Debate session (I):

CARVAR 논란: :
우리가 잃은 것은 무엇인가?

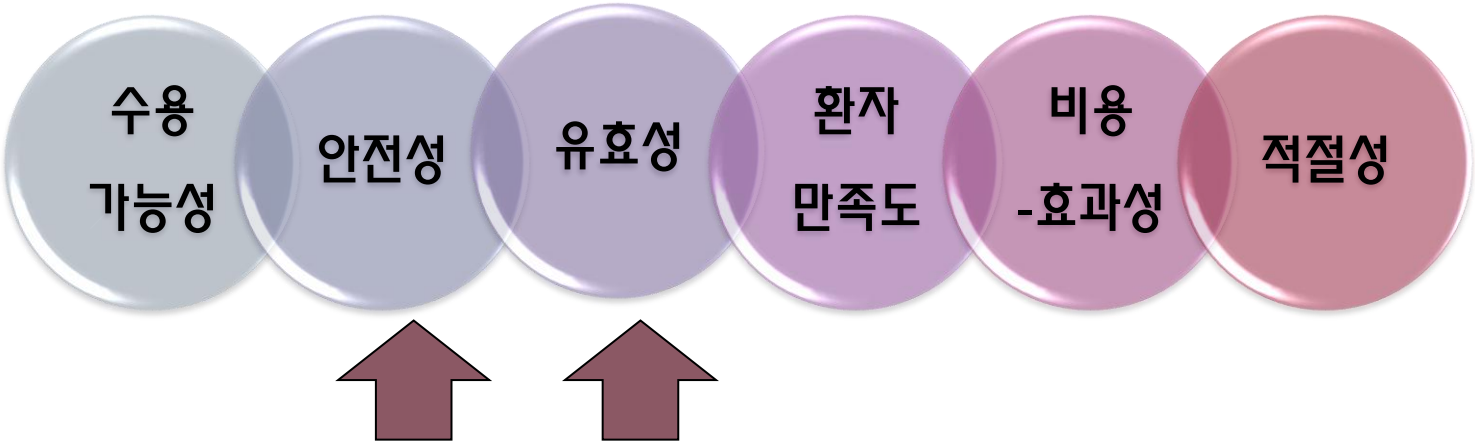
신의료기술- 임상역학자 관점

서울의대 예방의학교실

박병주

의료기술평가란?

- 다른 기술에 비해 **안전**하고 **효과**적이며 **비용-효율적**인 지를 **과학적이고 체계적이며 포괄적인 방법으로 평가**하여 의사결정자에게 제공하는 행위



가장 중요한 지표는?

근거중심의학

일상적인 의료현장에서 행해지는 보편적 진료

안전성과 효과가 입증된 것이라야 한다!

극히 상식적인 이야기. 그러나.....

실제 진료현장에서 의료기술이 가지고 있는 실체와는 다르게 적용되거나 왜곡되는 경우도 발생한다.

근거중심의학의 발전배경:

안전하고, 효과적인 치료를 받을 환자의 권리

- **비만환자의 위축소 수술**

  - 외국의 경우
    - 도입초기부터 사회적 관심
    - 1992년 미국국립보건원에서 합의한 도출 프로그램을 통해 동 기술에 대한 합의
    - 각국 의료시술평가기구에서 동 시술을 평가

  - 우리나라
    - 객관적이고 독립적인 평가기구가 없이 방치
    - 미용수술로 오해하는 국민들

근거중심의학의 발전배경:

안전하고, 효과적인 치료를 받을 환자의 권리

새로운 의료기술을 환자진료에 사용하기 전 고려사항 (미국외과학회)

1. 신기술이 **안전성**과 **유효성** 면에서 적절하게 **임상시험**을 거쳤는가?

2. 신기술이 최소한 **기존**에 존재하는 **기술**에 비해 **안전**하고 **효과**적인가?

3. 신기술이 **적합한 환자**에게 적용되는가?

4. **비용-효과적**으로 타당한가?

근거중심의학 발전배경:

근거나 효과가 불확실한 일부 보편화된 의료기술

근거에 입각한 진료의 수준

연구자	문헌	대상	근거에 입각한 진료
Ellis J	Lancet, 1995	일반진료, 대학의 지역분원병원(영국)	82%
Gill P	BMJ, 1996	일반진료, 교외수련종합병원	81%
Lee, JS	Ann Thorac Surg, 2000	흉부외과계 수술, 3차 및 종합병원(북미)	78%
Khan, AT	BMC womens Health, 2006	산부인과 영역의 진료, 3차병원(영국)	90%
Lai TYY	Br J Ophthalmol, 2003	안과진료, 안과병원(홍콩)	77%

Myocardial infarction	Experimental BMT	Purified bone marrow–derived hematopoietic	Intracardial	Reduction of infarcted area, improved cardiac hemodynamics	Orlic et al.[15]
			nous	Generation of donor-derived cardiomyocytes and endothelial	Jackson et al.[16]
				Decrease fracti hemo	
			Intravenous	Stimulation of and angio region	er et al.[24]
	G-CSF–mobilized peripheral-blood SCT	al- blood angioblas			
	Clinical BMT (autologous)	Bone marrow cells	Intracoronary	Decreased infarct size, improved ventricular function and myocardial perfusion†	Strauer et al.[43]
	Clinical BMT (autologous)	Purified bone marrow–derived hematopoietic stem cells	Intramyocardial	Enhanced left ventricular function, improved infarct tissue perfusion‡	Stamm et al.[44]
	Clinical BMT (autologous)	Bone marrow or peripheral-blood cells	Intracoronary infusion	Improved left ventricular ejection fraction, improved regional wall motion in infarct zone†	Assmus et al.[45]

Phase 1 studies have confirmed the feasibility of intracoronary injections of autologous mononuclear BMC a few days after myocardial infarction, and the results have indicated improvement of left ventricular function

RCTs to further investigate the effects of this treatment!!

† Patients underwent revascularization with the use of balloon angioplasty and subsequent stent implantation before infusion of bone marrow cells.

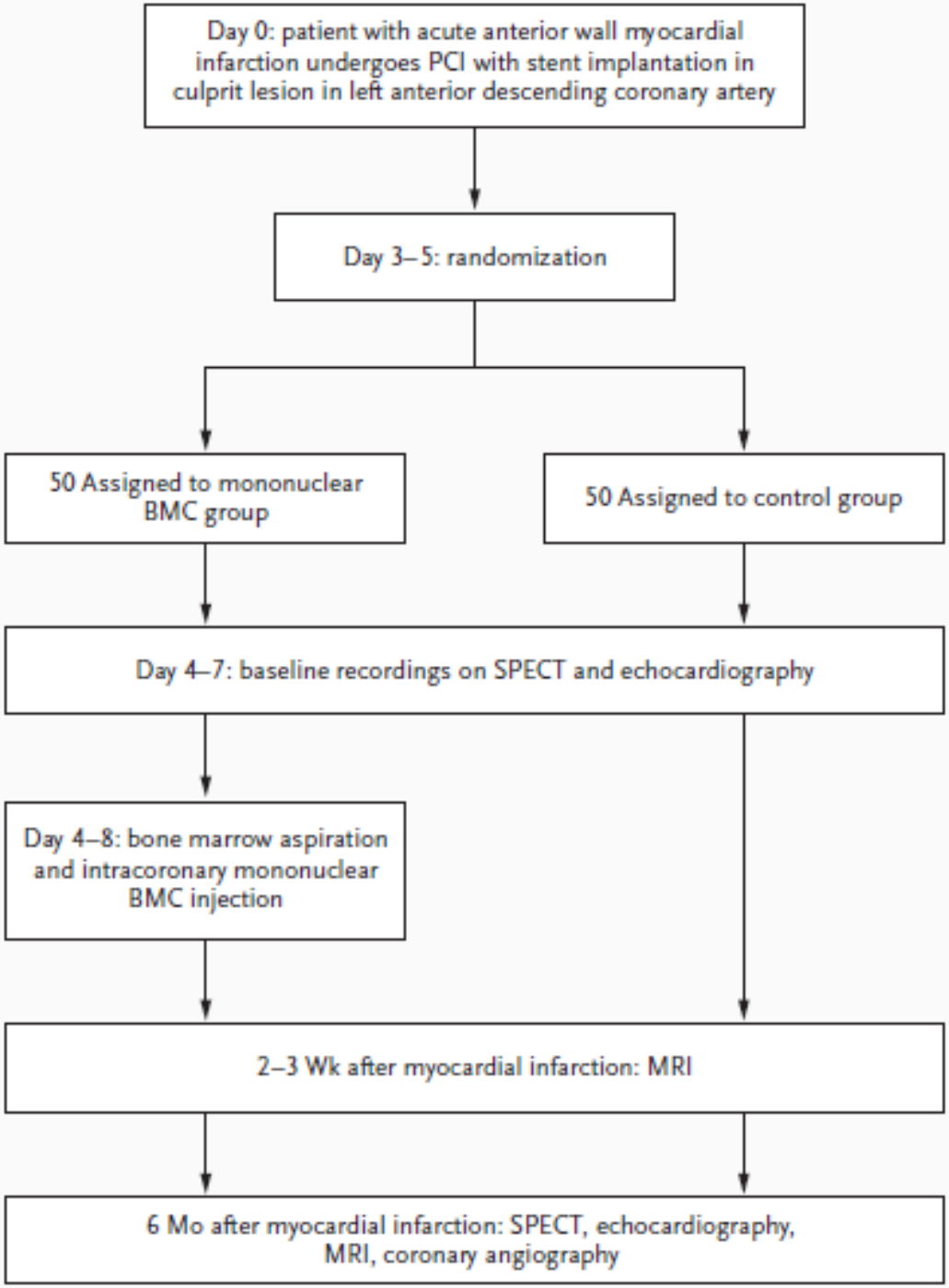
N Engl J Med 2003;349:570-82.

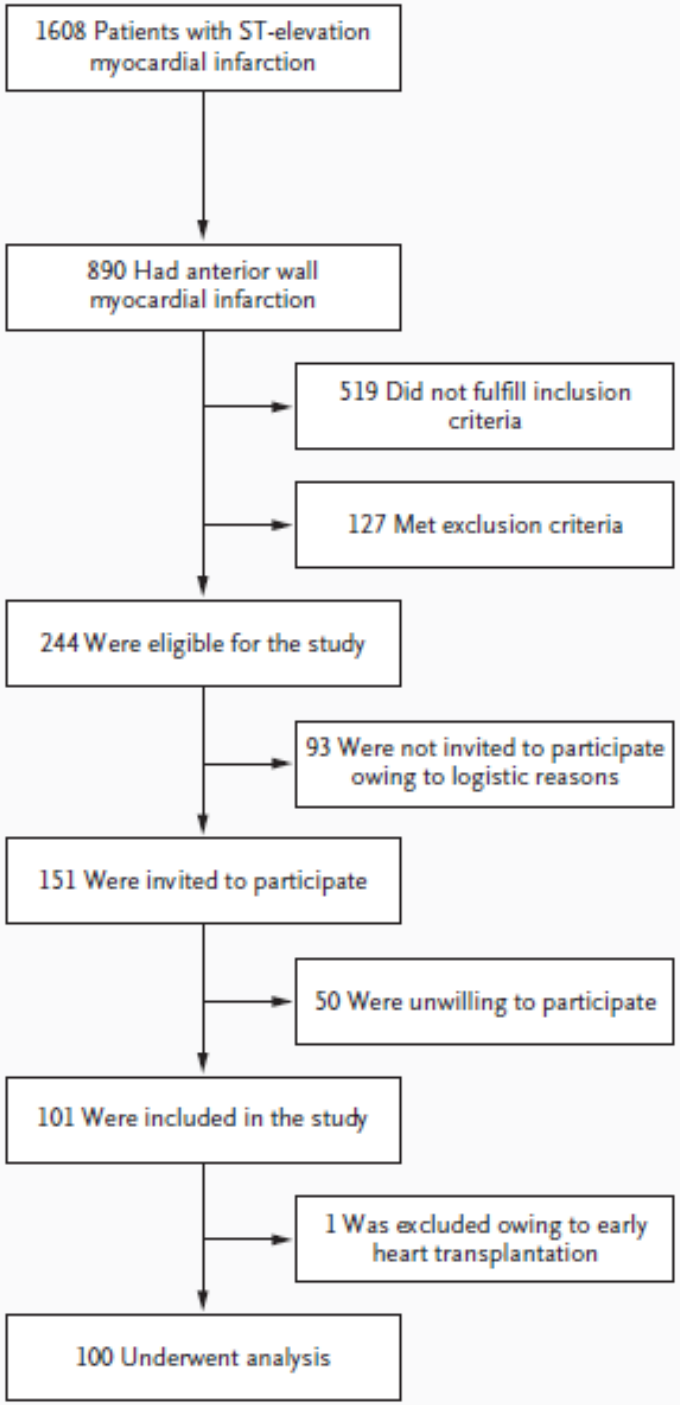
ASTAMI study

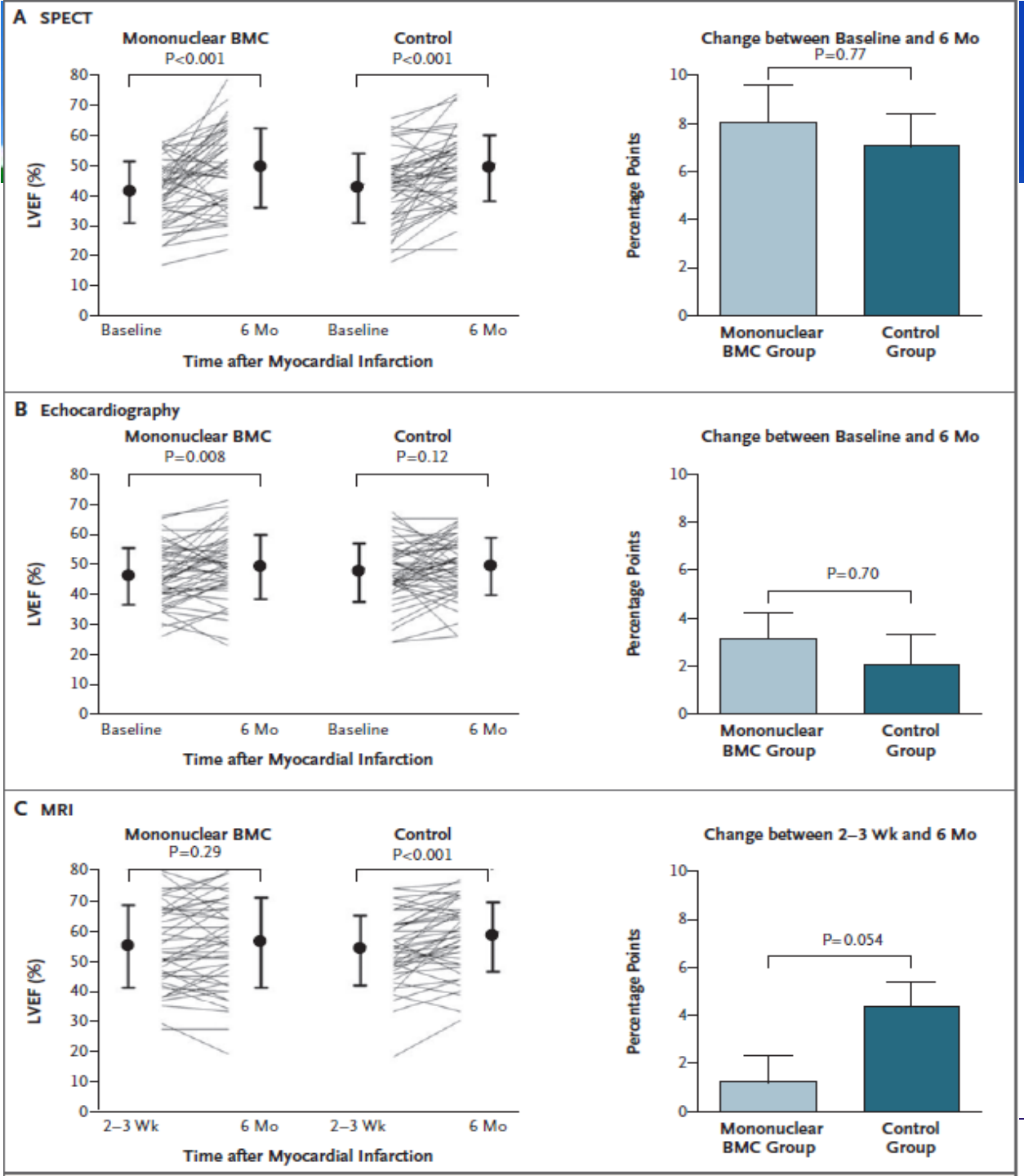
- **Autologous Stem-Cell Transplantation in Acute Myocardial Infarction**
  - effects on left ventricular function of intracoronary injections of autologous mononuclear bone marrow stem cell (BMC) 4 to 8 days after myocardial infarction treated with acute percutaneous coronary intervention
  - anterior-wall infarction only (greatest effect on LV function)

N Engl J Med 2006;355:1199-209.

- **Primary aim of the study**
  - Clinically important improvement in LV function as measured by the left ventricular ejection fraction (LVEF)
- **Sample size calculation: 50 for each group**
  - 80% power, 5% alpha error
  - clinically important difference in LVEF between baseline and 6 months: 5 %
  - SD: 8.3%
  - 10% Drop out


Day 0: patient with acute anterior wall myocardial infarction undergoes PCI with stent implantation in culprit lesion in left anterior descending coronary artery
Day 3–5: randomization
50 Assigned to mononuclear BMC group
50 Assigned to control group
Day 4–7: baseline recordings on SPECT and echocardiography
Day 4–8: bone marrow aspiration and intracoronary mononuclear BMC injection
2–3 Wk after myocardial infarction: MRI
6 Mo after myocardial infarction: SPECT, echocardiography, MRI, coronary angiography

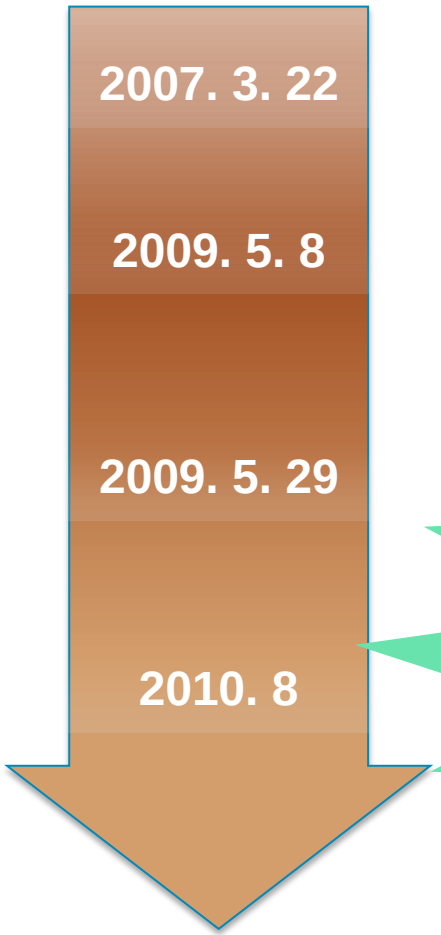

1608 Patients with ST-elevation myocardial infarction
890 Had anterior wall myocardial infarction
519 Did not fulfill inclusion criteria
127 Met exclusion criteria
244 Were eligible for the study
93 Were not invited to participate owing to logistic reasons
151 Were invited to participate
50 Were unwilling to participate
101 Were included in the study
1 Was excluded owing to early heart transplantation
100 Underwent analysis



no effects of intracoronary injection of autologous mononuclear BMC on global left ventricular function

CARVAR 논란에 대한 임상역학자적 관점

종합적 대동맥 근부 및 판막성형술(CARVAR)



심사평가원에 신의료기술 결정 신청

제 9차 건강보험정책심의위원회
평가연구 실시를 조건으로 비급여 시행, 3년 후 재평가

조건부 [illegible]

전향적 연구가 이루어져야 하나, 임의로 CARVAR수술이 계속 이루어짐

CARVAR 논란에 대한 임상역학자적 관점

- 우리나라 신의료기술평가 및 도입 과정상의 문제점

1 계획된 임상시험을 통한 근거를 생성하지 못함

(포함기준과 제외 연구대상수의 산출,

2 근거수준에 기 못함

3 의학연 을 받지 않음

4 허

CARVAR와 CAVIAAR

- **CAVIAAR**

  : 프랑스의 Lansac 박사에 의해 개발된 대동맥 근부 및 판막성형술의 일종

- 유효성·안전성의 평가를 위해 **2007년 5월**부터 다기관공동 무작위배정 비교임상시험 시작

  (미국 국립보건원(NIH)의 임상시험 등록사이트인 ClinicalTrials.gov (등록번호: NCT00478803)에 등록)

  http://clinicaltrials.gov/ct2/show/NCT00478803

CARVAR와 CAVIAAR

Conservative Aortic Valve Surgery for Aortic Insufficiency and Aneurysms of the Aortic Root. CAVIAAR

This study is currently recruiting participants.
Verified on May 2007 by Assistance Publique - Hôpitaux de Paris

First Received on May 24, 2007. Last Updated on May 3, 2011 History of Changes

Sponsor:	Assistance Publique - Hôpitaux de Paris
Information provided by:	Assistance Publique - Hôpitaux de Paris
ClinicalTrials.gov Identifier:	NCT00478803

Purpose

The primary objective of the CAVIAAR study is to prove that aortic valve sparing is associated with a 50% increase of 3 years-survival rate without increased mortality or serious increased morbidity events when compared to mechanical valve replacement.

The main hypothesis of this study is that a standardized procedure of valve sparing based on external aortic annuloplasty in patients with dystrophic aortic insufficiency and/or aortic root aneurysm increases survival rate without increased mortality or serious increased morbidity events when compared with patients undergoing mechanical aortic valve replacement.

Condition	Intervention	Phase
Aortic Valve Insufficiency	Procedure: external aortic annuloplasty Device: Expansile Prosthetic Aortic Ring	Phase III

Study Type: Interventional
Study Design: Allocation: Randomized
Endpoint Classification: Safety/Efficacy Study
Intervention Model: Parallel Assignment
Masking: Double Blind (Subject, Investigator)
Primary Purpose: Treatment

CARVAR와 CAVIAAR

Eligibility

Ages Eligible for Study:	18 Years and older
Genders Eligible for Study:	Both
Accepts Healthy Volunteers:	No

Criteria

Inclusion Criteria:

- Adult patients with indications for elective surgery of aortic root aneurysms and dystrophic aortic insufficiency superiority grade 1 conformed to AHA or ESC guidelines or Adult patients with indications for elective surgery of isolated dystrophic aortic insufficiency conformed to AHA or ESC guidelines
- signed informed consent

Exclusion Criteria:

- Valvular lesions not amenable to valve repair
- Aortic root aneurysms without any significant aortic insufficiency (≤ grade 1)
- Long-term indications for oral anticoagulation (arrythmia, intra-auricular thrombus)
- Concomitant other cardiac procedures (coronary bypass graft, mitral surgery, aortic arch surgery…)
- Acute or chronic ascending aorta dissections
- Redo cardiac surgery
- Contra-indications to oral anticoagulation treatment or to transoesophageal echocardiography
- Life expectancy < 36 mois
- Contra-indication for implantation of the expansile ring : patients are known to have sensitivity to polyester or silicone, the aortic wall is deemed unusually thin and/or friable above the native aortic annular base or local anatomy impairs the safe implantation of the device in the subvalvular position (hypertrophic cardiomyopathy with septal obstruction of the left ventricular outflow tract, calcifications, adhesions…)

CARVAR와 CAVIAAR

Primary Outcome Measures:

- morbidity or mortality, evaluated on a composite criteria, associating mortality; structural and non-structural valvular dysfunction, valve thrombosis, embolism, bleeding event, endocarditis, reoperations and permanent valve-related impairment [Time Frame: 3 years] [Designated as safety issue: No]

Secondary Outcome Measures:

- separate analysis of each component of main endpoint composite criteria [Time Frame: during the 3 years] [Designated as safety issue: No]
- minor bleeding events [Time Frame: during the 3 years] [Designated as safety issue: No]
- Analysis of details of the operative procedures and reasons for intra-operative conversions [Time Frame: during the intervention and in intensive care] [Designated as safety issue: No]
- cardiac rhythm (sinus rhythm or not) [Time Frame: at per-operation andduring the intervention] [Designated as safety issue: Yes]
- quality of life (Short Form SF-36) [Time Frame: during the 3 years] [Designated as safety issue: No]
- - Cardiac imaging (echocardiographic and CT-scan or MRI): coaptation height, systolic and diastolic diameters of the aortic root at the levels of the base of the aortic annulus, sinuses of valsalva, sino-tubular junction and ascending aorta [Time Frame: during the surgery and if there is reintervention] [Designated as safety issue: Yes]

CARVAR와 CAVIAAR

- **2009년 10월 - 연구의 중간결과 발표**

  : 수술의 효과를 나타내는 조기사망률 **(30**일 이내**),** 기능적 개선 정도 등과 같은 결과들 이외에도 재수술율과 그 이유, 수술에 의한 부작용 발생의 상세한 내용 또한 서술함

  Lansac E, et al. An aortic ring to standardise aortic valve repair: preliminary results of a prospective multicentric cohort of 144 patients, Eur J Cardiothorac Surg. 2010;38:147-154

Table 1
Patients' clinical and operative profile.

	Aortic root aneurysm
Number of patients	144
Mean age (years)	54.4 ± 14.1 (21–86)
Sex ratio (male/female)	119/25
Body surface area (m^2)	1.9 ± 0.2 (1.4–2.5)
Marfan syndrome	18 (12.5%)
Bicuspid valves	33 (22.9%)
Aneurysm diameter (mm)	54.6 ± 6.8 (50–97)
NYHA	1.7 ± 0.66 (1–3)
I	60 (41.7%)
II	70 (48.6%)
III	13 (9%)
IV	1 (0.7%)
Sinus rhythm	141 (97.9%)
Tube graft diameter (mm)	27.7 ± 1.6 (24–32)
Aortic ring diameter (mm)	27.2 ± 1.4 (24–32)
Cusp repair	58 patients (40.3%)–79
Plicating stitches	41 (57.7%)
Cusp resection	13 (18.3%)
Running suture	10 (14%)
Cusp decalcification	5 (7%)
Pericardial patch	1 (1.4%)
Direct suture of cusp defect	1 (1.4%)
Associated cardiac procedures	34 patients (23.6%)
Coronary bypass	14
Mitral valve repair	7
Closure of patent foramen ovale	6
Anterior arch replacement	4
Atrial fibrillation ablation	3
Second cardiopulmonary bypass run	8 (5.5%)
Re-repair of cusp prolapse	4 (2.8%)
Conversion for valve replacement	2 (1.4%)
Bypass on the right coronary	1 (0.7%)
Haemostasis on graft suture line	1 (0.7%)
ECC time (min)	169.3 ± 34 (101–315)
Aortic cross-clamping time (min)	
All patients (n = 144)	127.8 ± 30.5 (81–240)
Patients with cusp repair[a] (n = 44)	144 ± 26.7 (88–210)
Patients without cusp repair[a] (n = 64)	124.5 ± 25.7 (81–240)
Thirty-day mortality	4 (2.8%)
In hospital morbidity	54 patients–81 events
Valve related morbidity	
Structural valve deterioration	0
Non-structural dysfunction	6[b] (4.2%)
Valve thrombosis	0
Embolism (transient ischaemic attack)	3 (2%)
Stroke	1 (0.7%)
Bleeding	0
Operated valve endocarditis	0
Mediastinal re-exploration	7 (4.9%)
Cardiac morbidity	
Pericardial effusion requiring drainage	7 (4.9%)
Pacemaker implantation	5 (3.5%)
Mediastinitis	1 (0.7%)
Myocardial infarction	4 (2.8%)
Atrial fibrillation	37 (25.7%)
Multiple organ failure	1 (0.7%)
Cardiac assistance (ECMO)	1 (0.7%)
Other complications	
Pneumonia	3 (2%)
Phlebitis	1 (0.7%)
Acute renal insufficiency	4[c] (2.8%)

[a] Patients with associated cardiac procedure were excluded.
[b] Intra-operative residual cusp prolapse.
[c] Two transient dialysis. ECC: extracorporeal circulation, ECMO: extracorporeal membrane oxygenation.

Thirty-day mortality	4 (2.8%)
In hospital morbidity	54 patients—81 events
Valve related morbidity	
Structural valve deterioration	0
Non-structural dysfunction	6[b] (4.2%)
Valve thrombosis	0
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Operated valve endocarditis	0
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CARVAR 논란에 대한 임상역학자적 관점의 제언

새로운 의료기술들을 과학적으로 평가할 수 있는 효과적인 시스템 구축

새로운 치료법을 평가하는 연구가 윤리적이고 객관적으로 수행되는 체계 구축

수집된 안전성과 유효성에 대한 정보를 제3자가 확인할 수 있도록 투명하게 공개하는 풍토 조성


Thank You !