



# Extracorporeal Shockwave Myocardial Revascularization (ESMR)

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# Horizon Scanning

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## Extracorporeal Shockwave Myocardial Revascularization (ESMR)

### BASIC INFORMATION

Identification No.	H-SIGHT-2014-124
Report No.	H-SIGHT-2014-002
Technology type	Medical device, medical practice
Name of technology	Extracorporeal Shockwave Myocardial Revascularization (ESMR) or Cardiac Shock Wave Therapy (CSWT)
Product and Developer	Cardiospec™ (Medispec Ltd)/ U.S., Modulith®SLC (Storz Medical AG)/ Switzerland
Target group	Patients with refractory cardiovascular diseases
Purpose	To use extracorporeal shock wave therapy as a complementary and alternative health technology to improve symptoms experienced by patients with refractory cardiovascular disease, for whom medication is the only treatment option
Innovativeness	This particular technology, with a differentiated treatment mechanism from those of standard therapies, can be used for patients with refractory cardiovascular disease for whom there are no alternative treatment options (in whom standard procedures have failed or there is no indication for such procedures)
Estimated time point of market entry in South Korea	Five years and up
Stage of development	Currently being performed limitedly at specialty hospitals
Utilization(Licensing, reimbursement, and other approval)	Cardiospec™(U.S.), the equipment used for this technology, has received the CE mark and it is currently under assessment for FDA approval in the U.S. Authorization for importation into South Korea was given by KFDA in September 2006 (Import Authorization No. 06-1004). Modulith®SLC (Switzerland) has received the CE mark; however, it has not yet been authorized in South Korea.
Technology setting	Specialty (cardiology) hospitals or medical centers with cardiologists

### SUMMARY

- Extracorporeal Shockwave Myocardial Revascularization (ESMR) or Cardiac Shock Wave Therapy (CSWT) is a procedure developed to apply extracorporeal shock wave to the myocardium to improve symptoms of refractory cardiovascular disease in patients for whom medication is the only treatment option, or in whom traditional procedures such as Percutaneous Coronary Angioplasty (PCI) and Coronary Artery Bypass Graft (CABG) are not indicated.

## SUMMARY

- Eleven clinical studies (three randomized clinical trials, one cohort study, and seven case series studies) have been conducted to date, with an overall follow-up observation period of 6 months. Significant symptom improvement and effectiveness were observed in the majority of the studies reporting on the clinical results such as the CCS score, nitroglycerine dosage and left ventricular ejection fraction (LVEF).
- Safety concerns regarding the possibility of causing unintended damage with the extracorporeal shock wave to the cell membranes, cytoskeleton and small blood vessels exist. However, literature published to date has not reported any major adverse events or aggravated symptoms at 6 months follow-up.

## BACKGROUND AND BURDEN OF DISEASE

Ischemic heart disease or coronary artery disease (CAD) is characterized by insufficient blood supply to the myocardium resulting from a blockage or narrowing of the coronary artery. It causes more deaths and disability than any other disease and increases economic costs. In the U.S. alone, 6 million people are affected by angina pectoris and 7 million by myocardial infarction (Korean Association of Internal Medicine, 2010). In South Korea, 530,000 patients received treatment for angina pectoris in 2012; a 17% increase from 5 years ago (Health Insurance Review & Assessment Service, 2012).

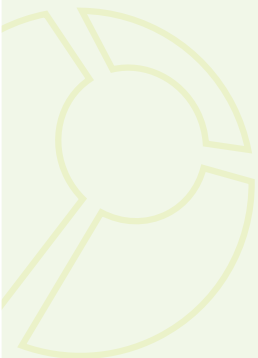
The recent advancements in medication and revascularization have increased the life expectancy of patients with CAD. However, there has been an increasing incidence of myocardial ischemia and clinical angina for which the current revascularization procedure cannot be performed.

## DESCRIPTION OF THE HEALTH TECHNOLOGY

A shock wave is a type of acoustic wave that can be generated by using high-speed, underwater discharge power and be delivered into the body in a non-invasive manner. ESMR involves delivery of an extracorporeal shock wave (ESW) to the myocardium for the purposes of pain relief and regeneration or rehabilitation of microvessels. The treatment mechanism can be summarized as follows<sup>1)</sup>:

- **Cavitation effect:** Delivering a shock wave to a tissue causes localized stress on cell membranes that resembles shear stress. The positive pressure and tension can cause tissue expansion and space formation resulting in improved blood supply.
- **Biochemical effect:** Non-enzymatic nitric oxide, synthesized from L-arginine and hydrogen peroxide, provides pain relief.
- **Neovascularization effect:** It promotes the synthesis of endothelial nitric oxides and proliferating cell antigens for the vascular endothelial growth factor (VEGF) to induce neovascularization.

The safety and effectiveness of ESMR have been proven in multiple specialty fields including urology, orthopedics, and rehabilitative medicine since the 1980s. Of particular note, the technology in question uses low energy (10% of that used in ESW lithotripsy)<sup>2)</sup>.



## Procedure

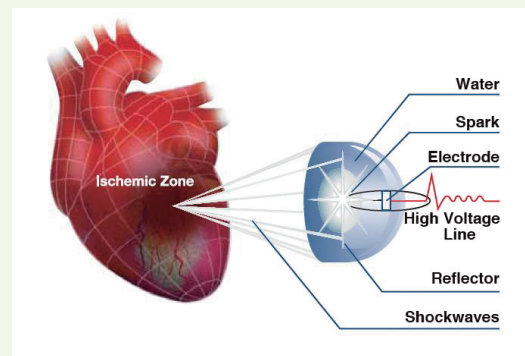
Each session consists of three procedures performed on alternating days in the course of a week. One session is carried out at weeks 1, 5, and 9 for a total of three sessions. Thus, the procedure is performed for a total of 9 times, in the following manner<sup>3)</sup>:

- 1) Patient is laid in the supine position, and the electrocardiogram, blood pressure, respiratory rate, and oxygen saturation is monitored.
- 2) The ultrasound probe is placed in order to view the myocardium, specifically, where necrosis was observed by using single photon emission computed tomography (SPECT) or other diagnostics, prior to the procedure.
- 3) The energy of the shock wave is gradually increased up to  $0.9\text{mJ}/\text{mm}^2$ .



<Fig. 1> ESW therapy for cardiovascular diseases

\*Source: copyright@ STORZ MEDICAL, AG



<Fig. 2> Major functional components of ESMR

\*Source: Medispec (2010)

## ALTERNATIVE, COMPLEMENTARY AND/OR CURRENT TECHNOLOGY

The treatment of ischemic heart disease is under the umbrella of internal medicine, however many patients seek help through invasive treatments such as Percutaneous Coronary Angioplasty (PCI) and Coronary Artery Bypass Graft (CABG). In cases where there are no indications for revascularization, or the patient experiences prolonged chest pain inhibiting day-to-day activities, alternative treatments must be sought (Korean Association of Internal Medicine, 2010).

Non-invasive treatments for refractory cardiovascular diseases include enhanced external counter pulsation (EECP)\* adopted in Korea and spinal cord stimulation\*\* adopted in Europe. Other alternative treatments such as genetic and stem cell therapy have been developed, but are also invasive treatments and require more research before being put into practice.

\* **Enhanced External Counterpulsation (EECP):** A tourniquet is applied to the upper and lower parts of the thighs and the buttocks and air is delivered into the space to create pressure. This enhances blood flow in the arteries and veins, thereby improving blood and oxygen supply. This technique was recognized as a new health technology in South Korea in 2012.

\*\* **Spinal Cord Stimulation:** This technique involves inserting an electrode at the C7-T1 spinal level in order to exert electrical stimulation for one hour, three times a day.

Currently in South Korea, ESW therapy cannot be used in treatment of cardiovascular diseases. However, ESW lithotripsy (Ja-350) in treatment of kidney diseases and ESW

in treatment of musculoskeletal diseases (Jo-84) have been registered on the health insurance benefits coverage list and are being used in diverse clinical contexts.

## Health Technology Assessment

### Safety

ESW therapy is a non-invasive treatment, which in the case of musculoskeletal diseases, can be performed without the risks associated with surgical procedures. Additionally, the rate of complications resulting from ESW therapy is considered negligible<sup>4</sup>. However, there are concerns regarding the possibility of causing unintended damage to the cell membranes, cytoskeleton and small vessels, resulting in irreversible muscle cell damage<sup>5</sup>.

The eleven clinical studies included in our literature review did not report any adverse events or symptom aggravation, but the limitations of these studies include a short follow-up period (6 months).

### Effectiveness

Clinical effectiveness was reviewed based on the findings of the eleven clinical studies. The effect on pain relief was assessed by using the grading scale of the Canadian Cardiovascular Society (CCS). Nine of the studies included CCS results and all reported significant improvement of pain<sup>1)2)3)6)7)8)9)10)11)</sup>. Also, of the five studies that included results related to the grading scale of the New York Heart Association (NYHA), four reported effective pain relief<sup>3)7)8)9)10)</sup>. The nitroglycerine dosage was reported in seven studies; all found significant improvement<sup>1)2)3)6)7)8)9)</sup>.

Four studies reported findings related to the left ventricular ejection fraction (LVEF) based on echocardiographic measurements, and they all found significant functional improvement<sup>2)3)6)7)</sup>. Moreover, of the six studies that included the results of single photon computed tomography (SPECT), five showed improvement in the blood flow<sup>1)3)7)9)10)12)</sup>.

### International Health Technology Assessment Report

In 2011, HealthPACT, a health technology assessment committee in Australia, issued a brief technology report<sup>13)</sup>. According to the report, there is a need for a long-term, randomized clinical trial for better analysis as the available studies all had a small subject pool and lacked long-term follow-up data; some had a low level of evidence. HealthPACT has recommended that it is unlikely that this technology will be taken up by Australian clinicians in the short-term, therefore long-term clinical data should be accumulated for further research.

## COST INFORMATION

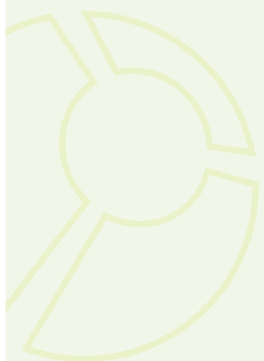
### Medical Device

According to the HealthPACT report, the Medispec equipment cost \$150,000 per unit in 2011<sup>13)</sup>.

### Medical Practice

Treatment costs cannot be determined as the ESW procedure has not yet been introduced in the clinical setting for the treatment of cardiovascular diseases. However, for reference purposes, the health insurance benefit payment (as of 2014) for ESW lithotripsy

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(for treatment of kidney, ureteral or gallstones, and pancreatoliths) (Ja-350) is \$640 to \$710, while the ESW therapy (for treatment of musculoskeletal diseases) (Jo-84) is not covered by health insurance.

## ONGOING RESEARCH

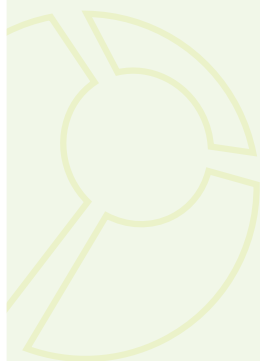
Clinicaltrials.gov and the Cochrane Library were searched for research protocols, clinical trials, and systematic reviews that are currently being conducted, but none were found.

## SOCIAL IMPACT (EXPERT OPINION)

It is expected that the ESMR can serve as a non-invasive complementary and alternative treatment to improve symptoms of refractory cardiovascular disease in patients for whom there are no other available treatment options. Extracorporeal shock wave therapy is a relatively safe procedure that is currently being used to treat musculoskeletal diseases, and it is worth attempting to apply it as a new option for cardiovascular disease treatment. However, the evidence available at this time is from a small number of studies with short-term follow-up data and retrospective studies that have analytical limitations. Based on these factors, the experts believe it would be difficult to assess the treatment mechanisms and the effectiveness of the health technology based on the current evidence alone. Other concerns include low impact and cost-effectiveness in the clinical setting. Thus, it is deemed necessary to generate further evidence to support the treatment mechanism and effectiveness by accumulating more data through well-designed randomized clinical trials.

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This report was compiled to provide objective information on an emerging health technology that is currently under development. Reference to the materials reviewed was made at the Committee meeting held to deliberate on Extracorporeal Shockwave Myocardial Revascularization (ESMR), for which a New Health Technology Assessment was requested in 2013. Further information was derived through a literature review and consultation with medical specialists in the relevant field. Further, please note that the National Evidence-based Healthcare Collaborating Agency and the researchers who compiled this report have no conflicts of interest with any of the enterprises that specialize in the medical field in question.

### [ATTACHMENT] Summary of Preceding Studies

As of May 2014, there were eleven studies on extracorporeal shockwave myocardial revascularization, of which three were randomized clinical trials, one was a cohort study, and seven were case series studies.

#	Year	Author	Study design	Study population	No. of patients	Treatment	Follow-up periods (mo)	Conflicts of interest
<b>Device: Cardiospec™ (Medispec Ltd)</b>								
1	2014	Andrew et al. <sup>12)</sup>	Case series/ multi-center	Refractory angina (class III/IV angina)	15	ESMR 9 times	2, 4	Not reported
2	2012	Zuoziene et al. <sup>6)</sup>	Case series	Angina (CCS class III-IV)	20	ESMR 9 times	6	Some+ (Medispec) †One received honoraria
3	2010	Vasyuk et al. <sup>3)</sup>	Case series	Ischemic heart failure	19	ESMR 9 times	3, 6	The study was supported by research grant from Medispec
<b>Device: Modulith®SLC (Storz Medical AG)</b>								
4	2013	Schmid et al. <sup>14)</sup>	Randomized controlled trial	Chronic refractory angina pectoris and myocardial ischemia	21 (11/10)	- CSWT 9 times (11) - Control (10)	3	None
5	2013	Yang et al. <sup>7)</sup>	Randomized controlled trial	Coronary heart disease	25 (14/11)	- CSWT 9 times (14) - Control (11)	6	Not reported
6	2012	Wang et al. <sup>8)</sup>	Randomized controlled trial	Severe coronary artery disease	55 (14/20/21)	- Drugs(14) - CSWT 3 times (20) - CSWT 9 times (21)	3, 6, 12	None
7	2010	Kikuchi et al. <sup>2)</sup>	Case series (cross-over)	Severe angina pectoris	8	Cross-over manner with an interval of 3 months - CSWT 9 times - Placebo	3	Not reported
8	2010	Wang et al. <sup>9)</sup>	Case series	Coronary heart disease	9	CSWT 9 times	1	None
9	2006	Fukumoto et al. <sup>1)</sup>	Case series	End-stage coronary artery disease with coronary revascularization	9	CSWT 9 times	12	None
<b>Device: Unknown</b>								
10	2012	Kazmi et al. <sup>10)</sup>	Prospective cohort study	End-stage coronary artery disease and were no option	86 (43/43)	- CSWT 9 times (43) - Placebo (43)	6	None
11	2009	Prinz et al. <sup>11)</sup>	Case report	Coronary artery disease	1	CSWT 18 times	6	Not reported

\* Control: acoustic simulation was performed without shock wave energy application



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