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Early Assessment of Extracorporeal Shock Wave Myocardial Revascularization (ESMR)

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ABSTRACT

Objectives: To predict the social impact of introducing extracorporeal shock wave myocardial revascularization (ESMR) on refractory cardiovascular disease.

Methods: We used a horizon-scanning system to prioritize and select promising health technologies, and evidence assessment and peer review to analyze current clinical evidence and predict the social impact.

Results: Analysis of the current evidence revealed that the non-invasive health technology ESMR, which can be performed using low-energy shock waves, is promising for refractory cardiovascular disease treatment. Its effectiveness regarding improvements in pain relief, nitroglycerine dosage, and blood flow have been reported in the absence of adverse events. However, these reports were based on short-term studies that lacked comparison groups, and treatment mechanisms have not been elucidated. According to expert opinions, it is currently difficult to assess and predict the social impact of this technology.

Conclusion: ESMR is promising, although stronger evidence of its safety, effectiveness, and treatment mechanism is needed.

INTRODUCTION

Ischemic heart disease, or coronary artery disease (CAD), which is characterized by insufficient blood supply to the myocardium resulting from blockage or narrowing of the coronary artery, is associated with greater mortality and morbidity than any other disease, as well as high economic costs. In the USA alone, 6 and 7 million people are affected by angina pectoris and myocardial infarction, respectively. In South Korea, according to health insurance assessment data 557,000 patients received treatment for angina pectoris in 2013, representing a 24% increase over the 2008 data ^[1]. Although recent advancements in medication and revascularization have increased the life expectancy of patients with CAD, the incidence of myocardial ischemia and clinical angina, for which current revascularization procedures cannot be performed, has increased.

Many patients seek invasive treatments such as percutaneous coronary angioplasty (PCI) and coronary artery bypass graft (CABG) for refractory ischemic heart disease ^[2]. However, in cases where revascularization is not indicated or the patient experiences prolonged chest pain that inhibits day-to-day activities, alternative treatments must be sought. Non-invasive

treatments for refractory cardiovascular diseases include enhanced external counter-pulsation and spinal cord stimulation, which have been adopted in the USA and Europe, respectively [3,4]. Other alternative treatments such as genetic and stem cell therapies have been developed; however, these are invasive and require more research before being put into practice [5,6].

Since the late 1990s, extracorporeal shock wave myocardial revascularization (ESMR), or cardiac shock wave therapy (CSWT), has been proposed as an effective and non-invasive therapy for refractory CAD or angina. This procedure involves the delivery of an extracorporeal shock wave (ESW), a type of sonic wave that can be generated using high-speed, underwater discharge power and delivered into the body non-invasively to the myocardium for the purposes of pain relief and micro vessel regeneration or rehabilitation [7]. ESMR is therefore intended to improve the symptoms of refractory cardiovascular disease in patients for whom medication is the only treatment option or traditional procedures such as PCI and CABG are not indicated.

According to manufacturers, the known mechanism of ESMR can be summarized as follows. First, ESMR causes a cavitation effect, whereby the delivery of a shock wave to a tissue causes localized cell membrane stress that resembles shear stress. The positive pressure and tension can cause tissue expansion and space formation, thus improving blood supply. Second, ESMR has a biochemical effect whereby non-enzymatic nitric oxide is synthesized from L-arginine and hydrogen peroxide and provides pain relief. Third, ESMR has a neovascularization effect by promoting the synthesis of endothelial nitric oxides and proliferating cell nuclear antigens for vascular endothelial cell growth factor (VEGF) to induce neovascularization [7].

Since the 1980s, ESW therapy has been proven to be safe and effective in the contexts of various specializations, including urology, orthopedics, and rehabilitative medicine. Notably, this technology requires lower energy (10% of that used in ESW lithotripsy) [8]. Each session consists of three procedures performed on alternating days during the course of a week. One session each is conducted during weeks 1, 5, and 9, for a total of three sessions. Thus, the procedure is performed a total of nine times in the following manner [9]: first, the patient is laid in the supine position with electrocardiogram, blood pressure, respiratory rate, and oxygen saturation monitoring; second, the ultrasound probe is placed to allow a specific view of the myocardial area where necrosis was observed using single-photon emission computed tomography (SPECT) or other diagnostics prior to the procedure; and third, the shock wave energy is gradually increased up to 0.9 mJ/mm² [7-9].

ESW therapy has not yet been introduced in South Korea for the treatment of cardiovascular diseases. However, this technique has been introduced for the treatment of kidney diseases (via lithotripsy) and musculoskeletal diseases, and is registered on the health insurance benefits coverage list for application in those clinical contexts. The purpose of this study was to assess the available clinical evidence and thus predict the social impact of ESMR on the Korean healthcare system through horizon scanning activities to supply information to stakeholders about the safety, effectiveness, and potential impacts on patients or healthcare services in the near future.

METHODS

Horizon scanning

We identified 136 research-phase health technologies that had been rejected in the new health technology assessment in 2013 and were not listed in the Korean health insurance system. From among these identified health technologies, we filtered eight innovative technologies that could be possibly introduced into the Korean healthcare system within 1–5 years. Next, we prioritized the eight filtered technologies based on seven weighted prioritization criteria (burden of disease, clinical impact, degree of innovation, economic impact, acceptability in the Korean healthcare system, social impact, and clinical evidence). To calculate the weighted score for each criterion, we surveyed 54 Korean healthcare professionals acquainted with health technology assessment (HTA). The weighted scores of the prioritization criteria were evaluated using a five-point rating scale with a range of 0–5 to achieve the following results: burden of disease: 3.8, clinical impact: 2.8, degree of innovation: 3.4, economic impact: 2.8, acceptability in the Korean healthcare system: 2.7, social impact: 3.0, and clinical evidence: 2.2. Finally, ESMR was selected as one of four highly ranked health technologies (remaining technologies: catheter-based renal denervation in patients with resistant hypertension, bronchial thermoplasty, and implantation of polyurethane scaffold in partial meniscal lesions). ESMR was mainly selected as a high priority because it is a noninvasive but innovative technology for the treatment of refractory cardiovascular disease. Subsequently, we assessed the clinical evidence and predicted the social impact of ESMR through a literature review and expert consultation.

We sought expert counsel concerning the social impact of ESMR from four healthcare professionals who were randomly selected from a pool of 826 health technology assessment specialists at NECA. These selected specialists comprised five experts from the concerned medical field (four) and health technology assessment methodology (one). The experts were asked to score eight areas of a social impact assessment on a scale of 1–5 (fulfillment of unmet needs; improvement in patients' health; impact on health disparities; impact on healthcare delivery system; acceptability to patients; acceptability to clinicians; change in healthcare costs; and social, ethical, and legal impact) and give subjective opinions about various aspects of the expected impact of the technology.

After seeking counsel, we also received peer reviews of the final ESMR assessment report from the same healthcare professionals. Following this expert peer review, we sent a final assessment report to the related medical device import industry to confirm the information regarding the extracorporeal shock wave device.

Literature review

To examine the evidence relevant to our study purpose, we conducted a literature review of the databases Ovid-MEDLINE (1946 to May Week 3, 2014), Ovid-Embase (1974 to May Week 3, 2014), and Google Scholar and the Korean databases KoreaMed and KMBase without any time limitations on May 13–14, 2014. Cardiovascular disease, coronary artery disease, angina, extracorporeal cardiac shock wave, and combinations of these terms were used to identify relevant studies. The inclusion criteria were all human studies in the English and Korean languages. Studies that reported patient outcomes, including randomized controlled trials, case reports, case series, or observational studies, were selected. Reviews, letters, and conference abstracts were excluded. Titles and abstracts of retrieved articles were screened to determine whether they fulfilled the inclusion criteria. In addition, to identify research protocols, clinical trials, and systematic reviews that were ongoing as of May 2014, we searched Clinicaltrials.gov and the Cochrane Library using the same search terms mentioned above but did not identify any appropriate entries. Next, the full texts of eligible studies were reviewed. No Korean studies related to this topic were found. Overall, 45 articles on ESMR were identified, of which 35 were excluded because they did not meet the inclusion criteria. One article was added following a manual search. A total of 11 studies were included in our analysis.

RESULTS

As of May 2014, 11 studies had been published concerning ESMR for patients with severe CAD and no indication for PCI or CABG, of which three were randomized clinical trials, one was a cohort study, and seven were case series. The overall follow-up observation period was less than 12 months. **Table 1** shows the details of these studies.

Safety of ESMR

ESW therapy is non-invasive and, 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^[10], with no reports of arrhythmias, heart failure, syncope, palpitations, breathing difficulty, bleeding, embolism, shock, or troponin^[7-9,11-18]. However, concerns remain regarding the possibility of unintended damage to the cell membrane, cytoskeleton, and small vessels, resulting in irreversible muscle cell damage^[19].

Table 1. “Summary of preceding studies.”

#	Year	Author	Study design	Study population	No. of patients	Treatment	Follow-up period (mo)	Conflicts of interest	Results	
									Safety	Effectiveness
Device: Cardiospec™ (Medispec Ltd.)										
1	2014	Andrew et al. ^[16]	Case series/multicenter	Refractory angina (class III/IV angina)	15	ESMR 9 times	2, 4	Not reported	No adverse events	- Exercise treadmill test: (+) - Vasodilator-SPECT(SSS, SRS, and SDS): (-)
2	2012	Zuoziene et al. ^[10]	Case series	Angina (CCS class III–IV)	20	ESMR 9 times	6	One received honoraria (Medispec)	No significant arrhythmias	- CCS class: (+) - Use of nitroglycerin: (+) - TID: (+) - LVEF: (+)
3	2010	Vasyuk et al. ^[6]	Case series	Ischemic heart failure	19	ESMR 9 times	3, 6	The study was supported by research grant from Medispec	No adverse events	- CCS class: (+) - NYHA class: (+) - Use of nitroglycerin: (+) - 6-minute walk test: (+) - MLHF: (+) - Quality of life(physical subscore): (+) - LVEF: (+) - SPECT(SSS, SRS): (+)
Device: Modulith®SLC (Storz Medical AG)										
4	2013	Schmid et al. ^[4]	Randomized controlled trial	Chronic refractory angina pectoris and myocardial ischemia	21 (11/10)	- CSWT 9 times(11) - Control (10)	3	None	No complications - no arrhythmias - no troponin rise	- SF-36(8 items)in the treatment: (+) - Cardiopulmonary exercise testing: (-)

5	2013	Yang et al. [11]	Randomized controlled trial	Coronary heart disease	25 (14/11)	- CSWT9 times (14) - Control (11)	6	Not reported	No serious adverse effects	- CCS class: (+) - NYHA class: (+) - SAQ scale: (+) - Use of nitroglycerin: (+) - 6-minute walk test: (+) - Cardiac enzymes: (-) - LVEF: (+) - LVEDD: (+) - Dual-isotope SPECT test: (+)
6	2012	Wang et al. [12]	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	12-month follow-up without heart failure, syncope, palpitations, breathing difficulty, bleeding, embolism, or shock	- CCS class: (+) - NYHA class (+) - SAQ score: (+) - 6-minute walk test (+) - Use of nitroglycerin: (+) - PSSR: (+) - MPI scores: (-)
7	2010	Kikuchi et al. [5]	Case series (cross-over)	Severe angina pectoris	8	Cross-over manner with an interval of 3 months - CSWT 9 times - Placebo	3	Not reported	No procedural complications or adverse effects	- CCS class: (+) - Use of nitroglycerin: (+) - 6-minute walk test: (+) - Max. exercise: (-) tended to improve - Peak VO ₂ : (-) tended to improve - LVEF: (+) - LVSV: (+) - LV end-diastolic volume: (-) - Plasma brain natriuretic peptide level: (-)
8	2010	Wang et al. [13]	Case series	Coronary heart disease	9	CSWT 9 times	1	None	No serious cardiovascular complications (heart failure, bleeding, thrombosis, shock or death)	- CCS scale: (+) - NYHA class: (-) - SAQ scale: (-) - Use of nitroglycerin: (+) - 6-minute walk test: (-) - Enzyme markers: (+) - SPECT, SE images: improved blood flow - MPI: (-) - PSSR: (+)
9	2006	Fukumoto et al. [8]	Case series	End-stage coronary artery disease with no indication of coronary revascularization	9	CSWT 9 times	12	None	No procedural complications or adverse effects	- CCS class: (+) - Use of nitroglycerin: (+) - 6-minute walk test: (-) tended to improve - Exercise treadmill test: (-) tended to improve - Dipyridamole stress thallium (SPECT): perfusion was improved - Coronary angiography: (-)

Device: Unknown

10	2012	Kazmi et al. [14]	Prospective cohort study	End-stage coronary artery disease and were no treatment option	86 (43/43)	- CSWT 9 times (43) - Placebo (43)	6	None	No adverse events	- CCS class: (+) - NYHA class: (+) - Exercise time: (+) - ^{99m} Tc-MIBI-gated SPECT: size of ischemia reduced
11	2009	Prinz et al. [15]	Case report	Coronary artery disease	1	CSWT 18 times	6	Not reported	No adverse effects	- Cardiac enzyme levels: normal - CCS II: improvement - 2D ECG: (-) - PET imaging: improvement
* Control: acoustic simulation was performed without shock wave energy application										
** (+): statistical significance; (-): statistical non-significance										

Abbreviations: CCS, Canadian Cardiovascular Society; ECG, Electrocardiography; ETT, exercise treadmill test; LVEDD, left ventricular end-diastolic dimension; LVEF, left ventricular ejection fraction; LVSV, left ventricular stroke volume; MLHF, Minnesota Living With Heart Failure; MPI, myocardial perfusion imaging; NYHA, New York Heart Association; PET, positron-emission tomography; PSSR, peak systolic strain rate; SAQ, Seattle Angina Questionnaire; SDS, summed difference score; SPECT, single photon emission computed tomography; SRS, summed rest score; SSS, summed stress score; TID, transient ischemic dilatation.

The 11 clinical studies included in our literature review did not report any adverse events or symptom aggravation; however, the limitations of these studies include a short follow-up period (less than 12 months).

Effectiveness of ESMR

Clinical effectiveness was reviewed according to the findings of the 11 clinical studies. The effect of ESMR on pain relief was assessed using the Canadian Cardiovascular Society (CCS) grading scale. Nine of the studies included CCS results, and all reported significant improvements in pain [8,9,11-17]. Also, of the five studies that included results related to the New York Heart Association (NYHA) grading scale, four reported effective pain relief [9,13-16]. Nitroglycerine dosage was reported in seven studies, all of which reported significant improvement [8,9,11-15]. Of the four studies that assessed effectiveness related to left ventricular ejection fraction (LVEF), determined from echocardiographic measurements, all reported significant functional improvement [8,9,12,13]. Moreover, of the six studies that included SPECT results, five showed improvements in blood flow [9,11,13,15,16,18]. One study assessed the quality of life using the eight-component SF-36 questionnaire; although no significant changes in any components were observed in the placebo group, improvements in three components (physical function, general health perception, and vitality) were observed in the treatment group [7].

Social Impact of ESMR

Expected social impacts following the introduction of a selected technology into the domestic market are assessed through reflection of the grounds to date and the opinions of relevant experts. Based on our consultation with experts, we have presented the social impact of ESMR in two ways (mean scores for the eight areas and overall opinions; **Figure 1 and Table 2**). Note that a positive score indicates a positive social impact and a negative score indicates a negative social impact. (**Figure 1 and Table 2**).

ESMR is expected to serve as a non-invasive, complementary, and alternative treatment intended to improve the symptoms of refractory cardiovascular disease in patients for whom there are no other available treatment options. This relatively safe procedure is currently used to treat musculoskeletal diseases, and its application as a new option for cardiovascular disease treatment is worth attempting. However, the evidence available at this time is derived from a small number of studies with short-term follow-up data and retrospective studies with analytical limitations. Therefore, the experts believed that it would be difficult to assess the treatment mechanisms and effectiveness of this health technology. Other concerns included a low impact and cost-effectiveness in clinical settings. Accordingly, it was deemed necessary to generate further evidence to support the treatment mechanism and effectiveness of ESMR by accumulating more data through well-designed randomized clinical trials.

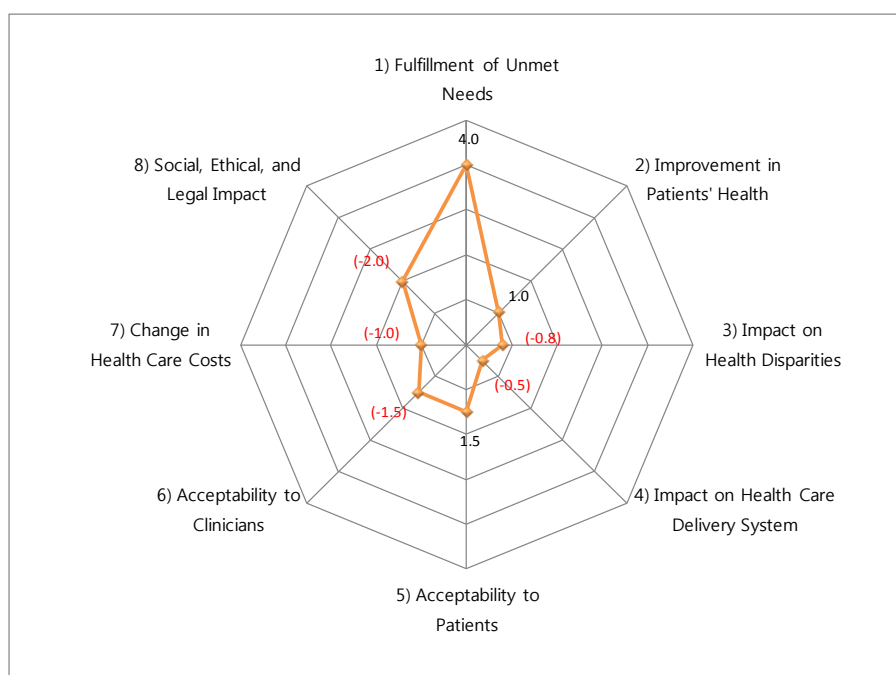
Cost information of ESMR

According to the HealthPACT report, the cost per Medispec equipment unit was \$ 150,000 in 2011 [20]. However, treatment costs could 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 (for the treatment of nephrolith, ureterolith, and pancreatoliths; Ja-350) was \$ 640 to \$ 710, whereas ESW therapy (for treatment of musculoskeletal diseases; Jo-84) was not covered by health insurance.

DISCUSSION

This study used a horizon-scanning toolkit to conduct a pilot horizon scanning analysis of high-priority research-phase technologies not listed in the Korean health insurance system with the intent to provide information about the current clinical evidence, social impact, and potential value to healthcare policymakers, payers, patients, and researchers [21,22]. Pilot Korean horizon-scanning analysis indicated ESMR as one of these high-priority technologies [21,22]. Although many regenerative gene,

cytokine, and stem cell-based therapies have been developed for incurable or refractory ischemic cardiovascular disease since the early 1990s, in humans these treatments have not yielded the consistent results observed in animal studies [5,6,23-25]. Notably, as various factors are involved in angiogenesis, no single factor or therapy could achieve myocardial revascularization. ESMR was also developed for myocardial revascularization and has been tested in European countries since the late 1990s. Although safety concerns exist regarding the possibility of unintended damage to the cell membranes, cytoskeleton, and small blood vessels, the literature published to date concerning ESW therapy has not reported any major adverse events or aggravated symptoms after a 12-month follow-up. In addition, the ability of ESMR to elicit significant improvements in symptoms was observed in the majority of the studies reporting clinical results such as CCS scores, nitroglycerine dosages, and LVEF [8,9,12,13,15-18]. Therefore, ESMR is quite useful and can be used repeatedly and safely without surgery or anesthesia. In addition, it is easily applied to elderly patients with severe CAD.



* We evaluated the scores using the 10-rating scale, range is from -5 to 5.

Interpretation of each social impact :

- 1) Fulfillment of Unmet Needs – could this technology can fulfill the unmet needs of stakeholders?
- 2) Improvement in Patient’s Health – could this technology improve patient’s health outcomes?
- 3) Impact on Health Disparities – could this technology create differences in access to, use of, and quality of care such that it affects health status or patient-oriented health outcomes?
- 4) Impact on Health Care Delivery System – could this technology change the care process?
- 5), 6) Acceptability – could this technology affect willingness to use for patients or clinicians?
- 7) Change in Health Care Costs – could this technology affect the costs of care for the intended patients and health care system?
- 8) Social, Ethical, and Legal Impact – could this technology affect our social, ethical, legal, political and cultural environment?

ESMR, Extracorporeal Shock Wave Myocardial Revascularization

Figure 1. “The result of scoring* social impacts of ESMR.”

Table 2. “Expert opinions on the social impact of ESMR.”

Overall opinion	
Positive	Negative
<ul style="list-style-type: none"> - A non-invasive complementary and alternative treatment for refractory cardiovascular disease in patients for whom there are no other available treatment options - Would be worth attempting to apply as a new option for refractory cardiovascular disease - Relatively safe procedure that is currently being used to treat musculoskeletal diseases 	<ul style="list-style-type: none"> - Lack of evidence for the mechanism underlying revascularization and treatment effectiveness - Low impact in a clinical setting - Doubt about the treatment mechanisms - Possibility of low cost-effectiveness - Need for well-designed randomized controlled trials for strong evidence

However, until now, ESMR use has not been widespread, and this technology remains under investigation in most countries because of the lack of clinical evidence from well-designed studies regarding long-term safety and effectiveness. Similarly, in Korea, ESMR is considered a research-phase technology that did not pass the new health technology assessment because of the above-mentioned lack of evidence, and therefore is not covered by health insurance. Accordingly, randomized and placebo-controlled studies involving large numbers of patients are needed to verify the long-term safety and effectiveness of ESMR [11]. Furthermore, low-energy shock wave therapy has been reported to upregulate the activity of multiple angiogenic pathways through

the expression of angiogenesis-related growth factors (e.g., VEGF, Fms-related tyrosine kinase 1 [Flt-1], stromal cell-derived factor 1 [SDF-1], and nitric oxide synthase); however, this phenomenon has only been demonstrated in preliminary animal studies [26,27]. In addition, angiogenesis mainly depends on the differentiation of bone marrow precursor cells into vascular stem cells and the recruitment of progenitor cells to lesions via the enhanced expression of chemoattractants; therefore, the precise mechanism underlying shock wave-induced angiogenesis in humans must also be elucidated in future studies [10,27,28]. For these reasons, the publication of additional clinical studies would necessitate an update to our horizon scanning results or periodic reassessment of selected health technologies for the timely provision of useful information to healthcare decision-makers, payers, patients, researchers, and healthcare and HTA professionals.

This pilot horizon-scanning activity will serve as a prototype for future horizon-scanning activities in Korea. Through this activity, healthcare policy makers and payers can gain advance knowledge of newly developed health technologies, and relevant health technology researchers or developers can anticipate platforms for technological development. Additionally, patients can learn more about newly developed, promising, but not yet introduced health technologies. These horizon-scanning results will facilitate the prioritization of research and development (R&D) items or the allocation of limited R&D resources to promising health technologies. Such a link between horizon-scanning activity and R&D could serve as a driving progressive force in the Korean healthcare industry (**supplementary file**).

This study had several limitations. First, although we conducted a pilot horizon-scanning activity, we did not have an evaluation system for this activity. In the near future, we plan to develop a horizon-scanning activity evaluation system together with relevant experts, and subsequently verify the efficiency, social impact, and prediction accuracy of each activity based on this system. Second, the numbers of participating patients in the 11 included studies were small (1–55 patients), creating the possibility of uneven patient characteristic distribution. Therefore, when the horizon scanning report is updated, the size and distribution of each study population must be considered. Third, among the 11 included clinical articles, five declared that the authors had no conflicts of interest; two declared that the authors had conflicts of interest regarding manufacturers, and the remaining four articles did not mention possible conflicts of interest. Although these articles attempted to present results objectively, manufacturers might have been inclined to conceal negative results. Therefore, the possibility of unreported results exists. In the future, conflicts of interest should be investigated in detail through contact with authors or relevant expert counsel.

CONCLUSION

This Korean pilot horizon-scanning activity was the first study to assess the current evidence and evaluate the social impact of ESMR using horizon-scanning tools. We found that the non-invasive, easily applicable ESW shows promise for the improvement of refractory cardiovascular disease symptoms. However, there is a lack of long-term clinical evidence regarding the safety and effectiveness of this technique, as well as its mechanism of action. Accordingly, well designed long-term follow-up studies and mechanistic investigations are required in the future. In conclusion, although ESMR is not currently listed in the Korean healthcare insurance system, this study provides useful information for related medical device developers, HTA professionals, healthcare professionals, patients, decision-makers, and insurance payers.

REFERENCES

1. <http://www.nhis.or.kr/bbs7/boards/B0039/13486>
2. Legrand V. Percutaneous coronary interventions vs coronary artery bypass grafting for patients with stable angina pectoris. *Rev Prat.* 2015;65:352–356.
3. Sharma U, et al. The role of enhanced external counter pulsation therapy in clinical practice. *Clin Med Res.* 2013;11:226–232.
4. Andrell 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;96:1132–1136.
5. Losordo DW, et al. Intramyocardial transplantation of autologous CD34⁺ stem cells for intractable angina: A phase I/IIa double-blind, randomized controlled trial. *Circulation.* 2007;115:3165–3172.
6. Van Ramshorst J, et al. Intramyocardial bone marrow cell injection for chronic myocardial ischemia: A randomized controlled trial. *JAMA.* 2009;301:1997–2004.
7. Schmid J, et al. Cardiac shock wave therapy for chronic refractory angina pectoris. A prospective placebo-controlled randomized trial. *Cardiovasc Ther.* 2013;31:e1-e6.
8. Kikuchi 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.
9. Vasyuk Y, et al. Initial clinical experience with extracorporeal shock wave therapy in treatment of ischemic heart failure. *Congest Heart Fail.* 2010;16:226–230.
10. Wang CJ. Extracorporeal shockwave therapy in musculoskeletal disorders. *J Orthop Surg Res.* 2012;7:11.

11. Fukumoto Y, et al. Extracorporeal cardiac shock wave therapy ameliorates myocardial ischemia in patients with severe coronary artery disease. *Coron Artery Dis.* 2006;17:63–70.
12. Zuoziene G, et al. Extracorporeal shockwave myocardial revascularization improves clinical symptoms and left ventricular function in patients with refractory angina. *Coron Artery Dis.* 2012;23:62–67.
13. Yang P, 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.
14. Wang Y, et al. A modified regimen of extracorporeal cardiac shock wave therapy for treatment of coronary artery disease. *Cardiovascular Ultrasound.* 2012;10:35.
15. Wang Y, 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.
16. Kazmi W, et al. Noninvasive therapy for the management of patients with advanced coronary artery disease. *Coron Artery Dis.* 2012;23:549–554.
17. Prinz C, et al. Extracorporeal cardiac shock wave therapy ameliorates clinical symptoms and improves regional myocardial blood flow in a patient with severe coronary artery disease and refractory angina. *Case Rep Med.* 2009;2009:639594.
18. Cassar A, et al. Safety and efficacy of extracorporeal shock wave myocardial revascularization therapy for refractory angina pectoris. *Mayo Clin Proc.* 2014;89:346-354.
19. Jargin SV. Shock wave therapy of ischemic heart disease in the light of general pathology. *Int J Cardiol.* 2010;144:116–117.
20. <http://www.health.qld.gov.au/healthpact/docs/briefs/WP090.pdf>
21. http://www.neca.re.kr/center/paper/report_view.jsp?boardNo=GA&seq=145&q=63706167653d3226666c61673d3126626f6172644e6f3d474126736561726368436f6c3d2673656172636856616c3d2673656172636853596561723d2673656172636845596561723d
22. Jooyeon P, et al. Establishment of Horizon Scanning System for New and Emerging Health Technology. *Evidence and Value.* 2014;6:12-23.
23. Gupta R, et al. Human studies of angiogenic gene therapy. *Circ Res.* 2009;105:724–736.
24. Epstein SE, et al. Therapeutic interventions for enhancing collateral development by administration of growth factors: Basic principles, early results and potential hazards. *Cardiovasc Res.* 2001;49:532–542.
25. Dimmer S, et al. Unchain my heart: The scientific foundations of cardiac repair. *J Clin Invest.* 2005;115:572–583.
26. Nishida T, et al. Extracorporeal cardiac shock wave therapy markedly ameliorates ischemia-induced myocardial dysfunction in pigs in vivo. *Circulation.* 2004;110:3055–3061.
27. Oi K, et al. Extracorporeal shock wave therapy ameliorate hindlimb ischemia in rabbits. *Tohoku J Exp Med.* 2008;214:151–158.
28. Wang CJ, et al. Shock wave therapy induces neovascularization at the tendon-bone junction. A study in rabbits. *J Orthop Res.* 2003;21:984–989.