Biomarkers in VTE

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Definition of Biological Markers

❖ **Measurable** and **quantifiable** biological parameters

▶ specific enzyme concentration, specific hormone concentration, specific gene phenotype distribution in a population, presence of biological substances

Year introduced: 1989 ***MeSH database***

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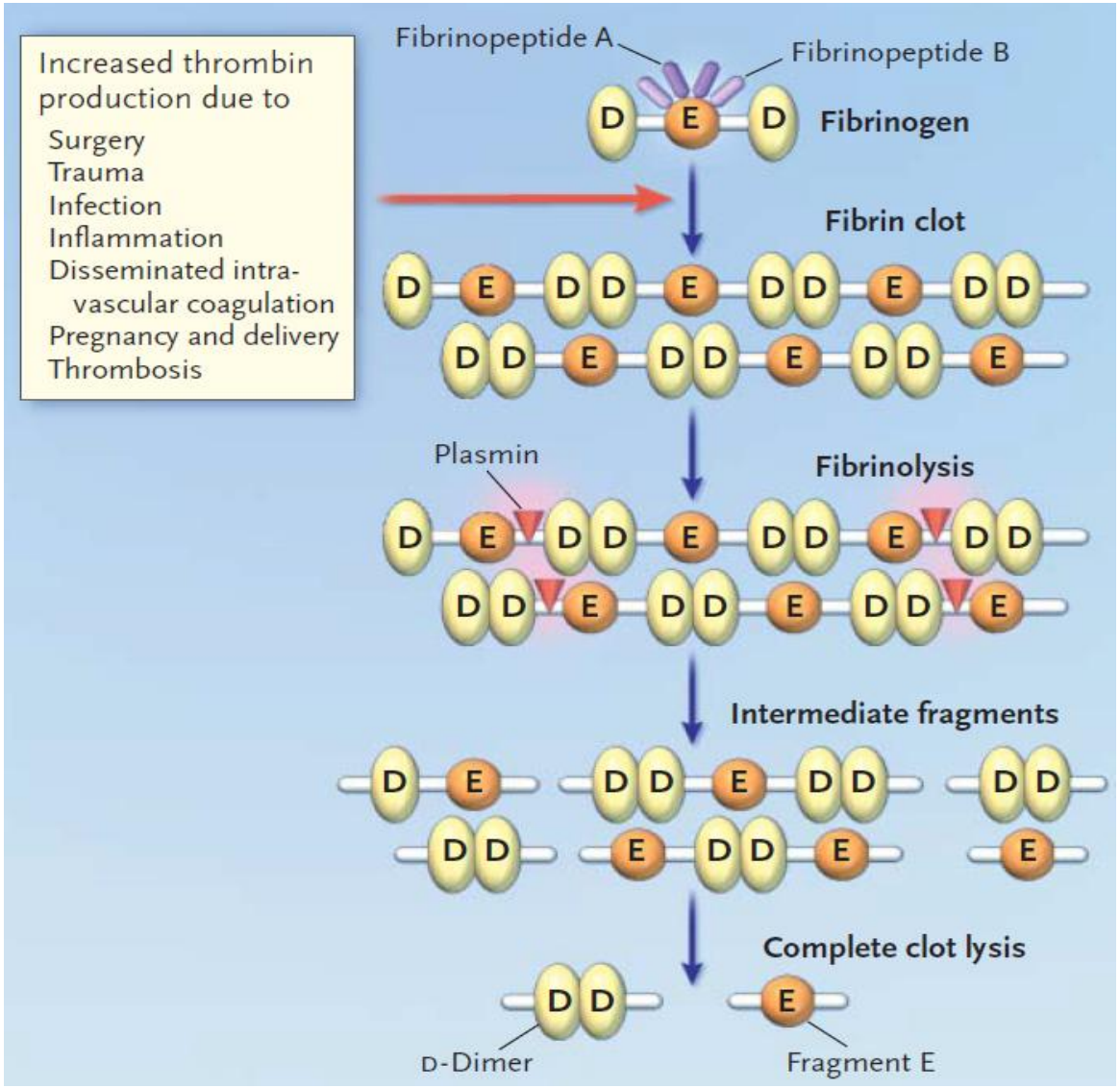
D-dimer

Plasmin degradation of a fibrin clot



▶The presence of D-dimer is a telltale clue that **blood clotting has been initiated.**

N Engl J Med 2003;349(13):1203-4

D-dimer

Detection Methods

1. Enzyme-linked immunosorbent assay (VIDAS)

: highly sensitive but not specific for DVT,
quantitative results, technically time-consuming

2. Latex-agglutination assay (IL-Test)

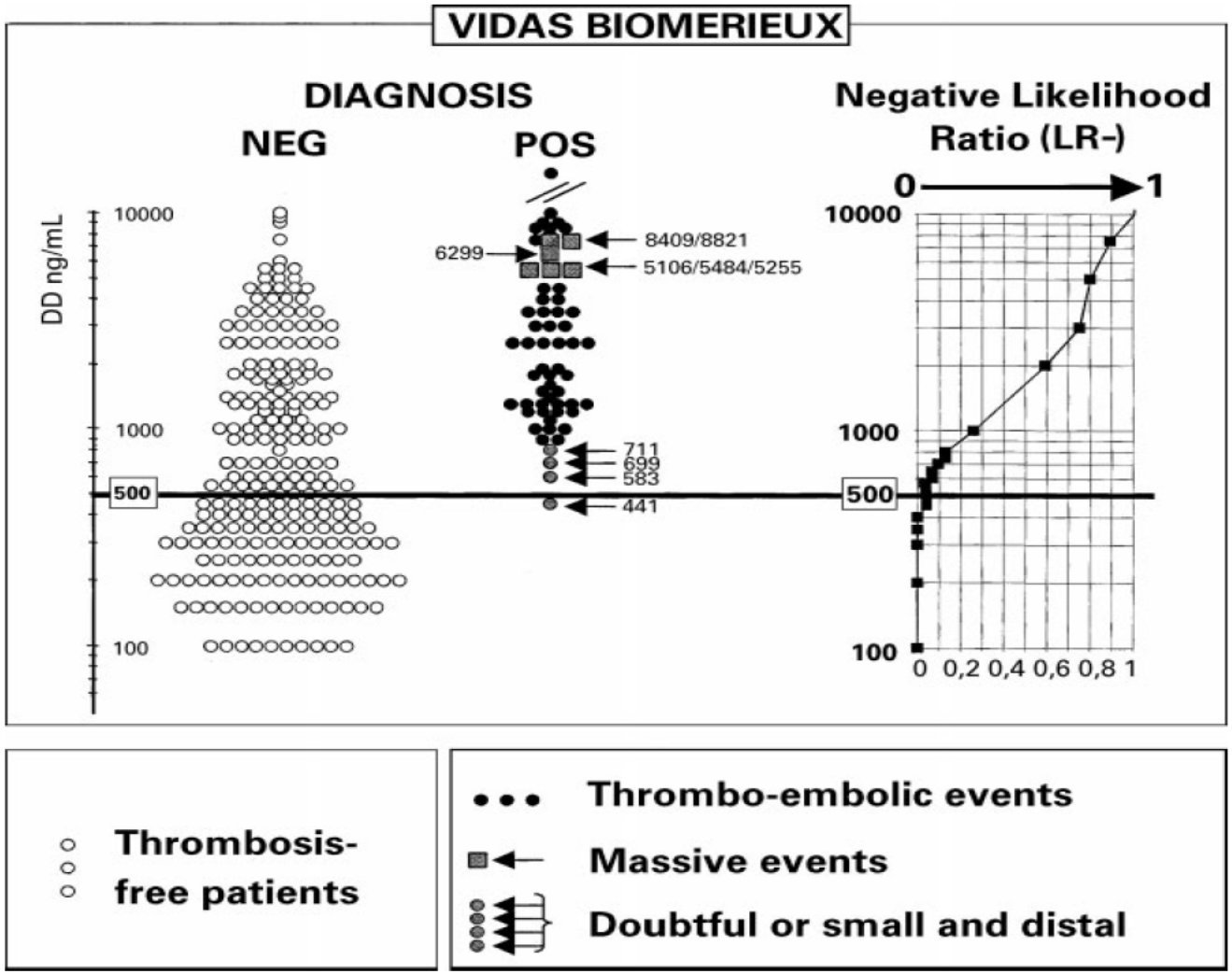
: inexpensive, rapid, quantitative, but 80% sensitivity

3. Whole-blood agglutination (SimpliRED)

: qualitative, red-cell agglutination assays,
monoclonal antibody specific for d-dimer
operator-dependent

N Engl J Med 2003;349(13):1203-4

D-dimer



▶High Sensitivity & High NPV (negative predictive value) (~100%)

Semin Vasc Med 2005;5(4):328-339

폐색전증 진단을 위한 진료실에서의 예비검사

High clinical likelihood of PE

PE likely > 4

임상적 특징	점 수
심부정맥혈전증의 임상적 증상 및 징후	3.0
폐색전증을 우선적 진단으로 고려하는 경우	3.0
심박수가 분당 100회를 초과	1.5
지난 4주 동안에 수술이나 3일 이상 거동이 안된 경우	1.5
심부정맥혈전증이나 폐색전증의 과거력	1.5
객혈	1.0
활동중인 암 (6개월 이내에 치료를 받았거나 보존적 치료)	1.0

Wells PS et al. Thromb Haemost 2000;83:416

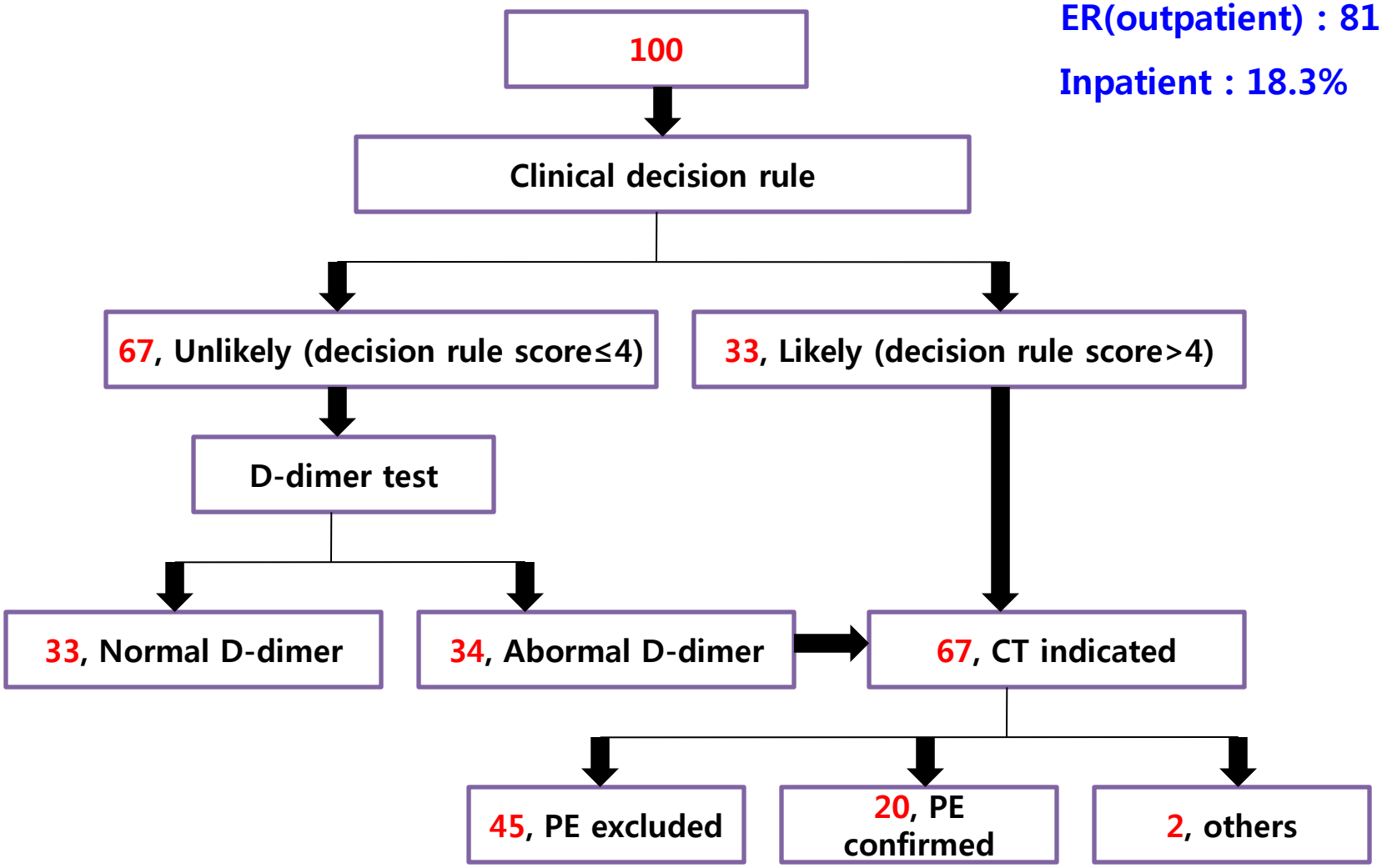
Incidence rate of PE using D-dimer and Wells score

Score by model	PE rate with -DD	PE rate with +DD	PE rate overall
≤ 4	1.7% [2/118] (0.2%-6.0%)	11.7% [7/60] (4.8%-22.6%)	5.1%[9/17] (2.3%-9.4%)
>4	10.3 [3.29] (2.2%-27.4%)	60% [24/40] (43.3%-75.1%)	39.1%[27/69] 27.6%-51.6%)

( ) = 95% confidence interval: DD = D-dimer

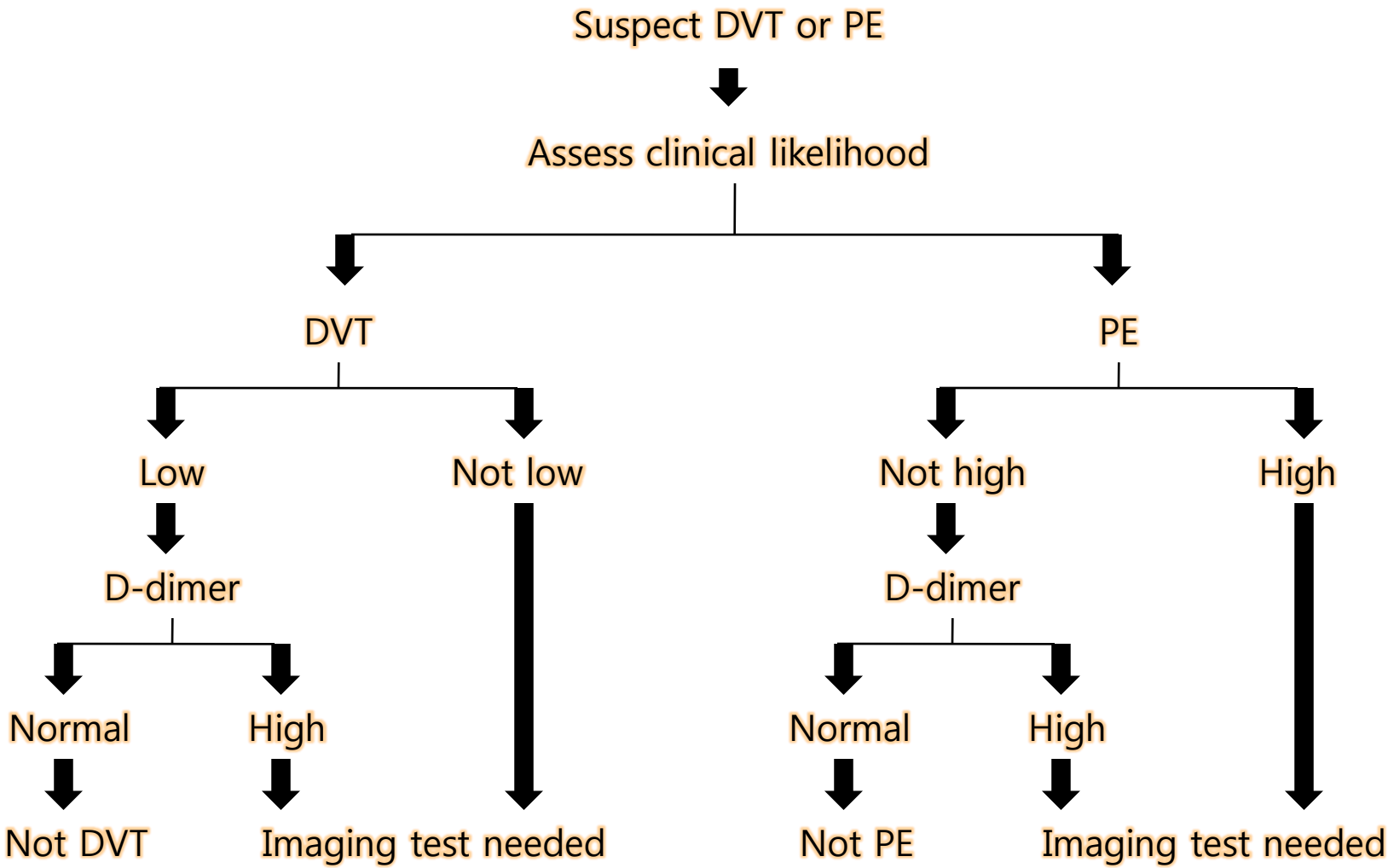
Thromb Haemost 2000;83:416

Diagnostic algorithm of PE using D-dimer



JAMA 2006;295:172-9

Algorithm for Diagnostic Imaging



Harrison's Internal Medicine 17th ed.

Summary of D-dimer

❖ **D-dimer 는 체내에 혈전생성이 시작되었음을 의미**

❖ **D-dimer 는VTE에서 증가하지만 기타 수술, 출혈, 외상, 악성종양, 패혈증, 고령, 임신(2기, 3기) 등과 관련해서도 증가할 수 있다.**

❖ **VTE를 진단에서 배제하는데 유용한 검사법**

▶민감도가 높지만 VTE가 없는 환자의 90% 이상에서 정상으로 높은 NPV

❖ **D-dimer 검사는 임상적 가능성(clinical probability)에 대한 평가와 함께 임상적으로 이용된다.**

▶임상적 평가는 Wells score, Geneva score를 사용

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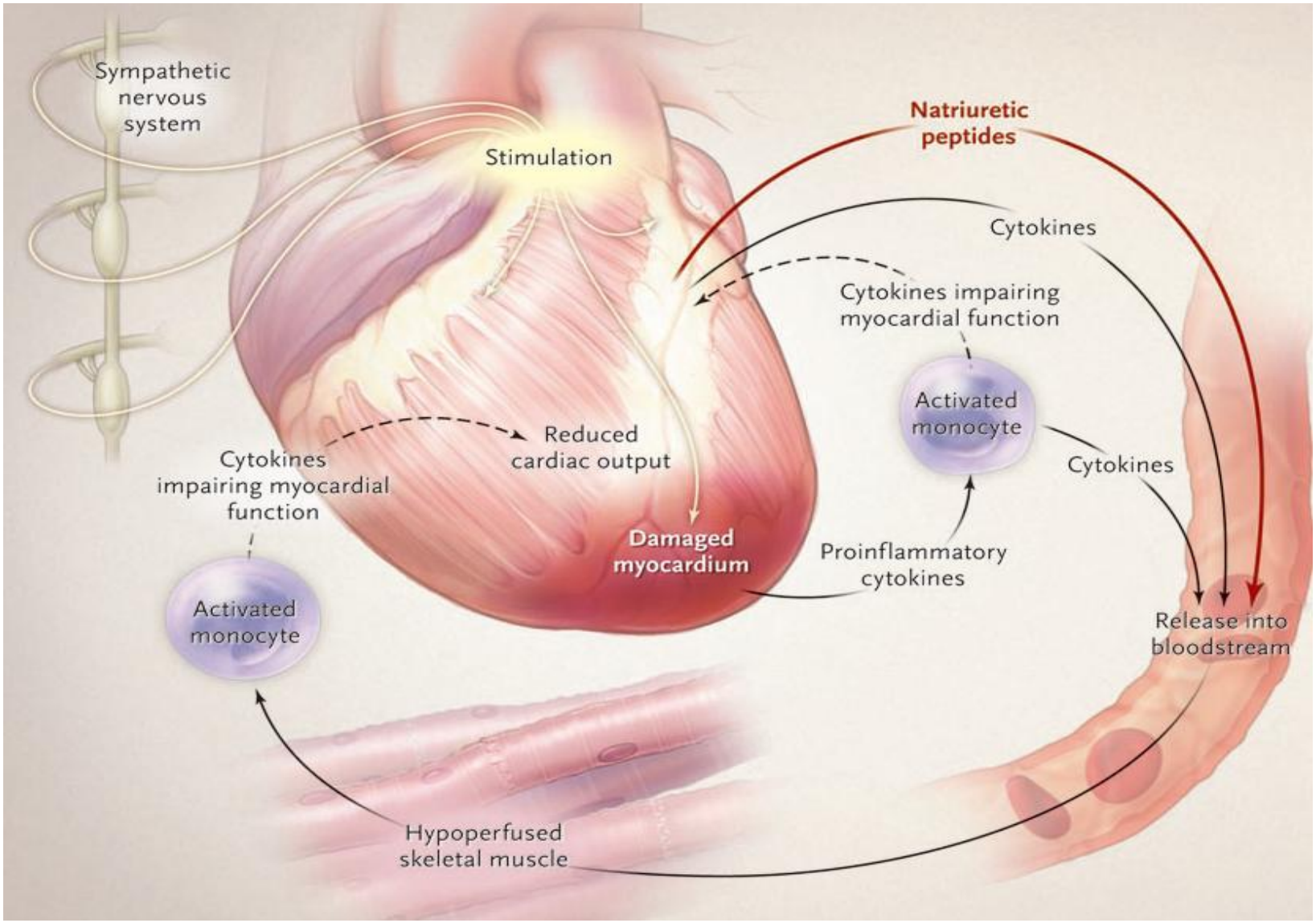
BNP(Brain Natriuretic peptide)



N Engl J Med 2008;358:2148-59

BNP(Brain Natriuretic peptide)

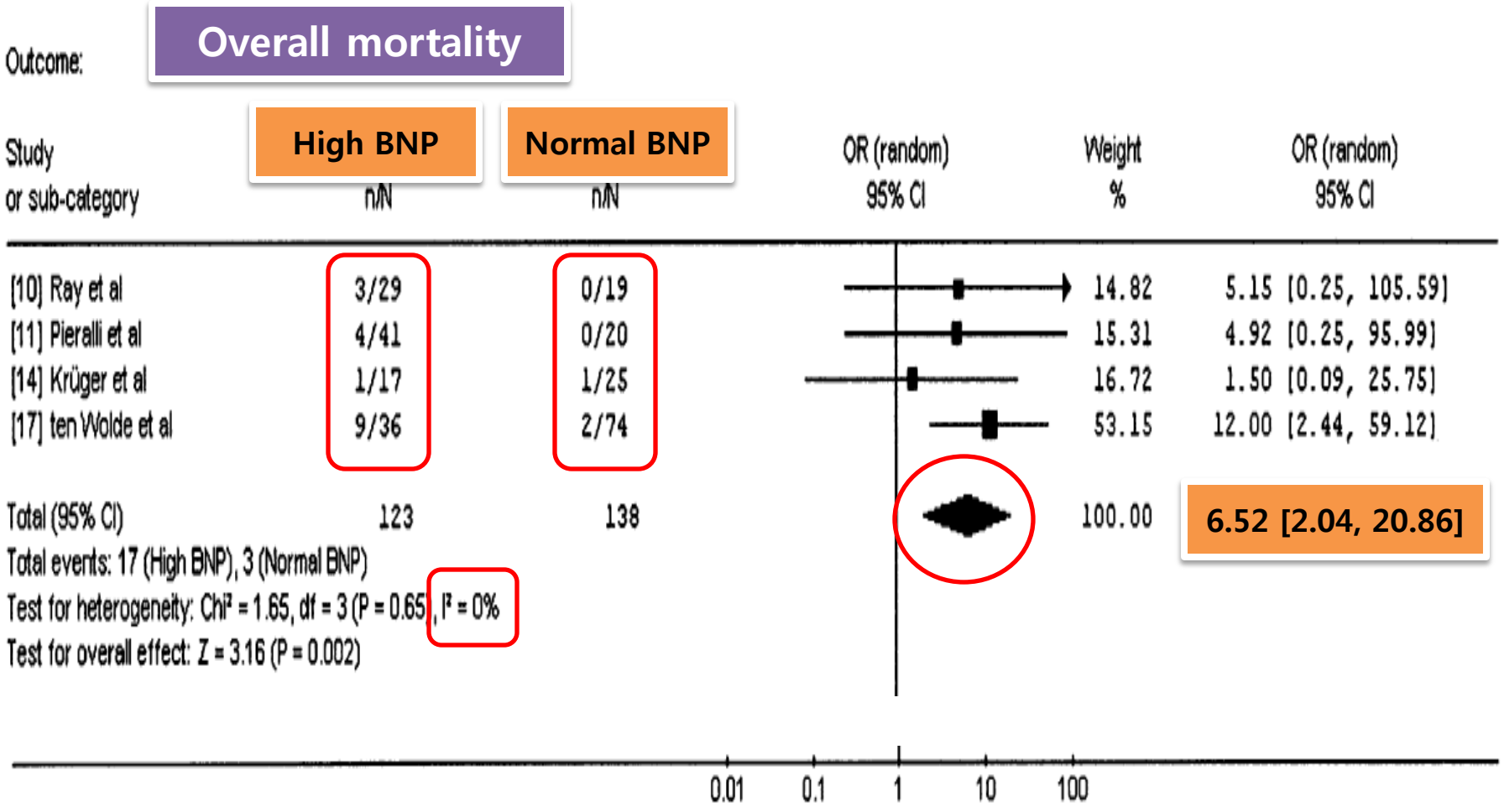
❖ BNP(Brain natriuretic peptide)는 **심근세포**에서 합성되는 호르몬

❖ 전구물질인 pro-BNP는 **심장의 용적확대(volume expansion)**와 **압력과부하(pressure overload)**로 인한 심근자극 후에 active BNP와 inactive NT-pro-BNP(N-terminal-proBNP)로 분해

❖ 급성 폐색전증에서 **우심실의 전단응력(shear stress)이 높아지면** BNP 혹은 NT-pro-BNP가 상승하고 이는 **우심실 기능이상(right ventricular dysfunction)**을 나타내는 표시자로 사용된다.

❖ 결과에 영향을 미치는 인자로는 환자의 나이, 체질량지수(body mass index, BMI), 신장기능이 있다.

BNP(Brain Natriuretic peptide)



Am J Respir Crit Care Med 2008;178(4):425-30

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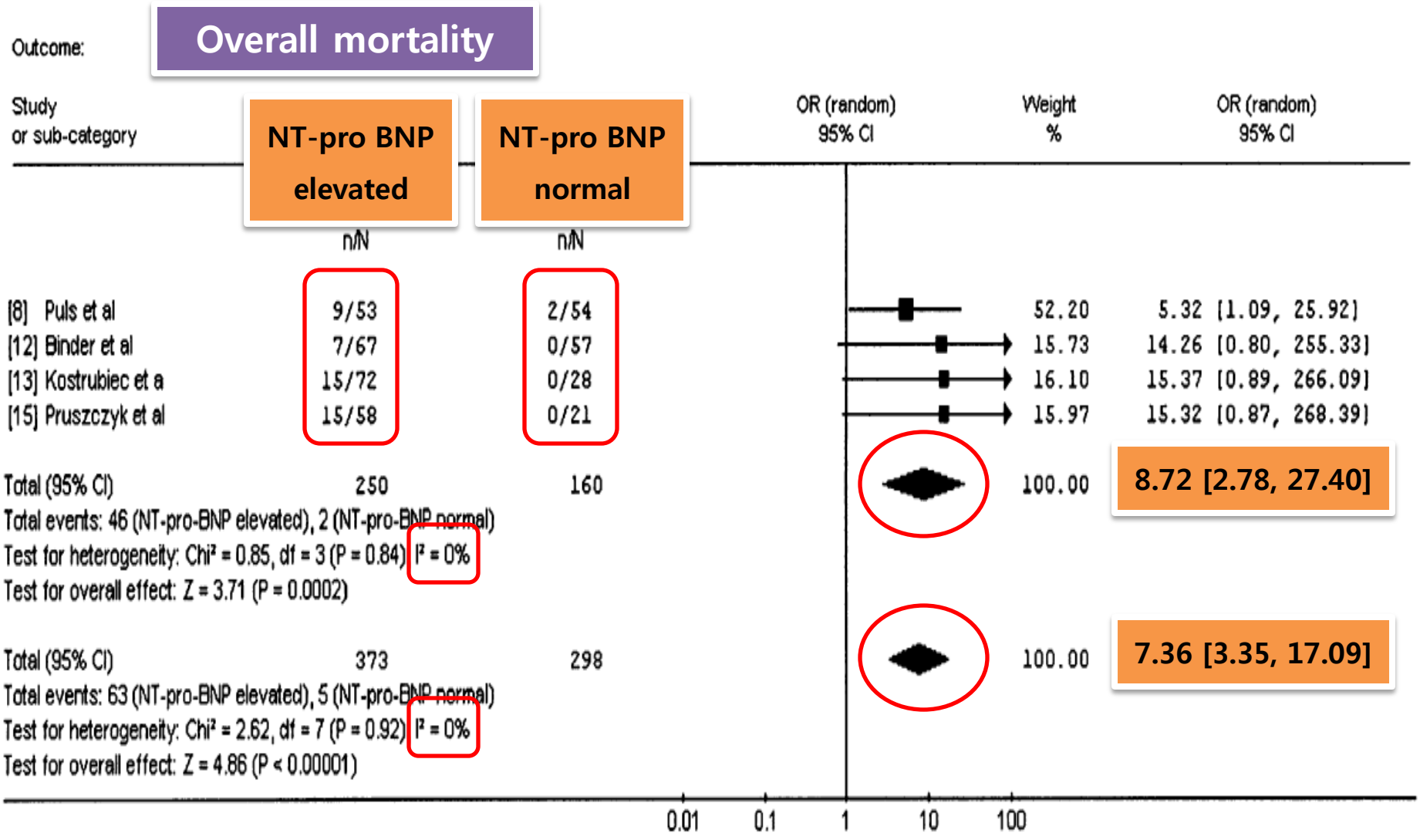

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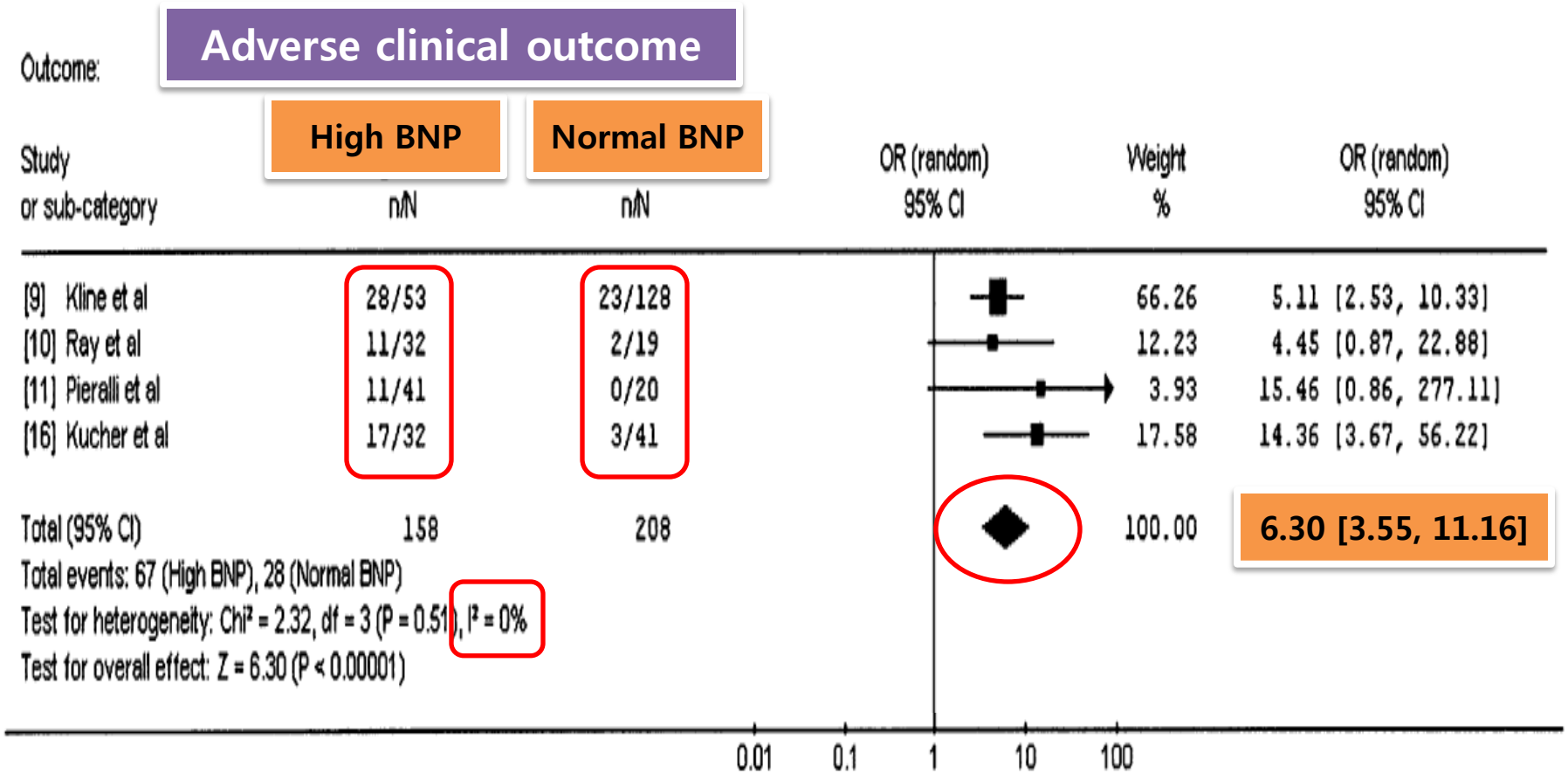

Adverse clinical outcome defined as the occurrence of any of the following: **death, CPR, mechanical ventilation, use of vasopressors, thrombolysis, thrombosuction, open surgical embolectomy, or admission to the ICU.**

Am J Respir Crit Care Med 2008;178(4):425-30

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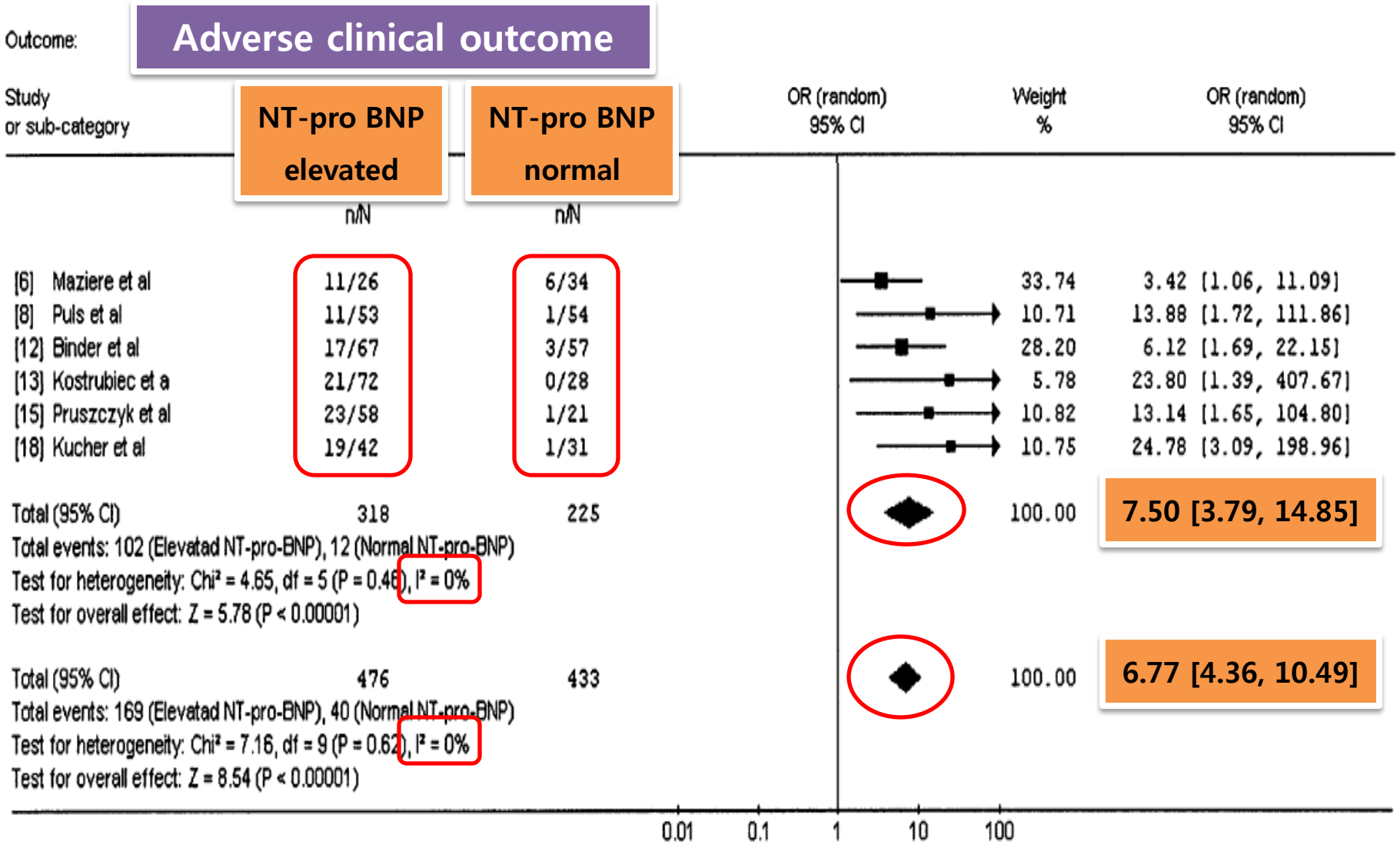

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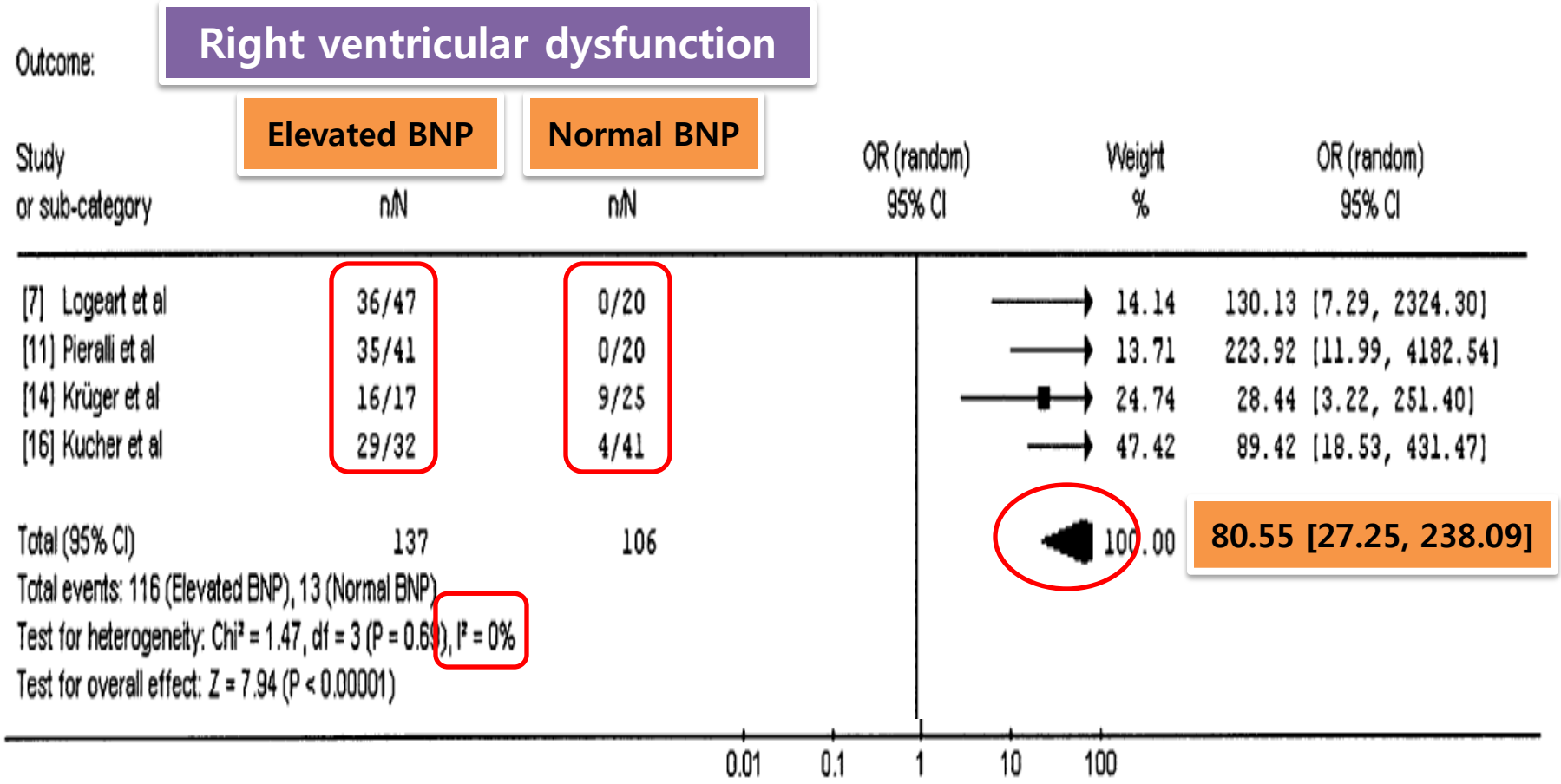

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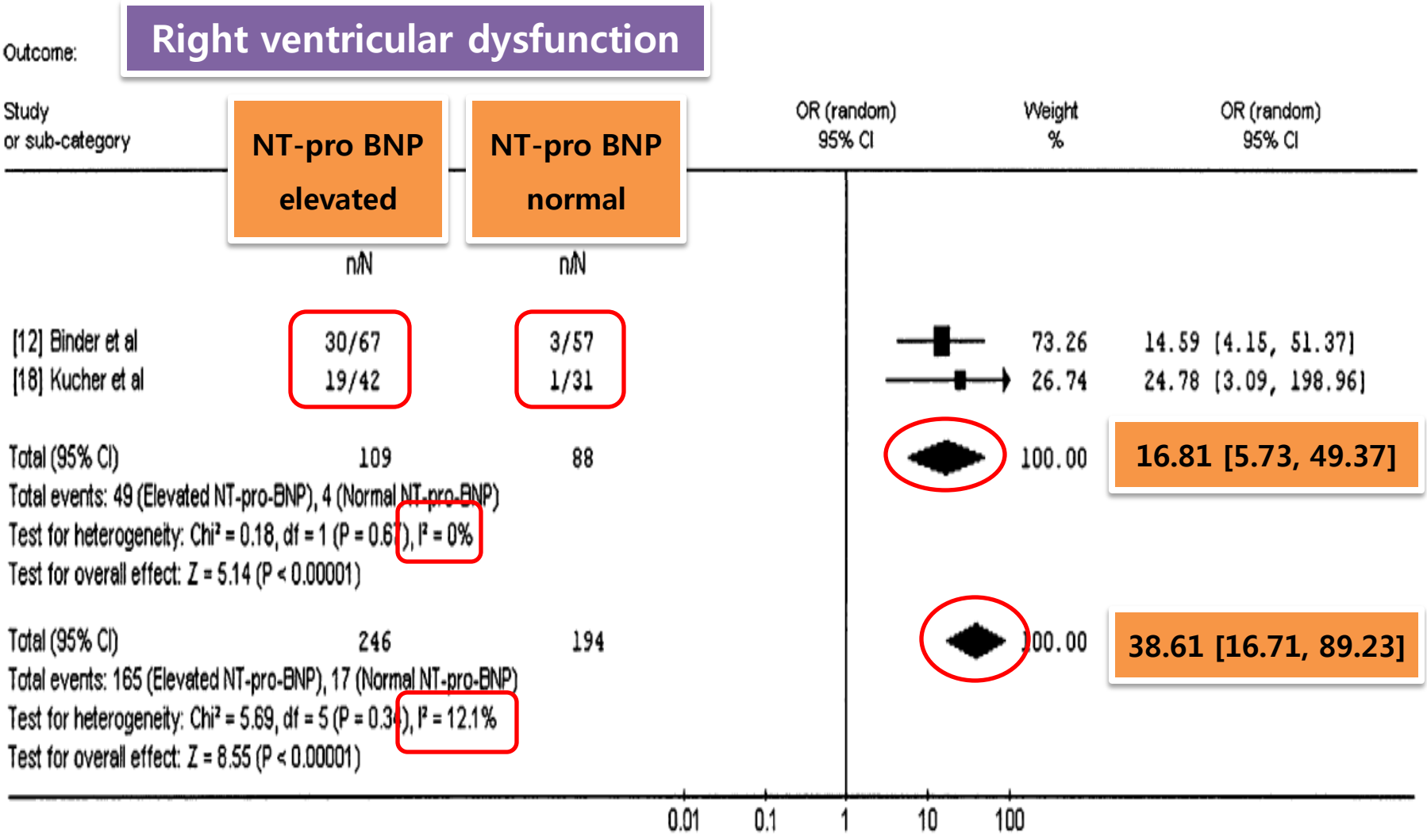
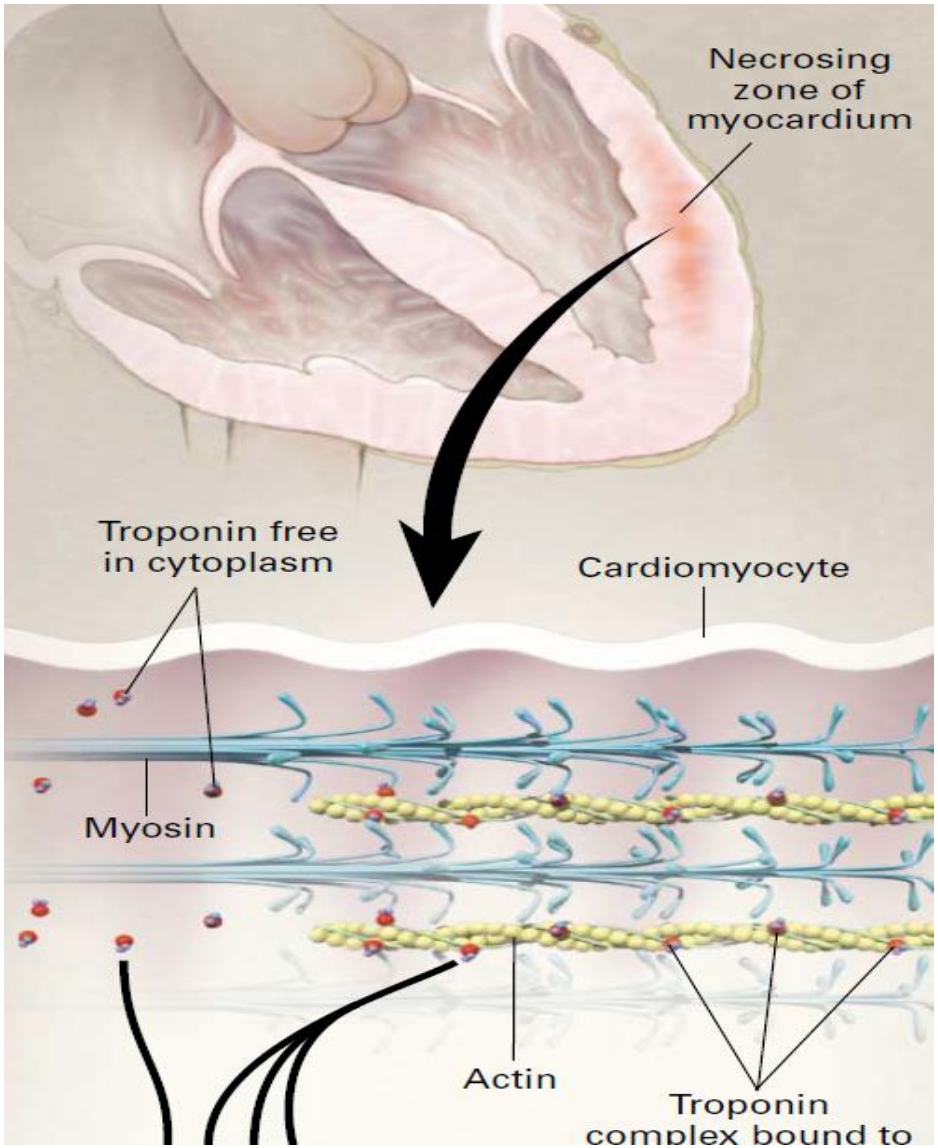
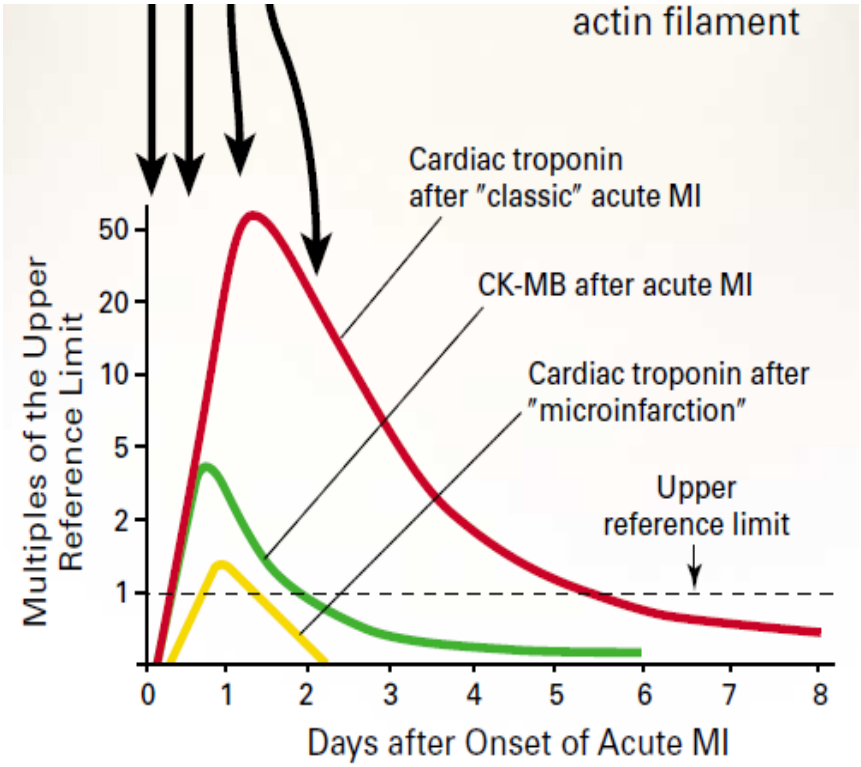


Am J Respir Crit Care Med 2008;178(4):425-30

Troponin





N Engl J Med 2002;346(26):2079-82

Troponin

❖ 심장 Troponin I(cTnT) 와 troponin T(cTnI)는 **횡문근(striated muscle)**에 있는 근육 단백질

❖ **심근괴사(myocardial necrosis)**가 있는 경우 혈류로 유리

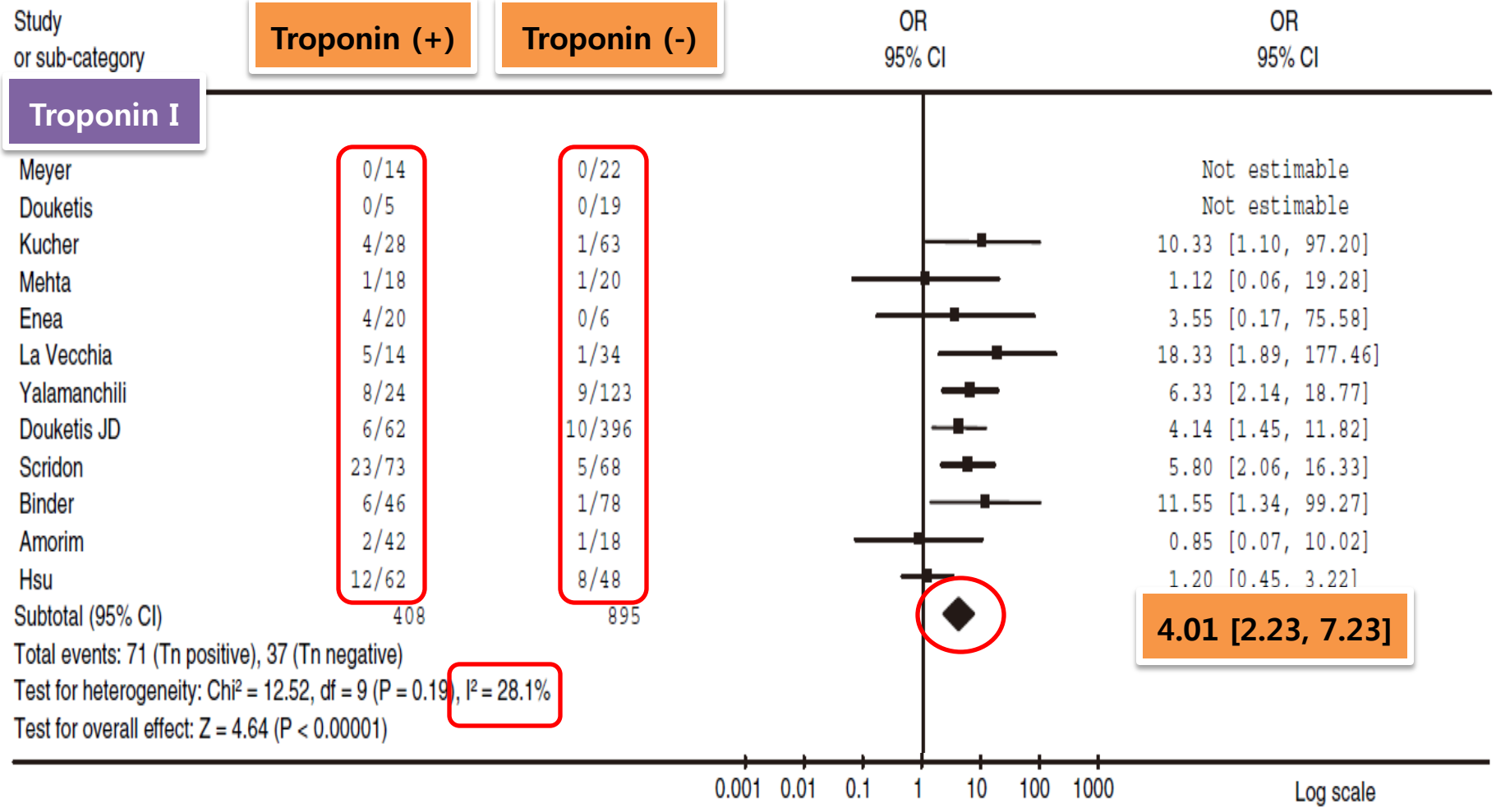
❖ 주로 심근경색증과 협심증에서 심근허혈로 인하여 증가되지만 폐색전증에서도 **중증의 우심실 압력 과부하(pressure overload)** 혹은 **우심실의 장기간의 압력 과부하 후에 발생하는 경미한 심근손상**에도 증가

❖ 폐색전증에서 troponin 의 상승은 **우심실의 기능이상이나 확장과 관련**

J Am Coll Cardiol 2000;36:1632-6

Troponin

Death based on serum Troponin I and T



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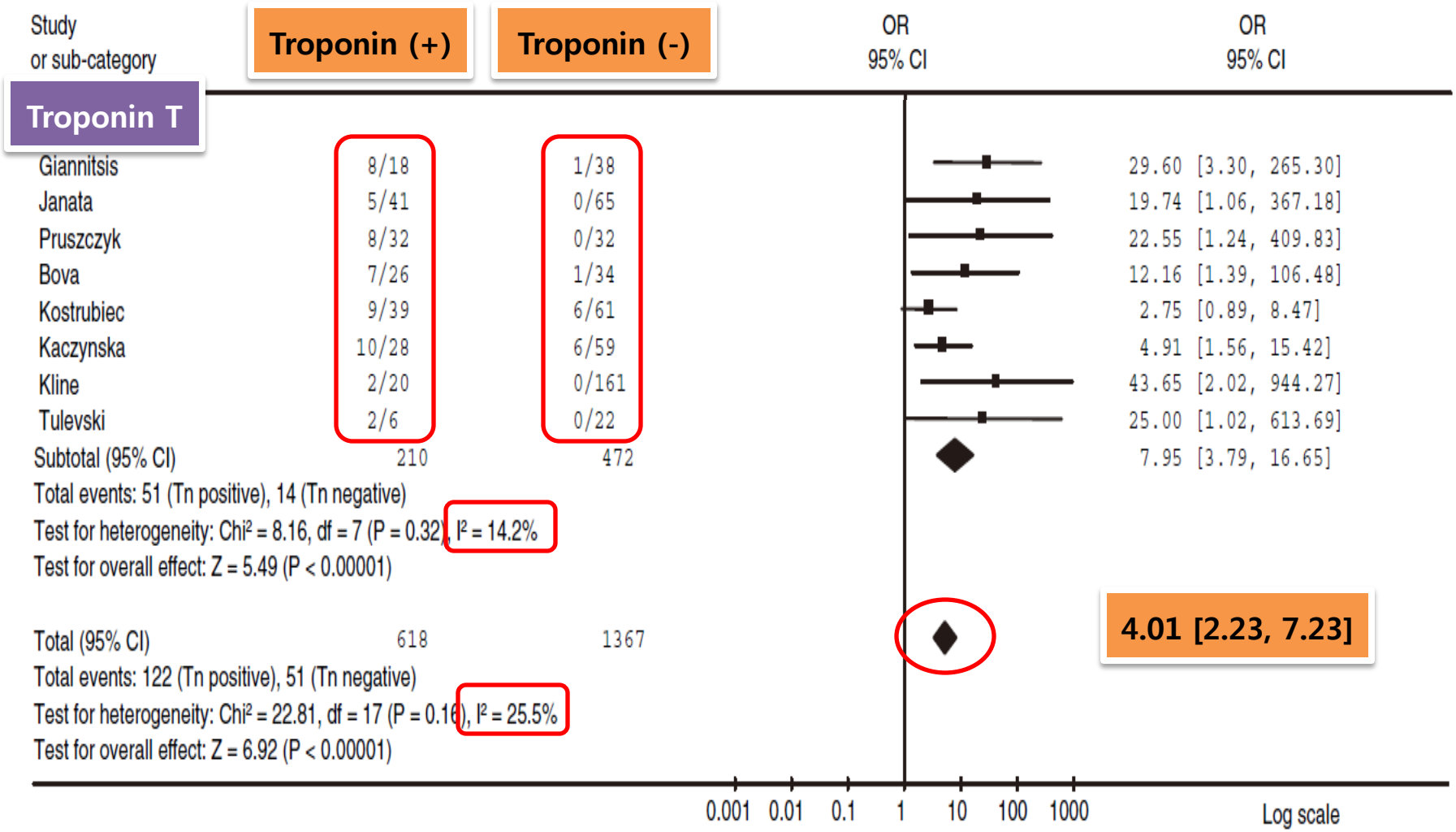
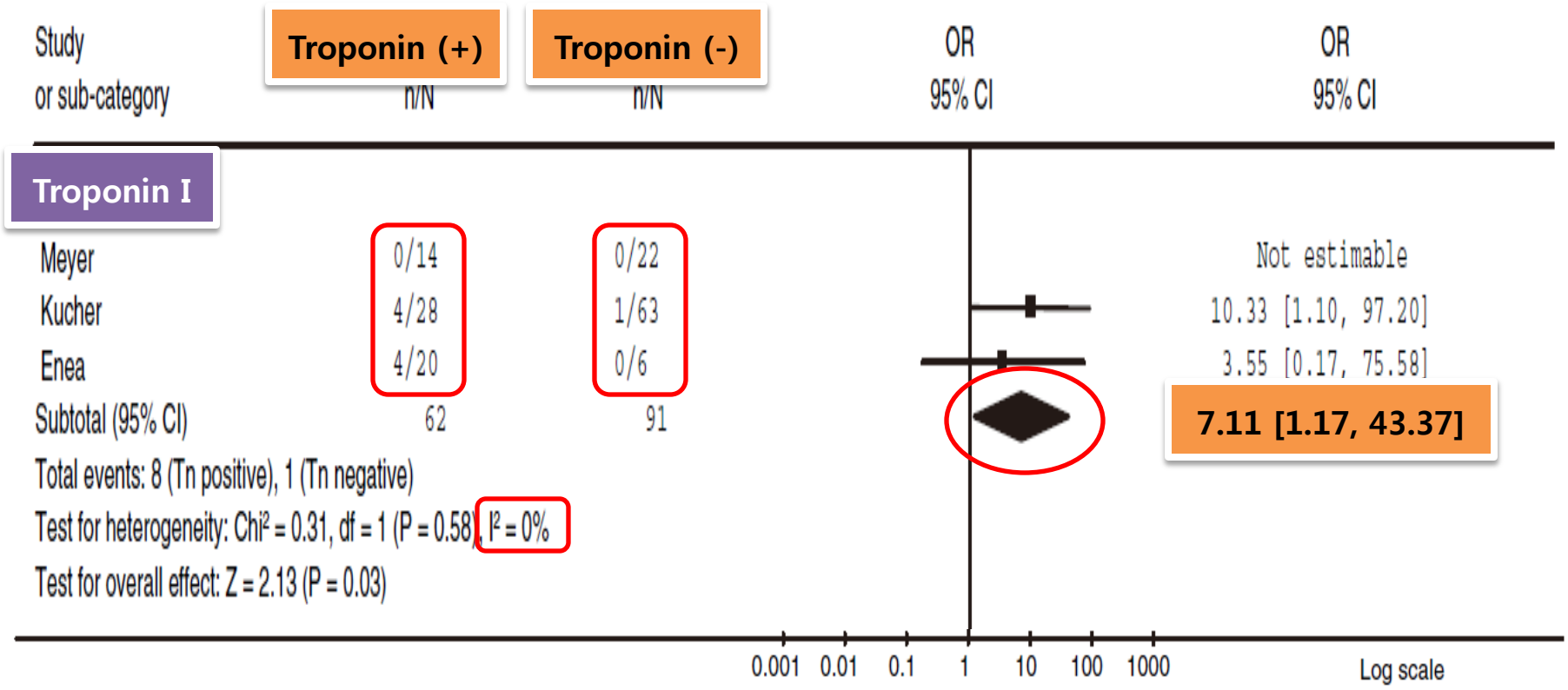


Troponin

Death resulting from PE based on serum Troponin I and T



Troponin

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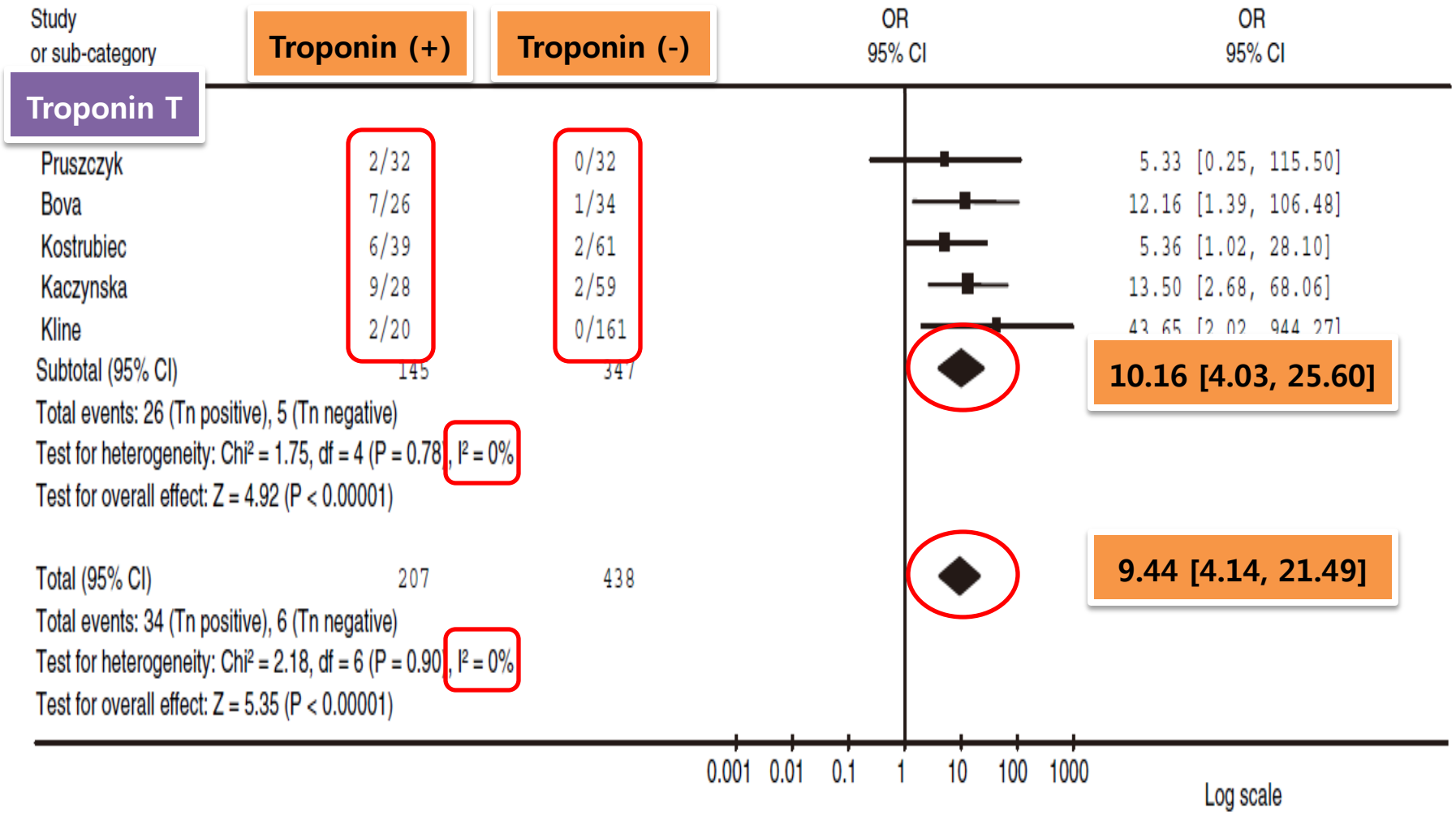


Pooled diagnostic indexes for various tests

- RV dysfunction predicting death in PE showing stable haemodynamics

	Echocardio -graphy	CT	BNP	Pro-BNP	Cardiac troponin
Sensitivity (%) (95% CI)	**70** (46–86)	**65** (35–85)	**88** (65–96)	**93** (14–100)	**81** (23–100)
Specificity (%) (95% CI)	**57** (47–66)	**56** (39–71)	**70** (64–75)	**58** (14–92)	**84** (77–90)
NPV (%) (95% CI)	**60** (55–65)	**58** (51–65)	**76** (73–79)	**81** (65–97)	**73** (68–78)
PPV (%) (95% CI)	**58** (53–63)	**57** (49–64)	**67** (64–70)	**63** (50–76)	**75** (69–80)

NPV : negative predictive value, PPV : positive predictive value

Eur Heart J 2008;29:1569–1577

Simplified PESI(Pulmonary Embolism Severity Index)

Variable	Points
Age > 80 years	1
History of cancer	1
History of chronic cardiopulmonary disease	1
Pulse ≥110 beats/min	1
Systolic blood pressure <100 mmHg	1
Arterial oxyhemoglobin saturation (SaO2) <90%	1

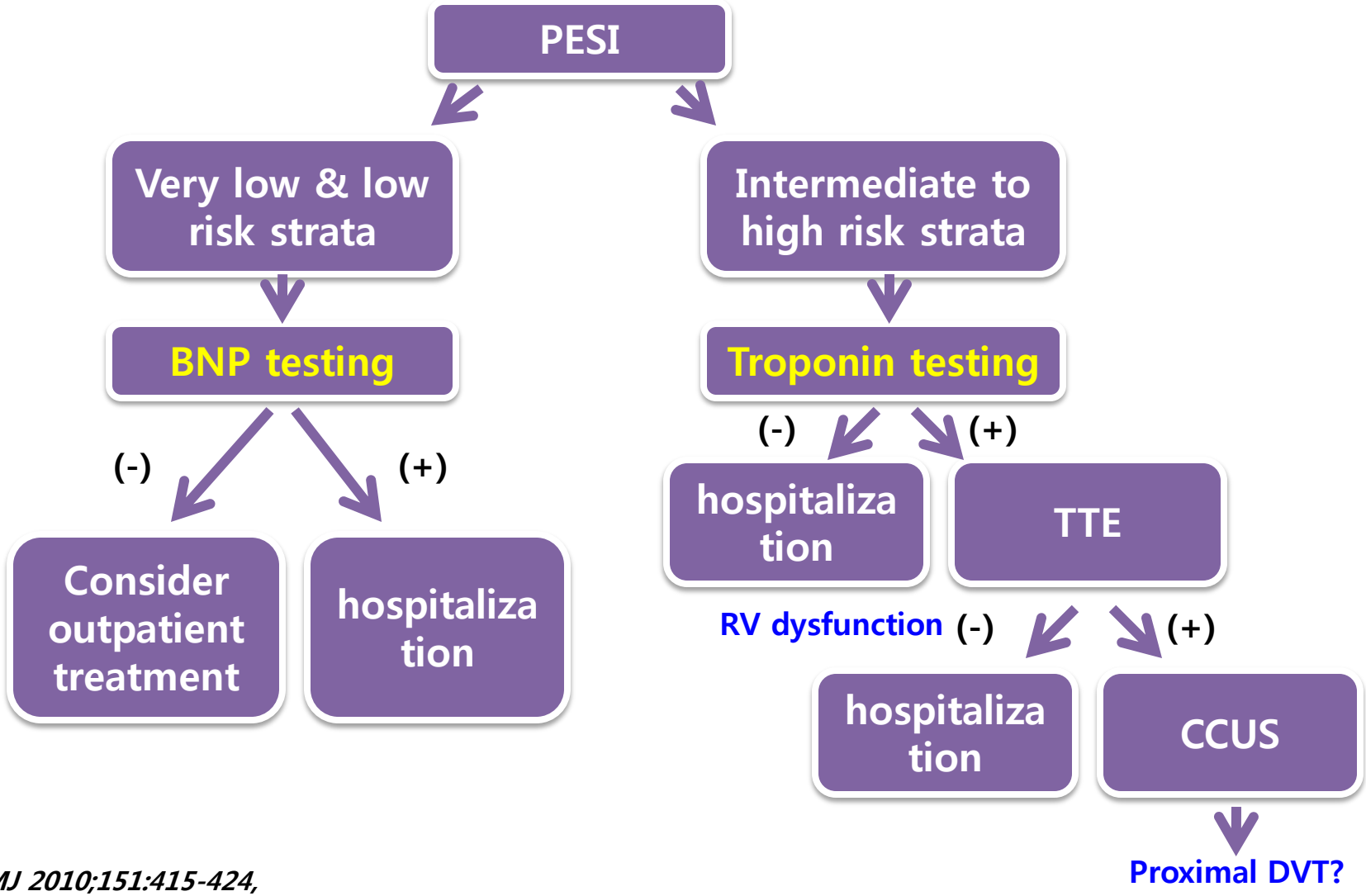
A total point score for a given patient is obtained by summing the points. The score corresponds with the following risk classes: 0, low risk; ≥ 1, high risk.

Am J Respir Crit Care Med 2005;172(8):1041-6

Arch Intern Med 2010;170(15):1383-9

Testing and treatment algorithm for hemodynamically stable PE

- acute symptomatic PE diagnosed in the ER or OPD setting



BMJ 2010;151:415-424,
Lancet 2011; 378: 41–48

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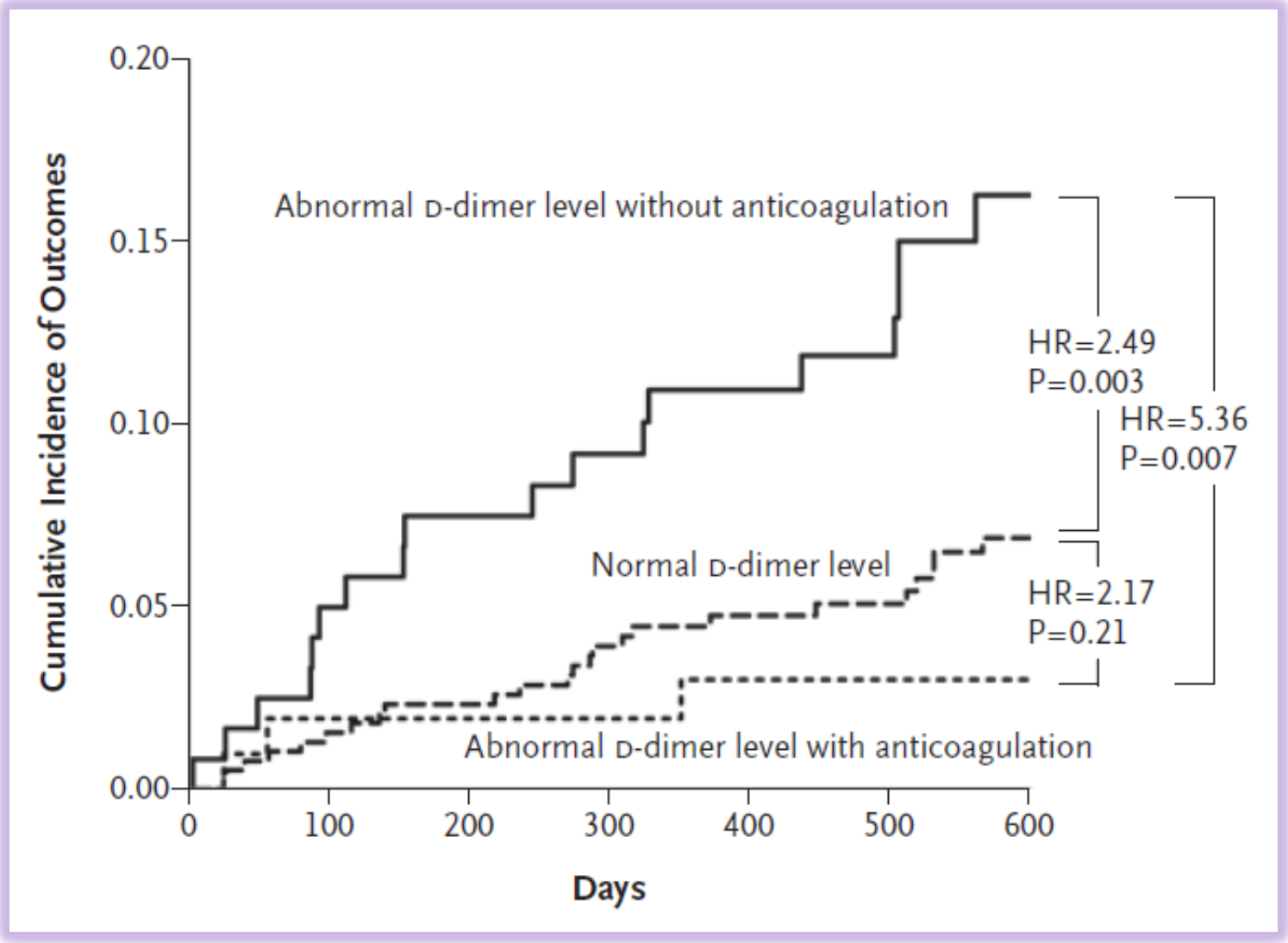
D-dimer

❖ D-dimer가 **항응고치료 종료 후 증가**한다는 것은 **비정상적인**

혈액응고 과정을 교정하기 위한 섬유소용해 과정이 활성화되었

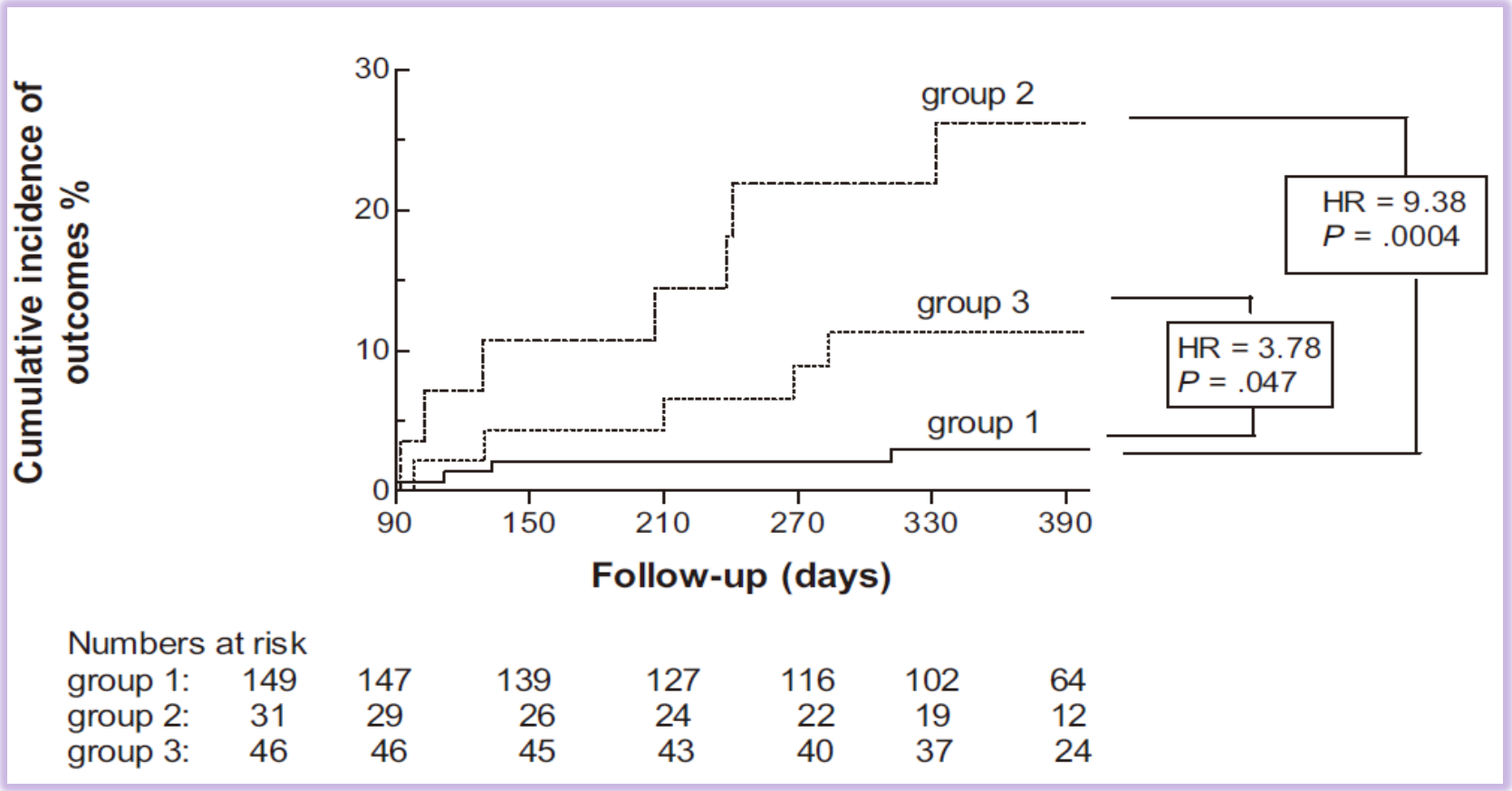
다는 것을 의미

D-Dimer Testing to determine the duration of anticoagulation therapy (PROLONG study)



New Engl J Med 2006; 355: 1780-9

Usefulness of repeated D-dimer testing after stopping anticoagulation (PROLONG II)



Group 1: Patients in whom D-d was normal at T90 and afterward (with D-d becoming abnormal only once).
Group 2: Patients in whom D-d became abnormal at T90 and afterward remained altered persistently or at least twice.
Group 3: Patients in whom D-d became abnormal after T90 and afterward remained abnormal persistently or at least twice.

Blood 2010;115:481-488

Annualized Risk for Recurrent VTE, by Timing of D-Dimer Testing After Anticoagulation

Variable	(-) D-Dimer Result	(+) D-Dimer Result
Timing of D-dimer testing after anticoagulation	Annualized Risk for Recurrent VTE Per 100 Patient-Years (95% CI)	
< 3 weeks	**2.0** (1.1–2.0)	**8.2** (2.1-13.9)
3-5 weeks	**4.2** (3.8-4.5)	**10.2** (7.3-13.5)
> 5 weeks	**3.0** (2.3-4.1)	**7.4** (3.9-12.0)

D-Dimer result (positive vs. negative) **HR 2.59** (1.90–3.52)

Ann Intern Med. 2010;153:523-531

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Microparticles

❖ Microparticles은 **0.1~1.0μm** 크기의 작은 **막소포(membranous vesicle)**들

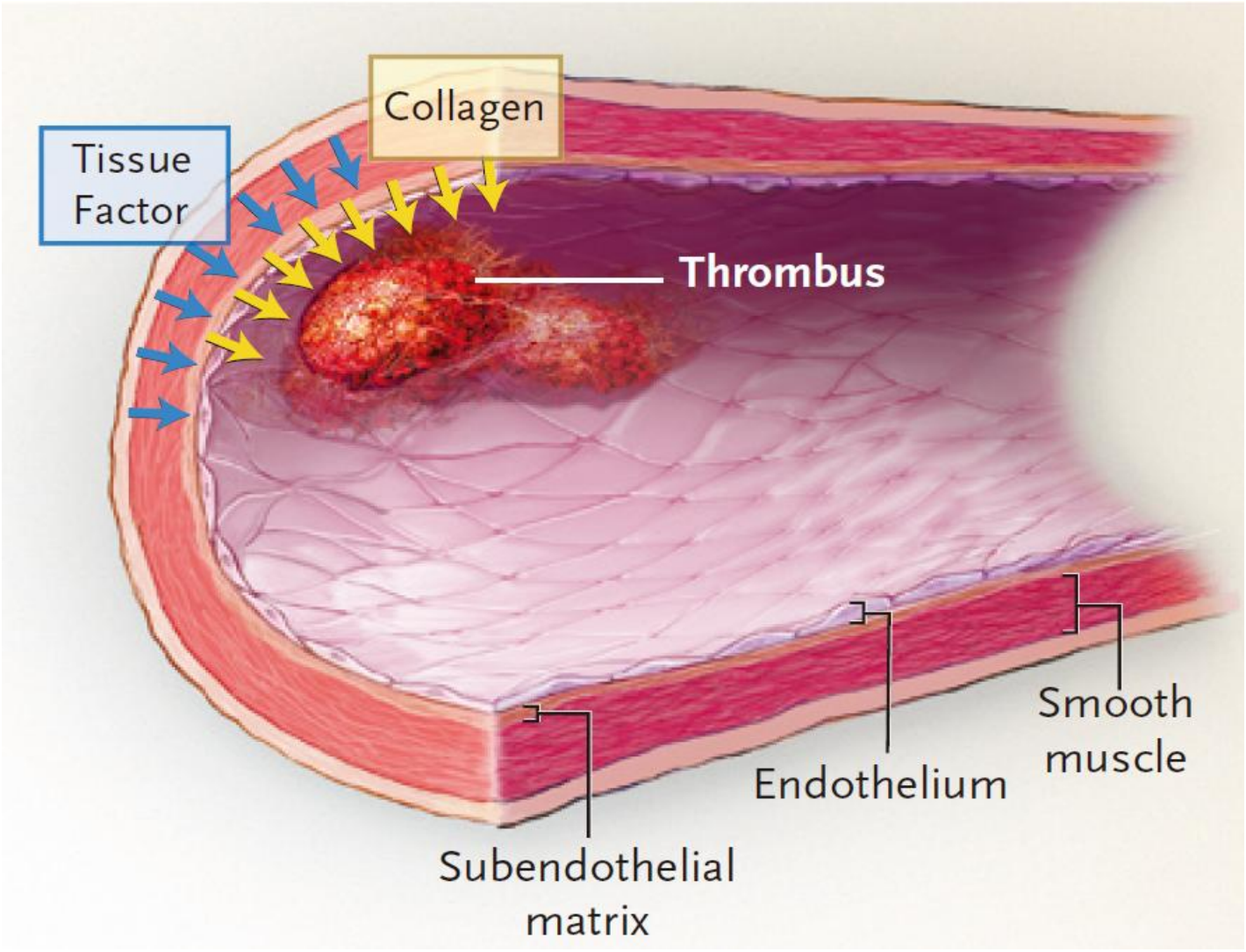
❖ **세포자멸(apoptosis)** 혹은 **세포활성(cellular activation)**에 대한 반응으로 혈소판, 백혈구, 적혈구 및 내피세포의 원형질막(plasma membrane)으로부터 유리

❖ Microparticles은 **염증(inflammation), 응고(coagulation) 및 혈관기능(vascular function)**에 역할을 할 것으로 추정

❖ **circulating tissue factor(TF)의 주된 운반자(carrier)**이자 **혈관내 혈전증(intravascular thrombosis)의 중요한 개시자(initiator)**의 역할

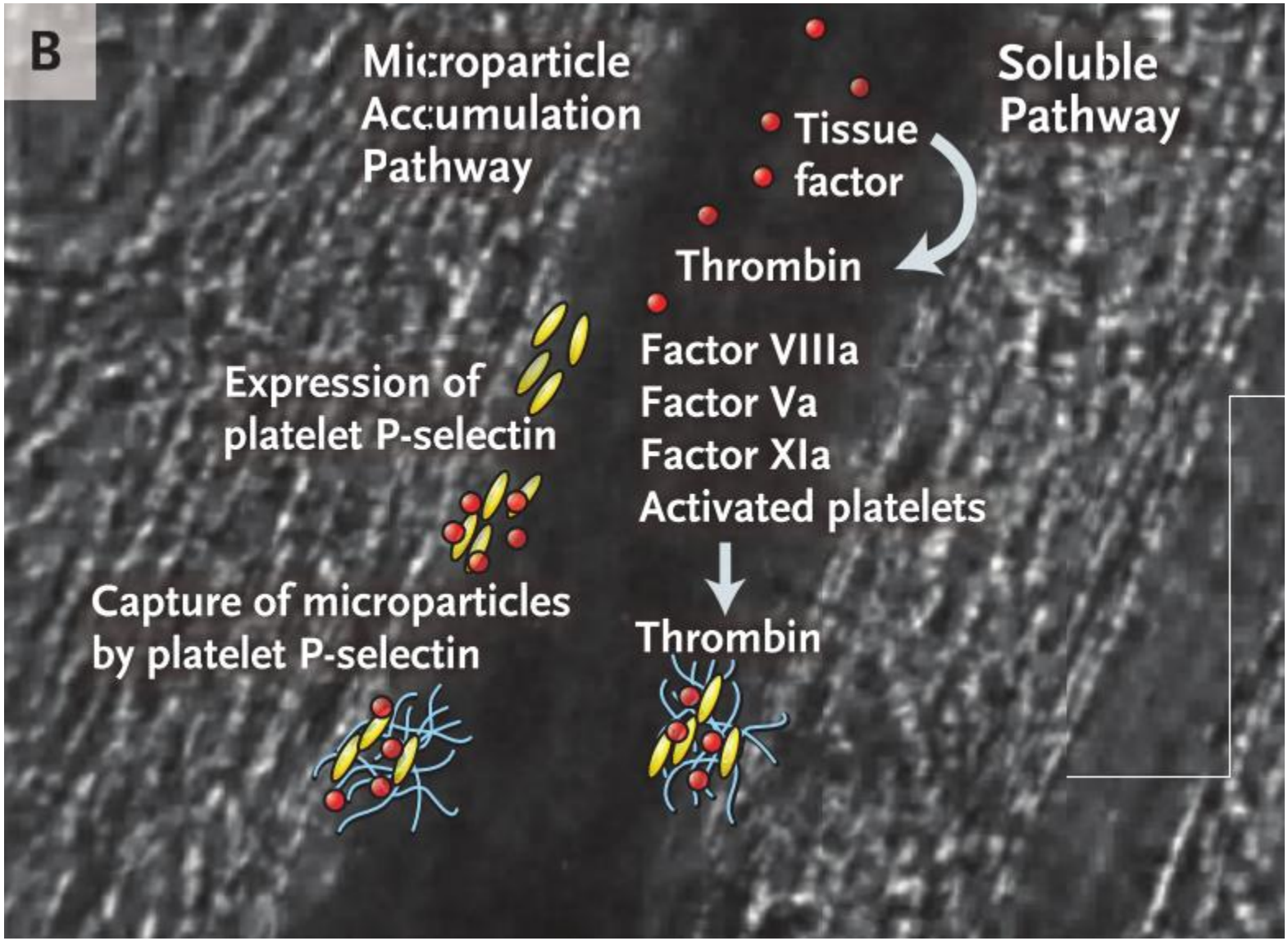
Thromb Res 2011;127:473-7

Response to vascular injury



N Engl J Med 2008;359:938-49

Microparticles



N Engl J Med 2008;359:938-49

Other biomarkers for thrombogenic potentials

- P-selectin
- Factor VIII
- Thrombin Generation
- Fibrin monomer

경청해 주셔서 감사합니다