
	Control group (n=14)	Baseline	2 (2, 3)	1 (0, 4)	2 (1, 3)	63.21±11.89
		Follow up	2 (1, 2.3)	0 (0, 2)	1 (1, 2.3)	60.14±12.82
Yang P. 2012[b] [186]	Test group (n=25)	Baseline	2.72±0.46	2.35±0.86	2.16±0.69	65.96±11.78
		Follow up	1.46±0.58[c,d]	1.0±0.73[c,d]	1.48±0.65[c,d]	76.4±11.78[c,d]
	Placebo group (n=20)	Baseline				
		Follow up	NSC	NSC	NSC	NSC
Nirala S. 2016[b] [181]	Test group (n=41)	Baseline	2.21±0.85	1.34±1.35	1.85±0.96	66.34±12.34
		Follow up	1.14±0.57	0.21±0.82[d]	1.04±0.49[d]	79.92±25.14
	Control group (n=11)	Baseline	1.81±0.75	1.36±1.62	1.36±0.67	84±7.61
		Follow up	2.18±0.75	2±1.18	2.09±0.94	72.72±12.33
Kikuchi Y. 2010[a] [179]	Test group (n=8)	Baseline	3.0	4.0	-	-
		Follow up	2.25[c]	1.0[c]	-	-
	Placebo group (n=8)	Baseline	2.75	4.0	-	-
		Follow up	2.75	3.0*	-	-
Kazmi W.H.[b] 2012 [180]	Test group (n=43)	Baseline	2.63±0.7	-	2.48±0.6	-
		Follow up	1.95±0.8[c]	-	1.95±0.5[c]	-
	Control group (n=43)	Baseline	2.63±0.7	-	2.48±0.6	-
		Follow up	2.63±0.7	-	2.46±0.6	-
Alunni G. 2015 [20]	Test group (n=43)	Baseline	2.67±0.75	26(60.5%)	2.51±0.74	-
		Follow up	1.33±0.57[d]	9 (20%)[d]	1.23±0.42[d]	-
	Control group (n=29)	Baseline	2.52±0.78	18 (41%)	2.32±0.79	-
		Follow up	1.92±0.69	13 (44.8%)	1.73±0.59	-

CCS - Canadian Cardiovascular Society Angina Class, nitroglycerine consumption is expressed as number of tablets per day, NYHA - New York Heart Association class, NSC - no significant changes, a - values expressed as median and interquartile range, b - values expressed as mean ± standard deviation, c - $p<0.05$, compared to baseline in corresponding group, d - $p<0.05$, compared with control group, e - standard treatment, f - modified treatment.

In CSWT patients CCS angina scale (31 studies) and NYHA class (13 studies) have reduced by median 1 (IQR 1, 1) and 1 (IQR 0, 1), respectively, compared with the baseline values. This symptomatic improvement was significant in comparison with controls in 5 out of 7 controlled trials. The frequency of weekly nitroglycerine use declined 40 - 75% (in 16 reporting studies).

4.1.3 Risk of Bias

Assessment of risk of bias in randomized controlled studies is shown in Table 11. Two RCT were eliminated from this analysis (1= heart failure population, 1= not full length manuscript). The high risk of bias in patients' attribution to groups, blinding of personnel, outcome assessment and sample size calculation was determined.

4.1.4 Meta-analysis of cardiac shock wave therapy effect on exercise capacity

Two studies investigating ischemic heart failure population were excluded from meta-analysis [167, 183].

From remaining 37 studies only 22 studies provided data suitable to be included in meta-analysis to evaluate the impact of CSWT on the parameters of exercise tolerance (including mean and standard deviation or standard error of mean values, both baseline and post procedure), (Figure 12, Table 12).

TABLE 11. **Assessment of risk of bias in 6 randomized controlled studies**

	Wang Y. 2012 [183]	Zhao L. 2015 [184]	Yang P. 2012 [186]	Leibowitz D. 2012 [147]	Schmid J.P. 2013 [22]	Yang P. 2013 [187]
Random sequence generation	high risk	low risk	high risk	high risk	high risk	high risk
Allocation concealment	high risk	high risk	high risk	high risk	high risk	high risk
Blinding of participants	high risk	low risk	high risk	low risk	low risk	high risk
Blinding of personnel who provide CSWT treatment	high risk	high risk	high risk	high risk	high risk	high risk
Blinding of outcome assessment	unclear risk	high risk	high risk	high risk	high risk	high risk
Incomplete outcome data	high risk	high risk	low risk	high risk	high risk	low risk
Selective reporting	low risk	low risk	low risk	low risk	low risk	low risk
Blinding of CWST procedure	high risk	low risk	high risk	low risk	low risk	high risk
Endpoints were based on sample size calculation	high risk	high risk	high risk	high risk	high risk	high risk
Complete testing in both groups	low risk	low risk	low risk	low risk	low risk	low risk

CSWT - cardiac shock wave therapy.

FIGURE 12. **Forest plot for overall impact of cardiac shock wave therapy on exercise capacity**

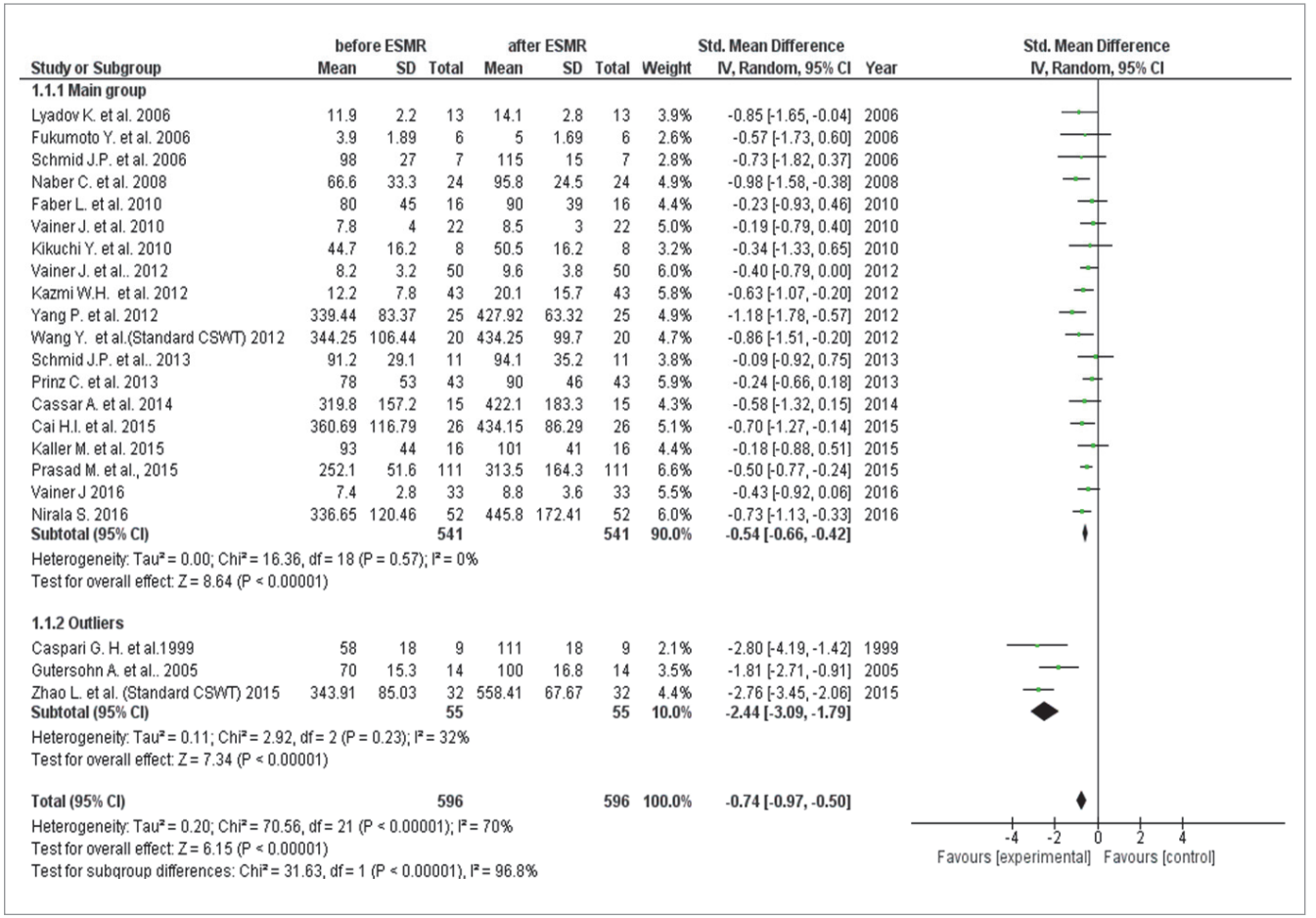


TABLE 12. **Effect of cardiac shock wave therapy on the parameters of exercise capacity**

Study (year)	Study type	Number of patients (Test/ Control)	Test group		Control group		Measurement unit
			Baseline	Follow up	Baseline	Follow up	
Caspari G.H. (1999) [130]	Single arm	9/-	58±18	111±18[f]	-	-	Wt
Gutersohn A. (2005) [156]	Single arm	14/-	70±15.3	100±16.8[f]	-	-	Wt
Lyadov K. (2006) [159]	Single arm	13/-	11.9±2.2	14.1±2.8	-	-	VO_2 ml/kg/min
Fukumoto Y. (2006) [158]	Single arm	9/-	3.9±1.9	5±1.7	-	-	Met
Schmid J.P. (2006) [185]	Randomized, Placebo controlled	7/8	98±27	115±15	88±21	92±30	Wt
Naber C. (2008) [162][a]	Single arm	24/-	66.6±33.3	95.8±24.5	-	-	Wt
Faber L. (2010) [165]	Single arm	16/-	80±45	90±39[f]	-	-	Wt
Vainer J. (2010) [166]	Single arm	22/-	7.8±4	8.5±3	-	-	Minutes
Kikuchi Y. (2010)[b] [179]	Placebo controlled	8/8	44.77±16.2	50.5±16.2	43±17	43±17	Wt
Vainer J. (2012) [169]	Single arm	50/-	8.2±3.2	9.6±3.8[f]	-	-	Minutes
Kazmi W.H. (2012) [180]	Controlled	43/43	12.2±7.8	20.1±15.7	10.5±3.6	10.1±4.2	Minutes
Yang P. (2012) [187]	Randomized, Placebo controlled	25/20	339.44±83.3	427.9±63.3	nd	nd	Meters
Wang Y. (2012) [183][c]	Randomized, controlled	31/14	344.3±106.4	434.3±99.7	363.9±150.9	325.9±157.3	Meters
Schmid J.P. (2013) [22]	Randomized, Placebo controlled	11/10	79.9±28	95.1±28[f]	98.3±28	106.8±23	Wt
Prinz C. (2013) [172]	Single arm	43/-	78±53	90±46[f]	-	-	Wt
Cassar A. (2014) [173]	Single arm	15/-	319.8±157.2	422.1±183.3[f]	-	-	Seconds
Zhao L. (2015) [184][c]	Randomized, controlled	32/25	343.9±85.0	489.4±72.2[f]	351.6±94.4	342.2±99.3	Seconds
Prasad M. (2015) [23]	Single arm	111/-	252.1±51.6[d]	313.5±164.3[f]	-	-	Seconds
			457.0±146.8[e]	606.0±126.4[f]	-	-	
Kaller M. (2015) [175]	Single arm	16/-	93±44	101±41	-	-	Wt
Cai HY. (2015) [176]	Single arm	26/-	360.7±116.8	434.2±86.3[f]	-	-	Meters
Nirala S. (2016) [181]	Controlled	41/11	336.7±120.5	445.8±172.4	491.7±91.9	388.9±83.0	Meters
Vainer J. (2016) [178]	Single arm	33/-	7.4±2.8	8.8±3.6[f]	-	-	Minutes

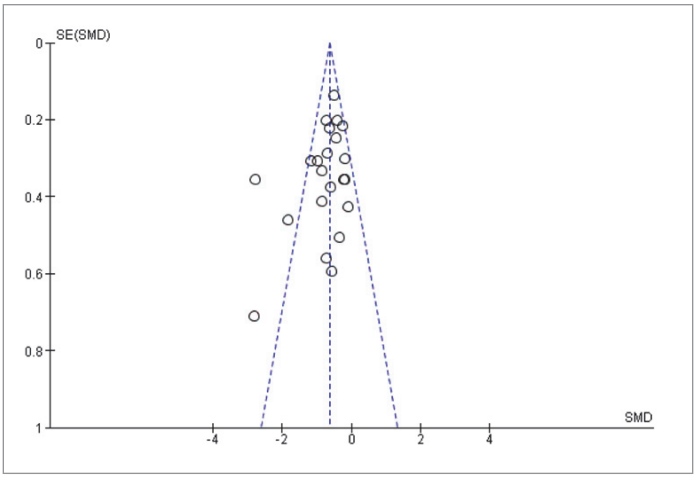
All values presented as mean ± SD, a - value presented as mean ± SE, SE calculated into SD using standard formulas; b - cross over design, c - group with standard CSWT protocol, d - Bruce protocol, e - modified Bruce protocol, f - $p<0.05$, compared to baseline in corresponding group.

Across 22 contributing studies (596 participants) the exercise capacity was significantly improved after CSWT, as compared with the baseline values (SMD = −0.74; 95% CI, −0.97 to −0.5; p<0.001, I^2=70%) (Figure 12); median follow up period of included studies made 4 months (IQR 3, 6) after end of treatment.

In order to explain heterogeneity, we performed sensitivity analysis by removing from analysis one of the studies at a time. Overall effect changed to -0.61, 95%CI (-0.78 to -0.44), p<0.001 when excluding study of Zhao L. et al. (2015) and to -0.77, 95% CI (-1.01 to -0.52), p<0.001 when excluding study of Prinz C. et al (2013).

Funnel plot analysis was performed in order to evaluate publication bias. It was founded that funnel plot graph was asymmetrical (Figure 13).

FIGURE 13. **Funnel plot diagram of publication bias**



The standardized mean difference (SMD) on the *x*-axis is plotted against the standard error (SE) of the log (SMD) on the *y*-axis. A symmetrical distribution of studies indicates the absence of publication bias. An asymmetrical distribution with, for example, relatively smaller studies with a positive result (in the *lower right part* of the plot) would suggest the presence of publication bias.

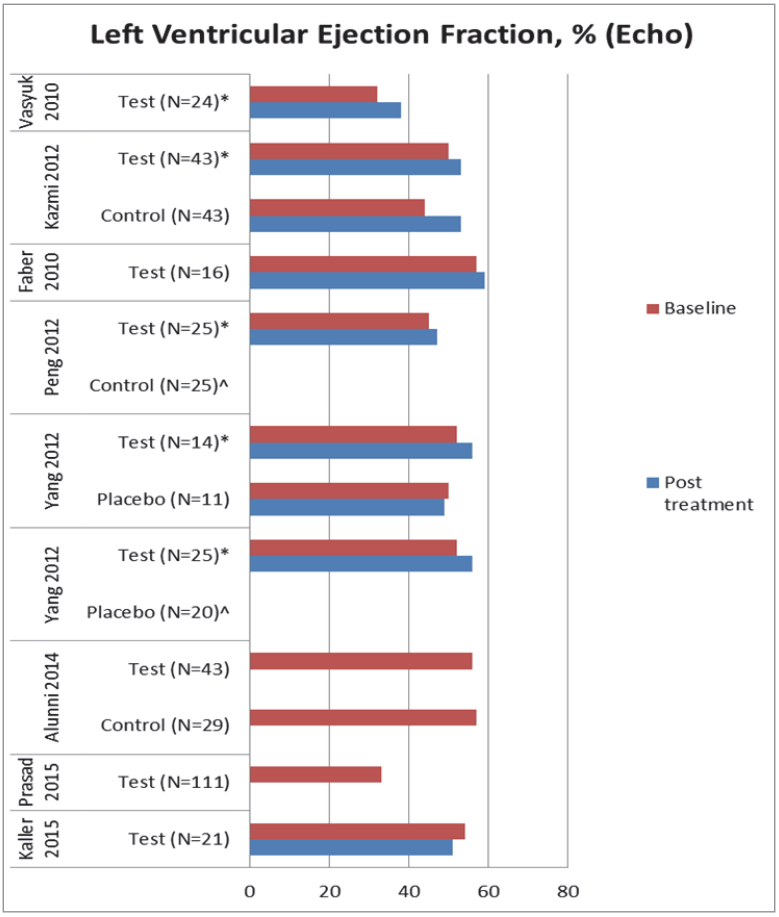
Three outliers were identified on a funnel plot representing studies of Caspari GH et al. (1999), Gutersohn A et al. (2005) and Zhao L. et al. (2015). Without these studies heterogeneity decreased to I^2=0%, p=0.57 with SMD=-0.54; 95% CI, −0.66 to −0.42; p<0.001 (see Figure 12).

Interestingly, in uncontrolled studies treatment effect was smaller than in controlled studies (SMD -0.59 (-0.81, -0.36) vs -0.93 (-1.44, -0.42)). However, data were not sufficient to perform comparison between CSWT and control groups across included studies.

4.1.5 Cardiac shock wave therapy effect on left ventricular function

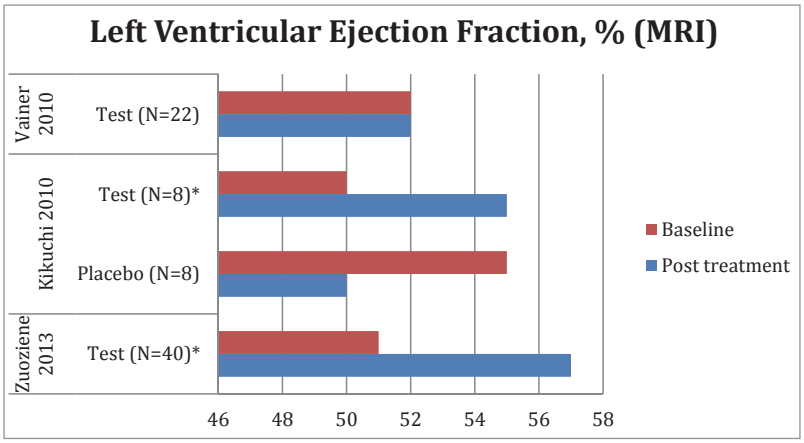
Figure 14 and Figure 15 demonstrate changes of rest left ventricular (LV) ejection fraction assessed by echocardiography and magnetic resonance imaging (MRI), respectively. Mean increase of rest LVEF 4.4±9.4% assessed by echocardiography was observed in 7 of 13 studies. Changes of LV end diastolic diameter are shown in Figure 16. Seven studies demonstrated significant LV ejection fraction improvement from baseline due to CSWT, while in eight studies no statistically significant changes were found. No comparisons with control groups were reported.

FIGURE 14. **Changes of left ventricular ejection fraction evaluated by echocardiography in cardiac shock wave therapy studies**



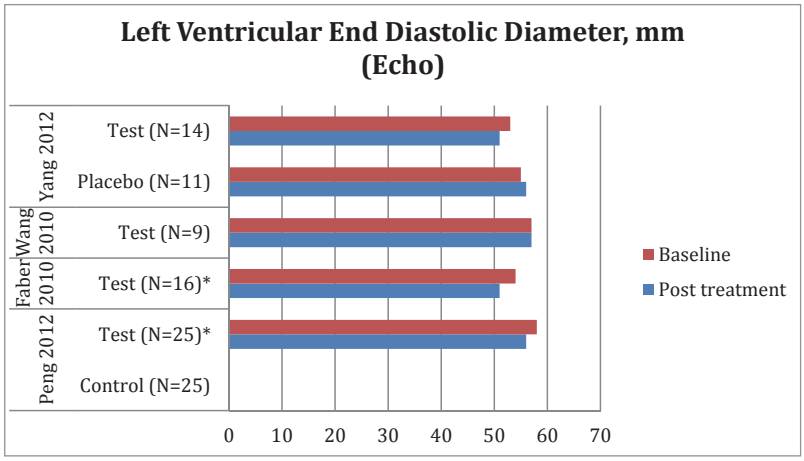
* = p<0.05 compared to baseline, ^ = no significant changes, no figures indicated.

FIGURE 15. **Changes of left ventricular ejection fraction evaluated by magnetic resonance imaging in cardiac shock wave therapy studies**



* - p<0.05 compared to baseline.

FIGURE 16. **Changes of left ventricular end diastolic diameter in cardiac shock wave therapy studies**



* - p<0.05 compared to baseline.

4.1.6 Cardiac shock wave therapy effect on myocardial perfusion

Significant improvement of myocardial perfusion was demonstrated by SPECT in 27 of 32 studies, and in 2 of 4 studies by PET. Beneficial changes of myocardial perfusion were associated with increase of LVEF by rest echocardiography. Cassar et al. [173] compared segments that were treated with CSW and those that were not,

and found that after 4 months of follow–up the progression of ischemic burden of untreated segments was significantly greater.

4.1.7 Cardiac shock wave therapy effect on angiogenesis markers

Angiogenesis markers were assessed in 4 studies. Increased VEGF concentration was revealed after CSWT in 3 single arm studies [163, 171, 176]. Kikuchi et al. in controlled trial found that the number of circulating progenitor cells (CD 34^+/KDR^+ and CD 34^+/KDR^+/c-kit^+) in peripheral blood remained unchanged at follow up in two study groups [179]. Cai et al. observed significant increase in the number of circulating progenitor cells ($CD45^{low}$/$CD34^+$/VEGFR2) in peripheral blood [176]. Again, these data were not investigated in comparison with controls.

4.2 Results of clinical randomized, triple blind, sham procedure controlled study

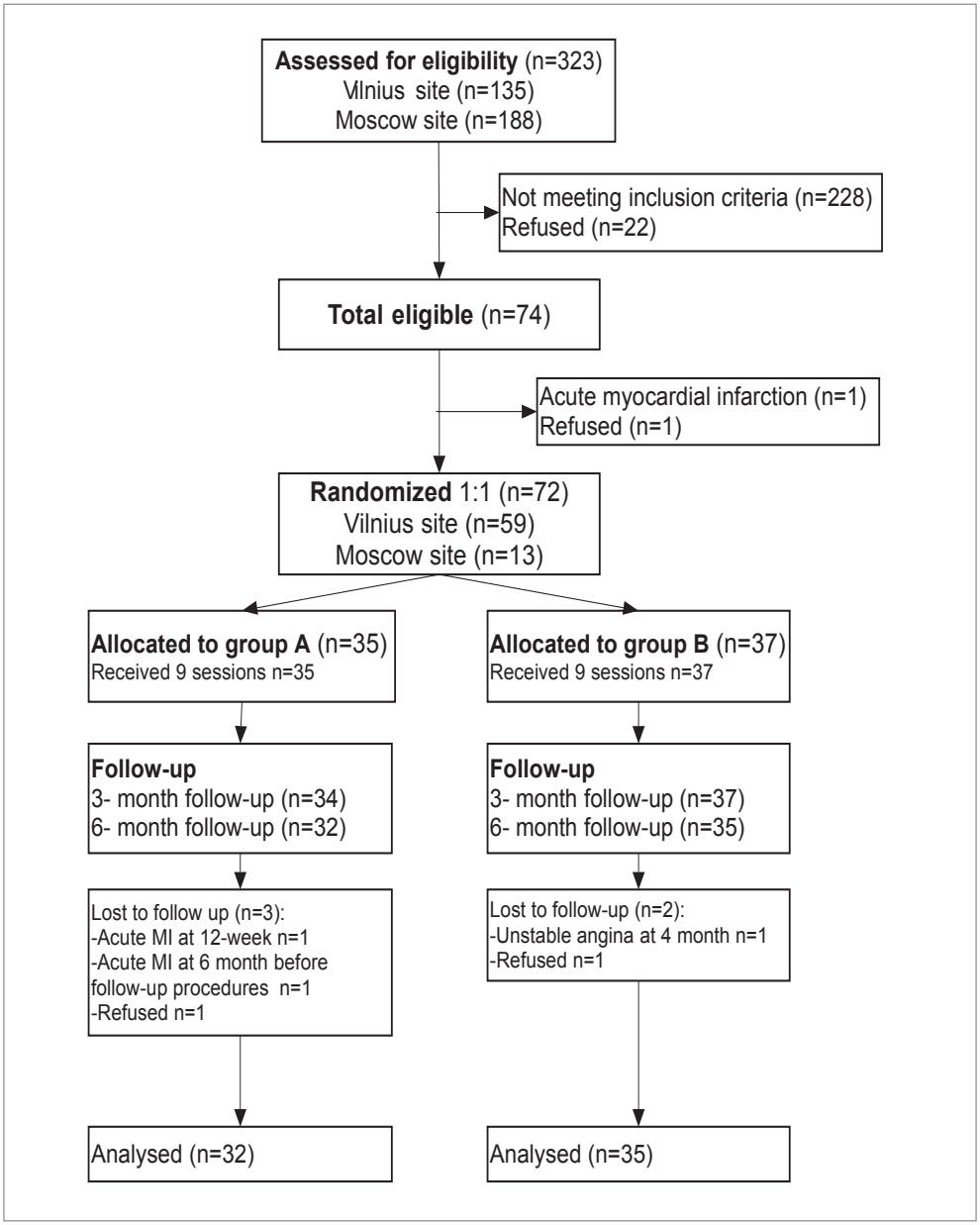
From June 2013 to December 2015, 323 patients were screened for eligibility and 72 of them were randomized at two centers: 59 of 135 in Vilnius University Hospital Santaros klinikos, and 13 of 188 in Moscow State University of Medicine and Dentistry, respectively (Figure 17). Specially for this trial professional statistician generated random sequence and only one principal investigator (JC) had access to digitally stored allocation sequence protected by password. Principle investigator (JC) performed allocation procedure being blinded to clinical and instrumental data of enrolled patient. The study investigator who performed patients' screening was blind to allocation sequence. According to random number table eligible patients were randomized (1:1) to group A (n=35) and group B (n=37) to undergo therapy with corresponding applicators in a double-blinded manner.

4.2.1 Baseline characteristics of clinical and functional status

The baseline characteristics of groups are presented in Table 13. The cardiac risk factor profile was high as each patient had at least two risk factors for cardiovascular disease. Majority of patients had undergone revascularization (percutaneous coronary intervention or coronary artery by-pass grafting surgery), and 9 patients in each group had indergone both procedures. Several significant differences in baseline characteristics were revealed between the two study groups: there were more history of myocardial infarction (p=0.005) and positive family history for cardiovascular

diseases (p=0.020) in OMT + placebo group. There were no significant differences between countries in any baseline characteristics (age, cardiovascular risk factors, medical history and clinical parameters, all p>0.005).

FIGURE 17. **Flow chart of study patients**



MI - Myocardial infarction.

TABLE 13. **Baseline characteristics of the study patients**

Variable	OMT + placebo group (n=35)	OMT + CSWT group (n=37)	*P* value
Demographic characteristics			
Age, years	68.8 ± 8.3	67.6 ± 8.3	0.546
Male sex, n (%)	29 (82.8)	23 (62.2)	0.053
Cardiovascular risk factors			
Hyperlipidemia, n (%)	30 (85.7)	31 (83.8)	0.824
Hypertension, n (%)	34 (97.1)	36 (96.3)	0.851
Diabetes, n (%)	10 (28.6)	8 (21.6)	0.496
Peripheral vascular disease, n (%)	12 (34.3)	10 (27.0)	0.505
Current smoker, n (%)	6 (17.1)	2 (5.4)	0.117
Positive family history for CVD, n (%)	20 (57.1)	11 (29.7)	**0.020**
Medical history			
Previous myocardial infarction, n (%)	29 (82.9)	19 (51.4)	**0.005**
Previous percutaneous intervention, n (%)	19 (54.3)	19 (51.4)	0.807
Previous CABG, n (%)	20 (57.1)	20 (54.1)	0.799
No revascularization, n (%)	7 (20.0)	7 (18.9)	0.906
Three-vessel disease, n (%)	22 (75.9), n=29	24 (80), n=30	0.161
Two-vessel disease, n (%)	2 (6.9), n=29	5 (16.7), n=30	
Previous stroke, n (%)	3 (8.6)	0 (0)	0.070
Paroxysmal atrial fibrillation, n (%)	10 (28.6)	7 (18.9)	0.336
Clinical parameters			
Body mass index, kg/m^2	30.1 ± 3.8	29.7 ± 4.1	0.647
Angina episodes/ week, median (25; 75%)	5.5 (2.3; 13.5)	6 (3; 14)	0.619
Nitroglycerine consumption (times/week), median (25;75%)	1 (0; 3.8)	2 (0.5; 2.5)	0.250
Left ventricular ejection fraction (echocardiographic), %	56.5 ± 7.1	54.5 ± 9.1	0.284
Systolic blood pressure, mmHg	129.2 ± 22	125.8 ± 21.7	0.831
Diastolic blood pressure, mmHg	78.8 ± 11.8	79.1 ± 11.8	0.239
Angina CCS class			
I, n (%)	1 (2.9)	3 (8.1)	0.506
II, n (%)	13 (37.1)	11 (29.7)	
III, n (%)	21 (60.0)	23 (62.3)	
SAQ scores			
Physical limitation, %	53.2 ± 22.6	52.5 ± 21.6	0.915
Angina stability, %	45.3 ± 29.7	39.1 ± 24.1	0.290
Angina frequency, %	58.1 ± 24.8	58.9 ± 31.1	0.776
Treatment satisfaction, %	75.5 ±17.1	68.3 ±16.2	0.190
Disease perception, %	55.7 ± 22.4	51.9 +20.8	0.662

CABG - Coronary artery bypass grafting, CCS - Canadian Cardiovascular Society, CSWT – Cardiac shock wave therapy, CVD – cardiovascular disease, OMT – optimal medical therapy, SAQ - Seattle Angina Questionnaire.

P <0.05 considered as significant.

In the screening phase, the participants were seen 3-4 times within minimum 28 days to ensure that angina was stable, to evaluate blood pressure profile and quality of life, to determine the ischemic threshold and/or symptom limited stress level. Blood pressure measurements, lipid profiles and clinical status were obtained during first visit; based on these parameters, the antihypertensive, antihyperlipidemic and antianginal medications were adapted according to the guidelines [27]. All patients (100%) were on statins and antiplatelet therapy; over 90% were on β-blockers and ACE inhibitors (Table 14). Four-week period before randomization was kept to ensure clinical stability and stable dose of medication. After this period patients underwent screening testing. From this point on, the medications were not changed further, except sublingual nitroglycerine use for angina attacks relief.

TABLE 14. **Medical treatment at baseline**

Medication	**OMT + placebo group (n=35)**	**OMT + CSWT group (n=37)**	***P* value**
ACE inhibitors / ARB, n (%)	33 (94.3)	36 (97.3)	0.527
Beta-blockers, n (%)	34 (97.1)	35 (94.6)	0.599
Long acting nitrates, n (%)	16 (45.7)	20 (54.1)	0.479
Calcium channel blockers, n (%)	19 (54.3)	18 (48.7)	0.637
Trimetazidine, n (%)	15 (42.9)	21 (56.8)	0.242
Ivabradine, n (%)	8 (22.9)	8 (22.2)	0.944
Ranolazine, n (%)	2 (5.7)	1 (2.8)	0.543
Diuretics, n (%)	18 (51.4)	17 (46.0)	0.649
Statins, n (%)	36 (100)	37 (100)	-
Antiplatelets, n (%)	36 (100)	37 (100)	-
Dual-antiplatelet therapy, n (%)	12 (34.3)	5 (13.5)	0.059
Oral anti-diabetic, n (%)	9 (25.7)	4 (10.8)	0.103
Number of antianginal medication	2.8 ± 0.9	3.0 ± 1.0	0.948

ACE - Angiotensin converting enzyme, ARB - Angiotensin II receptor blocker, CSWT - Cardiac shock wave therapy, OMT – optimal medical therapy.

P <0.05 considered as significant.

Systolic and diastolic blood pressures were within optimal range as recommended in the ESC guidelines for the hypertension management [188] in both groups at baseline and during all phases of study.

Prior to the CSWT treatment, there were no significant differences between the groups in any of the clinical variables (CCS class, SAQ scores, total exercise duration, nitroglycerine consumption, all p>0.05, Table 13). Over 70% of study patients were in CCS class III at baseline.

4.2.2 Tolerability of intervention

Both CSWT and placebo procedures were well tolerated in all patients, and all patients completed therapy. During or after the treatment procedures no changes of heart rate and blood pressure and no relevant arrhythmias were documented. During the follow up no patient died in both groups; few cardiovascular events occurred in both study groups (Table 15).

TABLE 15. **Incidence of cardiovascular events and hospitalization during study period**

	OMT + placebo group (n=35)	**OMT + CSWT group (n=37)**
Related with CSWT procedure	0	0
Acute myocardial infarction	3	0
Unstable angina	0	1
Revascularization (PCI)	2	0
Acute limb ischemia	0	1
Cumulative events	**5**	**2**

CSWT - Cardiac shock wave therapy, OMT – optimal medical therapy, PCI – percutaneous coronary intervention.

4.2.3 Results of exercise treadmill test

Exercise capacity was reduced in all patients at baseline (METS was 4.7 ± 2.1 in females and 4.9 ± 1.5 in males) without difference between the study groups (Table 16). Study interventions significantly improved mean exercise time at 3- and 6-month follow up in both study arms without difference between them (Table 16).

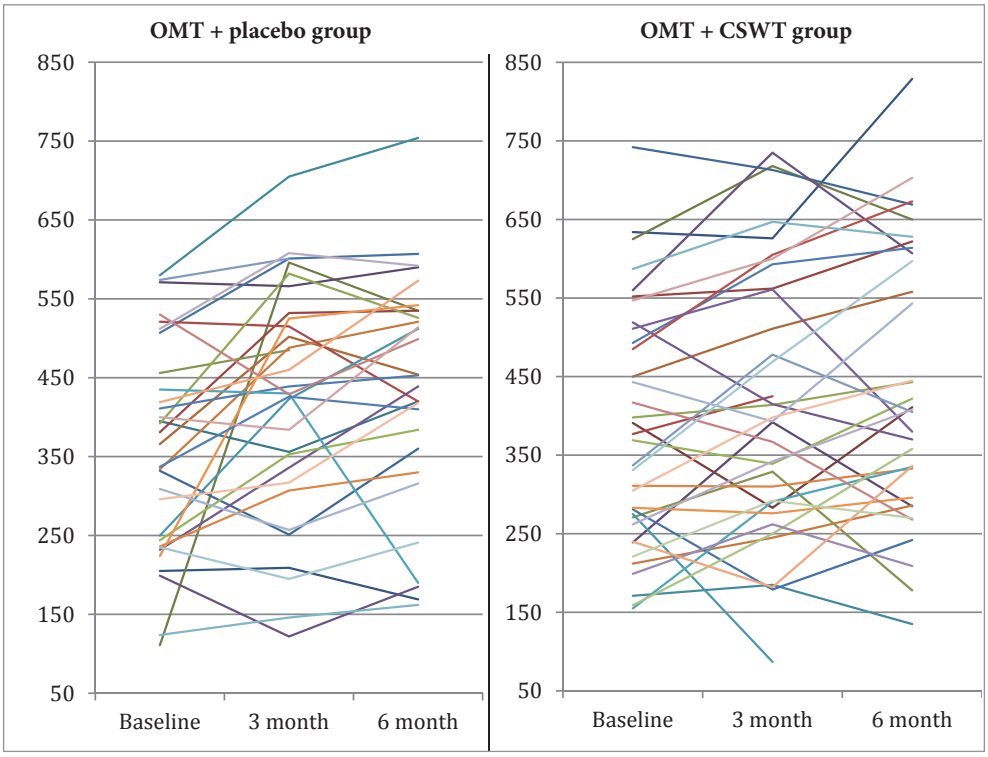
The dynamics of exercise duration was calculated as total exercise duration at 3 or 6 months minus that at baseline. In OMT + CSWT group mean increase of exercise duration made 25.5 seconds (95% CI: -6.4, 57.4) at 3 months and 48.8 seconds (95% CI: 12.2, 85.3) at 6 month follow up compared with 68.3 seconds (95% CI: 18.7, 107.9) and 80.4 seconds (95% CI: 34.0, 126.9) in OMT + placebo group, respectively. Similarly, number of patients with increased exercise duration by more than 90 seconds also did not differ between the groups: 10 (28.6%) and 13 (37.1%) patients in OMT + CSWT group and 12 (40%) and 15 (46.9%) in OMT + placebo group at 3 and 6 months follow up, respectively (p=0.337 and p=0.420). Individual duration of exercise changes is shown in Figure 18.

TABLE 16. **Exercise measurements during ECG treadmill stress test**

Variable	OMT + placebo group					OMT + CSWT group					*P* value comparing two groups	
	Baseline (n=35)	3 month (n=30)	P_{B-3}	6 month (n=32)	P_{B-6}	Baseline (n=37)	3 month (n=35)	P_{B-3}	6 month (n=35)	P_{B-6}	3 month	6 month
Exercise duration, sec	380.5 ± 150.7	432.2 ± 146.0	**0.004**	447.4 ± 139.9	**0.001**	380.9 ± 152.5	414.0 ±170.7	**0.026**	432.8 ± 176.1	**0.010**	0.655	0.710
METS	4.8 ± 1.7	5.2 ± 1.7	**0.008**	5.5 ± 1.8	**0.001**	4.8 ± 1.4	5.1 ± 1.7	0.067	5.3 ± 1.9	**0.046**	0.724	0.667
Angina on exertion, n (%)	29 (80.6)	10 (32.3)	**<0.001**	7 (21.2)	**<0.001**	28 (75.7)	18 (51.4)	**0.033**	12 (34.3)	**<0.001**	0.120	0.232
Max ST depression, mm	1.5 ±0.5	1.2 ± 0.7	**0.008**	1.3 ± 0.5	**0.002**	1.3 ± 0.6	1.0 ±0.7	**0.038**	0.9 ± 0.6	**0.001**	0.246	**0.001**
ST-segment depression												
<1mm, n (%)	1 (2.9)	5 (16.1)	**0.020**	3 (9.4)	0.096	3 (8.1)	11 (30.6)	**0.008**	17 (48.6)	**0.001**	0.325	**0.002**
1-1.9 mm, n (%)	24 (68.6%)	19 (61.3%)		22 (68.8%)		26 (70.3%)	20 (55.6%)		14 (40.0%)			
≥ 2 mm, n (%)	10 (28.6%)	7 (22.6%)		7 (21.9%)		8 (21.6%)	5 (13.9%)		4 (11.4%)			

BP – blood pressure, CSWT - Cardiac shock wave therapy, HR – heart rate, METS - metabolic equivalent, OMT – optimal medical therapy, ST - ST segment.
P <0.05 considered as significant.

FIGURE 18. **Exercise duration changes in study groups**



CSWT - Cardiac shock wave therapy, OMT – optimal medical therapy.

At baseline, more patients discontinued exercise treadmill test for cardiac reasons (angina or angina equivalent; 75.7% in CSWT treatment and 80.6% in placebo group) than at 3 months (51.4% and 32.3%, respectively, p=0.120) and at 6 months follow up (34.3% and 21.2%, respectively, p=0.232). During follow up, more patients stopped exercise test due to non-cardiac reasons (for example, leg cramps or back pain).

At 6-month follow up, the magnitude and the frequency of peak exercise ST segment depression significantly reduced in CSWT + OMT group compared with OMT + placebo group (p=0.001 and 0.002), see in Table 16.

At baseline peak ST segment deviation ≥1mm during exercise treadmill test was recorded in 91.9% and 97.1% of OMT + CSWT group and OMT + placebo group, respectively (p=0.664). Number of patients with ST deviation ≥1mm recorded during peak exercise decreased significantly to 71.4% and 51.4% in OMT + CSWT group compared with 86.7% and 90.6% in OMT + placebo group at 3- and 6- months follow up, respectively (p=0.038 and p=0.001).

4.2.4 Changes in quality of life and functional status

At baseline only 4 patients in OMT+ placebo group and 1 in OMT+ CSWT group reported being free of angina (i.e. had an angina frequency score of 100 on SAQ). During the study percentage of angina-free patients progressively increased in both groups: at 6 months follow up there were 9 and 7 angina free patients in OMT + CSWT and OMT + placebo group, respectively (p=0.663). Mean values of SAQ scores are shown in Table 17. The scores were similar in both study groups at baseline and improved significantly in both groups for 4 of 5 domains of the SAQ at 3- and 6- month follow up; no differences were found between groups at follow up. Interestingly, relevant reduction in physical limitation was reported at 3-, but not replicated at 6-months period by the patients regardless of the intervention. This subjective evaluation of physical capacity at the end of the study did not match objective parameters of exercise tolerance, which remained improved throughout the whole study duration. Besides that, satisfaction with treatment improved in all study patients being significantly higher in patients of OMT + placebo group compared with OMT + CSWT group at 6 month follow up (p=0.030).

TABLE 17. **Results of Seattle Angina Questionnaire**

Month	OMT + placebo group (*n=35*)[a]		OMT + CSWT group (*n=37*)[b]		*P between the groups*
	Mean value ± SD	*P compared to baseline*	Mean value ± SD	*P compared to baseline*	
Physical limitation					
0	53.2 ± 22.6	-	52.5 ±21.6	-	0.915
3	60.0 ± 22.7	**0.001**	59.1 ± 18.5	**0.039**	0.888
6	58.7 ± 22.0	0.131	58.8 ±16.1	0.091	0.939
Angina stability					
0	45.3 ± 29.7	-	39.1 ± 24.1	-	0.290
3	72.1 ± 23.3	**<0.0001**	74.4 ± 31.3	**<0.0001**	0.505
6	71.1 ± 28.5	**0.001**	76.5 ± 30.0	**<0.0001**	0.347
Angina frequency					
0	58.1 ± 24.8	-	58.9 ±31.1	-	0,776
3	74.9 ± 17.7	**<0.0001**	78.7 ± 35.1	**<0.0001**	0.630
6	77.5 ±20.3	**<0.0001**	81.8 ± 32.8	**<0.0001**	0.701
Treatment satisfaction					
0	75.5 ± 17.1	-	68.3 ± 16.2	-	0.190
3	84.5 ± 12.6	**0.001**	80.1 ± 15.4	**0.001**	0.181
6	88.2 ± 10.3	**<0.0001**	81.4 ± 14.0	**<0.0001**	**0.030**
Disease perception					
0	57.7 ± 22.4	-	51.9 ± 20.8	-	0.662
3	67.7 ± 20.1	**<0.0001**	68.3 ±17.5	**<0.0001**	0.767
6	71.7 ± 16.4	**<0.0001**	75.0 ± 19.3	**<0.0001**	0.272

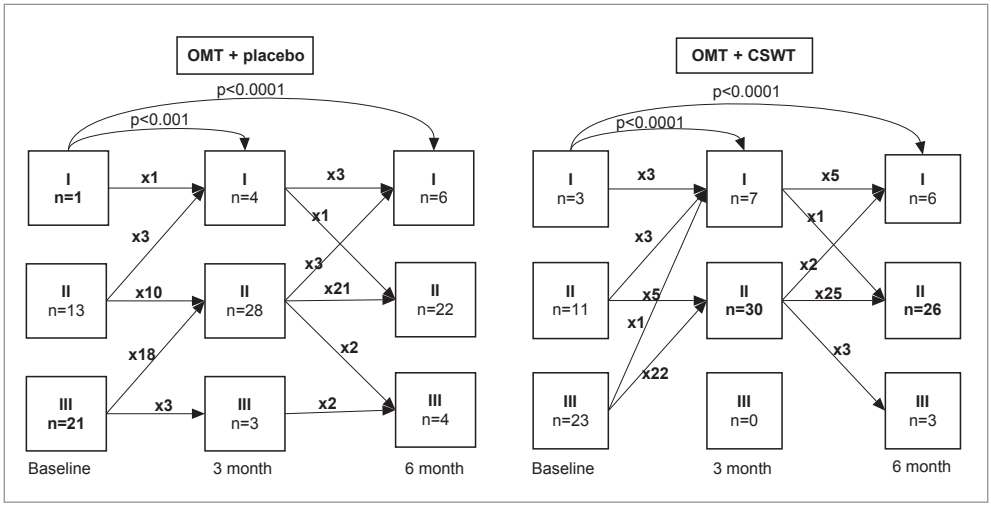
CSWT - Cardiac shock wave therapy, OMT – optimal medical therapy, SD – standard deviation, a - OMT + placebo group included 32 patients at 6 month follow up, b - OMT + CSWT group included 34 patients at 6 month follow up.

P <0.05 considered as significant.

Moreover, significant improvement of CCS angina class assessed by investigator was observed in both study groups (Figure 19) with no differences between groups at any time point.

Comparing with baseline reduction by at least one class in CCS score was achieved in 26 (70.3%) and 25 (73.5%) patients in OMT + CSWT group compared with 21 (60.0%) and 21 (67.7%) patients in OMT + placebo group at 3 and 6 month follow up, respectively (p=0.499 and p=0.776).

FIGURE 19. **Changes of Canadian Cardiovascular Society (CCS) class**



Number in the boxes indicates Canadian Cardiovascular Society (CCS) angina class, each line indicates change in CCS class. *P* values were calculated using Fishers' exact test between CCS class at baseline and at 3- and 6- months follow up.

CSWT - cardiac shock wave therapy, OMT - optimal medical therapy.

During follow up visits, number of angina attacks and short acting nitroglycerine usage for symptoms relief were reported by patients. The amount of angina attacks and nitroglycerine use per week were similar in both study groups at baseline. At follow up, the decrease of angina episodes was more prominent in OMT + CSWT group [mean decrease of 6.6 angina attacks (95% CI: 4.5 to 8.7)] compared with OMT + placebo group [mean decrease of 4.3 angina attacks (95% CI: 2.4 to 6.2)], Table 18, though the difference did not achieve statistical significance.

TABLE 18. **Dynamics of angina and short acting nitroglycerine consumption**

Month	**OMT + placebo group (*n=35)*[a]**		**OMT + CSWT group *(n=37)*[b]**		***P between the groups***
	Med (IQR 25%; 75%)	*P compared to baseline*	Med (IQR 25%; 75%)	*P compared to baseline*	
Angina episodes / week					
0	5.5 (2.3; 13.5)	-	6 (3; 14)	-	0.619
3	2 (0; 5)	**<0.0001**	2 (0; 4)	**<0.0001**	0.617
6	2 (0;4)	**<0.0001**	1 (0; 3.3)	**<0.0001**	0.344
Nitroglycerine consumption					
0	1 (0; 3.8)	-	2 (0.5; 2.5)	-	0.756
3	0 (0; 1)	**<0.0001**	0 (0; 1)	**<0.0001**	0.650
6	0 (0; 1)	**0.001**	0 (0; 1)	**<0.0001**	0.802

CSWT - Cardiac shock wave therapy, IQR – Interquartile range, OMT – optimal medical therapy. *P* <0.05 considered as significant.

a - OMT + placebo group included 32 patients at 6 month follow up, b- OMT + CSWT group included 34 patients at 6 month follow up in.

4.2.5 Changes of ventricular morphometric and functional parameters

Baseline and follow up results of rest echocardiography are given in Table 19. No major changes were documented in any structural or functional markers in OMT + placebo group. In contrast, significant decrease of both systolic and diastolic LV volumes in OMT + CSWT group was observed at 6 months; the trend of reduction in LV filling pressure was seen as well in the intervention group, however, without reaching statistical significance.

At 6 month follow up LVEF had improved at least 5% in 10 of 35 patients receiving CSWT on top of OMT, compared with 6 of 30 patients in the OMT + placebo group (p=0.426). The mean change of LVEF was 1.7% (95% CI: -0.3 to 3.7) and -1.3% (95% CI: -4.0 to 1.3) in OMT + CSWT and OMT + placebo group, respectively.

TABLE 19. Echocardiographic measurements

Variable	OMT + placebo group		OMT + CSWT group		*P between the groups*	
	Baseline (n=35)	Follow-up (n=29)	Baseline (n=37)	Follow-up (n=35)	Baseline	Follow-up
IVSDD, cm	1.0 ± 0.1	0.98 0.1	0.98 ± 0.13	0.96 ± 0.12	0.321	0.349
LVEDD, cm	5.17 ± 0.5	5.12 ± 0.5	5.22 ± 0.62	5.2 ± 0.65	0.729	0.649
LVPWDD, cm	0.96 ± 0.1	0.95 ± 0.1	0.93 ± 0.1	0.93 ± 0.07	0.348	0.415
LV index, cm/m^2	2.6 ± 0.24	2.6 ± 0.29	2.7 ± 0.3	2.7 ± 0.3	0.181	0.115
MMI, g/m^2	95.6 ± 16.8	93.7 ±23.7	94.1 ± 18.6	88.3 ± 24.0	0.724	0.351
LV end-diastolic volume, ml	115.4 ± 26.0	113.9 ± 28.9	113.9 ± 30.5	107.8 ± 28.1*	0.822	0.394
LV end-systolic volume ml	50.5 ± 15.2	50.7 ± 16.6	53.1 ± 21.6	48.1 ± 20.7*	0.554	0.571
LV Ejection fraction, %	56.5 ± 7.1	56.4 ± 7.5	54.5 ± 9.1	57.1 ± 9.3	0.284	0.678
E, m/s	0.63 ± 0.21	0.68 ± 0.24	0.63 ± 0.15	0.66 ± 0.19	0.983	0.690
A, m/s	0.74 ± 0.19	0.79 ± 0.23	0.69 ± 0.20	0.72 ± 0.18	0.318	0.172
E/A	0.94 ± 0.57	1.12 ± 1.18	0.99 ±0.46	0.96 ± 0.48	0.721	0.435
Deceleration time, ms	213.6 ± 76.8	203.8 ± 58.1	200.5 ± 58.6	196.1 ± 35.8	0.468	0.555
E'lat	8.3 ± 3.5	8.6 ± 3.8	8.5 ± 3.2	8.8 ± 2.9	0.748	0.782
E/E'lat	7.9 ± 3.5	8 ± 3.1	7.8 ± 4.1	7.6 ± 2.9	0.929	0.684
E/E'vid	9 ± 3.1	9.2 ± 3.2	9.1 ± 3.8	8.6 ± 2.8	0.739	0.401
TAPSE, cm	1.8 ± 0.5	1.9 ± 0.5	1.8 ± 0.5	1.8 ±0.5	0.630	0.192

CSWT - Cardiac shock wave therapy, IVSDD – inter ventricular septum diastolic diameter, LVEDD - left ventricular end-diastolic diameter, LVPWDD – left ventricular posterior wall diastolic diameter, OMT – optimal medical therapy, TAPSE - tricuspid annular plane systolic excursion.

*- *P* was paired in the group and considered as significant ($P < 0.05$).

4.2.6 Results of sub study of imaging stress tests

The sub-study of non-invasive cardiac imaging assessing the efficacy of CSWT on myocardial contractility and perfusion during stress was run at Vilnius site only.

All patients had undergone myocardial perfusion imaging by SPECT and dobutamine stress echocardiography at baseline. Cardiac magnetic resonance imaging study including perfusion with adenosine was possible to perform in 43 of 59 patients at baseline (7 patients had metal implants, 2 patient has claustrophobia, 7 patients refused). There were no significant differences in any of documented parameters of the multimodality imaging stress tests between the groups at baseline (Table 20).

TABLE 20. **Baseline parameters of multimodality imaging stress tests**

	OMT + placebo group (n=29)	**OMT + CSWT group (n=30)**	***P* value**
Dobutamine stress echocardiography			
Wall motion score at rest	23.8 ± 7.0	23.4 ± 7.8	0.753
Wall motion score at stress	26.3 ± 6.5	26.8 ± 7.0	0.945
Wall motion score index at rest	1.4 ± 0.4	1.4 ± 0.5	0.840
Wall motion score index at stress	1.6 ± 0.4	1.6 ± 0.4	0.783
Global peak systolic strain at rest, %	-14.1 ± 2.3	-14.8 ± 3.4	0.405
Global peak systolic strain at stress, %	-15.7 ± 4.5	-15.0 ± 3.2	0.958
LV ejection fraction at rest, %	48.5 ± 9.0	46.5 ± 10.6	0.450
LV ejection fraction at stress, %	51.6 ± 11	49.8 ± 11.2	0.668
ECG changes during stress, n (%)	19 (65.5)	22 (73.3)	0.519
Chest pain during stress, n (%)	18 (62.1)	23 (76.7)	0.227
Mean dobutamine dose, mcg/kg/min	31.1 ± 8.0	31.3 ± 8.6	0.920
Myocardial ischemia:			
No ischemia (WMS 0), n (%)	10 (34.5)	9 (30)	0.879
Mild (1-2), n (%)	4 (13.8)	4 (13.3)	
Moderate to severe (≥3), n (%)	14 (48.3)	17 (56.7)	
Myocardial perfusion imaging Single photon emission computed tomography			
Summed stress score	10.3 ± 9.2	10.5 ± 8	0.590
Summed rest score	3.9 ± 5.3	4.9 ± 8.1	0.819
Summed difference score (SDS)	6.4 ± 5.8	5.6 ± 3.7	0.903
Myocardial ischemia:			
No ischemia (SDS 0)	1 (3.4)	2 (6.7)	0.889
Mild (SDS 1-4), n (%)	8 (27.6)	7 (23.3)	
Moderate (SDS 4-7), n (%)	10 (34.5)	11 (36.7)	
Severe (SDS >7), n (%)	10 (34.5)	10 (33.3)	
Cardiac magnetic resonance imaging			
Wall motion score at rest	21.0 ± 4.6	21.7 ± 4.7	0.530
Wall motion score index	1.2 ± 0.3	1.3 ± 0.3	0.530
Number of segments with induced perfusion deficit per patient	3.9 ± 3.2	3.1 ± 2.2	0.570
Total late gadolinium enhancement score	6.6 ± 6.2	8.7 ± 9.7	0.622

CSWT - Cardiac shock wave therapy, OMT – optimal medical therapy.

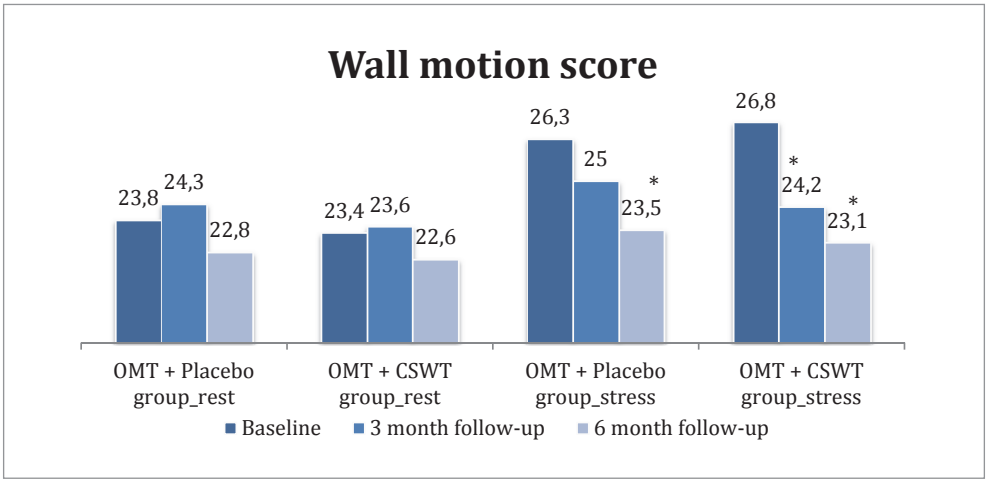
P <0.05 considered as significant.

4.2.6.1 Dynamics of myocardial ischemia evaluated by dobutamine stress echocardiography

Complete data of myocardial contractility by DSE were available in 28 patients of each group at 3 month follow up and in 28 patients of OMT + CSWT group and 26 patients of OMT + placebo group at 6 month follow up. Before the study treatment mean number of myocardial segments with induced contraction deterioration during stress made 3.6 ± 2.6 and 3.6 ± 2.8 per patient in OMT + placebo group and OMT + CSWT group, respectively. At baseline, inducible myocardial ischemia was similar in both groups, and moderate to severe ischemia was noted in 14 of 29 (48.3%) of OMT + placebo and 17 of 30 (56.6%) of OMT + CSWT group patients (p=0.527).

CSWT treatment caused significant reduction in stress-induced ischemia at 3 months in contrast to placebo applications (stress wall motion score decreased from 26.8 ± 7.0 to 24.2 ± 7.3, p=0.001). Interestingly, at 6 month follow up remarkable anti-ischemic effect was maintained in OMT + CSWT group (WMS 23.1 ± 5.8, p = 0.012 vs baseline) and at that time-point it appeared also in OMT + placebo group (WMS 23.5 ± 5.1, p=0.015 vs baseline, Figure 20). Wall motion score did not differ between the groups at 3- and 6- months follow-up; changes of WMS at stress in both groups are presented in Figure 21.

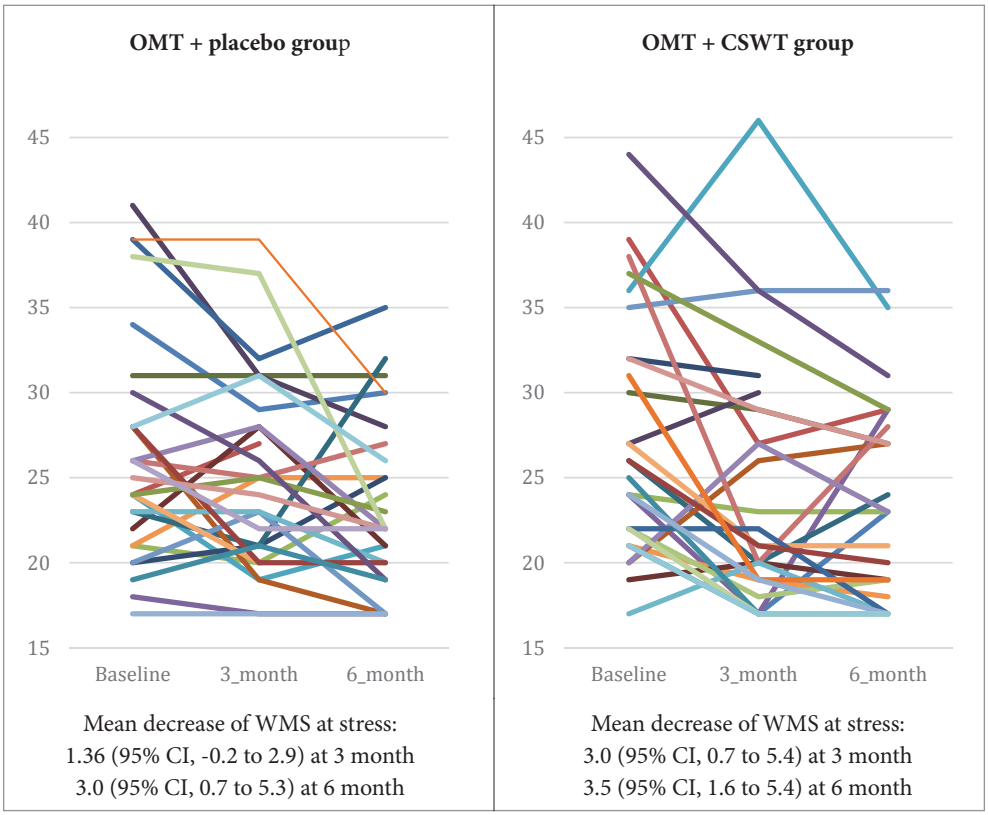
FIGURE 20. **Wall motion score changes during dobutamine stress echocardiography**



CSWT - Cardiac shock wave therapy, OMT – optimal medical therapy.

*- *P* was paired in the group and considered as significant (*P* <0.05).

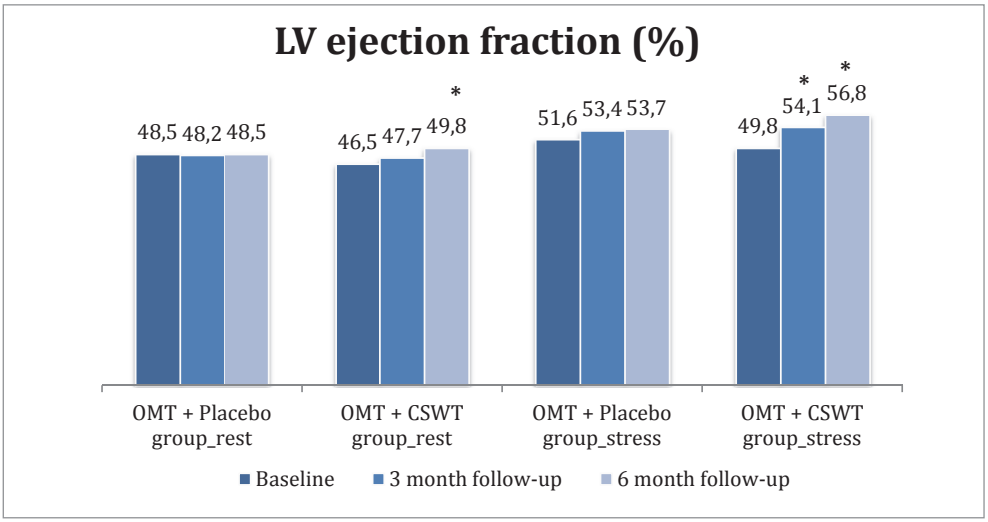
FIGURE 21. **Comparisons of changes in wall motion score during dobutamine stress echocardiography at stress at baseline, 3- and 6- month follow up**



CSWT – cardiac shock wave therapy, OMT – optimal medical therapy, WMS – wall motion score.

In addition to improvement of segmental myocardial function meaningful increase in global left ventricular ejection fraction was detected in OMT + CSWT group: during stress in both time-points (from 49.8% ± 11.2 to 54.1% ± 12.3 and 56.8% ± 9.4, p=0.014 and p=0.001) and at rest at the end of study (from 46.5% ± 10.6 to 49.8% ±8.6, p=0.014), whereas it was not the case in OMT + placebo group (Figure 22). The changes of LV EF during DSE at stress in both groups are presented in Figure 23. No significant differences were found between the groups at 3- and 6- months follow-up. The other measurements and hemodynamics during DSE are presented in Table 21.

FIGURE 22. **Evaluation of left ventricular ejection fraction during dobutamine stress echocardiography**



CSWT - Cardiac shock wave therapy, OMT – optimal medical therapy.

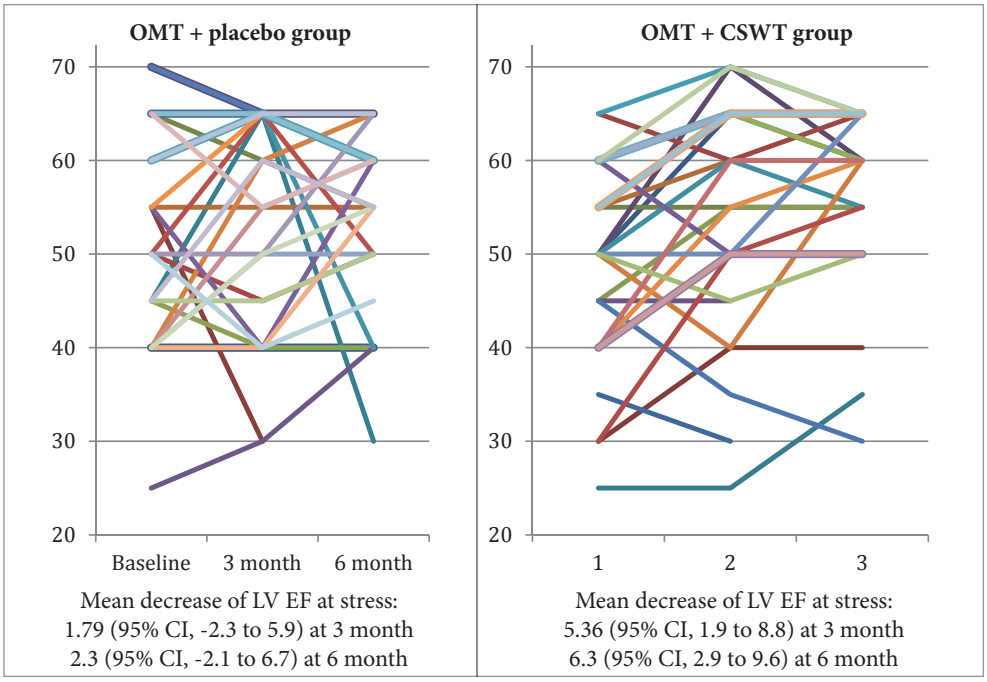
*- P was paired in the group and considered as significant (P <0.05).

At baseline the reduced mean global peak systolic strain (PSS) was found in all patients at rest and during stress. CSWT treatment demonstrated protective effect on myocardial deformation during the study period: strain values remained unchanged in contrast to OMT + placebo group, where global PSS decreased significantly at rest in 2-chamber view and at stress in 4-chamber view (see Table 21).

At baseline myocardial ischemia during DSE was induced in 66.7% and 62.1% of patients in OMT + CSWT group and OMT + placebo group, respectively (p=0.715). At 3- and 6- months follow up, number of patients with inducible ischemia decreased to 10 (35.7%) and 8 (28.6%) in OMT + CSWT group compared with 13 (46.4%) and 8 (42.3%) in OMT + placebo group, respectively (p=0.420 and p=0.297), Figure 24.

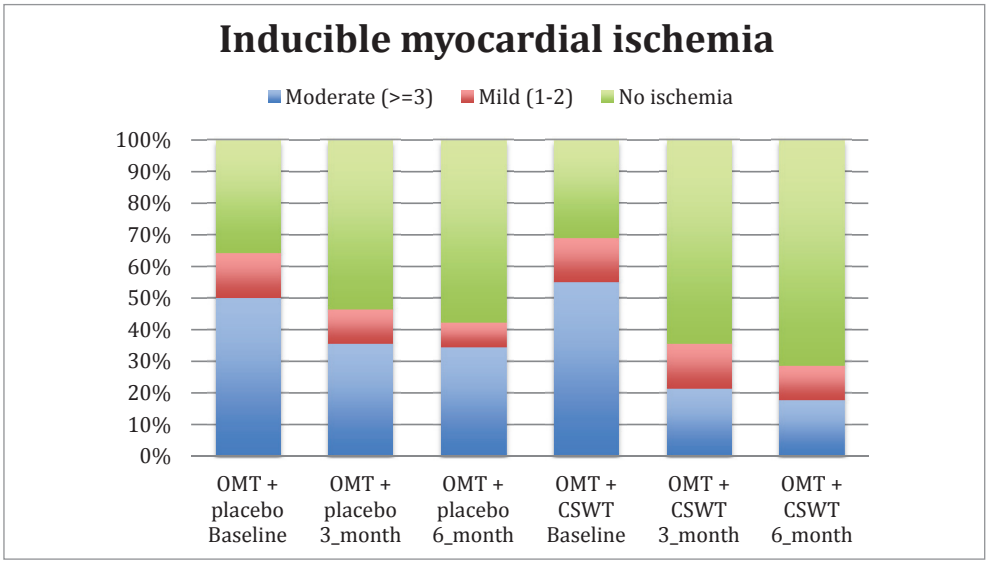
In OMT + CSWT group along with the diminished ultrasound signs of ischemia number of patients who presented with additional ischemic markers - stress angina and ST depression - significantly decreased at 3- and 6- month follow up (Table 21). Again, less angina was recorded also in OMT + placebo group, but only at 6 month follow up, similarly to changes in wall motion score (Table 21).

FIGURE 23. **Comparisons of changes in LV ejection fraction during dobutamine stress echocardiography at stress at baseline, 3- and 6- month follow up**



CSWT – cardiac shock wave therapy, LV EF – left ventricular ejection fraction, OMT – optimal medical therapy.

FIGURE 24. **Dynamics of inducible ischemia during dobutamine stress echocardiography**



Moderate ischemia defined as ≥3 segments with stress induced severe hypokinesis or akinesis. CSWT – cardiac shock wave therapy, OMT – optimal medical therapy.

TABLE 21. Hemodynamics and peak systolic strain changes during dobutamine stress echocardiography

	OMT + placebo group			OMT + CSWT group			*P between groups*		
	Baseline (n=29)	3- month (n=28)	6- month (n=26)	Baseline (n=30)	3- month (n=28)	6- month (n=28)	Base-line	3 month	6 month
Wall motion score index at rest	1.4 ±0.4	1.4 ± 0.4	1.3 ± 0.3	1.4 ± 0.5	1.4 ± 0.5	1.3 ± 0.4	0.753	0.608	0.499
Wall motion score index at stress	1.6 ± 0.4	1.5 ± 0.3	1.4 ± 0.3*	1.6 ± 0.4	1.4 ± 0.4*	1.4 ± 0.3*	0.945	0.282	0.334
HR at rest, beats/min	69.3 ± 11.4	72.3 ± 10.0	70.6 ± 9.4	66.7 ± 12.1	67.4 ± 11.2	64.6 ± 7.2	0.396	0.082	0.117
HR at stress, beats/min	130.1 ± 14.5	135.9 ± 15.7	130.5 ± 10.1	125.1 ± 14.2	124.8 ±16.1	125.5 ± 13.2	0.191	0.061	0.125
ECG changes during stress, n (%)	19 (65.5)	21 (75.0)	16 (61.5)	22 (73.3)	13 (46.4)*	13 (46.4)*	0.514	**0.029**	0.266
Angina during stress, n (%)	18 (62.1)	13 (46.4)	11 (42.3)*	23 (76.7)	12 (42.9)*	10 (35.7)*	0.223	0.788	0.619
Peak systolic strain global									
4 CH- rest, %	-13.7 ± 2.8	-13.7 ± 2.7	-12.6 ± 2.2	-13.8 ± 3.8	-12.2 ± 3.7	-13.6 ± 2.5	0.910	0.118	0.132
2 CH- rest, %	-15.1 3.3	-13.6 ± 3.4	-13.3 ± 2.1*	-15.9 ± 4.2	-13.2 ± 7.2	-14.3 ± 3.1	0.527	0.915	0.509
3 CH- rest, %	-13.5 ± 4.1	-13.2 ± 4.5	-13.1 ± 2.9	-14.8 ± 4.4	-13.8 ± 3.6	-14.2 ± 3.1	0.295	0.543	0.283
Total- rest, %	-14.1 ± 2.2	-13.5 ± 2.6	-13.0 ± 1.9	-14.8 ± 3.4	-13.2 ± 3.8	-13.9 ± 2.7	0.405	0.756	0.209
4 CH- stress, %	-15.3 ± 4.8	-14.2 ± 3.9	-12.9 ± 2.5*	-14.1 ± 3.4	-14.1 ± 3.9	-13.9 ± 3.0	0.138	0.835	0.135
2 CH- stress, %	-14.9 ± 4.6	-12.7 ± 4.0	-14.3 ± 3	-15.7 ± 4.4	-13.2 ± 4.1	-14.4 ± 3.1	0.588	0.809	0.668
3 CH- stress, %	-13.9 ± 5.5	-13.5 ± 4.1	-13.9 ± 3.1	-14.8 ± 4.9	-12.5 ± 3.8	-13.2 ± 2.8	0.713	0.304	0.270
Total- stress, %	-15.1 ± 4.5	-13.7 ± 3.6	-13.6 ± 2.4	-15.0 ± 3.2	-13.7 ± 3.0	-14.0 ± 2.3	0.958	0.801	0.587

CH – chamber view, CSWT - Cardiac shock wave therapy, HR – heart rate, OMT – optimal medical therapy.

*- *P* was paired in the group and considered as significant ($P < 0.05$).

Though at 3 and 6 months follow up, number of patients with reduced wall motion score by equal or more than 3 points at stress was larger in OMT + CSWT group: 16 (57.1%) and 19 (67.9%) compared with 9 (32.1%) and 14 (53.9%) in OMT + placebo group, respectively, this difference did not reach statistical significance (p=0.060 and p=0.244).

4.2.6.2 Dynamics of myocardial ischemia evaluated by single photon emission computed tomography

Complete data of myocardial perfusion imaging by SPECT were available in 25 and 26 patients of OMT + placebo group and OMT + CSWT group, respectively. Before the study intervention mean number of myocardial segments with induced reversible ischemia was 3.5 ± 2.6 and mean 3.4 ± 2.2 per patient in OMT + placebo and OMT + CSWT group, respectively. At baseline, extent of ischemia was similar in both groups, and moderate to severe ischemia was noted in 21 of 29 (72.4%) of OMT + placebo and 22 of 30 (73.3%) of OMT + CSWT group patients (p=0.889).

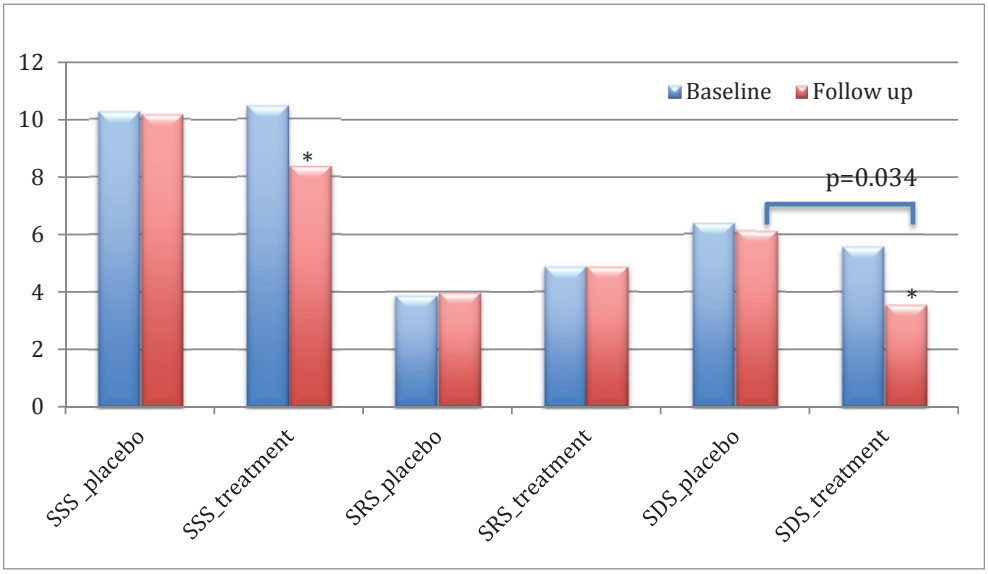
At 6 months follow-up the extent and severity of myocardial hypoperfusion (SSS) and amount of ischemia (SDS) significantly reduced in OMT + CSWT group compared with OMT + placebo group (Figure 25 and Table 22). The reductions of SSS and SDS were consistent in the treated patients; changes of SDS in both groups are shown in Figure 26.

TABLE 22. **Evaluation of myocardial perfusion during single photon emission computed tomography**

Variable	**OMT + Placebo group (n=25)**			**OMT + CSWT group (n=26)**			***P between groups***	
	Baseline	Follow-up	*P*	Baseline	Follow-up	*P*	Base-line	Follow-up
SSS	11.3 ±9.4	10.2 ±8.8	0.060	10.2 ±8.5	8.4 ± 9.9	**0.029**	0.590	0.268
SRS	4.2 ± 5.6	4 ±5.2	0.551	4.8 ± 8.6	4.9 ± 9.2	0.975	0.819	0.644
SDS	6.4 ± 5.9	6.2 ± 5	0.110	5.4 ± 3.7	3.6 ± 3.8	**0.006**	0.903	**0.034**
TPD at stress, %	16.1±13.2	14.9±12.9	0.096	14.8±12.6	12.4±14.5	**0.040**	0.660	0.277
TPD at rest, %	5.7 ± 7.2	5.8 ± 7.5	0.888	7.2±13.5	7.2 ±13.5	0.592	0.837	0.652
TPD difference, %	10.4 ± 8.7	9 ± 7.4	0.147	7.9 ±5.6	5.2 ± 5.6	**0.006**	0.970	**0.034**

SSS - Summed stress score, SRS - Summed rest score, SDS - Summed difference score, TPD – total perfusion defect, P <0.05 considered as significant.

FIGURE 25. **Results of myocardial perfusion imaging by single photon emission computed tomography**

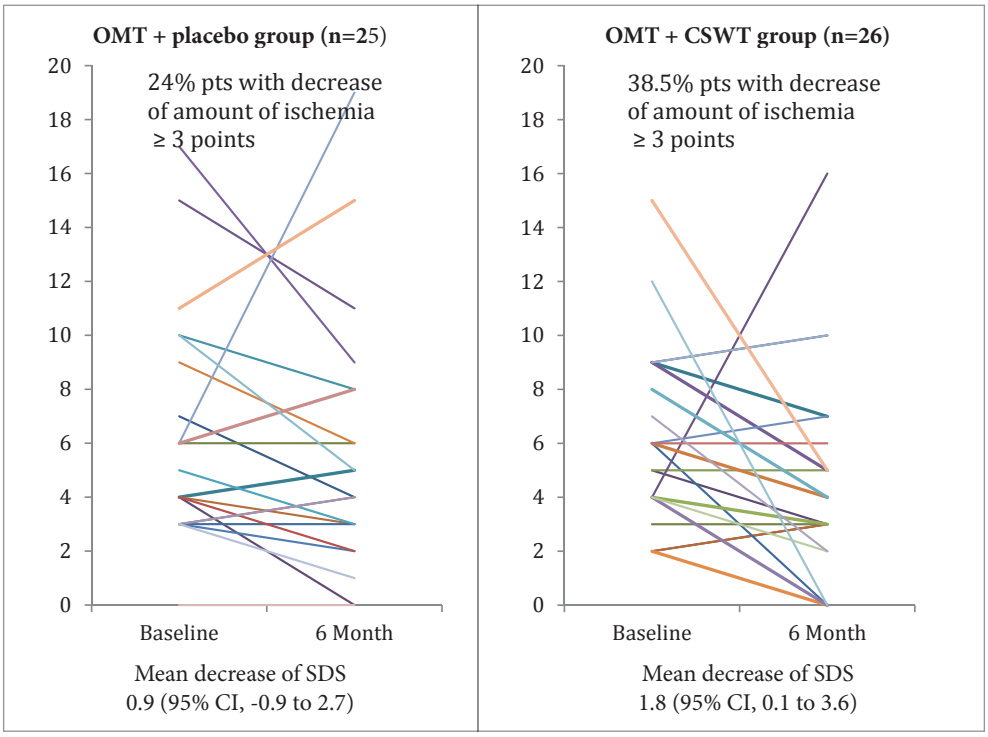


SSS – summed stress score, SRS – summed rest score, SDS – summed difference score, placebo – optimal medical therapy + placebo group, treatment – optimal medical therapy + cardiac shock wave therapy group, *- *P* was paired in the group and considered as significant (*P* <0.05).

At 6 month follow up number of patients with moderate to severe inducible myocardial ischemia decreased to 12 (46.2%) in OMT + CSWT group and 17 (68%) in OMT + placebo group (p=0.296); while number of patients with no ischemia increased significantly to 8 (30.8%) in OMT + CSWT group compared to 2 (8%) in OMT + placebo group (p=0.042), Figure 27.

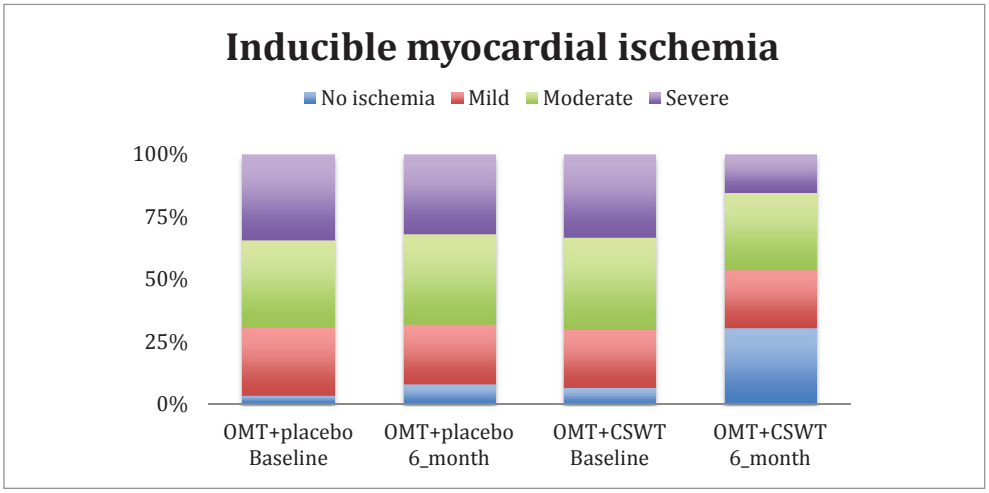
Again, this effect was not attained: at 6 month follow up mean decrease of SDS was 1.8 (95% CI: 0.1, 3.5) in OMT + CSWT group; in OMT + placebo group it made 0.9 (95% CI: -0.8, 2.7). Though in the course of true CSWT treatment clearly more patients achieved SDS more than 3 points compared to placebo arm: 38.5% vs 24% (see Figure 26), this difference was not significant.

FIGURE 26. **Comparison of changes in inducible ischemia during SPECT at baseline and 6 months follow up**



CSWT - Cardiac shock wave therapy, OMT – optimal medical therapy, SDS – summed difference score.

FIGURE 27. **Dynamics of amount of inducible myocardial ischemia**



Amount of inducible ischemia expressed as summed difference score (SDS). No ischemia, SDS=0; Mild ischemia, SDS 1-4; Moderate ischemia, SDS 4-7; Severe ischemia, SDS > 7.
CSWT - Cardiac shock wave therapy, OMT – optimal medical therapy.

4.2.6.3 Dynamics of myocardial ischemia and LV size and function evaluated by cardiac magnetic resonance imaging

Complete baseline and follow-up data of CMRI conducted in 16 patients of OMT + placebo group and 21 patient of OMT + CSWT group are presented in Table 23. At 6 month follow up significant improvement in regional contractility at rest is demonstrated in OMT + CSWT group in contrast to OMT + placebo group: WMS decreased from 21.7 ± 4.7 to 20.8 ± 4.7 and from 21 ± 4.6 to 21.7 ± 5, respectively (p=0.018 and p=0.603). But improvement of WMS did not reach significant difference between groups (p=0.617). No changes in LV volumes, myocardial perfusion and late gadolinium enhancement scores were found.

TABLE 23. **Stress perfusion and morphometric parameters of cardiac magnetic resonance imaging**

	OMT + placebo group (n=16)		**OMT + CSWT group (n=21)**		***P between groups***	
Variable	Baseline	Follow-up	Baseline	Follow-up	Baseline	Follow-up
Wall motion score	21 ± 4.6	21.7 ± 5.0	21.7 ± 4.7	20.8 ± 4.7*	0.530	0.617
WMSI	1.2 ± 0.3	1.3 ± 0.3	1.3 ± 0.3	1.2 ± 0.3*	0.530	0.617
Number of segments with induced perfusion deficit per patient	3.9 ± 3.2	4.4 3.3	3.1 ± 2.2	2.9 ± 2.6	0.570	0.122
Late gadolinium enhancement score	6.6 ± 6.2	7.8 ± 7.1	8.7 ± 9.7	8.4 ± 10	0.622	0.722
LV EF, %	58.1 ± 9.7	61 ± 9.1	57.3 ± 14.1	62 ± 13.2	0.765	0.743
LV EDV, ml	136 ±39.4	130.6 ± 48	146.9 ± 43.4	147.8 ± 42.2	0.438	0.098
LV ESV, ml	57.8 ±25.2	52.1 ± 28	66.7 ± 39.7	60.2 ± 38.2	0.724	0.713
IVSdd, mm	12.3 ± 2	12.8 ± 2.4	11.4 ± 1.3	11.5 ± 1.7	0.065	0.056
LV EDD, mm	48.6 ± 7.1	48.6 ± 7.59	51 ± 7.1	50.9 ± 7.2	0.372	0.283
LV PWdd, cm	8.9 ± 1.7	9.3 ± 1.4	8.7 ± 2.6	9.1 ± 1.8	0.725	0.728

LV - left ventricular, EDD - end-diastolic diameter, EDV - end-diastolic volume, ESV - end-systolic volume, EF - ejection fraction, WMSI - wall motion score index. *- *P* compared to baseline and considered as significant (*P* <0.05).

4.2.7 Number needed to treat

The number needed to treat (NNT) for improvement of clinical, functional and imaging parameters after cardiac shock wave treatment are presented in Table 24. The NNT between study endpoints reports not high figures, and ranged between 3.5 and 15.2.

TABLE 24. **Number need to treat to improvement of study endpoints to one patient**

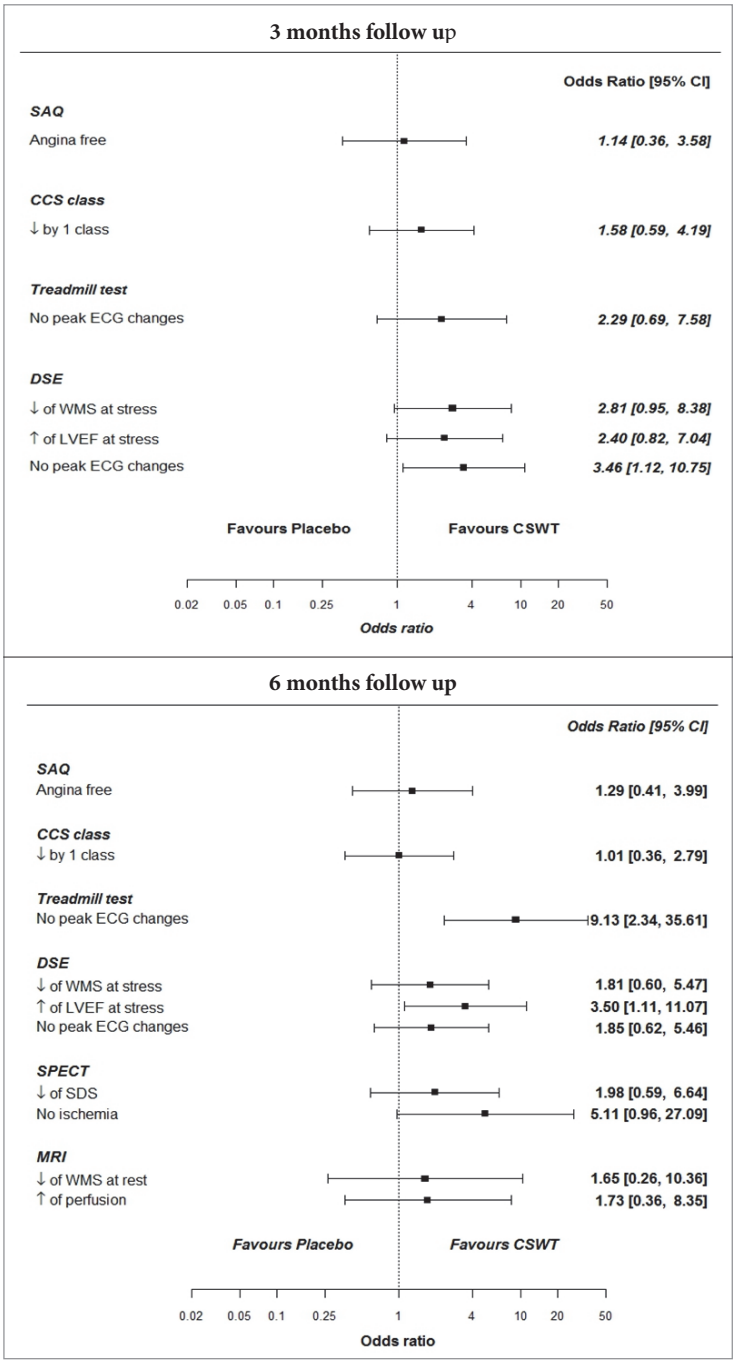
	3 month			6 month		
	OMT+ placebo	**OMT + CSWT**	**NNT**	**OMT+ placebo**	**OMG + CSWT**	**NNT**
Treadmill test						
Improvement of exercise duration at least 90 s	12/30	10/35	**8.8**	15	13	**10.2**
No significant ST depression at peak	5/30	11/35	**6.8**	3/32	17/35	**2.6**
DSE						
Decrease of WMS at least 3 points at stress	9/28	16/28	**4**	14/26	19/28	**7.1**
Improvement of LV EF at least 5% at stress	12/28	18/28	**4.7**	12/26	21/28	**3.5**
No significant ST depression at peak	7/28	15/28	**3.5**	10/26	15/28	**6.6**
SPECT						
Decrease of SDS at least 3 points	-	-	-	6/25	10/26	**6.9**
No ischemia	-	-	-	2/25	8/26	**4.4**
Cardiac MRI						
Improvement of WMS at least 3 points	-	-	-	2/16	4/21	**15.2**
Decrease in number of segments with inducible perfusion deficit at least 2	-	-	-	3/16	6/21	**10.2**

CSWT - cardiac shock wave therapy, DSE – dobutamine stress echocardiography, OMT – optimal medical therapy, LVEF left ventricular ejection fraction, MRI – magnetic resonance imaging, NNT – number needed to treat, SDS – summed difference score

4.2.8 Summary of study treatment effects

The summary effect of treatment with SW compared to placebo on investigated clinical, functional and imaging parameters are shown in Figure 28. There was no significant difference between the two study groups with respect to the primary endpoint for the improvement of exercise duration. Although, he addition of CSWT to OMT resulted in effective reduction of numerous ischemia signs than OMT alone, and normalization of myocardial perfusion and contraction during stress was significantly more common in CSWT + OMT group. This suggests that CSWT is able to reduce ischemic burden of myocardium.

FIGURE 28. **Treatment effect of CSWT compare with placebo**



CCS – Canadian Cardiovascular Society angina class, DSE – dobutamine stress echocardiography, SAQ – Seattle angina questionnaire, SPECT – single photon emission computed tomography.

4.2.9 Search of patients' characteristics predictive for CSWT effectiveness. Insights for future research

The patient profile, which benefits most from treatment with SW, is not clear yet. Thus we initiated analysis, which aimed to explore associations between patient's characteristics and reduction of myocardial ischemia in patients treated with SW on top of OMT in order to provide practical recommendations.

This analysis included only data of CSWT + OMT group patients. Two datasets were created for analysis of improvement separately of myocardial perfusion (by SPECT scores, n=26) and contractility (by DSE scores, n=28). The variables of choice included cardiovascular risk factors, history of CAD and medications at baseline, SAQ scores, clinical and functional parameters, DSE and SPECT stress tests results at baseline and at 6 month follow up. The improvement in myocardial contractility and perfusion was defined as decrease in WMS during DSE and SDS during SPECT, respectively, at least by 2 points at 6 months follow up compared to baseline. In each dataset patients with improved parameters comprised subgroup of responders, remaining patients entered the subgroup of non-repsonders. The comparison of characteristics of these subgroups is presented in Table 25 and Table 26.

Our attempts to describe responder profile additionally included use of several statistical approaches, such as conditional interference trees algorithm, decision forest method and hierarchical cluster analysis. Detailed descriptions of the methodology are not provided due inconsistent results and limitation of thesis volume. However, we briefly show some of obtained models as demonstrating hypotheses generating signals.

The decision forest of myocardial contractility and perfusion is shown in Figure 29. Random forest returns several measures of variable importance. The most reliable measure is based on the decrease of classification accuracy when values of a variable in a node of a tree are permuted randomly [189-190], and this is the measure of variable importance.

The clusterograms of myocardial contractility and perfusion are shown in Figure 30. In hierarchical cluster analysis we used dendrograms to visualize how clusters are formed. The main purpose of this visualization is to get the patients' clusters and properties of their features. The dendrogram's horizontal axis is naturally determined by the tree. We chose to use the mean to determine the coordinate. The "distance" was used as the second axis. "Distance" naturally determines the number of clusters.

TABLE 25. **Comparison of patients with and without improvement in myocardial contractility**

	Responders (n=18)		**Non responders (n=10)**		P value	
	Baseline	6-month	Baseline	6-month	Baseline	6-month
Age	67.7±8	-	66.4±7.7	-	0.68	-
Exercise time duration, sec	345.1±129.9	373.8±141.4	357.7±143.2	466.8±192.2	0.805	0.155
Echocardiography						
LVEDV, ml	108.5±31.0	101.8±28.4	118.8±28.3	111.2±24.6	0.363	0.387
LVESV, ml	48.1±18.5	44.1±21.1	58.5±23.6	53.3±19.5	0.186	0.268
LVEF, %	56.2±8.4	58.4±8.5	51.8±10.9	53.2±9.8	0.220	0.156
LVMI, g/m^2	90±16.2	87±16	100±15.1	96.9±21	0.116	0.169
Seattle Angina Questionnaire						
PL	54.1±22.9	55.2±19.2	48.1±19.7	54.9±11	0.484	0.950
AS	45.8±19.6	75±30.9	24.6±18.5	87.5±21.2	**0.006**	0.267
AF	56.1±18.8	78.3±24.8	53.3±17.8	77±20	0.689	0.886
TS	65.1±15	80.7±12.0	68.3±18	76.6±11.4	0.601	0.391
QL	55.1±19.2	72.2±17.4	46.5±16.8	75±22.2	0.220	0.717
Dobutamine stress echocardiography						
WMS rest	23.2±7.8	21.3±5	23.6±8.2	24.9±8.1	0.904	0.160
WMS stress	28.2±7.2	21.9±5.1	24.6±6.5	25.1±6.6	0.169	0.171
PSS rest	-15.5±3.7	-14±2.4	-14.4±2.9	-13.7±	0.470	0.858
PSS stress	-14.5±3	-14.3±2.8	-15.7±2.7	-15.6±1.3	0.339	0.408
Single photon emission computed tomography						
SSS	9±3.9	6.8±5.6	12.3±11.7	11.2±14.5	0.269	0.284
SRS	2.7±2.8	2.4±3	8.8±11.9	9.1±13.9	**0.047**	0.072
SDS	6.3±3.4	4.4±4.1	4.5±4.3	2.1±2.5	0.204	0.118

Values are presented as mean ± standard deviation.

LVEDV – left ventricular end diastolic volume, LVESV – left ventricular end systolic volume, LVEF – left ventricular ejection fraction, LVMI – left ventricular mass index, PL – physical limitation, AS – angina stability, AF – angina frequency, TS – treatment satisfaction, QL – quality of life, WMS – wall motion score, PSS – peak systolic strain, SSS – summed stress score, SRS – summed rest score, SDS – summed difference score.

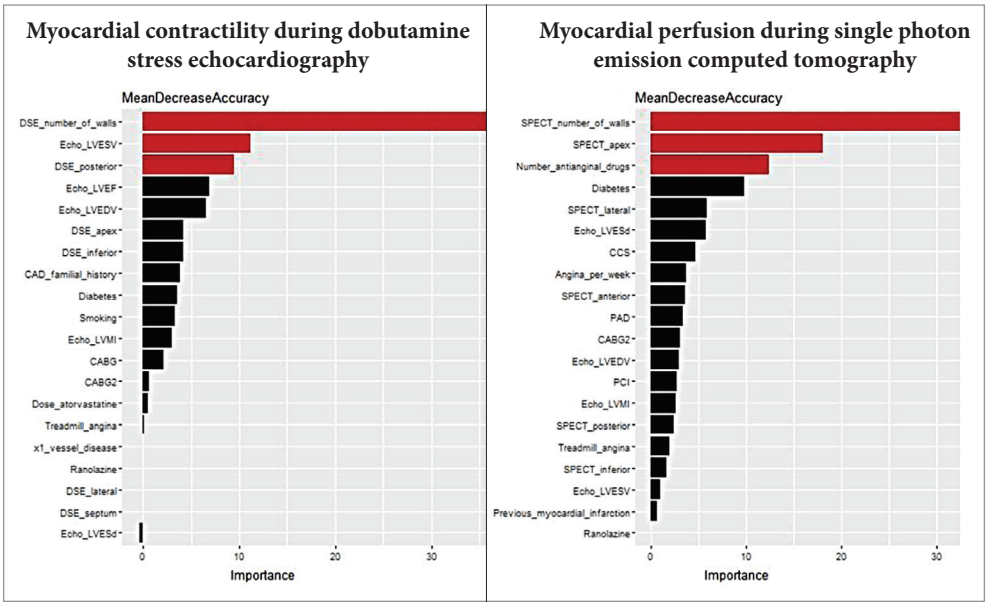
TABLE 26. **Comparison of patients with or without improvement in myocardial perfusion**

	Responders (n=13)		Non responders (n=13)		P value	
	Baseline	6-month	Baseline	6-month	Baseline	6-month
Age	66.4±7.6	-	68±7.1	-	0.581	-
Exercise time duration, sec	351.5±146.5	408.7±186.9	375.3±127.1	414.6±158.9	0.661	0.931
Echocardiography						
LVEDV, ml	100.9±30.8	99.2±28.6	125.5±25.2	113.5±23.5	**0.035**	0.183
LVESV, ml	43.2±17.5	43.5±19.5	58.6±22.1	52.9±22.2	0.059	0.300
LVEF, %	57.4±7.6	57.7±8	54.4±10.5	54.8±10.9	0.410	0.534
LVMI, g/m^2	88±14.6	85.0±14.8	97.9±17.4	93.8±20.8	0.127	0.315
Seattle Angina Questionnaire						
PL	58.8±21.5	54.2±18.6	49.4±20.6	56.2±10.8	0.266	0.667
AS	38.5±21.9	84.6±24	38.5±24.2	76.9±29.7	1	0.475
AF	59.2±14.4	83.9±17.6	52.3±21.7	74.6±24.7	0.347	0.283
TS	66.2±14.4	81±11.7	67.1±17.7	79.2±11.8	0.880	0.711
QL	51.3±18.6	69.2±22.4	53.2±20.6	78.2±14.2	0.805	0.235
Dobutamine stress echocardiography						
WMS rest	21.9±8.4	21.5±5.6	24.3±7.7	24.5±7.1	0.455	0.256
WMS stress	25.7±7.6	22.1±5.3	27.6±7.6	24.8±6.2	0.524	0.248
PSS rest	-15.3±3.9	-13.8±2.9	-15.2±3.4	-13.9±2.8	0.927	0.954
PSS stress	-15.2±2.6	-14.8±1.9	-15.1±3.3	-15.1±3	0.963	0.819
Single photon emission computed tomography						
SSS	10.1±5.7	5.8±6.2	10.2±10.9	11.2±12.4	0.965	0.180
SRS	2.9±4.8	3.1±5.1	7.1±11.2	6.8±12.1	0.230	0.310
SDS	7.2±3.5	2.8±2.3	3.2±2.9	4.3±4.7	**0.004**	0.297

Values are presented as mean ± standard deviation.

LVEDV – left ventricular end diastolic volume, LVESV – left ventricular end systolic volume, LVEF – left ventricular ejection fraction, LVMI – left ventricular mass index, PL – physical limitation, AS – angina stability, AF – angina frequency, TS – treatment satisfaction, QL – quality of life, WMS – wall motion score, PSS – peak systolic strain, SSS – summed stress score, SRS – summed rest score, SDS – summed difference score.

FIGURE 29. **Decision forests for prediction of responders**

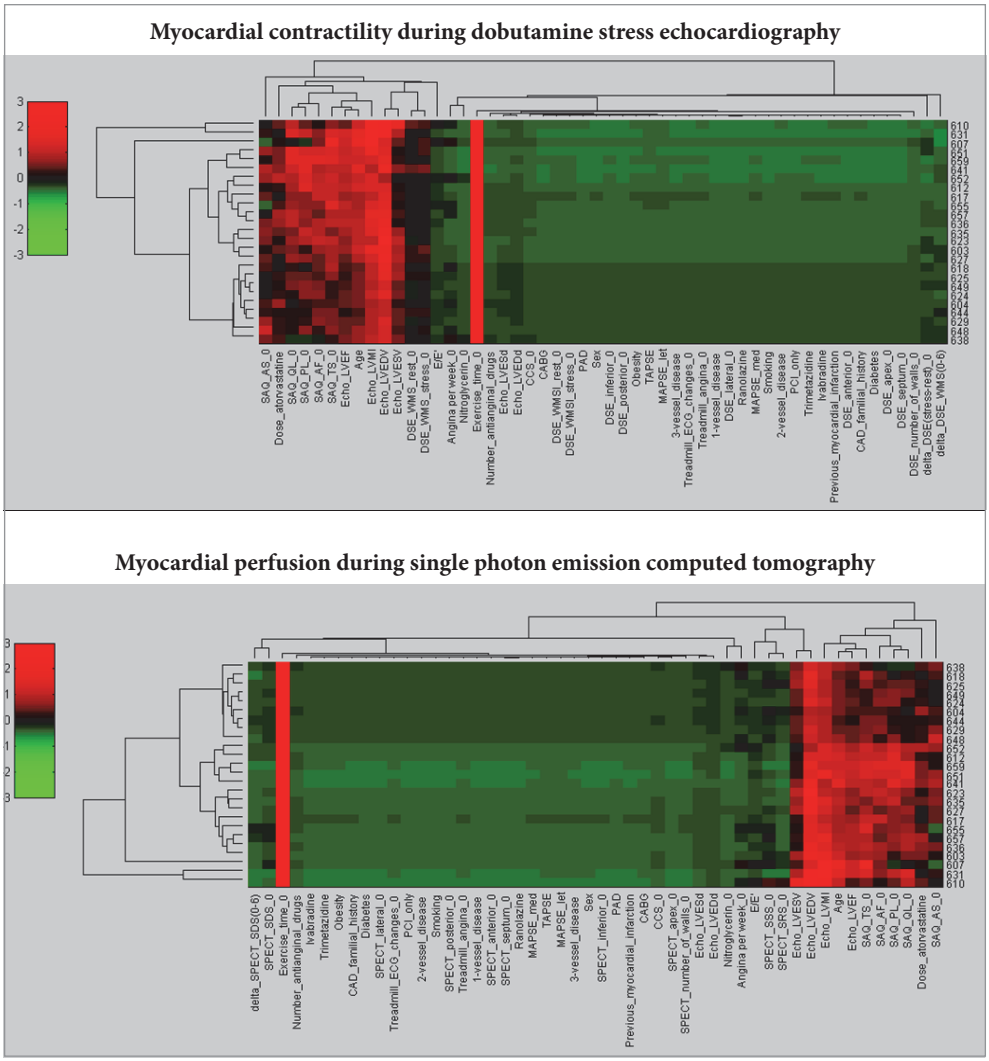


The most important predictors are shown in red: (1) for improvement in myocardial contractility: LV ESV, number of walls with inducible ischemia and inducible ischemia in posterior wall during DSE; (2) for improvement in myocardial perfusion: number of antianginal drugs, number of walls with inducible perfusion deficit and inducible perfusion deficit in the apex during SPECT.

The positive correlation was observed for characteristics including age, LVEDV, LVESV, LVMI, LVEF, dose of atorvastatine and SAQ scores in both models.

Though our study is underpowered and was not specifically oriented to provide definite results on responders' profile, presented data generate new hypotheses for the design of future randomized controlled trial. The signals come that CSWT on top of OMT may be more effective in younger patients with sufficient amount of inducible myocardial ischemia and not significantly dilated LV without extensive scar tissue. These statements could be tested in the adequately powered trial with pre-specified patient stratification to appropriate subgroups using the calculation of response probability using hazard ratio prediction methods; calculation of correlation and Granger causality between characteristics and improvement in myocardial contractility and perfusion and labeled regression analysis.

FIGURE 30. **The clusterograms of responders**



The most positive correlated features are in red color, negative correlated in green one. The collumns represent individual variables, rows – individual study participants.

5. DISCUSSION

Despite major advances in the management of coronary artery disease, this condition is recognized to be a leading reason of adult mortality worldwide, responsible for 20% of deaths each year in Europe [191], and stable angina is the most frequent clinical presentation. The death rate for ischemic heart disease in Lithuania was as high as 529.6 deaths per 100,000 inhabitants in 2016 [192], which is much higher than mean death rate in Europe [193]. It is the second most frequent chronic disease in Lithuania with the prevalence of angina pectoris being 4561 cases per 100,000 in general population [194].

Many patients experience persistent symptoms despite revascularization procedures and modern medical treatment. Thus, there is a crucial need for development and investigation of novel pharmacological, invasive or non-invasive treatment modalities, aimed of improving care and quality of life for this challenging patient population.

Experimental studies demonstrated that cardiac shock wave therapy might promote angiogenesis and improve myocardial function in a model of myocardial ischemia [128]. Since 1999 [130], cardiac shock-wave therapy has been investigated for the management of refractory angina in a considerable number of clinical studies.

The purpose of our study was to study the impact of CSWT on exercise tolerance, angina symptoms, myocardial perfusion and contraction during stress in patients with coronary artery disease and objective evidence of myocardial ischemia, who are not candidates for traditional revascularization and experience angina despite optimal medical therapy.

First we performed systematic review and meta-analysis of currently available CSWT studies in humans and subsequently carried out a randomized, triple blind, sham-procedure controlled study. The data analysis showed that available publications provided only low to moderate-quality scientific results on clinical benefits of CSWT. Keeping in mind modest penetration of this promising but time- and resource-consuming method into practice, it seemed relevant to perform rigorously designed clinical study of CSWT potential to improve exercise tolerance confirmed by reduction of myocardial ischemia provoked during stress. Furthermore, for the first time effect of CSWT on regional and global mycardial contractility is studied in RCT using multimodality and deformation imaging.

5.1 Systematic review and meta-analysis

In an effort to get evidence on the efficacy of the alternative non-invasive method for treatment of stable angina we summarized the results and evaluated the quality of currently accumulated data about cardiac shock wave therapy from trials published since 1999 to April 2016. Our systematic review expands previously published analysis [24] by including 23 recent studies, and confirms the beneficial effects of CSWT in a larger pooled sample size of patients with stable CAD. The strength of this analysis is a comprehensive character of review, an inclusion in meta-analysis studies with single clinical indication and a uniform treatment protocol, and assessment of bias risk in randomized trials in accordance to Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement [131]. In contrast to our study, recently published meta-analysis of Wang and co-authors covered only a limited period of publications, from 2010 to 2014, and included not only English but also Chinese articles [25]. As a result, our work presents the largest contemporary review of human CSWT trials incorporating all historical research period. Like in the previous analyses the majority of detected trials were relatively small (largest study sample consisted of 111 patients, but control group was absent [23]), single center, single arm, some of them insufficiently reported methodology and results. Largest RCT sample consisted of 87 patients, but study personnel was not blinded to treatment allocation [184]; placebo applicators were used only in one published study [147]. In order to avoid substantial heterogeneity and publication bias reported by Wang, we excluded from meta-analysis studies, which targeted at different population of ischemic heart failure, and also non-English articles as potentially producing more beneficial results. Our study focused on the stable CAD patients and confirmed consistent positive anti-anginal effect of CSWT.

Our review and meta-analysis show that in the majority of published CSWT studies, nitroglycerine consumption and angina frequency decreases, CCS angina class, Seattle angina questionnaire scores and NYHA class improves, myocardial perfusion and exercise capacity increases significantly. The positive impact could be observed as early as in the first month, suggesting the contribution of an early local vasodilating effect of SW. Those beneficial effects persisted up to 1-year of follow up, probably related to angiogenesis and other tissue reactions [175].

Total exercise capacity is one of the most accepted variables used to assess efficacy of any anti-anginal treatment. Our meta-analysis of 596 participants suggests at least a moderate improving effect of CSWT on exercise tolerance. We evaluated data from

randomized clinical studies along with several non-controlled studies of good quality, though certain extent of heterogeneity is not avoided.

However, most of the studies included in the review and meta-analysis are single-center and uncontrolled, making the likelihood of bias towards larger intervention effect substantial. Different methodological quality, inadequate design or unbalanced analysis compels cautious interpretation of the real CSWT effect. We confirmed the conclusion made by Wang who stated that quality of published controlled trials methodology was low [25]. We found the majority of the randomized studies having high risk of bias in terms of attribution, sample size calculation, blinding of participants and outcome assessment.

Our review and meta-analysis combined data from randomized and non-randomized clinical trials (RCT). The rationale to include data from non-randomized trial was the lack of evidence about CSWT efficacy as treatment method for CAD. This meta-analysis combines the aggregate data from the trials.

Despite very good tolerance, virtually absence of side effects, considerable symptomatic effect and non-invasive nature of CSWT it has not been widely put into practice. This may be associated with the need of special average-cost equipment, particular skills of ultrasound scanning and CSWT application, and with the significant time consumption for the whole therapy course as well. Therefore, CSWT can be considered not as a substitutive but as adjunct therapy in case of limited efficacy of optimal medical treatment. It seems that the tentative phase of this novel treatment has lasted long enough, and still there is a lack of high quality evidence. Thus, larger scale randomized placebo-controlled trial is justified to get more data providing a rationale for CSWT widespread use.

5.2 Randomized, sham-procedure controlled, triple blind study

The novelty and better quality evidence in this study include several aspects. Patients were enrolled to a multicenter, randomized, sham-procedure controlled trial on the basis of myocardial ischemia proven by several stress tests. Mean extent of stress-induced changes in perfusion and wall motion corresponded to moderate amount of ischemia. For assessment of myocardial mechanics at rest and during stress we utilized not only visual assessment but also innovative markers of deformation imaging. The protocol was created in accordance to Consolidated Standards of Reporting Trials (CONSORT) statement [26]. The study was conducted in two centres and randomization was performed centrally. The multicentre design

reduces bias that may be inevitable consequence in single center studies. Next, the specific sham applicator with external appearance and the same behaviour as active applicator was used in this study (Figure 10).

The stress tests for evaluation of myocardial perfusion and contractility were performed in accordance to European guidelines for cardiovascular imaging and stress testing [141, 195, 196, 197]. Furthermore, the competence of stress echocardiography and SPECT laboratories at the time of the present study was approved by the core specialists of International Study of Comparative Health Effectiveness with Medical and Invasive Approaches (ISCHEMIA) for independent assessment of ischemia during stress. The definitions of moderate to severe ischemia for myocardial perfusion imaging (MPI) and echocardiography were chosen according to ISCHEMIA study methodology [198]. Moreover, blinding of participants, healthcare providers, investigators of outcome assessments and statistician was kept during all period of study conduction. Therefore, in comparison to previous randomized CSWT trials we consider our study to be at low risk of bias in terms of methodology.

The study included 72 patients with coronary artery disease, who were not candidates for further traditional revascularization and experienced limiting angina despite optimal medical therapy, from 2 centres. Majority of patients were selected from out-patient department of Cardiology and eligibility was based on objective evidence of myocardial ischemia proven by stress tests.

Last, the new treatment protocol is produced in order to provide application of shock waves to all segments of LV. In previously published studies, SWs were applied only to ischemic segments of LV, defined by imaging stress tests. The idea of new protocol is to extend the indications for widespread use of CSWT, which would not be based on the results of sometimes unavailable any imaging tests or coronary angiography. Application of shock waves to all segments of LV may provide beneficial therapeutics effects not only by reducing ischemia, but additionally by attenuating inflammation and suppressing oxidative stress and fibrosis in non-ischemic segments as well, what potentially may prevent LV remodelling.

Measurement of total exercise tolerance, time to ischemic ECG changes or development of symptoms during ETT are widely used outcomes in CAD studies. The way to assess subjective physical and emotional impact of angina pectoris is the Seattle angina questionnaire [137]. The SAQ is commonly used for measuring health status in coronary patients, which has been confirmed as a valid, reproducible and sensitive performance measure for assessing the quality of CAD care [199].

Therefore, ETT, CCS class and SAQ scores were chosen as efficacy parameters in our study. Advantages of these tests are their simplicity, safety, negligible cost, and wide accessibility.

Regardless of treatment assignment, the majority of patients from both treatment groups showed significant improvement in exercise capacity and quality of life, angina class and less dependence on nitroglycerine for symptom relief at 3 and 6 months follow up. There was no significant difference between the two study groups with respect to the primary endpoint meaning neutral result of intervention for the improvement of exercise duration.

However, it should be acknowledged that measurement of exercise duration susceptible to such errors as variable encouragement by the test supervisor, non-cardiac reasons for test termination such as skeletal muscle deconditioning because of lack of physical exercise, degenerative skeletal diseases, chronic pain disorders, depression [200]. The time to ST-depression or time to chest pain are more sensitive to changes in angina status [201]. The total exercise time could be of limited value at the end of our study due to the cessation of the test by more than half of the patients due to non-cardiac reasons. A complimentary example is a study, where patients did not improve their maximum exercise capacity at one year after one-vessel PCI, despite being relieved of angina symptoms and myocardial hypo-perfusion [202-203].

The sample size calculation for primary outcome was performed to detect at least 90 seconds improvement in exercise duration in patients treated with CSWT on top of OMT; this value is based on the previous studies of anti-anginal treatment (Table 27). In pharmacological studies exercise duration increased by 115.6 seconds in ranolazine groups (pooled) compared to 91.7 seconds in the placebo group ($p=0.01$), by 86 seconds in trimetazidine group compared to 24 seconds in the placebo group ($p=0.01$), and by 24.3 seconds in ivabradine group compared to 7.7 seconds in the placebo group ($p<0.001$).

In CSWT studies Prasad et al. [23] and Cassar et al. [173] reported the improvement of mean exercise time of 149 and 103 seconds, respectively. The increase in exercise duration in our study is modest in comparison to previously published CSWT studies: 48.8 seconds in OMT + CSWT group compared with 80.4 seconds in OMT + placebo group ($p=0.710$). Leibowitz et al. did not found significant changes in exercise duration at follow up between study groups in double blind, placebo controlled study [147].

TABLE 27. **Effects of antianginal medications and non-pharmacological therapeutic methods on the improvement of exercise duration**

	Test group			Control group			P value	Reference
	N	Baseline	Follow up	N	Baseline	Follow up		
Antianginal medications								
Ranolazine[a,b,c]	533	-	Δ 115.6 ± 8.1[f]	258	-	Δ 91.7 ± 8.3[f]	0.01	[205]
Ivabradine[a]	441	-	Δ 24.4 ± 65.3[f]	434	-	Δ 7.7 ± 63.8	<0.001	[7]
Trimetazidine[a]	168	420 ± 108	485 ± 122	179	432 ± 110	458 ± 134	0.01	[206]
Non-invasive methods								
Enhanced external counterpulsation[a]	28	586 ± 193.5	773.6 ± 263.2[f]	14	597.1 ± 181.6	612.1 ± 175.6	<0.001	[74]
Cardiac shock wave therapy[a]	35	380.9 ± 152.5	Δ 48.8	32	380.5 ± 150.7	Δ 80.4	0.710	Our study
Invasive methods								
Spinal cord stimulation[d,e]	10	121±98	191 ± 81	9	175 ± 100	140 ± 78	NS	[71]
Transmyocardial laser revascularization[a, b]	98	393 ± 154.2	431.2 ±175.4[f]	102	358.6 ± 146.8	395.3 ± 177.9	0.334	[207]
Coronary sinus reduction[a]	52	441 ± 191	Δ 59	52	464±257	Δ 4	0.07	[208]
Cell based therapies[a]	55[g] 56[h]	-	Δ 140 ± 171 Δ 103 ± 162	56	-	Δ 58 ± 146	0.014 0.097	[12]
Protein and gene based therapies[a,b,c]	171	-	Δ 36.6	156	-	-	NS	[93]

a- blinded, randomized, placebo controlled study, b- pooled test group; c – results presented as mean ±SE, d- randomized, controlled, e- 6MWT was used, f- $p<0.05$ of the comparison of follow up to baseline, g- low dose group, h- high dose group, NS – non significant.

Importantly, the research in the field of several other alternative anti-anginal methods showed similar evolution: from positive single-arm small-scale studies to randomized controlled studies, which failed to show significant benefit in exercise tolerance. This was the case in the studies of spinal cord stimulation, enhanced external counterpulsation, gene therapy and other CSWT studies [10, 74, 93, 147, 204].

Expected improvement in exercise time was not reached, but anti-ischemic benefit of CSWT was shown in decrease of patient number with peak ST segment deviation ≥1mm during exercise treadmill and dobutamine stress echocardiography tests. Patients randomized to OMT + CSWT group more commonly experienced a significant reduction in ischemia (peak ST segment deviation <1 mm) during exercise treadmill test compared with those receiving OMT + placebo (48.6% versus 9.4%, p=0.001).

The addition of CSWT to OMT resulted in more effective reduction of several objective ischemia signs than OMT alone, and normalization of myocardial perfusion and contraction during stress was significantly more common in CSWT + OMT group. This signifies the positivity of secondary study outcomes assessed by imaging stress tests.

In imaging tests sub-study, analysis of dobutamine stress echocardiography data revealed that CSWT is able to improve regional myocardial contractility and LV ejection fraction during stress. Wall motion score reduced significantly during DSE stress phase at 3 and 6 month follow up. Improvement in rest wall motion score at 6 month follow up was also observed during cardiac MRI. For the first time we show the significant additive impact of CSWT on regional and global systolic function evaluted visually both by ultrasound and MRI on top of OMT. Due to particular study design (i.e. repetitive DSE testing at 3 and 6 months after the treatment initiation), we are able to demonstrate significant reduction in stress induced ischemia assessed by semi-quantitative wall motion score at 3 months only in CSWT + OMT group compared to baseline. As additional confirmation of anti-ischemic impact, at 3 month follow up significant improvement of LVEF during stress in DSE test was observed in OMT + CSWT group. This early improvement of myocardial contractility during stress confirms the beneficial effect of shock acoustic waves, which may be attributed to angiogenetic and vasoactive mechanisms. Importantly, positive effect on regional myocardial function, most likely related to enhanced coronary circulation, was maintained further until the end of study at 6 months after the CSWT initiation,

along with markedly higher LVEF not only during stress, but also at rest. To our knowledge, this is the first study that evaluates the effects of CSWT on LVEF during DSE test.

On the other hand, our study reveals the potential of optimal medical treatment to result in the anti-ischemic action in longer period of treatment as was found in the changes of stress WMS at 6 months (but not at 3 months) after placebo application.

For assessment of myocardial mechanics at rest and during stress we utilized not only visual assessment but also innovative markers of deformation imaging. Previous CSWT studies analysed changes of peak systolic strain rate (PSSR) [181, 183]. The results showed significant increase of PSSR at 6 and 12 months follow up in CSWT group compared with controls, accompanied by singnificant increase in the amplitude of regional myocardial motion in M-mode compared to baseline [181, 183]. We did not find any previuos reports of systolic strain dynamics in CSWT trials. The purpose of inclusion of these objective functional parameters was to register probable subtle differences in contractility in the course of treatment which sometimes can not be seen by naked eye. We found that application of SW to all LV segments has a protective effect on myocardial deformation: peak systolic strain values remained unchanged in contrast to placebo group, where global PSS decreased significantly at the end of the study. This important finding suggest that CSWT might inhibit progression of ischemic burden. Additionally, in OMT + placebo group at 6 month follow up the trend of increase in number of segments with late gadolinium enhancement on MRI scans was observed, while opposite trend was seen in OMT + CSWT group.

The myocardial perfusion imaging results demonstrated that the adjunct of CSWT to OMT resulted in significant reduction of ischemia amount compared to OMT alone, and the complete normalization in perfusion scores was more common in patients assigned to OMT + CSWT group. The extent and severity of ischemia (summed stress score - SSS) and amount of inducible ischemia (summed difference score – SDS) significantly decreased in CSWT + OMT group at 6 month follow up compared with OMT + placebo group (as method associated with radiation exposure and more resource-consuming it was not repeated at 3 months time point). Previous studies also demonstrated CSWT ability to improve myocardial perfusion in ischemic settings in patients with refractory angina. Alunni et al. demonstrated a significant reduction of mean SSS from 21.3±10.3 to 14.1±10.1 ($p=0.003$) compared with baseline, but SPECT was not performed in controls at follow up [20]. Kazmi et al. reports increased numbers of patients with reduced severity of ischemia at follow

up compared with baseline [180]. However, this is the first study to evaluate the direct effects on local perfusion using analysis of SPECT images comparing treatment groups in a triple blind, randomized study design.

In studies with angina patients, CCS class and nitroglycerine consumption are the most frequently chosen variables for evaluation of clinical status. The effects of CSWT to changes of angina and nitroglycerine consumption were the secondary endpoints with neutral result in our trial.

Majority of CSWT studies (including single arm and controlled) reported the significant decrease in CCS class (mean decrease at least by one class) and weekly nitroglycerine use (40 - 75%) after the treatment with CSWT [63]. In present study, both groups showed considerable reduction in CCS class, angina frequency and use of nitroglycerine at follow up compared to baseline with no significant difference between study groups. These finding are in line with research data previously published by Nirala et al. [181]. Moreover, the SAQ scores increased significantly in both study groups. Clinical improvement equally exhibited in intervention and placebo group presumably is related to robust anti-ischemic, anti-inflammatory, vasoactive and anti-atherosclerotic action of optimal medical treatment. Enhanced motivation of adherence to medications, stable doses during clinical study may play a role.

Both study groups were exposed to the same size of placebo effect, which may particularly affect clinical parameters, SAQ score, and exercise capacity. For CCS angina class, which is usually scored by the investigator and not by the patient himself, one trial found that 28% of the improvement was due to investigator bias [209]. The VIVA trial (Vascular endothelial growth factor in Ischemia for Vascular Angiogenesis) demonstrated that placebo may have a significant ameliorating effect on a subjective outcome measurements, such as angina [13]. Both patient and investigator tend to be biased towards an improvement over time due to treatment. Thus, in our study probably modest degree of clinical CSWT effect may be masked by prominent placebo effect, while objective test parameters, such as myocardial perfusion scores during SPECT or wall motion scores during DSE or MRI, revealed significant differences between CSWT and placebo. The assessment of SPECT and WMS were performed by blinded to clinical data investigators, thus eliminating bias. For the interpretation of the present study results it is important to recognize that the correlation between exercise capacity and myocardial perfusion changes is weak [210].

Due to numerous exclusion criteria of the main and sub-study of RCT the screen failure rate was high (77.4%) undermining generalizability of the results. As treatment area needs to be localized, the patients without an adequate echocardiographic window (e.g., overweight, pulmonary disease) cannot receive CSWT. Also, the safety of CSWT use in patients with pacemakers or implantable defibrillators is not defined. Beyond these points no other technical limitations are described. Our study was underpowered to investigate the impact of CSWT on patients' prognosis.

Our systematic review of CSWT studies in stable CAD demonstrated a significant improvement of clinical variables including angina class and quality of life, as well as positive changes in LV function and perfusion. Meta-analysis showed moderate improvement in exercise capacity. Overall, CSWT is a potentially effective new non-invasive option for patients with CAD, but up till now evidence was limited to small, single-centre studies with high risk of bias due to the absence of credible control and allocation procedures.

The anti-ischemic CSWT effect is clearly proven by cardiac imaging techniques and ECG changes during stress in our triple blind RCT. Exercise time duration of treadmill stress test, angina symptoms, angina class, nitroglycerine consumption and quality of life improved in both intervention and placebo groups, with no additional benefit of CSWT on top of standard medical therapy in these clinical variables. Thus, this strictly designed randomized sham-procedure controlled study showed neutral result of CSWT regarding primary endpoint of exercise tolerance. Significant but modest positive effect of CSWT on perfusion, contractility and extent of myocardial ischemia did not translate to meaningful clinical benefit comparing to placebo. Our study presumably shows the substantial reserve of symptomatic improvement in optimizing medical treatment and patients' adherence.

6. CONCLUSIONS

1. Meta-analysis of the effect of cardiac shock wave therapy demonstrates the significant moderate improvement in exercise capacity.
2. Currently published studies provide weak evidence for clinical application of cardiac shock wave therapy, due to inadequate design and high risk of bias from small studies.
3. The primary endpoint of the randomized, sham-procedure controlled study for improvement in exercise duration during exercise treadmill test in patients treated with cardiac shock wave therapy on top of optimal medical therapy is not achieved.
4. The randomized, sham-procedure controlled study met secondary endpoints:
   - CSWT significantly reduced extent and severity of myocardial hypo-perfusion and amount of ischemia during single photon emission computed tomography in intervention group compared with placebo;
   - CSWT significantly improved stress wall motion score and left ventricular ejection fraction during dobutamine echocardiography at 3 and 6 month follow up in OMT + CSWT group patients compared with baseline.
5. CSWT exhibited neutral effect on quality of life and level of angina.
6. Cardiac shock wave therapy demonstrates possibly earlier anti-ischemic effect than optimization of medical treatment.

7. CLINICAL IMPLICATIONS

1) Cardiac shock wave therapy may be effectively used for treatment of patients with refractory angina, who are not amenable to revascularization, and optimal medical treatment is not sufficient.
2) The application of shock waves to all left ventricular segments may be sufficiently effective and does not require imaging stress tests prior to treatment.
3) Seattle angina questionnaire can be useful for monitoring of the efficacy of cardiac shock wave therapy.
4) Thorough optimization of medical treatment and enhancement of patients' adherence still shows significant potential for relief of symptoms, improvement in exercise capacity and quality of life.

8. REFERENCES

1. Go AS, Mozaffarian D, Roger VL, et al. Heart disease and stroke statistics—2013 update: a report from the American Heart Association. Circulation. 2013; 127(1):e6-e245.
2. Nichols M, Townsend N, Luengo-Fernandez R, et al. European Cardiovascular Disease Statistics 2012. European Heart Network, Brussels, European Society of Cardiology, Sophia Antipolis; 2012.
3. Andrell P, Ekre O, Grip L, et al. Fatality, morbidity and quality of life in patients with refractory angina pectoris. Int J Cardiol 2011; 147(3):377–82.
4. Willams B, Menon M, Satran D et al. Patients with coronary artery disease not amenable to traditional revascularization: prevalence and 3-year mortality. Catheter Cardiovasc Interv. 2010;75(6):886-891.
5. Mannheimer C, Camici P, Chester MR, et al. The problem of chronic refractory angina; report from the ESC Joint Study Group on the Treatment of Refractory Angina. Eur Heart J 2002; 23:355-370.
6. Wilson SR, Scirica BM, Braunwald E, et al. Efficacy of ranolazine in patients with chronic angina observations from the randomized, double-blind, placebo-controlled MERLIN-TIMI (Metabolic Effi- ciency With Ranolazine for Less Ischemia in Non-ST-Segment Elevation Acute Coronary Syndromes) 36 Trial. J Am Coll Cardiol. 2009;53(17):1510-1516.
7. Tardif JC, Ponikowski P, Kahan T, ASSOCIATE Study Investigators. Efficacy of the I(f) current inhibitor ivabradine in patients with chronic stable angina receiving beta-blocker therapy: a 4 month, randomized, placebo-controlled trial. Eur Heart J. 2009;30(5):540-548.
8. Arora RR, Chou TM, Jain D, et al. The multicenter study of enhanced external counterpulsation (MUST-EECP): effect of EECP on exercise-induced myocardial ischemia and anginal episodes. J Am Coll Cardiol 1999; 33:1833-1840.
9. Hautvast RW, DeJongste MJ, Staal MJ, van Gilst WH, Lie KI. Spinal cord stimulation in chronic intractable angina pectoris: a randomized, controlled efficacy study. Am Heart J. 1998;136(6):1114-1120.
10. Zipes DP, Svorkdal N, Berman D, et al. Spinal cord stimulation therapy for patients with refractory angina who are not candidates for revascularization. Neuromodulation 2012;15(6):550-9.

11. Buschmann EE, Utz W, Pagonas N, et al. Arteriogenesis Network (Art. Net.) Improvement of fractional flow reserve and collateral flow by treatment with external counterpulsation (Art.Net.-2 Trial). Eur J Clin Invest 2009;39:866–875.
12. Burkhoff D, Schmidt S, Schulman SP, et al. Transmyocardial laser revascularisation compared with continued medical therapy for treatment of refractory angina pectoris: a prospective randomised trial. ATLANTIC Investigators. Angina Treatments-Lasers and Normal Therapies in Comparison. Lancet 1999; 354:885-890.
13. Henry TD, Annex BH, McKendall GR, et al. The VIVA trial: Vascular endothelial growth factor in Ischemia for Vascular Angiogenesis. Circulation. 2003;107(10):1359-65.
14. Kastrup J, Jørgensen E, Rück A, et al. Direct intramyocardial plasmid vascular endothelial growth factor-A165 gene therapy in patients with stable severe angina pectoris A randomized double-blind placebo-controlled study: the Euroinject One trial. J Am Coll Cardiol. 2005;45(7):982-8.
15. Patel AN, Geffner L, Vina RF, et al. Surgical treatment for congestive heart failure with autologous adult stem cell transplantation: a prospective randomized study. J Thorac Cardiovasc Surg. 2005 Dec;130(6):1631-8.
16. Losordo DW, Henry TD, Davidson C, and the ACT34-CMI Investigators. . Intramyocardial, autologous CD34+ cell therapy for refractory angina. Circ Res. 2011;109(4):428-436.
17. Gotte G, Amelio E, Russo S, Marlinghaus E, Musci G, Suzuki H. Short-time non-enzymatic nitric oxide synthesis from L-arginine and hydrogen peroxide induced by shock waves treatment. FEBS Lett. 2002 Jun 5;520(1-3):153-5.
18. Ciampa AR, de Prati AC, Amelio E, et al. Nitric oxide mediates anti-inflammatory action of extracorporeal shock waves. FEBS Lett. 2005 Dec 19;579(30):6839-45.
19. Fu M, Sun CK, Lin YC, et al. Extracorporeal shock wave therapy reverses ischemia-related left ventricular dysfunction and remodeling: molecular-cellular and functional assessment. PloS One 2011; 6:e24342.
20. Alunni G, Marra S, Meynet I, et al. The beneficial effect of extracorporeal shockwave myocardial revascularization in patients with refractory angina, Cardiovasc. Revasc. Med. 2015;16:6–11.
21. Zuoziene G, Leibowitz D, Celutkiene J, et al. Multimodality imaging of myocardial revascularization using cardiac shockwave therapy, Int. J. Cardiol. 2015;187:229–230.

22. Schmid JP, Capoferri, Wahl A, Eshtehardi P, Hess OM. Cardiac Shock Wave Therapy for Chronic Refractory Angina Pectoris. A Prospective Placebo-Controlled Randomized Trial. Cardiovascular Therapeutics 2013;31:e1-e6.
23. Prasad M, Wan Ahmad WA, Sukmawan RL, et al. Extracorporeal shockwave myocardial therapy is efficacious in improving symptoms in patients with refractory angina pectoris – a multicenter study. Coron Artery Dis 2015; 26:194-200.
24. Ruiz-Garcia J, Lerman A. Cardiac shock-wave therapy in the treatment of refractive angina pectoris. Interv Cardiol 2011;3(2).
25. Wang J, Zhou C, Liu L, Pan X, Guo T. Clinical effect of cardiac shock wave therapy on patients with ischemic heart disease: a systematic review and meta-analysis. Eur J Clin Invest 2015; 45(12):1270-1285.
26. Moher D, Hopewell S, Schulz KF, et al. CONSORT 2010 Explanation and elaboration: updated guidelines for reporting parallel group randomized trials. BMJ 2010;340:c869. Doi:10.1136/bmj.c869.
27. Montalescot G, Sechtem U, Achenbach S, et al. 2013 ESC guidelines on the management of stable coronary artery disease: The Task Force on the management of stable coronary artery disease of the European Society of Cardiology. Eur Heart J 2013;34(38):2949–3003.
28. Gould KL, Lipscomb K. Effects of coronary stenoses on coronary flow reserve and resistance. Am J Cardiol 1974;34:48–55.
29. Huang AL, Vita JA. Effects of systemic inflammation on endothelium-dependent vasodilation. Trends Cardiovasc Med 2006;16:15-20.
30. Vita JA. Endothelial function. Circulation 2011;124:e906-e912.
31. Koenig W, Khuseyinova N. Biomarkers of atherosclerotic plaque instability and rupture. Arterioscler Thromb Vasc Biol 2007;27:15–26.
32. Hachamovitch R, Berman DS, Shaw LJ, et al. Incremental prognostic value of myocardial perfusion single photon emission computed tomography for the prediction of cardiac death: differential stratification for risk of cardiac death and myocardial infarction. Circulation 1998;97:535-543.
33. Baigent C, Keech A, Kearney PM, for the Cholesterol Treatment Trialists' (CTT) Collaborators. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. Lancet 2005;366:1267–1278.

34. Al-Mallah MH, Tleyjeh IM, Abdel-Latif AA, Weaver WD. Angiotensin-converting enzyme inhibitors in coronary artery disease and preserved left ventricular systolic function: a systematic review and meta-analysis of randomized controlled trials. J Am Coll Cardiol 2006;47:1576–1583.
35. Antithrombotic Trialists' Collaboration. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. BMJ 2002;324:71–86.
36. Suzuki T, Kohro T, Hayashi D, et al. Frequency and impact of lifestyle modification in patients with coronary artery disease: The Japanese Coronary Artery Disease (JCAD) Study. Am Heart J 2012; 163:268-273.
37. Lin J, O'Connor E, Evans C, et al. Behavioral counseling to promote a healthy lifestyle in persons with cardiovascular risk factors: A systematic review for the U.S. Preventive Services Task Force. Ann Intern Med 2014;161:568–578.
38. Hemingway H, Langenberg C, Damant J, Frost C, Pyorala K, Barret-Connor E. Prevalence of angina in women versus men Circulation 2008; 117:1526-1536.
39. Fihn SD, Gardin JM, Abrams J, et al. 2012 ACCF/ AHA/ ACP/ AATS/ PCNA/ SCAI/ STS guideline for the diagnosis and management of patients with stable ischemic heart disease: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, and the American College of Physicians, American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. Circulation. 2012;126:e354-471.
40. Fox K, Ford I, Steg PG, for the BEAUTIFUL investigators. Ivabradine for patients with stable coronary artery disease and left-ventricular systolic dysfunction (BEAUTIFUL): a randomised, double- blind, placebo-controlled trial. Lancet 2008; 372: 807–816.
41. Fox K, Ford I, Steg PG et al. Ivabradine in stable coronary artery disease without clinical heart failure. N Engl J Med 2014;371:1091-1099.
42. IONA study group. Effect of nicorandil on coronary events in patients with stable angina: the Impact Of Nicorandil in Angina (IONA) randomized trial. Lancet 2002;359:1269-1275.
43. Horinaka S, Yabe A, Yagi H, et al. Effects of nicorandil on cardiovascular events in patients with coronary artery disease in the Japanese Coronary Artery Disease (JCAD) study. Circ. J. 2010;74:503–509.

44. Stone PH, Chaitman BR, Stocke K, et al. The anti-ischemic mechanism of action of ranolazine in stable ischemic heart disease. J. Am. Coll. Cardiol. 2010;56:934–942
45. Banon D, Filion KB, Budlovsky T, et al. The usefulness of ranolazine for the treatment of refractory chronic stable angina pectoris as determined from systematic review of randomized controlled trials. Am J Cardiol 2014;113:1075-82.
46. Kantor PF, Lucien A, Kozak R, et al. The antianginal drug trimetazidine shifts cardiac energy metabolism from fatty acid oxidation to glucose oxidation by inhibiting mitochondrial long-chain 3-ketoacyl coenzyme A thiolase. Circ. Res. 2000; 86:580–588.
47. Grabczewska Z, Białoszyński T, Szymański P, et al. The effect of trimetazidine added to maximal anti-ischemic therapy in patients with advanced coronary artery disease. Cardiol J 2008;15:344–50.
48. Phan TT, Shivu GN, Choudhury A, et al. Multi-centre experience on the use of perhexiline in chronic heart failure and refractory angina: old drug, new hope. Eur J Heart Fail 2009;11:881–6.
49. Rajendra NS, Ireland S, George J, et al. Mechanistic insights into the therapeutic use of high-dose allopurinol in angina pectoris. J. Am. Coll. Cardiol. 2011;58,:820–828.
50. George J, Carr E, Davies J, et al. High-dose allopurinol improves endothelial function by profoundly reducing vascular oxidative stress and not by lowering uric acid. Circulation 2006;114:2508–2516.
51. Windecker S, Kolh P, Alfonso F, et al. 2014 ESC/EACTS Guidelines on myocardial revascularization: The Task Force on Myocardial Revascularization of the Eu- ropean Society of Cardiology (ESC) and the European Association for Cardio-Tho- racic Surgery (EACTS) developed with the special contribution of the European As- sociation of Percutaneous Cardiovascular Interventions (EAPCI). Eur Heart J 2014; 35:2541-619.
52. Writing Group of the Bypass Angioplasty Revascularization Investigation (BARI) Investigators. Five-year cllinical and functional outcome comparing bypass surgery and angioplasty in patients with multivessel coronary disease. A multicenter randimized trial. JAMA. 1997;277:715-721.

53. Boden WE, O'Rourke RA, Teo KK, et al. COURAGE Trial Research Group. Optimal medical therapy with or without PCI for stable coronary disease. N Engl J Med. 2007;356:1503-1516.
54. Adamu U, Knollmann D, Alarawashdeh W, et al. Results of interventional treatment of stress positive coronary artery disease. Am J Cardiol. 2010;105:1535-1539.
55. Weintraub WS, Spertus JA, Kolm P, et al. COURAGE Trial Research Group. Effect of PCI on quality of life in patients with stable coronary disease. N Engl J Med. 2008;359(7):677-687.
56. Tonino PA, De Bruyne B, Pijls NH, et al. Fractional flow reserve versus angiography for guiding percutaneous coronary intervention. N Engl J Med 2009;360:213-24.
57. Alderman EL, Kip KE, Whitlow PL, et al. Native coronary disease progression exceeds failed revascularization as cause of angina after five years in the Bypass Angioplasty Revascularization Investigation (BARI). J Am Coll Cardiol 2004;44:766-74.
58. Marzilli M, Hugi A, Marrone D. Persistent angina: the Araba Phoenix of Cardiology. Am J Cardiovasc Drugs 2010;10(suppl 1):27-32
59. Jolicoeur EM, Cartier R, Henry TD, et al. Patients With Coronary Artery Disease Unsuitable for Revascularization: Definition, General Principles, and a Classification Can J Cardiol 2012; 28(2):S50-S59.
60. Henry TD, Datran D, Jolicoeur EM. Treatment of refractory angina in patients not suitable for revascularization. Nat Rev Cardiol 2014;11:78-95.
61. McGillion M, Arthur HM, Cook A, et al. Management of patients with refractory angina: Canadian Cardiovascular Society /Canadian Pain Society jpint guidelines. Can J Cardiol 2012;28(Suppl 2):S20-41.
62. Fihn SD, Blankenship JC, Alexander KP, et al. 2014 ACC/AHA/AATS/ PCNA/ SCAI/STS focused update of the guideline for the diagnosis and management of patients with stable ischemic heart disease: a report of the American College of Cardiology / American Heart Association Task Force on Practice Guidelines, and the American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. J. Am. Coll. Cardiol. 2014;64(18):1929-1949.

63. Burneikaite G, Shkolnik E, Celutkiene J, et al. Cardiac shock-wave therapy in the treatment of coronary artery disease: systematic review and meta-analysis. Cardiovascular Ultrasound 2017;15:11.
64. Rathore S, Katoh O, Matsuo H, et al. Retrograde percutaneus recanalization of chronic total occlusion of the coronary arteries: procedural outcomes and predictors of success in contemporary practice. Circ Cardiovasc Interv 2009; 2:124-132.
65. Christakopoulos GE, Christopoulos G, Carlino M, et al. Meta- analysis of clinical outcomes of patients who underwent percutaneous coronary interventions for chronic total occlusions. Am J Cardiol. 2015;115(10):1367-1375.
66. Grantham JA, Jones PG, Cannon L, Spertus JA. Quantifying the early health status benefits of successful chronic total occlusion recanalization: results from the FlowCardia's Approach to Chronic Total Occlusion Recanalization (FACTOR) trial. Circ. Cardiovasc. Qual. Outcomes. 2010; 3:284–290.
67. Park S-J. Optimal Medical Therapy With or Without Stenting For Coronary Chronic Total Occlusion - DECISION-CTO (Presentation). ACC 2017: American College of Cardiology Annual Scientific Session March 18, 2017, Washington, DC, USA.
68. Prager, J. P. What does the mechanism of spinal cord stimulation tell us about complex regional pain syndrome? Pain Med. 11, 1278–1283 (2010).
69. Taylor RS, De Vries J, Buchser E, Dejongste MJ. Spinal cord stimulation in the treatment of refractory angina: systematic review and meta-analysis of randomised controlled trials. BMC Cardiovasc Disord 2009;9:13.
70. Andréll P, Yu W, Gersbach P, et al. Long-term effects of spinal cord stimulation on angina symptoms and quality of life in patients with refractory angina pectoris--results from the European Angina Registry Link Study (EARL). Heart 2010;96:1132–6.
71. Eldabe S, Thomson S, Duarte R, et al. The Effectiveness and Cost-Effectiveness of Spinal Cord Stimulation for Refractory Angina (RASCAL Study): a pilot randomized controlled trial. Neuromodulation. 2016;19(1):60-70.
72. Sinvhal RM, Gowda RM, Khan IA. Enhanced external counterpulsation for refractory angina pectoris. Heart. 2003;89:830-833.
73. Michaels AD, Linnemeier G, Soran O, Kelsey SF, Kennard ED. Two-year outcomes after enhanced external counterpulsation for stable angina pectoris (from the International EECP Patient Registry [IEPR]). Am J Cardiol 2004; 93:461-464.

74. Braith RW, Conti CR, Nichols WW, et al. Enhanced external counterpulsation improves peripheral artery flow-mediated dilation in patients with chronic angina: a randomized sham- controlled study. Circulation. 2010;122(16):1612-1620.
75. Stys TP, Lawson WE, Hui JC, et al. Effects of enhanced external counterpulsation on stress radionuclide coronary perfusion and exercise capacity in chronic stable angina pectoris. Am J Cardiol. 2002;89(7):822-824.
76. Gloekler S, Meier P, de Marchi SF, et al. Coronary collateral growth by external counterpulsation: a randomised controlled trial. Heart 2010;96:202–7.
77. Bonetti PO, Barness GW, Keelan PC, et al. Enhanced external counterpulsation improves endothelial function in patients with symptomatic coronary artery disease. J. Am. Coll. Cardiol. 2003;41:1761-1768.
78. Lawson WE, Hui JCK, Zheng ZS, et al. Improved exercise tolerance following enhanced external counterpulsation: cardiac or peripheral effect? Cardiology 1996;87:271–5.
79. Allen KB, Dowling RD, Fudge TL, et al. Comparison of transmyocardial revascularization with medical therapy in patients with refractory angina. *The New England Journal of Medicine* 1999;341:1029–36.
80. van der Sloot JAP, Huikeshoven M, Tukkie R, et al. Transmyocardial revascularization using an XeCl excimer laser: Results of a randomized trial. *Annals of Thoracic Surgery* 2004;78(3): 875–81.
81. Leon MB, Kornowski R, Downey WE, et al. A blinded, randomized, placebo-controlled trial of percutaneous laser myocardial revascularization to improve angina symptoms in patients with severe coronary disease. J Am Coll Cardiol 2005; 46:1812-1819.
82. Briones E, Lacalle JR, Marin-Leon I, Rueda JR. Transmyocardial laser revascularization versus medical therapy for refractory angina. Cochrane Database Syst Rev 2015;2, CD003712.
83. Banai S, Ben Muvhar S, Parikh KH, et al. Coronary sinus reducer stent for the treatment of chronic refractory angina pectoris: A prospective, open-label, multicenter, safety feasibility first-in-man study. J Am Coll Cardiol 2007;49:1783–1789.
84. Ido A, Hasebe N, Matsuhashi H, Kikuchi K. Coronary sinus occlusion enhances coronary collateral flow and reduces subendocardial ischemia. Am. J. Physiol. Heart Circ. Physiol. 2001; 280:H1361–H1367.

85. Verheye S, Jolicoeur EM, Behan MW, et al. Efficacy of a device to narrow the coronary sinus in refractory angina. N Engl J Med 2015;372: 519–527.
86. Losordo DW, Dimmeler S. Therapeutic angiogenesis and vasculogenesis for ischemic disease: part II: cell-based therapies. Circulation 2004;109:2692-2697.
87. Khan AR, Farid TA, Pathan A, et al. Impact of cell therapy on myocardial perfusion and cardiovascular outcomes in patients with angina refractory to medical therapy: a systematic review and meta-analysis. Circ Res. 2016;118(6):984-993.
88. Henry TD, Schaer GL, Traverse JH, et al. Autologous $CD34^+$ cell therapy for refractory angina: 2-year outcomes from the ACT34-CMI Study. Cell Transplant. 2016;25(9):1701-1711.
89. Povsic TJ, Henry TD, Traverse JH, et al. The RENEW trial: Efficacy and Safety of Intramyocardial Autologous $CD34^+$ Cell Administration in Patients With Refractory Angina. JACC Cardiovasc Interv. 2016;9(15):1576-1585.
90. Giordano FJ, Ping P, McKirnan MD, et al. Intracoronary gene transfer of fibroblast growth factor-5 increases blood flow and contractile function in an ischemic region of the heart. Nat. Med. 1996; 2:534–539.
91. Kocher AA, Schuster MD, Szabolcs MJ, et al. Neovascularization of ischemic myocardium by human bone-marrow-derived angioblasts prevents cardiomyocyte apoptosis, reduces remodeling and improves cardiac function. Nat. Med. 2001;7:430–436.
92. Simons M, Annex BH, Laham RJ, et al. Pharmacological treatment of coronary artery disease with recombinant fibroblast growth factor-2: double-blind, randomized, controlled clinical trial. Circulation 2002;105:788–793.
93. Henry TD, Grines CL, Watkins MW, et al. Effects of Ad5FGF-4 in patients with angina: an analysis of pooled data from the AGENT-3 and AGENT-4 trials. J. Am. Coll. Cardiol. 2007;50:1038–1046.
94. Stewart DJ, Kutryk MJ, Fitchett D, et al. VEGF gene therapy fails to improve perfusion of ischemic myocardium in patients with advanced coronary disease: results of the NORTHERN trial. Mol. Ther. 2009;17:1109–1115.
95. Medispec Ltd. Optimal cardiacl neovascularization using the extra-corporeal shockwave myocardial revascularization. www.medispec.com/pdf/Cardiospec%20 Broschure%202008.pdf.
96. Apfel RE: Acoustic cavitation: a possible consequence of biomedical use of ultrasound. Br J Cancer 1982(Suppl.5):140-146.

97. Fisher AB, Chien S, Barakat AI, et al. Endothelial cellular response to altered shear stress. Am J Physiol 2001;281:L529-L533.
98. Wang FS, Wang CJ, Huang HJ, Chung H, Chen RF, Yang KD. Physical shock wave mediates membrane hyperpolarization and Ras activation for osteogenesis in human bone marrow stromal cells. BiochemBiophys Res Commun 2001;287:648-655.
99. Mariotto S, Cavalieri E, Amelio E, et al. Extracorporeal shock waves: from lithotripsy to anti-inflamatory action by NO production. Nitric Oxide 2005;12:89-96.
100. Zimpfer D, Aharinejad S, Holfield J, et al. Direct epicardial shock wave therapy improves ventricular function and induces angiogenesis in ischemic heart failure. J Thorac Cardiovasc Surg 2009;137:963-970.
101. Reher P, Doan N, Brandnock B, Meghiji S, Harris M. Effect of ultrasound on the production of IL-8, basic FGF and VEGF. Cytokine 1999;11:416-423.
102. Gutersohn A, Gaspari G. Shock waves upregulates vascular endothelial growth factor m-RNA in human umbilical vascular endothelial cells. Circulation 2000;102(Suppl.):18.
103. Aicher A, Heeschen C, Sasaki K, Urbich C, Zeiher AM, Dimmeler S. Low-energy shock wave for enhancing recruitment of endothelial progenitor cells: a new modality to increase efficacy of cell therapy in chronic hind limb ischemia. Circulation 2006;114:2823–2830.
104. Sheu JJ, Sun CK, Chang LT, et al. Shock wave-pretreated bone marrow cells further improve left ventricular function after myocardial infarction in rabbits. Ann Vasc Surg 2010;24:809–821.
105. Chavakis E, Koyanagi M, Dimmeler S. Enhancing the outcome of cell therapy for cardiac repair: progress from bench to bedside and back. Circulation 2010;121:325–335.
106. Risau W. Mechanisms of angiogenesis. Nature 1997; 386:671–674.
107. Longland CJ. The collateral circulation of the limb. New Ann R Coll Surg Engl 1953;13:161–164.
108. Buschmann I, Schaper W, Arteriogenesis Versus Angiogenesis: Two Mechanisms of Vessel Growth. New Physiol Sci 1999;14:121-125.
109. Heil M, Eitenmuller I, Schmitz-Rixen T, Schaper W. Arteriogenesis versus angiogenesis: similarities and differences. J Cell Mol Med 2006;10(1):45-55.

110. Heil M, Schaper W. Pathophysiology of collateral development. Coron Artery Dis 2004;15:373-378.
111. Carmeliet P: Angiogenesis in health and disease. Nat Med 2003;9:653-660.
112. Conway EM, Collen D, Carmeliet P. Molecular mechanisms of blood vessel growth. Cardiovasc Res 2001; 49:507-521.
113. Pugh CW, Ratcliffe PJ. Regulation of angiogenesis by hypoxia: role of the HIF system. Nat Med 2003; 9:677-684.
114. Wustmann K, Zbinden S, Windecker S, Meier B, Seiler C. Is there functional collateral flow during vascular occlusion in angiographically normal coronary arteries? Circulation 2003;107:2213-2220.
115. Pohl T, Seiler C, Billinger M, et al. Frequency distribution of collateral flow and factors influencing collateral channel development. Functional collateral channel measurement in 450 patients with coronary artery disease. J Am Coll Cardiol 2001; 38:1872-1878.
116. Chaussy C, Brendel W, Schmiedt E. Extracorporeally induced destruction of kidney stones by shock waves. Lancet. 1980;2:1265–8.
117. Turk C, Knoll T, Petrik A, et al. European Association of Urology, Guidelines on Urolithiasis. 2015. p. 1–71.
118. Tandan M, Reddy DN, Santosh D, et al. Extracorporeal shock wave lithotripsy of large difficult common bile duct stones: efficacy and analysis of factors that favour stone fragmentation. J Gastroenterol Hepatol. 2009;24:1370–4.
119. Parsi MA, Stevens T, Lopez R, Vargo JJ. Extracorporeal shock wave lithotripsy for prevention of recurrent pancreatitis caused by obstructive pancreatic stones. Pancreas. 2010;39:153–5.
120. Capaccio P, Torreta S, Pignataro L. Extracorporeal lithotripsy techniques for salivary stones. Otorungol Clin North Am. 2009;42:1139–59.
121. Zelle BA, Gollwitzer H, Zlowodzki M, Buhren V. Extracorporeal shock wave therapy:current evidence. J Orthop Trauma. 2010;24 Suppl 1:S66–70.
122. Wang CJ, Cheng JH, Kuo YR, Schaden W, Mittermayr R. Extracorporeal shockwave therapy in diabetic foot ulcers. Int J Surg. 2015. doi:10.1016/j.ijsu. 2015.06.024.
123. Wang CJ, Huang HY, Pai CH. Shock wave-enhanced neovascularization at the tendon-bone junction: an experiment in dogs. J Foot Ankle Surg. 2002;41:16–22.

124. Oi K, Fukumoto Y, Ito K, et al. Extracorporeal shock wave therapy ameliorates hind limb ischemia in rabbits. Tohoku J Exp Med 2008; 214(2):151-158.
125. Aicher A, Heeschen C, Sasaki K, Urbich C, Zeiher AH, Dimmeler S. Low-energy shock wave for enhancing recruitment of endothelial progenitor cells. Circulation 2006; 114: 2823-2830.
126. De Sanctis MT, Belcaro G, Nicolaides AN, et al. Effects of Shock Waves on the Microcirculation in Critical Limb Ischemia (CLI) Angiology 2000; 51: S69-78.
127. Belcaro G, Cesarone MR, Dugall M, et al. Effects of Shock Waves on the Microcirculation, Perfusion, and Pain Management in Critical Limb Ischemia. Angiology 2005; 56(4): 403-407.
128. Nishida T, Shimokawa H, Oi K, et al. Extracorporeal cardiac shock wave therapy markedly ameliorates ischemia-induced myocardial dysfunction in pigs in vivo. Circulation 2004; 110(19): 3055-3061.
129. Umatoku T, Ito K, Kohtaro A, et al. Extracorporeal cardiac shock wave therapy improves left ventricular remodeling after acute myocardial infarction in pigs. Coron Artery Dis 2007; 18(5):397-404.
130. Caspari GH, Erbel R. Revascularization with extracorporeal shock wave therapy: first clinical results. Circulation 1999;100(Suppl 18):84-89.
131. Moher D, Liberati A, Tetzlaff J, et al. The PRISMA Group (2009) Preferred Reporting Items for Systematic Reviews and Meta- Analyses: The PRISMA Statement. PLoS Med 2009; 6(7): e1000097. doi:10.1371/ journal.pmed.1000097.
132. Higgins JPT, Altman DG, Gøtzsche PC, et al. on behalf of Cochrane Bias Methods Group, Cochrane Statistical Methods Group The Cochrane Collaboration's tool for assessing risk of bias in randomized trials. BMJ 2011;343:d5928.
133. Cohen J. Statistical power analysis for the behavioral sciences. 2nd edition. Lawrence Erlbaum, New Jersey 1988, pp 567.
134. 2014 Review Manager (RevMan) [Computer program]. Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration. http://community.cochrane.org/tools/review-production-tools/revman-5/about.
135. Fletcher GF, Ades PA, Kligfield P, et al. Exercise Standards for Testing and Training: A Scientific Statement From the American Heart Association. Circulation 2013; 128:873-934.
136. Campeau L. Grading of angina pectoris. Circulation 1976;54:5223.

137. Spertus JA, Winder JA, Dewhurst TA, et al. Development and evaluation of the Seattle Angina Questionnaire: a new functional status measure for coronary artery dis- ease. *J Am Coll Cardiol*. 1995;25:333–341.
138. Lang RM, Badano LP, Mor-Avi V, et al. Recommendations for Cardiac Chamber Quantification by Echocardiography in Adults: An Update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J Am Soc Echocardiogr. 2015;28:1-39.e14.
139. Devereux RB, Alonso DR, Lutas EM, et al. Echocardiographic assessment of left ventricular hypertrophy: comparison to necropsy findings. Am J Cardiol. 1986;57:450–8.
140. Nagueh S, Appleton CP, Gillebert TC, et al. Recommendations for the evaluation of left ventricular diastolic function by echocardiography. J Am Soc Echocardiogr. 2009;22(2):107-33.
141. Sicari R, Nihoyannopoulos P, Evangelista A, et al. EAE guidelines: Stress echocardiography expert consensus statement. European Journal of Echocardiography 2008; 9:415-437.
142. Cerqueira MD, Weissman NJ, Dilsizian V, et al. Standardized Myocardial Segmentation and Nomenclature for Tomographic Imaging of the Heart A Statement for Healthcare Professionals From the Cardiac Imaging Committee of the Council on Clinical Cardiology of the American Heart Association. Circulation. 2002;105(4):539–42.
143. Shaw LJ, Berman ds, Picard MH, et al. Comparative Definitions for Moderate-Severe Ischemia in Stress Nuclear, Echocardiography, and Magnetic Resonance Imaging. JACC: Cardiovasc Imaging 2014;7:593-604.
144. Hachamovitch R, Berman DS, Kiat H, et al. Exercise myocardial perfusion SPECT in patients without known coronary artery disease: incremental prognostic value and use in risk stratification. Circulation 1996;93:905–914.
145. Berman DS, Abidov A, Kang X, et al. Prognostic validation of a 17-segment score derived from a 20-segment score for myocardial perfusion SPECT interpretation. *J Nucl Cardiol*. 2004;11:414 – 423.
146. Hachamovitc R, Hays SW, Friedman JD, Cohen I, Berman DS. Comparison of the short-term survival benefit associated with revascularization compared with medical therapy in patients with no prior coronary artery disease undergoing stress myocardial perfusion single photon emission computed tomography. Circulation. 2003; 107:2900-2907.

147. Leibowitz D, Weiss AT, Rott D, Durst R, Lotan C. The Efficacy of Cardiac Shock Wave Therapy in the Treatment of Refractory Angina: A Pilot Prospective, Randomized, Double-Blind Trial. Int J Cardiol 2013;167:3033-3034.
148. Zuoziene G. Evaluation of myocardium revascularization y cardiac shock wave therapy applying multimodal image analysis. Summary of doctoral dissertation. Vilnius University, 2013.
149. Popovic ZB, Thomas JD. Assessing observer variability: a user's guide. Cardiovasc Diagn Ther 2017;7(3):317-324.
150. Koo TK, Li MY. A Guideline of Selecting and Reporting Interclass Correlation Coeficients for Reliability Research. Journal of Chiropractic Medicine 2016; 15:155-163.
151. Portney LG, Watkins MP. Foundations of clinical research: applications to practice. New Jersey: Prentice Hall; 2000.
152. https://www.rdocumentation.org/packages/irr/versions/0.84/topics/icc
153. Wen L, Badgett R, Cornell J. Number needed to treat: a descriptor for weighing therapeutic options. Am J Health Syst Pharm. 2005;62(19):2031-6.
154. Kane SP. Number Needed to Treat (NNT) Calculator. ClinCalc: http://clincalc.com/stats/nnt.aspx. Updated October 24, 2015. Accessed June 23, 2017.
155. Gutersohn A, Caspari G, Erbel R. Cardiac shock wave therapy: New option for endstage cardiovascular disease. Atherosclerosis Suppl. 2003;3P-0626.
156. Gutersohn A, Caspari G, Erbel R. Autoangiogenesis Induced by Cardiac Shcok Wave Therapy (CSWT) Increases Perfusion and Exersice Tolerance in Endstage CAD Patients with Refractory Angina. Presented at the 69th Annual Scientific Meeting of the Japanese Circulation Society 2005.
157. Gutersohn A, Caspari G, Erbel R. Short and Long Term Clinical Improvement in Patients with Refractory Angina Using Cardiac Shock Wave Therapy (CSWT). Presented at the ACC 2006.
158. Fukumoto Y, Ito A, Uwatoku T, et al. Extracorporeal cardiac shock wave therapy ameliorates myocardial ischemia in patients with severe coronary artery disease. Coron Artery Dis 2006;17(1):63-70.
159. Lyadov K, Uvarov A. Cardiac shock-wave therapy: First Experience. Presented at the 6th Mediterranean congress of PRM. 2006;181-182.
160. Naber C, Ebralidze T, Lammers S, Hakim G, Erbel R. Non invasive cardiac angiogenesis shock wave therapy increases perfusion and exercise tolerance in endstage CAD patients. Eur J Heart Fail 2007;7:71.

161. Khattab A, Brodersen B, Schuermann-Kuchenbrandt D, et al. Extracorporeal cardiac shock wave therapy: First experience in the everyday practice for treatment of chronic refractory angina pectoris. Int J Cardiol 2007;121(1):84-85.
162. Naber C, Lammers S, Lind T, Müller N, Hakim G, Erbel R. Safety and Efficacy of Extracorporeal Low Energy Shockwave Application for the Treatment of Refractory Angina Pectoris and Myocardial Ischemia in Patients with End-Stage Coronary Artery Disease. Medispec 2008;1-16.
163. Takayama T, Saito S, Hirayama A, et al. Investigation into effectiveness of Shock Wave treatment for Angina Pectoris patients post-bypass surgery. Eur Heart J 2008; 29:200.
164. Wang Y, Guo T, Cai HY, et al. Cardiac Shock Wave Therapy Reduces Angina and Improves Myocardial Function in Patients With Refractory Coronary Artery Disease. Clin Cardiol 2010;33:693–699.
165. Faber L, Lindner O, Prinz C, et al. Echo-guided Extracorporeal Shock Wave Therapy for Refractory angina improves regional myocardial blood flow as assessed by PET imaging. J Am Coll Cardiol 2010;55(10A):A120.
166. Vainer J, Habets J, Lousberg A, Brans B, Schalla S, Waltenberger J. Cardiac shockwave therapy in patients with end-stage coronary artery disease and chronic refractory angina pectoris – mid term results. Eur Heart J 2010;31(Abstract Supplement):198.
167. Vasyuk Y, Hadzegova A, Shkolnik E, et al. Initial Clinical Experience With Extracorporeal Shock Wave Therapy in Treatment of Ischemic Heart Failure. Congest Heart Fail 2010;16:226-230.
168. Alunni G, D'amico M, Meynet I, et al. A new treatment for patients with refractory angina: extracorporeal shockwave myocardial revascularization. Eur Heart J 2011;32(Abstract Supplement):575.
169. Vainer J, Habets J, De Pont C, et al. Extracorporeal shockwave myocardial revascularization therapy (ESMR): an alternative for patients with end-stage coronary artery disease and chronic refractory angina pectoris? Eur Heart J 2012;33(Abstract Supplement):782.
170. Alunni G, Meynet I, D'Amico M, Garrone P, Checco L, Marra S. Extracorporeal shockwave myocardial revascularization: a promising therapy for refractory angina. Cardiology 2013;126(Suppl 2):390.

171. Gabrusenko S, Malakhov V, Shitov V, et al. An experience of the use of a curative metod of cardiac shock wave therapy in patients with ischemic heart disease. Kardiologiya 2013;53:20-26.
172. Prinz C, Faber L, Lindner O, et al. Echo-guided extracorporeal shock wave therapy for refractory angina improves regional myocardial blood flow as assessed by PET imaging. Eur Heart J 2013;34(suppl 1):P4007.
173. Cassar A, Prasad M, Rodriguez-Porcel M, et al. Safety and Efficacy of Extracorporeal Shock Wave Myocardial Revascularization Therapy for Refractory Angina Pectoris. Mayo Clin Proc 2014;89:346-354.
174. Faber L, Prinz C, Lindner O, et al. Echo-guided extracorporeal shock wave therapy for refractory angina improves regional left ventricular function along with myocardial blood flow. Eur Heart J 2014;35(Abstract Supplement):658.
175. Kaller M, Faber L, Bogunovic N, Horstkotte D, Burchert W, Lindner O. Cardiac shock wave therapy and myocardial perfusion in severe coronary artery disease. Clin Res Cardiol 2015;104(10):843-849.
176. Cai HY, Li L, Guo T, et al. Cardiac shockwave therapy improves myocardial function in patients with refractory coronary artery disease by promoting VEGF and IL-8 secretion to mediate the proliferation of endothelial progenitor cells. Exp Ther Med 2015;10:2410-2416.
177. Liu BY, Li WC, Zhang RS, Chen CX, Yao ZM, He Q. Application of extracorporeal cardiac shock wave therapy in treating coronary heart disease in the elderly. J Am Geriatr Soc 2015;63:S408.
178. Vainer J, Habets JHM, Schalla S, et al. Cardiac shockwave therapy in patients with chronic refractory angina pectoris. Neth Heart J 2016;24:343-349.
179. Kikuchi Y, Ito K, Ito Y, et al. Double-Blind and Placebo-Controlled Study of the Effectiveness and Safety of Extracorporeal Cardiac Shock Wave Therapy for Severe Angina Pectoris. Circ J 2010;74:589-591.
180. Kazmi WH, Rasheed SZ, Ahmed S, Saadat M, Altaf S, Samad A. Noninvasive therapy for the management of patients with advanced coronary artery disease. Coron Artery Dis 2012;23:549–554.
181. Nirala S, Wang Y, Peng YZ, Yang P, Guo T. Cardiac shock wave therapy shows better outcomes in the coronary artery disease patients in a long term. Eur Rev Med Pharmacol Sci 2016;20:330-338.

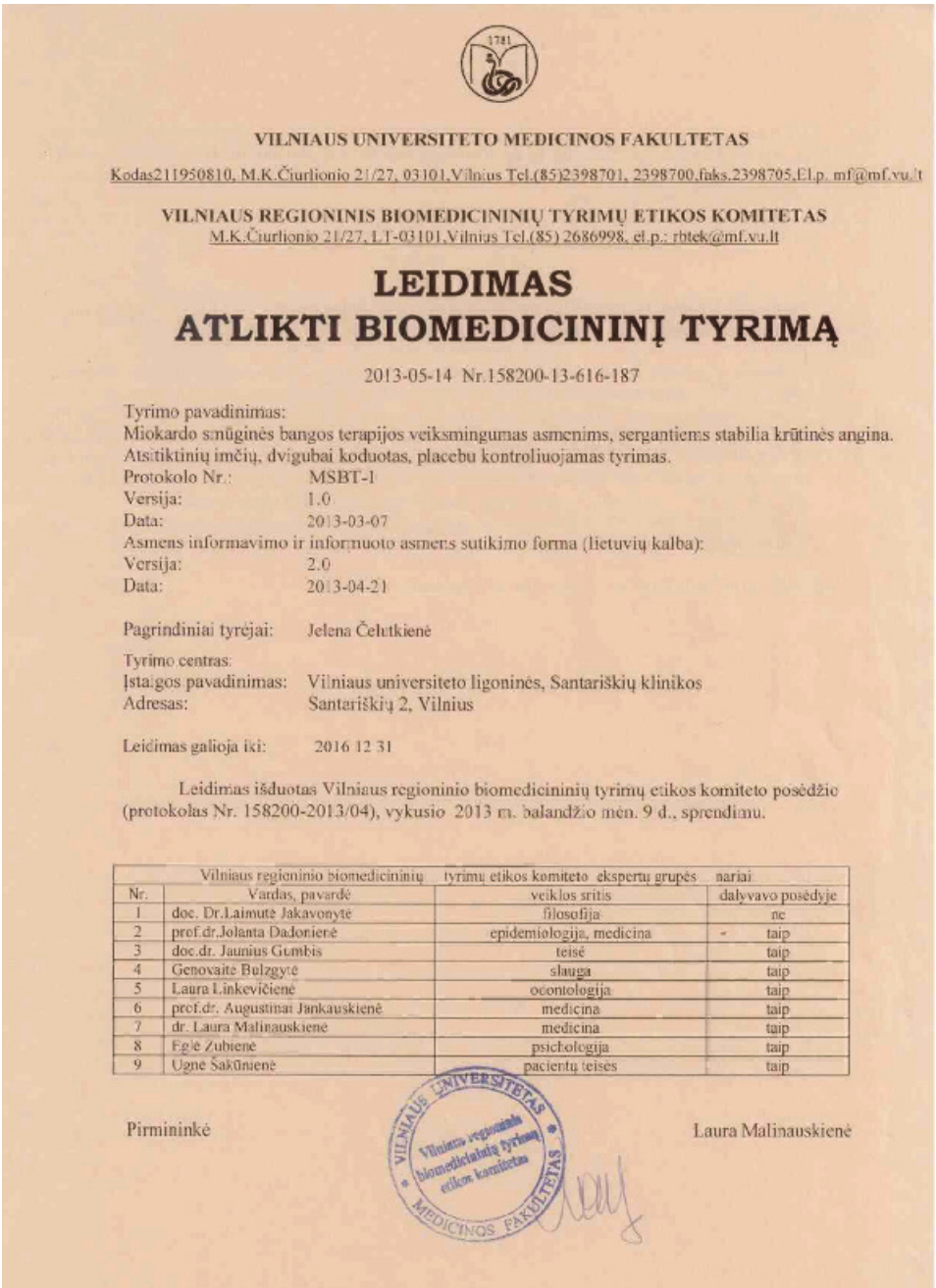
182. Peng YZ, Guo T, Yang P, et al. Effects of extracorporeal cardiac shock wave therapy in patients with ischemic heart failure. Zhonghua Xin Xue Guan Bing Za Zhi 2012;40:141-146.
183. Wang Y, Guo T, Ma T, et al. A modified regimen of extracorporeal cardiac shock wave therapy for treatment of coronary artery disease. Cardiovascular Ultrasound 2012;10:35.
184. Zhao L, Yang P, Tang Y, et al. Effect of cardiac shock wave therapy on the microvolt T wave alternans of patients with coronary artery disease. Int J Clin Exp Med 2015;8:16463-16471.
185. Schmid JP, Capoferri M, Schepis T, et al. Extracorporeal Shock Wave for Therapy of Refractory Angina Pectoris: The Shock Trial. Presented at the American College of Cardiology 55th Annual Scientific Session, March 11 – 14, Atlanta, Georgia 2006.
186. Yang P, Peng Y, Guo T, Wang Y,Cai H, Zhou P. A Clinical study of the Extracorporeal Cardiac Shock Wave Therapy for Coronary Aretery Disease. Heart 2012;98(Suppl 2):E163–E164.
187. Yang P, Guo T, Wang W, et al. Randomized and double-blind controlled clinical trial of extracorporeal cardiac shock wave therapy for coronary heart disease. Heart Vessels 2013;28:284–291.
188. Mancia G, Fagard R, Narkiewicz K, et al. 2013 ESH/ESC guidelines for the management of arterial hypertension: the Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *Eur Heart J*. 2013;34(28):2159-2219.
189. Rokach L. Decision forest: twenty years of research. Information Fusion 2016; 27:111-125.
190. Breiman L. Random forests. Machine Learning 2001; **45:**5-32.
191. European cardiovascular statistics 2017. European Heart Network. Accessed 23 May 2017.
192. Mirties priežastys 2016 (išankstiniai duomenys)-Causes of death (provisional data) / Higienos instituto Sveikatos informacijos centras. Vilnius, 2017, 131 p. ISSN 1392-9186.
193. European cardiovascular statistics 2017. European Heart Network. Accessed 23 May 2017.
194. Gaidelytė R, Garbuvienė M, Madeikytė. Lietuvos gyventojų sveikata ir sveikatos priežiūros įstaigų veikla 2016 m. (išankstiniai duomenys) / LR SAM Higienos instituto Sveikatos informacijos centras. Vilnius 2017, 127 p. ISSN 1392-8155.

195. Hesse B, Lindhardt TB, Acampa W, et al. EANM/ESC guidelines for radionuclide imaging of cardiac function. Eur J Nucl Med Mol Imaging. 2008;35:851–885.
196. Hundley WG, Bluemke D, Bogaert JG, et al. Society for Cardiovascular Magnetic Resonance guidelines for reporting cardiovascular magnetic resonance examinations.J Cardiovasc Magn Reson 2009; **11:** 5.
197. Gibbons RJ, Balady GJ, Bricker JT, et al. ACC/AHA 2002 guideline update for exercise testing: summary article: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Update the 1997 Exercise Test- ing Guidelines). Circulation 2002;106:1883–92.
198. www.ischemiatrial.org. Accessed 7 April 2017.
199. Chan PS, Jones PG, Arnold SA, Spertus JA. Development and Validation of a Short Version of the Seattle Angina Questionnaire. Circ Cardiovasc Qual Outcomes. 2014; 7(5):640–7.
200. Sylvén C, Eriksson B. Thorax. In Wall & Melzacks Textbook Of Pain. Edited by McMahon SB, Koltzenburg M. Philadelphia: Elsevier/Churchill Livingstone; 2005: 737-751.
201. Stewart RAH, Kittelson J, Kay P. statistical methods to improve the precision of the treadmill exercise test. JACC. 2000; 36:1274-9.
202. Hambrecht R, Walther C, Mobius-Winkler S, et al. Percutaneous coronary angioplasty compared with exercise training in patients with stable coronary artery disease: a randomized trial. Circulation 2004; 109:1371-1378.
203. Kendziorra K, Walther C, Foerster M, et al. Changes in myocardial perfusion due to physical exercise in patients with stable coronary artery disease. Eur J Nucl Med Mol Imaging 2005; 32:813-819.
204. Gloekler S, Meier P, de Marchi SF, et al. Coronary collateral growth by external counterpulsation: a randomised controlled trial. Heart 2010;96:202–7.
205. Chaitman BR, Pepine CJ, Parker JO, Skopal J, Chumakova G, Kuch J, et al. Effects of ranolazine with atenolol, amlodipine, or diltiazem on exercise tolerance and angina frequency in patients with severe chronic angina: a randomized controlled trial. JAMA 2004;291:309– 316.
206. Szwed H, Sadowski Z, Elikowski W, et al. Combination treatment in stable effort angina using trimetazidine and metoprolol: results of a randomized, double-blind, multicentre study (TRIMPOL II). TRIMetazidine in POLand. Eur Heart J. 2001;22:2267–2274.

207. Leon MB, Kornowski R, Downey WE, et al. A blinded, randomized, placebo-controlled trial of percutaneous laser myocardial revascularization to improve angina symptoms in patients with severe coronary disease. J Am Coll Cardiol 2005; 46:1812-1819.
208. Verheye S, Jolicoeur EM, Behan MW, et al. Efficacy of a device to narrow the coronary sinus in refractory angina. N Engl J Med 2015;372: 519–527.
209. Oesterele SN, Sanborn TA, Ali N, et al. percutaneous transmyocardial laser revascularization for severe angina: the PACIFIC randomized trial. The Lancet. 2000; 356:1705-10.
210. Diaz LA, Brunken RC, Blackstone EH, et al. Independent contribution of myocardial perfusion defects to exercise capacity and heart rate recovery for prediction of all-cause mortality in patients with known or suspected coronary heart disease. J Am Coll Cardiol 2001;37(6):1558-1564.

9 ANNEXES

9.1 Regulatory permission for study conduction



VILNIAUS UNIVERSITETO MEDICINOS FAKULTETAS

Kodas211950810, M.K.Čiurlionio 21/27, 03101,Vilnius Tel.(85)2398701, 2398700,faks.2398705,El.p. mf@mf.vu.lt

VILNIAUS REGIONINIS BIOMEDICININIŲ TYRIMŲ ETIKOS KOMITETAS
M.K.Čiurlionio 21/27, LT-03101,Vilnius Tel.(85) 2686998, el.p.: rbtek@mf.vu.lt

LEIDIMAS
ATLIKTI BIOMEDICININĮ TYRIMĄ

2013-05-14 Nr.158200-13-616-187

Tyrimo pavadinimas:
Miokardo smūginės bangos terapijos veiksmingumas asmenims, sergantiems stabilia krūtinės angina. Atsitiktinių imčių, dvigubai koduotas, placebu kontroliuojamas tyrimas.
Protokolo Nr.: MSBT-1
Versija: 1.0
Data: 2013-03-07
Asmens informavimo ir informuoto asmens sutikimo forma (lietuvių kalba):
Versija: 2.0
Data: 2013-04-21

Pagrindiniai tyrėjai: Jelena Čelutkienė

Tyrimo centras:
Įstaigos pavadinimas: Vilniaus universiteto ligoninės, Santariškių klinikos
Adresas: Santariškių 2, Vilnius

Leidimas galioja iki: 2016 12 31

Leidimas išduotas Vilniaus regioninio biomedicininių tyrimų etikos komiteto posėdžio (protokolas Nr. 158200-2013/04), vykusio 2013 m. balandžio mėn. 9 d., sprendimu.

Vilniaus regioninio biomedicininių tyrimų etikos komiteto ekspertų grupės nariai			
Nr.	Vardas, pavardė	veiklos sritis	dalyvavo posėdyje
1	doc. Dr.Laimutė Jakavonytė	filosofija	ne
2	prof.dr.Jolanta Dadonienė	epidemiologija, medicina	taip
3	doc.dr. Jaunius Gumbis	teisė	taip
4	Genovaitė Bulzgytė	slauga	taip
5	Laura Linkevičienė	odontologija	taip
6	prof.dr. Augustinai Jankauskienė	medicina	taip
7	dr. Laura Malinauskienė	medicina	taip
8	Eglė Zubienė	psichologija	taip
9	Ugnė Šakūnienė	pacientų teisės	taip

Pirmininkė Laura Malinauskienė

VILNIAUS UNIVERSITETAS Vilniaus regioninis biomedicininių tyrimų etikos komitetas MEDICINOS FAKULTETAS

9.2 Publication list related to this thesis

Publications

1. **Burneikaite G**, Shkolnik E, Celutkiene J, Zuoziene G, Butkuviene I, Petrauskiene B, Serpytis P, Laucevisius A, Lerman A. Cardiac shock-wave therapy in the treatment of coronary artery disease: systematic review and meta-analysis. Cardiovascular Utrasound 2017;15:11. (ISI, Impact factor-1.598)
2. Celutkiene J, **Burneikaite G**, Petkevicius L, Balkeviciene L, Laucevicius A. Combination of single quantitative parameters into multiparametric model for ischemia detection is not superior to visual assessment during Dobutamine stress echocardiography. Cardiovascular Ultrasound 2016;14:13. (ISI, Impact factor-1.46)
3. Zuoziene G, Leibowitz D, Celutkiene J, **Burneikaite G**, Ivaskeviciene L, Kalinauskas G, Maneikiene VV, Palionis D, Janusauskas V, Valeviciene N, Laucevicius A. Multimodality imaging of myocardial revascularization using cardiac shock wave therapy. International Journal of Cardiology 2015;187:229–230. (ISI, Impact factor-4.638)

Meeting abstracts

1. **Burneikaite G**, Zuoziene G, Celutkiene J, Palionis D, Valevicienė N, Laucevicius A. "Efficacy of Myocardial Shockwave Therapy Depends on Left Ventricular Function". Poster presentation at "The 61st Annual Conference of the Israel Heart Society", 30 April – 1 May 2014, Tel Aviv, Israel. Abstract book:79.
2. **Burneikaite G**, Zuoziene G, Celutkiene J, Laucevicius A. "The potential of myocardial shockwave therapy to cause reverse remodeling in patients with ischemic cardiomyopathy". Poster presentation at "The Heart Failure Congress 2014 and the 1st World Congress on Acute Heart Failure", 14-20 May 2014, Athens, Greece (European Journal of Heart Failure 2014;16(Suppl 2):298-298).
3. **Burneikaite G**, Zuoziene G, Celutkiene J, Butkuviene I, Laucevicius A. "Myocardial shockwave therapy improves global and regional left ventricular function in patients with stable ischemic heart disease regardless of baseline contractility". Poster presentation at "ESC Congress 2014", 30 August – 3 September 2014, Barcelona, Spain (European Heart Journal 2014;35(Abstract Supplement:322)).

4. Shkolnik E, **Burneikaite G**, Celutkiene J, Zuoziene G, Butkuviene I, Petrauskiene B, Laucevicius A, Lerman A. "Cardiac shock-wave therapy in the treatment of coronary artery disease: systematic review and meta-analysis". Poster presentation at 65th Annual Scientific Session and Expo of the American-College-of-Cardiology (ACC), Apr 02-04, 2016, Chicago, IL. Journal of the American College of Cardiology 2016;67(13)Suppl:2149-2149.
5. Vajauskas D, **Burneikaite G**, Celutkiene J, Komiagiene R. "Inter-observer variability of reporting myocardial perfusion imaging". Poster presentation at "International Conference on Integrated medical Imaging in Cardiovascular Diseases (IMIC 2016), 10-14 October 2016, Viena, Austria. Book of Abstracts:34.
6. **Burneikaite G**, Celutkiene J, Valeviciene N, Glaveckaite S, Palionis D, Zuoziene G, Puronaite R, Butkuviene I, Petrauskiene B, Steponeniene R, Laucevicius A. Does Cardiac shock wave therapy able to improve global and regional left ventricular function in patients with stable angina? Data from double blind, randomized, placebo-controlled study. Oral abstract presentation at EuroCMR2017: 15th Annual Meeting on CMR of The European Association of Cardiovascular Imaging (EACVI), 25-27 May, 2017, Prague, Czech Republic.
7. **Burneikaite G**, Celutkiene J, Vajauskas D, Ciburiene E, Zuoziene G, Petrauskiene B, Butkuviene I, Sadauskiene E, Laucevicius A. SPECT fits better than Dobutamine echocardiography for the evaluation of the cardiac shock wave therapy effect: data from double blind, randomized, placebo-controlled study. Poster presentation at International Conference on Integrated medical Imaging in Cardiovascular Diseases (IMIC 2016), 10-14 October 2016, Viena, Austria. Book of Abstracts:34.

Oral presentation

1. **Burneikaite G.** Biomarkers of angiogenesis during cardiac shock wave therapy. 2nd International Meeting On Heart Diseases and The Moroccan Society of Cardiology. 4 - 6 May 2017, Rabat, Marocco.