Coronary Artery Disease (CAD) and Diltiazem

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Contents

The Mechanism of Diltiazem
: Anti-Ischemia

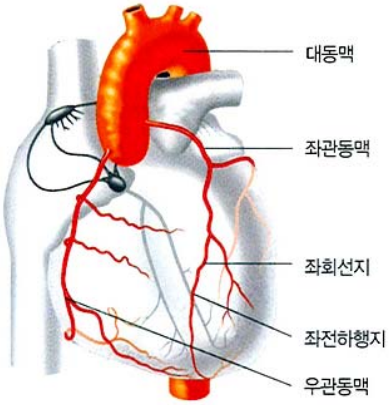
Compared of CCB-CV Effects

	DHP Nifedipine	Benzodiazepine Diltiazem	Phenylalkylamine Vasolan	2nd generation DHP Amlodipine
Coronary dilation	+++	++	+	+++
Conducting System Inhibition	±	+	++	±
Heart Rate	↑	↓	↓	→
Peripheral Vasolidation	++	+	+	++

Nikkei Medical. 2001

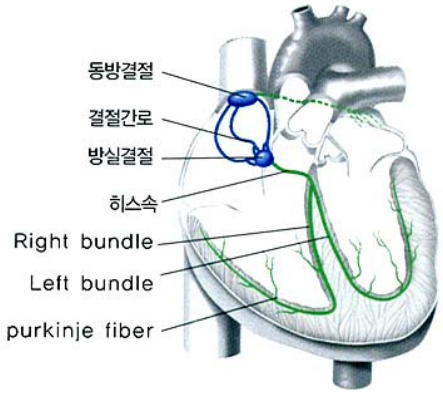
Mechanisms of Diltiazem

관상동맥



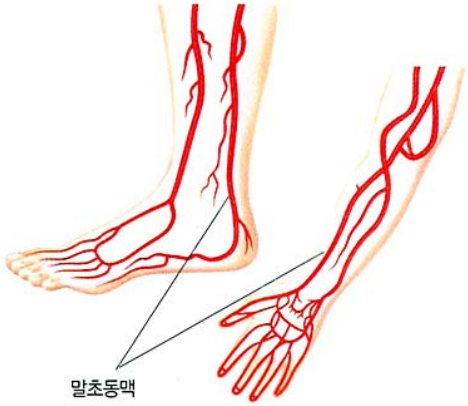
관동맥 확장
Ca^{2+} 유입을 억제하여
관연축 예방

자극생성·전도계



동방결절, 방실결절에
작용, 심박수를 감소시켜
심실의 확장시간 연장

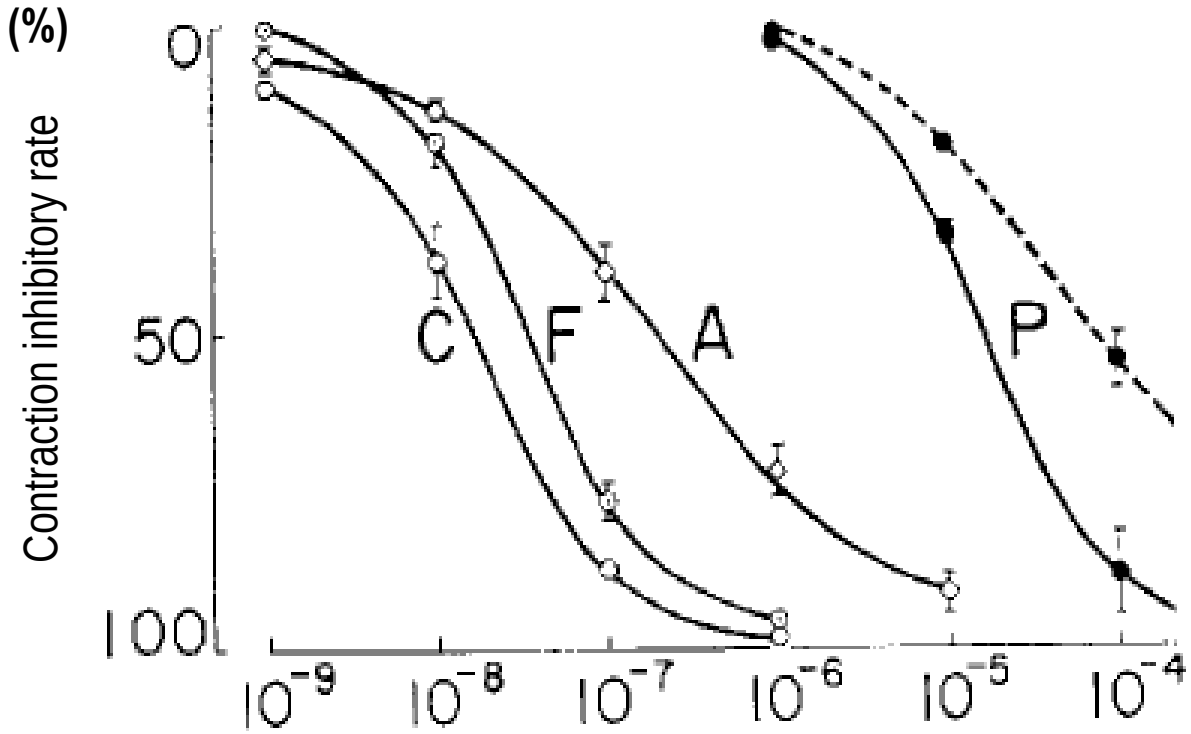
동맥



말초동맥 확장

Diltiazem : Selective Coronary Dilating Effect

Diltiazem acts on coronary artery at lower dose

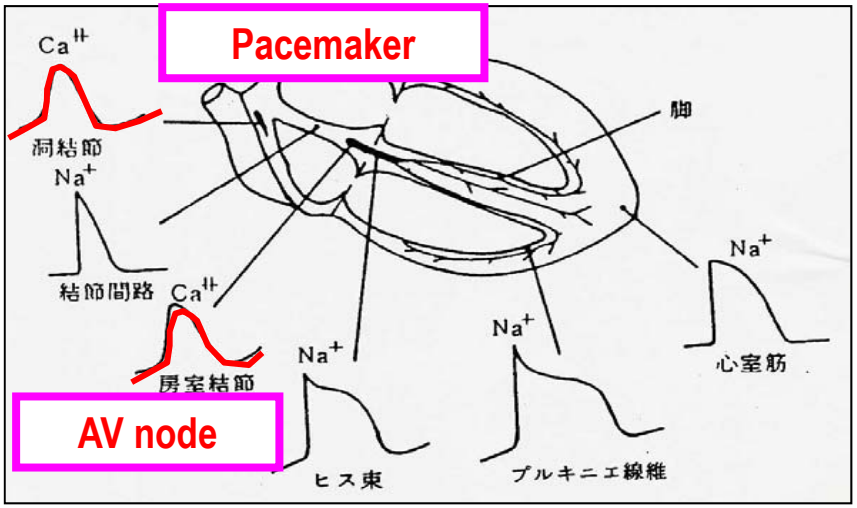


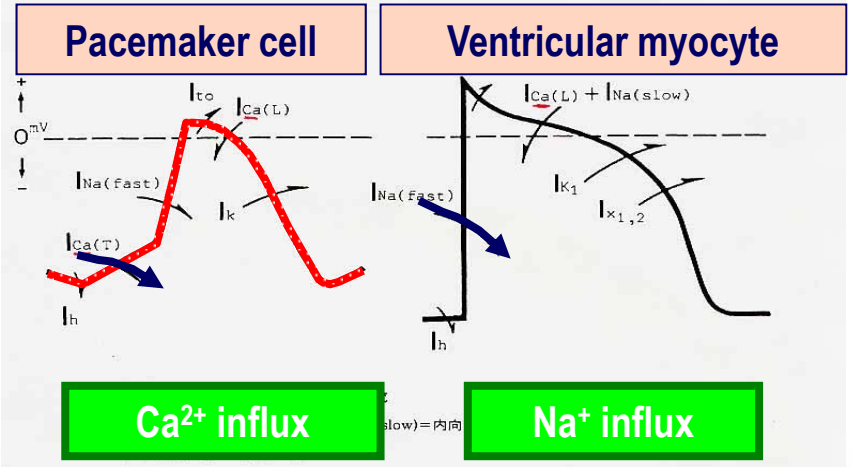
C: Coronary artery
F: Femoral artery
A: Aorta
P: Papillary muscle

Methods: After coronary artery, aorta and myocardium (papillary muscle) isolated from rabbits were contracted by ouabain (10^{-6} M), various concentrations of diltiazem were added to *in vitro* culture and contraction inhibitory rates were measured.

H. Nakajima: Jpn J Pharmacol **27**, 910 (1977)

Diltiazem : Anti-ischemia by mechanism of SA,AV





In sinus node (pacemaker cells) and stimulus conducting pathway (atrioventricular node), Ca^{2+} influx induces action potential.

Diltiazem inhibits Ca^{2+} influx in pacemaker cell and AV node.

Reduction in Heart Rate!

Diltiazem : Endocardial blood flow

Decreased heart rate extends cardiac diastole and makes coronary blood flow reach endomyocardial layer which tends to be ischemic.

Diltiazem decrease HR

▼

Extend the time of diastole

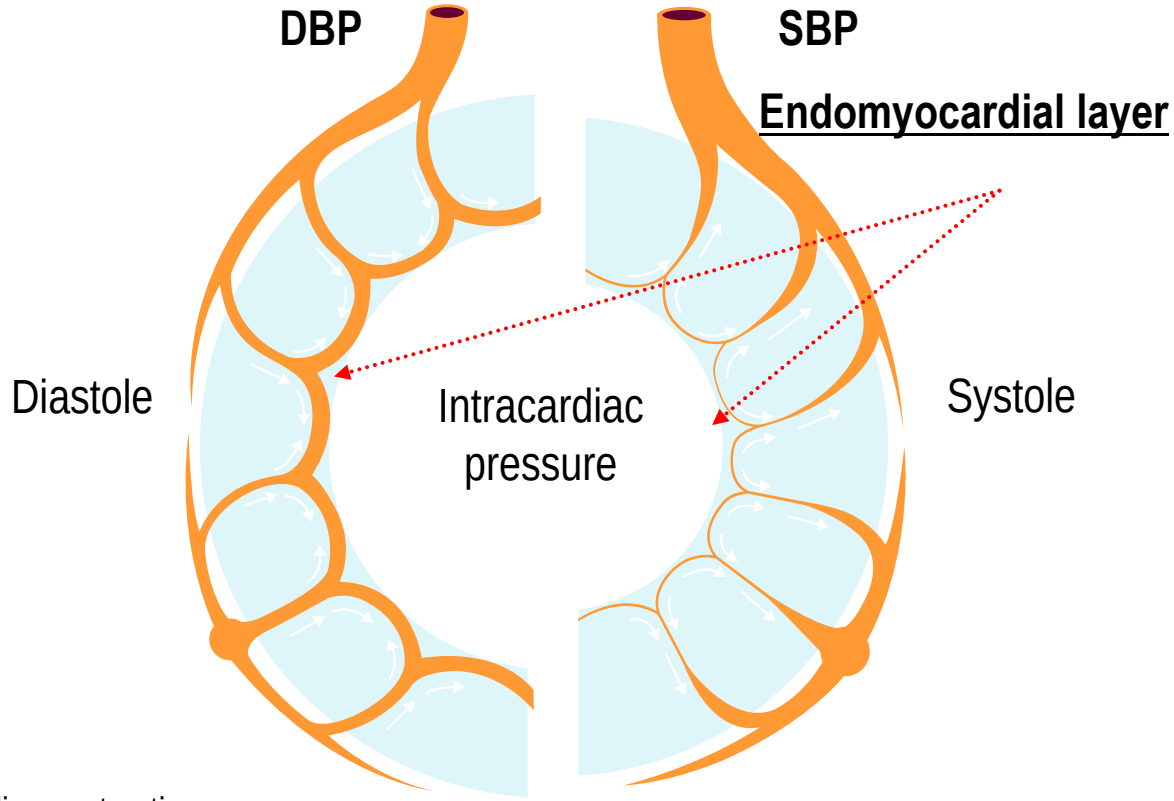
▼

Increase endocardial blood flow

▼

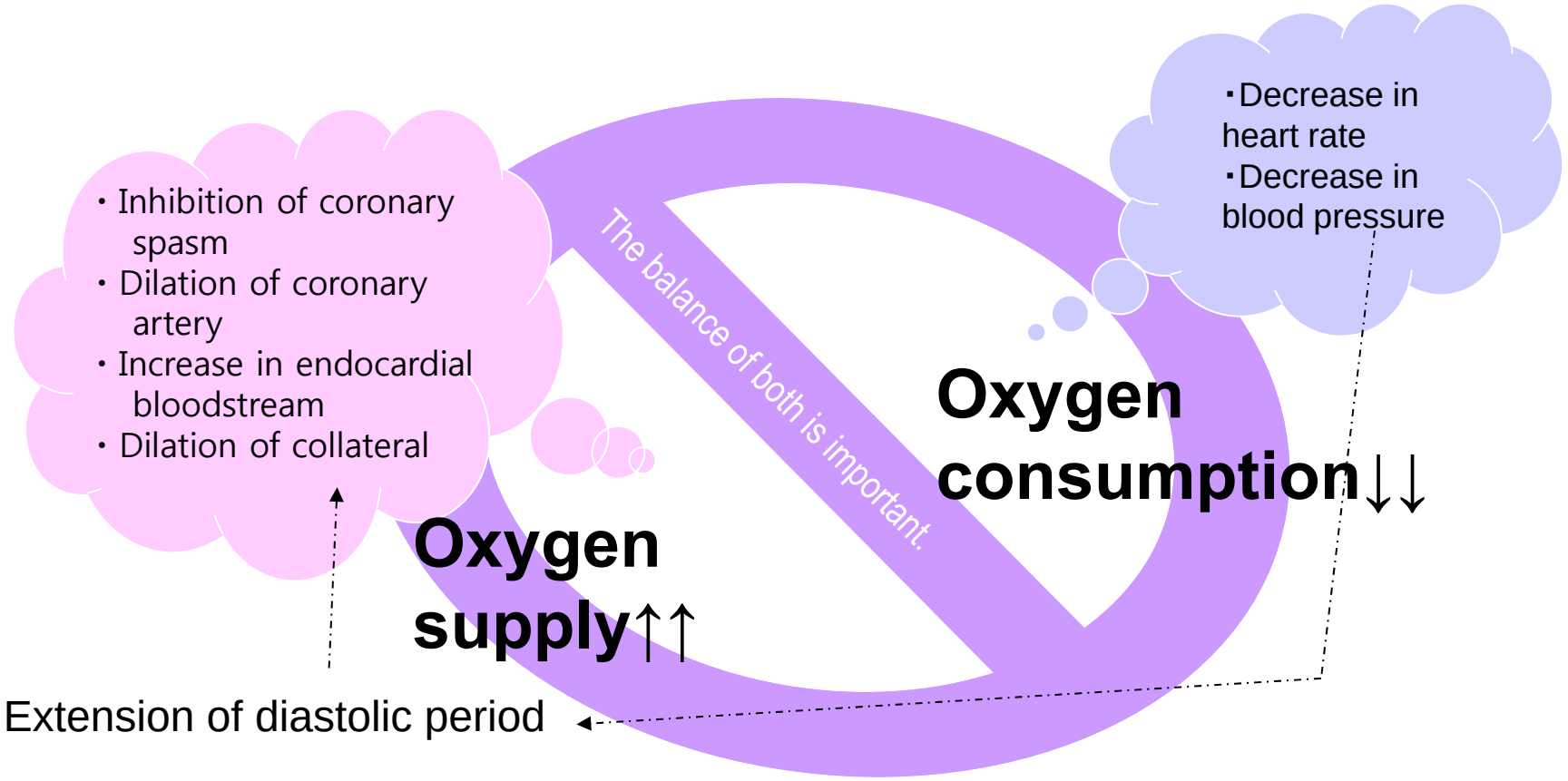
improvement in

myocardial ischemia



- In systole, intracardiac pressure caused by cardiac contraction oppresses coronary artery in the endocardial layer, thus coronary bloodstream temporarily refluxes and decreases.
- In diastole, intracardiac pressure decreases and coronary blood flow is maintained.

Diltiazem : O_2 Balance

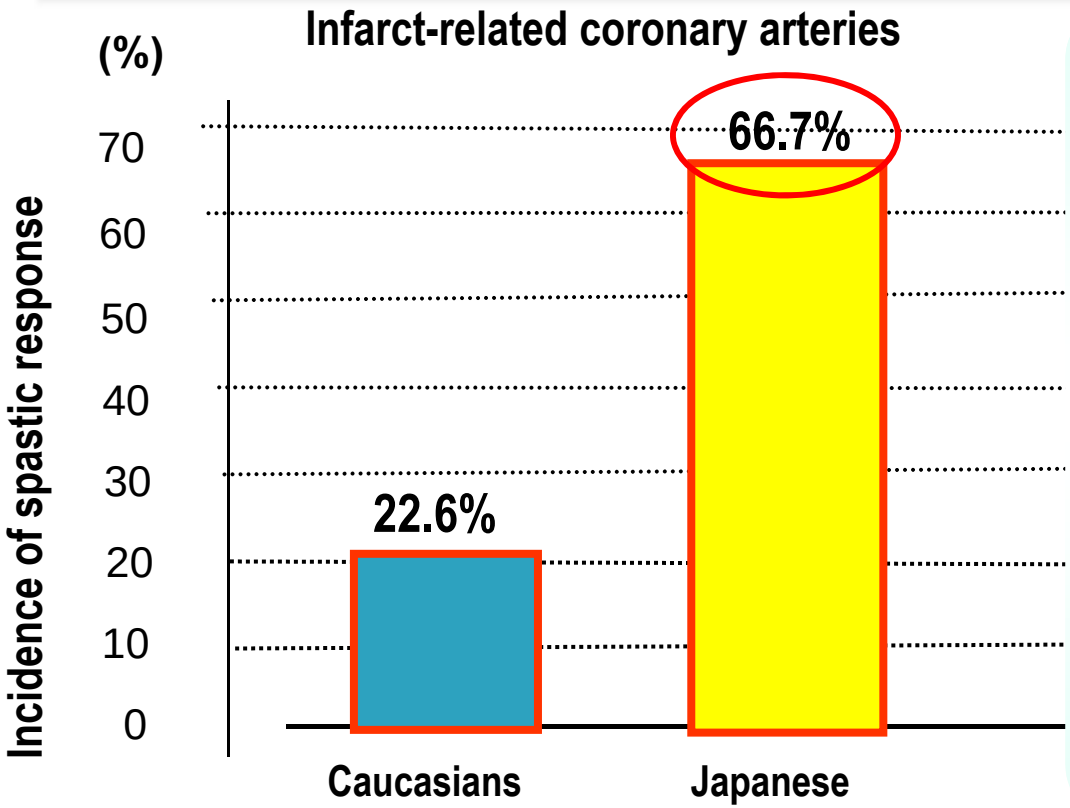


・For ischemic heart disease: Improvement in anginal pain of various angina
・For hypertension with cardiac complaint (palpitation, chest discomfort)

Coronary Spasm

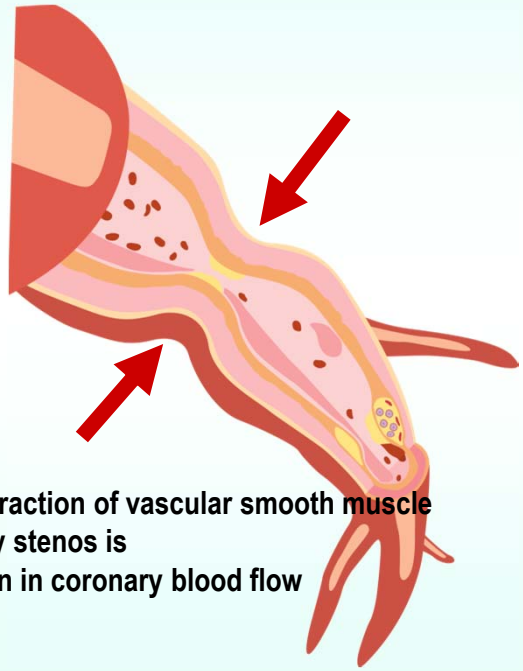
Onset time	Frequent from late at night to early morning
Pathogenesis	Pathogenic mechanism remains to be elucidated, so the pathogenesis is also unknown. However, enhanced coronary vascular tonus is considered to be related because of decreased sympathetic nerve activity and increased parasympathetic nerve activity late at night. [Two theories of pathogenic mechanism of coronary spasm] • Kumamoto Unit theory: Coronary endothelial NO dysfunction • Kyusyu/Kobe Unit theory: Hyper responsiveness of coronary smooth muscle

Coronary Spasm



Subjects: AMI patients (Japanese and Caucasian)
※Coronary spasm was induced by acetylcholine.

Coronary spasm



Hyperconstraction of vascular smooth muscle
→ coronary stenos is
→ reduction in coronary blood flow

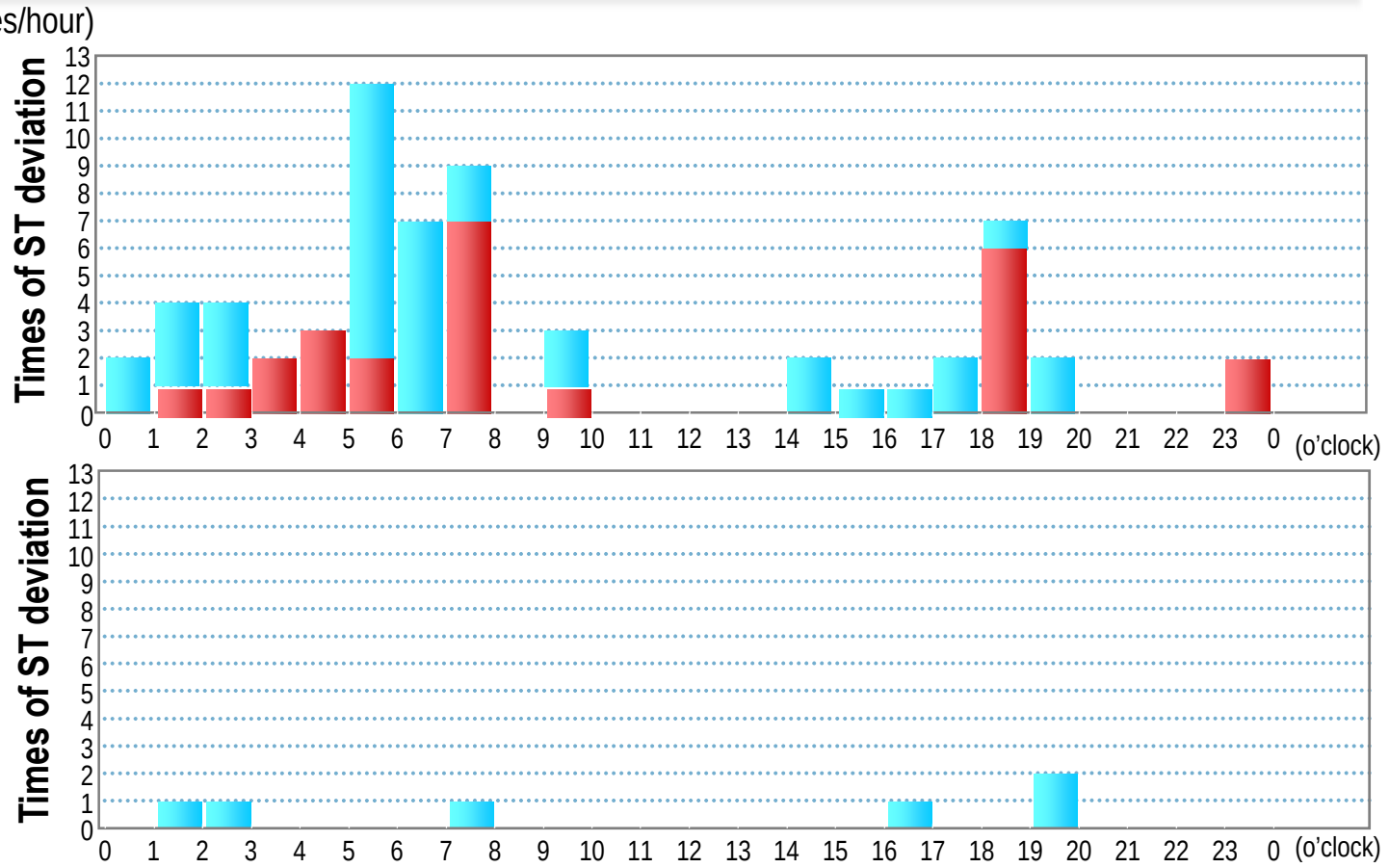
In oriental people, prevention of coronary spasm is important!

C. Pristipino, et al.: Circulation. 101, 1102 (2000)

Diltiazem : Coronary Spasm & Variant Angina

Observation period

Treatment period



Subjects: 11 variant angina patients with ST deviation
Methods: 100-200 mg of Herben R (QD) were administered after dinner for 4 weeks, and ST segments were analyzed based on Holter monitor record.

CARDIOANGIOLOGY 26, 327 (1989)

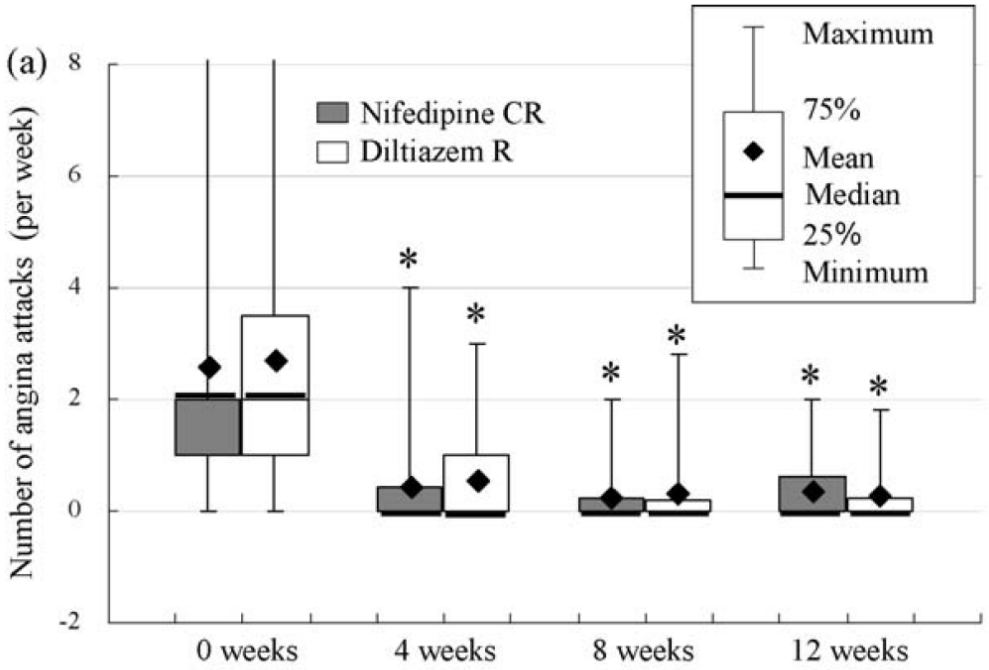
Original article

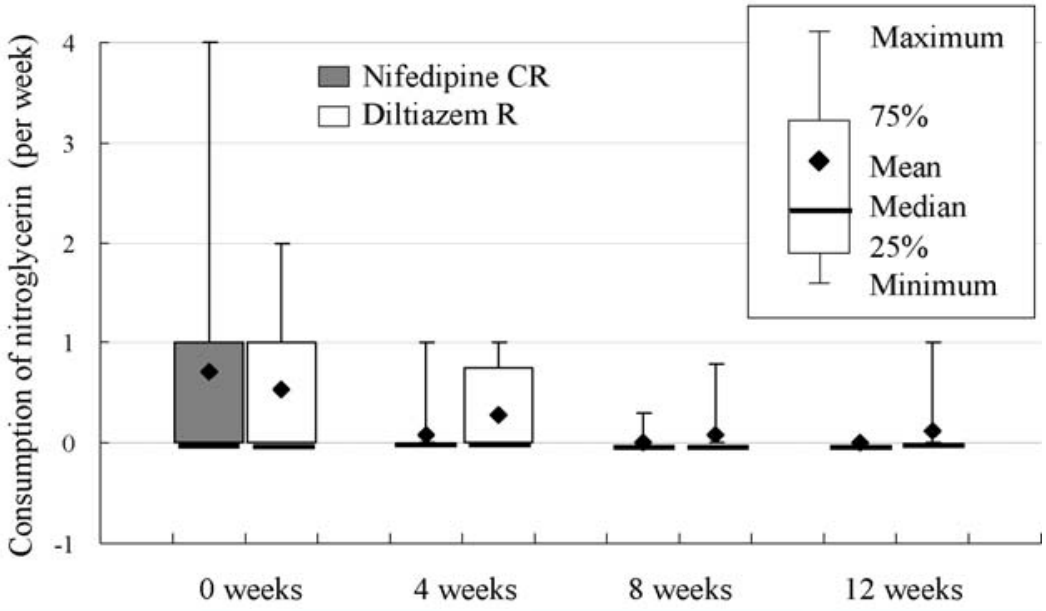
Comparison of the effects of long-acting nifedipine CR and diltiazem R in patients with vasospastic angina: Aomori coronary spastic angina study

Takumi Higuma (MD)[a], Koichi Oikawa (MD)[a], Takeshi Kato (MD)[b], Yasuhiro Mori (MD)[b], Takeshi Kudo (MD)[c], Takeru Yamamoto (MD)[c], Yoshiki Hoshi (MD)[d], Kunihiko Kameda (MD)[d], Naoyuki Suto (MD)[e], Norio Fujita (MD)[f], Yoichi Inokubo (MD)[g], Atsushi Konta (MD)[h], Tomohiro Osanai (MD)[a], Ken Okumura (MD,FJCC)[a,*]

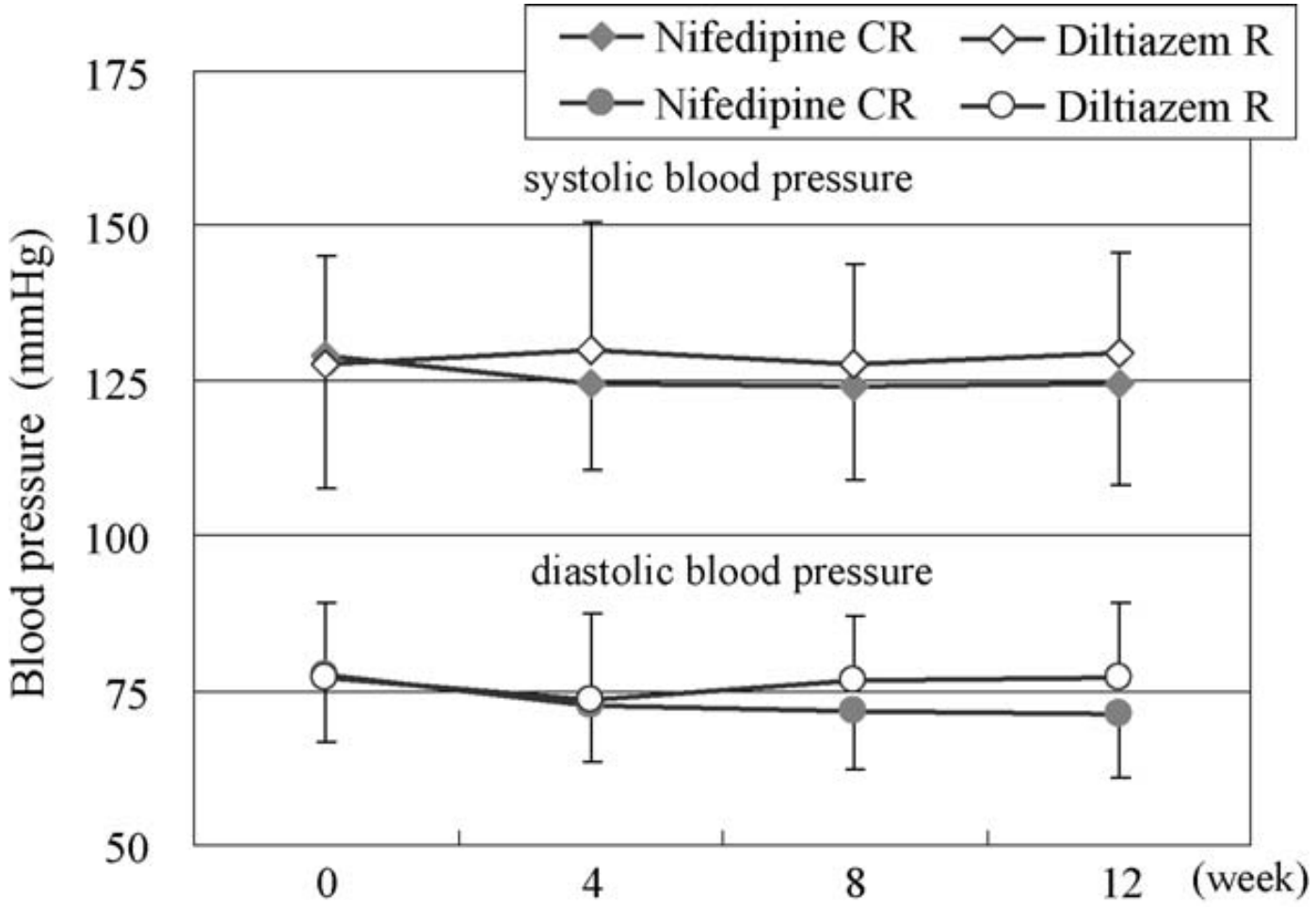
Diltiazem vs. Nifedipine
In variant angina

Journal of Cardiology (2010) 56, 354—360

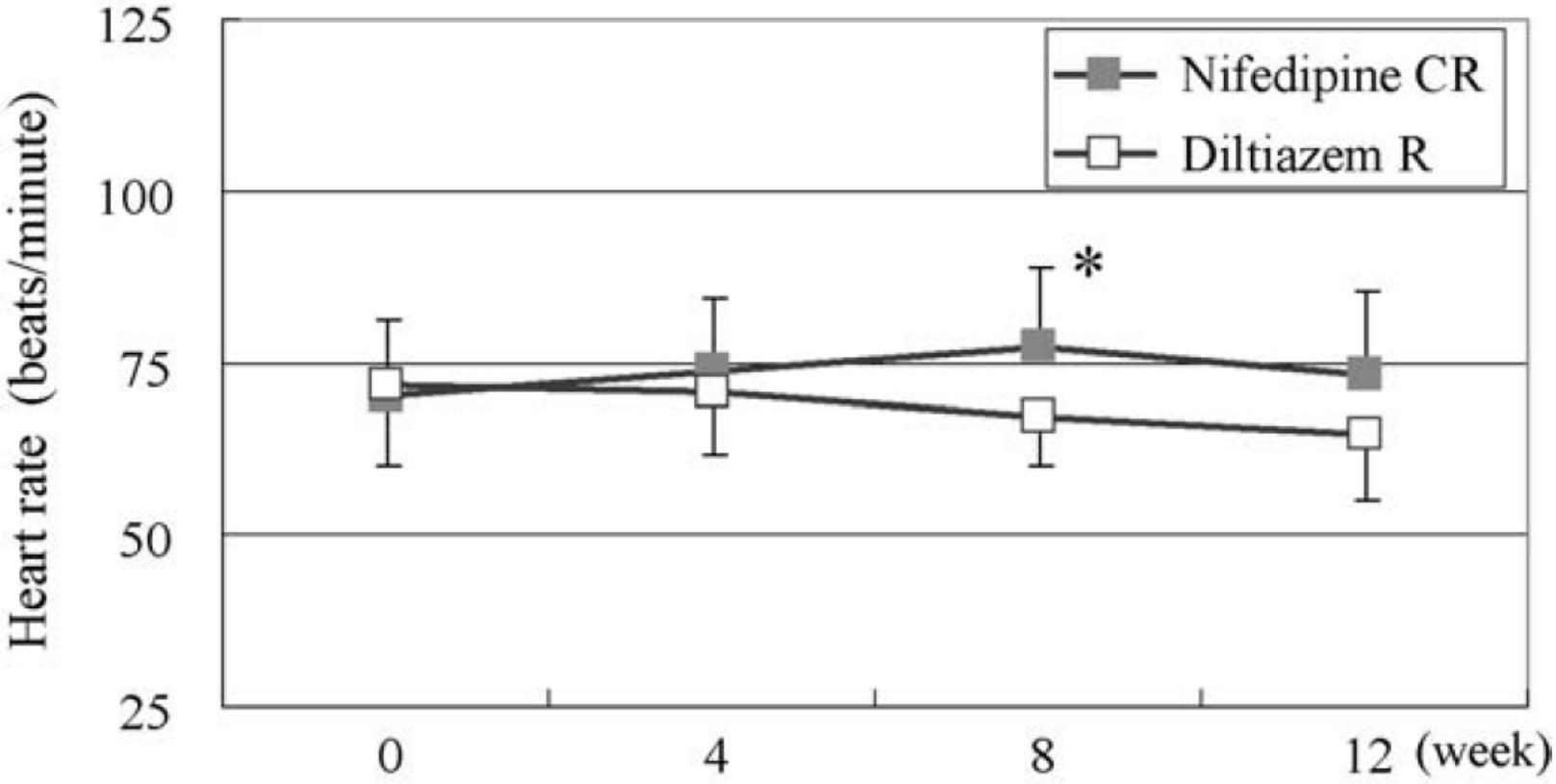

(a)
Number of angina attacks (per week)
8
6
4
2
0
-2
Nifedipine CR
Diltiazem R
Maximum
75%
Mean
Median
25%
Minimum
*
0 weeks
4 weeks
8 weeks
12 weeks


Consumption of nitroglycerin (per week)
4
3
2
1
0
-1
Nifedipine CR
Diltiazem R
Maximum
75%
Mean
Median
25%
Minimum
0 weeks
4 weeks
8 weeks
12 weeks

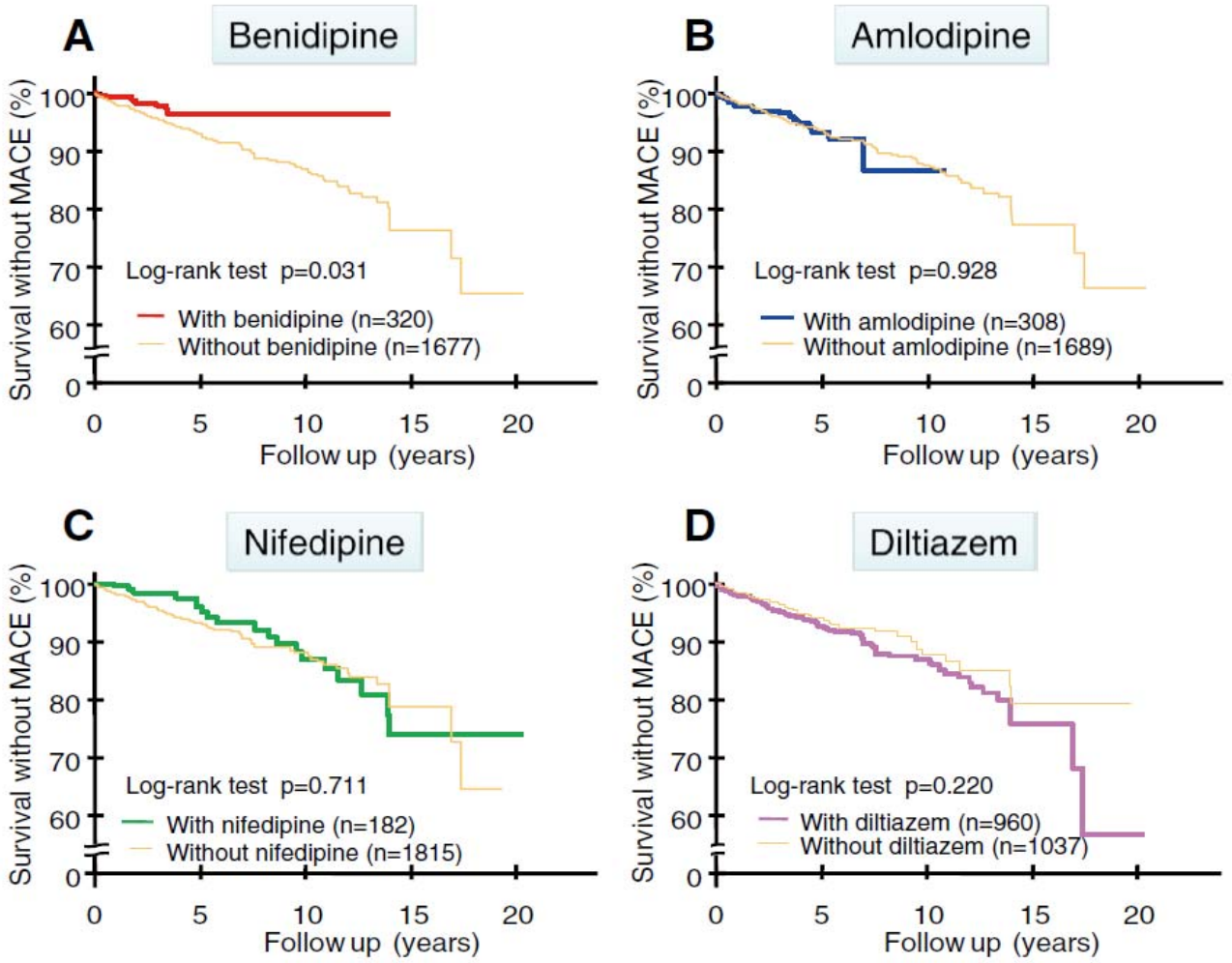
Changes in systolic and diastolic blood pressures in each group during the study period. No significant change was observed in either group



Changes in heart rate in each group. The heart rate remained unchanged until 4 weeks after the start of treatment, but was increased significantly after 8 weeks in the nifedipine



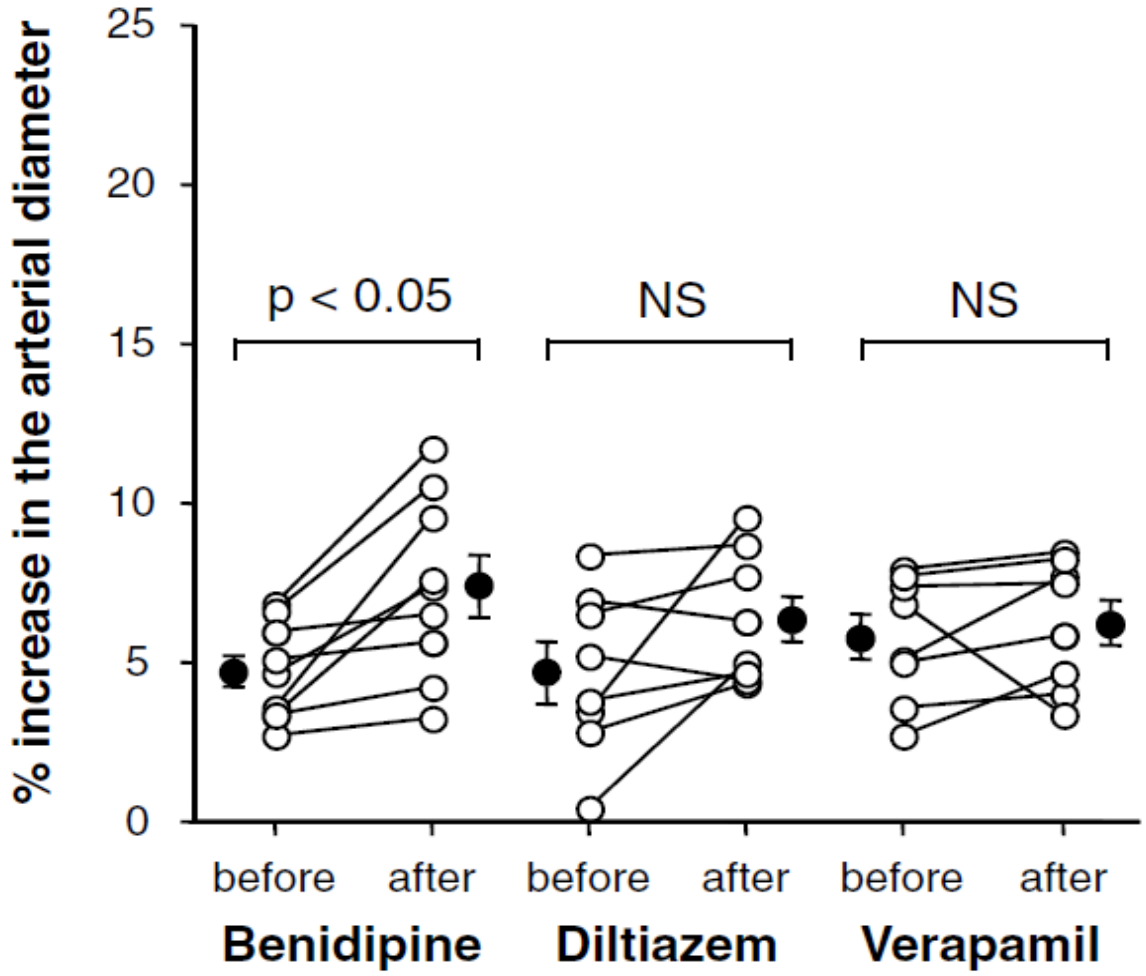
Major adverse cardiovascular events (MACE)-free survival in vasospastic angina patients treated with each calcium channel blocker (n=1,997 in total). (A) benidipine, (B) amlodipine, (C) nifedipine, and (D) diltiazem



Circ J 2010; 74: 1943 – 1950

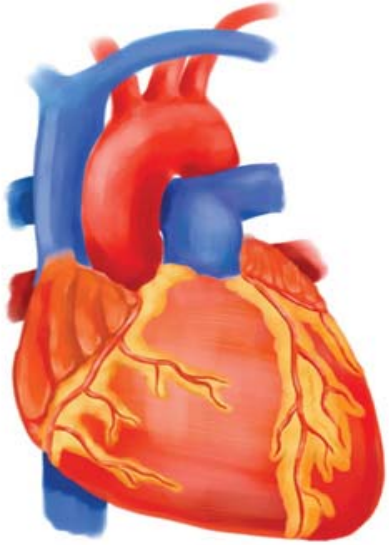
	No. of pts.	MACE		Non-adjustment			Adjustment*		
		n	(%)	Hazard rate		p value	Hazard rate		p value
					0.1 1 10			0.1 1 10	
Benidipine	320	8	(2.5)	0.46		0.035	0.41		0.016
Amlodipine	308	17	(5.5)	1.02		NS	0.98		NS
Nifedipine	182	19	(10.4)	0.91		NS	0.88		NS
Diltiazem	960	83	(8.6)	1.23		NS	1.15		NS

Percent increase in vessel diameter induced by flow-mediated dilatation (FMD) in patients with coronary spastic angina before and after 3-month treatment with benidipine, diltiazem or verapamil



Circ J 2009; 73: 713 – 717

Diltiazem : Angina Pectoris



- Coronary vasodilation
- Antispasmatic
- Heart rate reduction
- Reduction of afterload

Current Management of CAD

Acute Therapy

- Oxygen, Bed rest, ECG Monitoring
- Nitroglycerin
- Beta-Blocker
- ACE Inhibitor
- Anti-platelet Therapy
- Anti-coagulant Therapy

Maintenance Therapy

- Antiplatelet Therapy
- Beta-Blocker
- **Calcium Channel Blocker**
- Lipid Lowering Agent
- ACE Inhibitor

Large-Scale Clinical Trials of Diltiazem

For patients with experience of myocardial infarction

- DRS : Non-Q-wave myocardial infarction / n=576 (N Eng J Med, 1986)
- MDPIT : Myocardial infarction / n=2,466 (N Eng J Med, 1988)
- INTERCEPT : Myocardial infarction treated with thrombolytic therapy / n=874 (Lancet, 2000)

For patients with idiopathic dilated cardiomyopathy

- DiDi trial : DCM / n=186 (Circulation, 1996)

For patients with unstable angina

- DAISY : UAP / n=129 (Lancet, 1995 , Eur Heart J 1998)

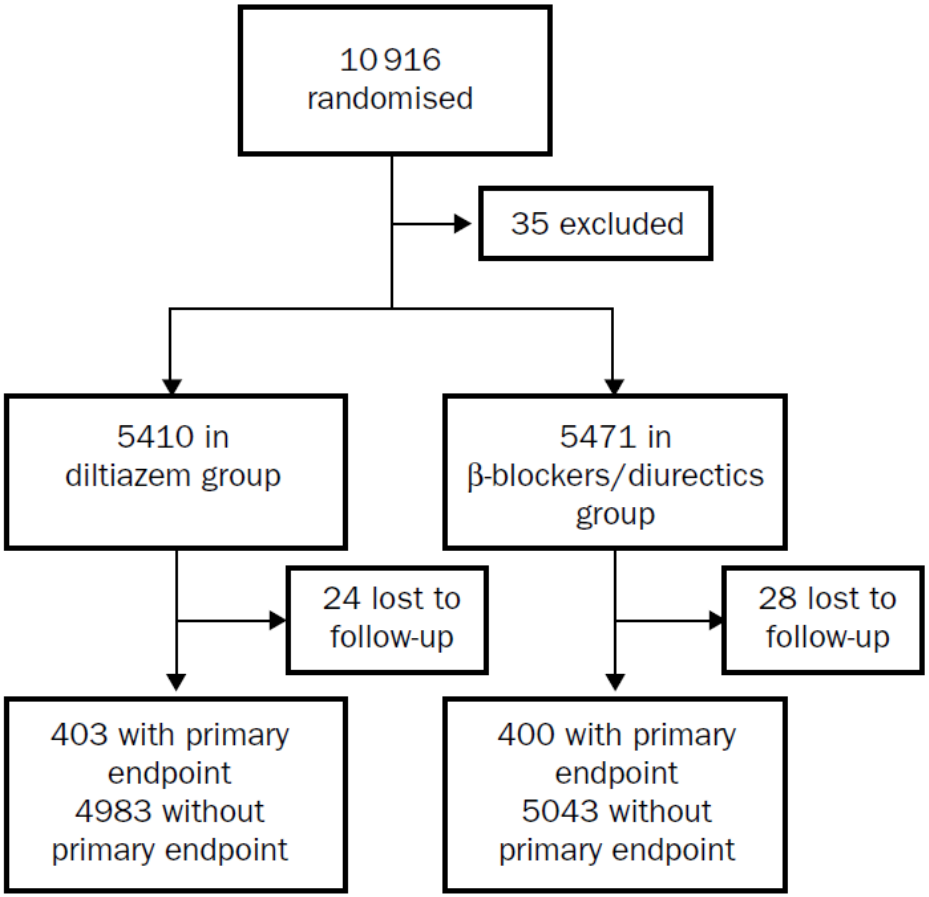
For patients with hypertension

- NORDIL : Hypertension / n=10,881 (Lancet, 2000)

Hypertension

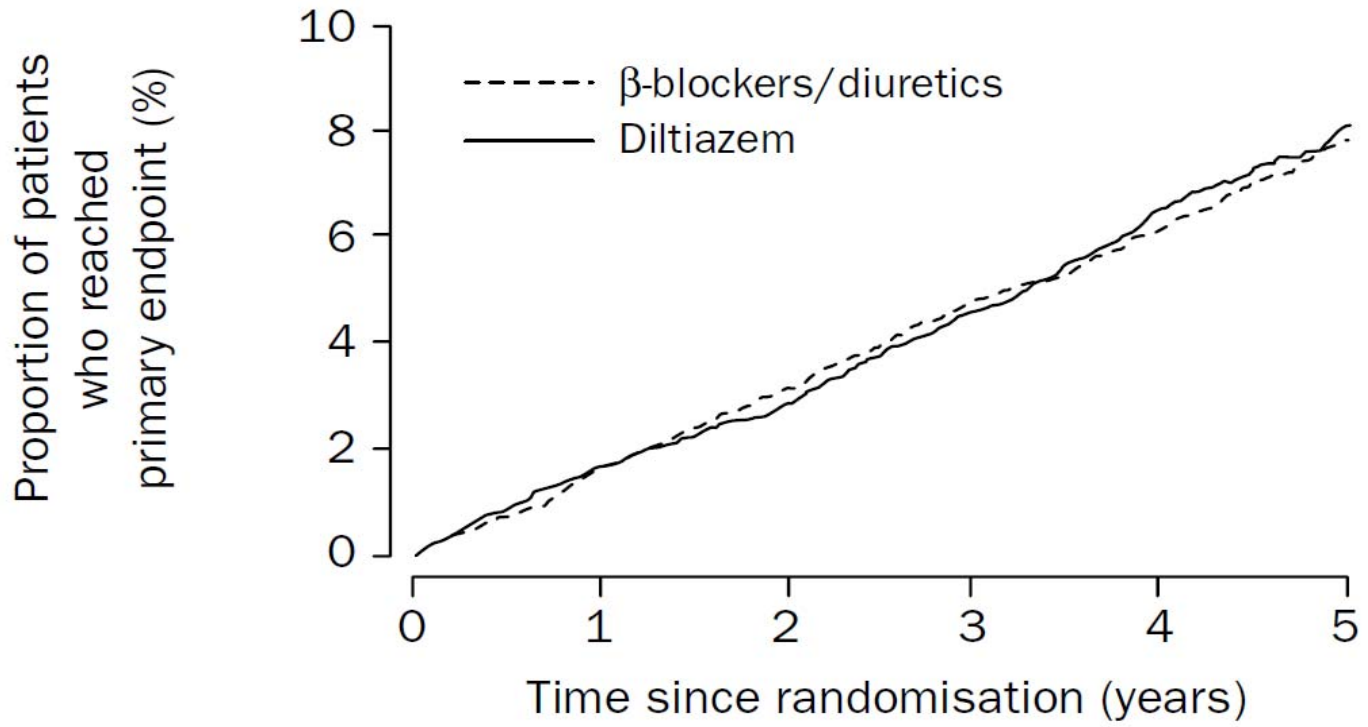
Randomised trial of effects of calcium antagonists compared with diuretics and β-blockers on cardiovascular morbidity and mortality in hypertension: the Nordic Diltiazem (NORDIL) study

*Lennart Hansson, Thomas Hedner, Per Lund-Johansen, Sverre Erik Kjeldsen, Lars H Lindholm, Jan Otto Syvertsen, Jan Lanke, Ulf de Faire, Björn Dahlöf, Bengt E Karlberg, for the NORDIL Study Group**



Lancet 2000; 356: 359–65

Combined primary endpoint was fatal and non-fatal stroke, myocardial infarction, and other cardiovascular death



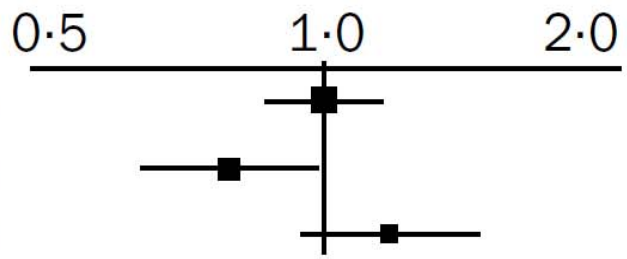
Patients at risk

β-Blockers/ diuretics	5471	5363	5244	4975	3486	1921
Diltiazem	5410	5299	5217	4932	3409	1865

Lancet 2000; 356: 359–65

Combined primary endpoint was fatal and non-fatal stroke, myocardial infarction, and other cardiovascular death

	Relative risk* (95% CI)	p
Primary endpoint	1·00 (0·87–1·15)	0·97
Stroke, fatal and non-fatal	0·80 (0·65–0·99)	0·04
Myocardial infarction, fatal and non-fatal	1·16 (0·94–1·44)	0·17

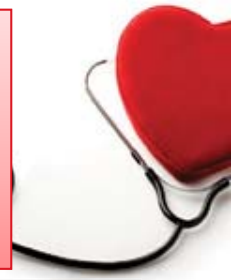


Adverse event	Diltiazem group	Diuretics and β-blocker group
Dizziness	505 (9·3%)	488 (8·9%)
Arthralgia	418 (7·7%)	391 (7·1%)
Headaches*	458 (8·5%)	311 (5·7%)
Chest discomfort	310 (5·7%)	322 (5·9%)
Coughing	303 (5·6%)	298 (5·4%)
Fatigue*	239 (4·4%)	353 (6·5%)
Back pain	253 (4·7%)	298 (5·4%)
Depression	198 (3·7%)	186 (3·4%)
Abdominal pain	187 (3·5%)	186 (3·4%)
Dyspnoea†	157 (2·9%)	212 (3·9%)
Myalgia	172 (3·2%)	188 (3·4%)
Impotence*	126 (2·3%)	202 (3·7%)

Lancet 2000; 356: 359–65

The Role of Diltiazem
: Unstable Angina

Anti-inflammatory action of diltiazem in patients with unstable angina



Postgrad Med J 2006;**82**:594–597. doi: 10.1136/pgmj.2006.045302

Background and Aims: Plasma concentrations of anti-inflammatory cytokine interleukin 10 (IL10) have been shown to be decreased in patients with unstable angina (UA) suggesting that reduced concentrations of IL10 may favour plaque instability and the development of acute coronary syndromes. Diltiazem has been shown to exert beneficial effects in patients with acute coronary syndrome. However, the potential influence of diltiazem on the anti-inflammatory cytokine IL10 in patients with UA has not been investigated. This study was designed to find out the effects of diltiazem on IL10 in UA patients.

Methods and Results: Thirty patients with UA were divided into two groups: group R and group D (n = 15). Group R was given routine pharmacotherapy for UA, and group D was given routine pharmacotherapy plus diltiazem. Plasma concentrations of IL10 in these groups were measured before the start of the treatment and 28 days after treatment. Plasma concentrations of IL10 in 15 normal subjects (group N) were also measured. Patients with UA had decreased concentrations of IL10 compared with normal group. Four weeks after treatment, plasma concentrations of IL10 significantly increased in group D compared with that before treatment, but the increase in IL10 values in group R was not significant.

Anti-inflammatory action of diltiazem in patients with unstable angina

	Group N	Group R	Group D
Mean age (years)	60 (3)	61 (5)	61 (6)
Men (n)	11 (74%)	12 (80%)	12 (80%)
HTN (n)	6 (40%)	10 (67%)*	11 (74%)*
DM (n)	4 (27%)	5 (34%)	5 (34%)
Hyperlipidaemia (n)	3 (20%)	3 (20%)	2 (14%)
Current smoking (n)	3 (20%)	9 (60%)*	10 (67%)*
Echocardiography			
Diameter of left atrium (mm)	31.05 (4.21)	32.14 (4.30)	31.23 (4.02)
Diameter of left ventricle (mm)	48.25 (7.45)	49.34 (8.06)	48.39 (8.19)
Ejection fraction (%)	60.12 (11.42)	59.29 (12.20)	58.34 (11.31)

*$p<0.01$ v group N. Data are mean (SD) unless shown otherwise.

Postgrad Med J. 2006 Sep;82(971):594-7.

Anti-inflammatory action of diltiazem in patients with unstable angina

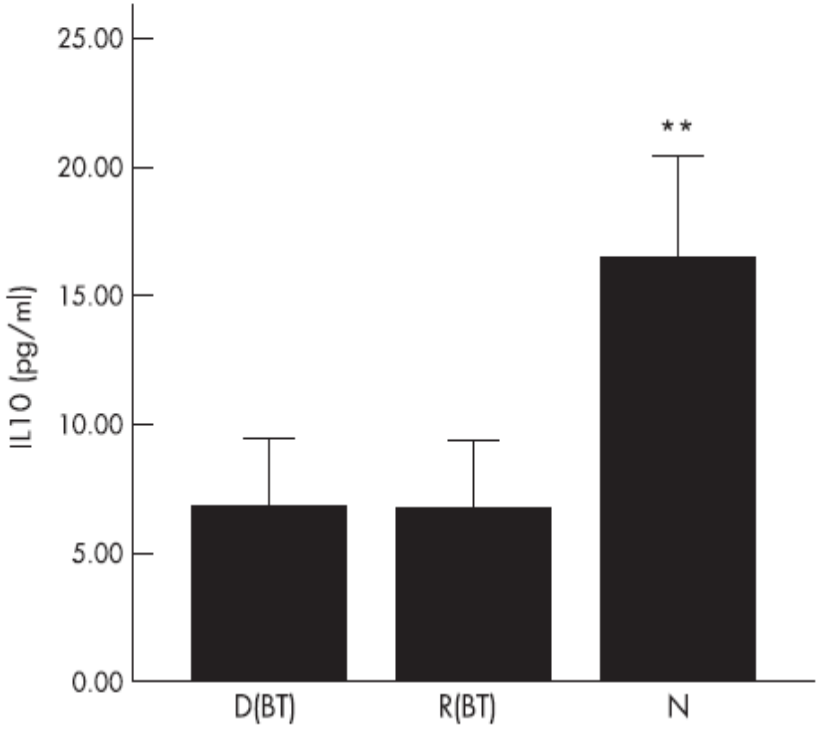


Figure 1 Comparison of IL10 in group R and group D before treatment (BT) with group N. **p<0.01 v R (B) and D (B).

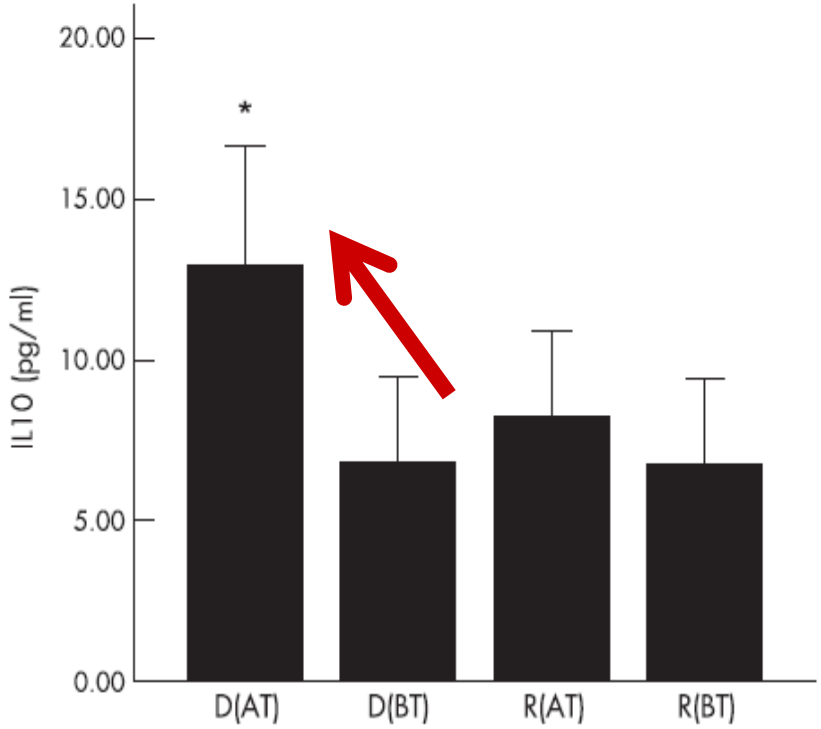


Figure 2 Comparison of IL10 in group D and group R after treatment (AT) with that before treatment (BT). Concentration of IL10 in group R (AT) was not significant (NS) compared with that before treatment R (AT). *p<0.05 v D (B).

Postgrad Med J. 2006 Sep;82(971):594-7.

Long-term follow-up after early intervention with intravenous diltiazem or intravenous nitroglycerin for unstable angina pectoris with early intervention

- **Aims**

In a double-blind randomized trial in unstable angina, it was shown that intravenous diltiazem reduced ischaemic events in the first 48 h after inclusion better than intravenous nitroglycerin. The present study was performed to establish the long-term prognosis of the randomized patients, with respect to their initial treatment assignment.

- **Methods and Results**

One year follow-up data on ischaemic end-points and anti-ischaemic medication were recorded. Results were available for all of the 121 randomized patients. One hundred and sixty-seven primary endpoint events were recorded, of which 54 occurred in the first 48 h and 113 during the follow-up. Survival analysis showed that event-free survival was significantly better in the diltiazem group (45.0%) than in the nitroglycerin group(34.4%), P=0·04. The incidence rate after 48 h and one year for cardiac death are, respectively, 0% and 4.1%. The trend in anti-ischaemic medication was higher in the nitroglycerin group. For beta-blockers, this trend became significant after 12 months (P=0·03).

Eur Heart J. (1998) 19, 1208–1213.

Long-term follow-up after early intervention with intravenous diltiazem or intravenous nitroglycerin for unstable angina pectoris

•***Baseline Characteristics***

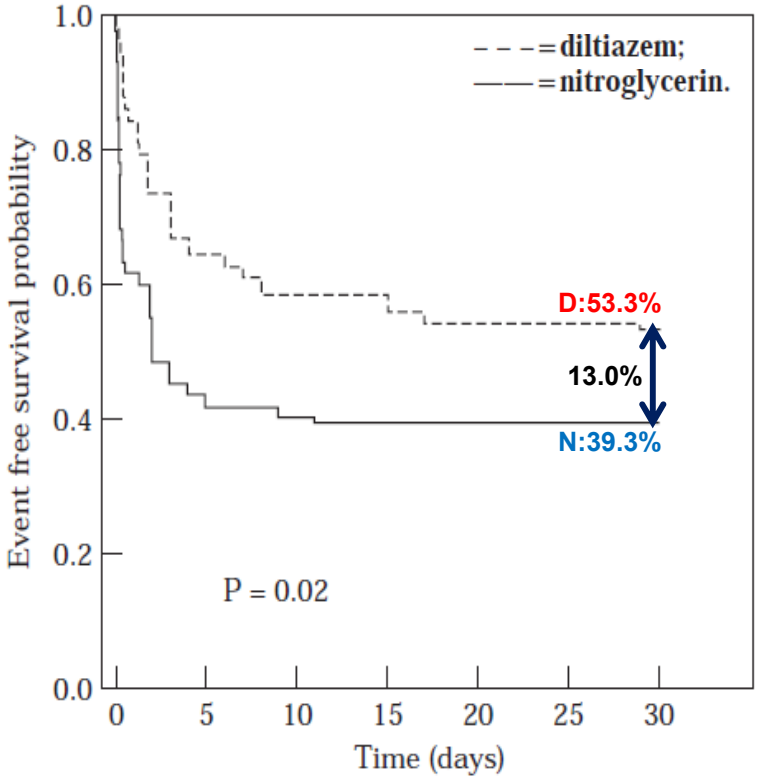
	Nitroglycerin	Diltiazem
Total number	61	60
Age (median+range)	63 (40–79)	65 (40–80)
Sex (M/F)	48/13	38/22
Medical history		
Smoking	34 (55%)	22 (37%)
Hypertension	19 (31%)	24 (40%)
Diabetes	7 (12%)	9 (15%)
Family history of CAD	16 (26%)	17 (28%)
Myocardial infarction	19 (31%)	21 (35%)
PTCA	4 (7%)	9 (15%)
CABG	10 (16%)	5 (8%)
Medication on admission		
Calcium channel blockers	13 (21%)	20 (33%)
Nitrates	16 (26%)	17 (28%)
Beta-blockers	14 (23%)	22 (37%)
ACE-inhibitors	6 (10%)	8 (12%)

There were no statistical differences in any baseline variables. CAD=coronary artery disease;

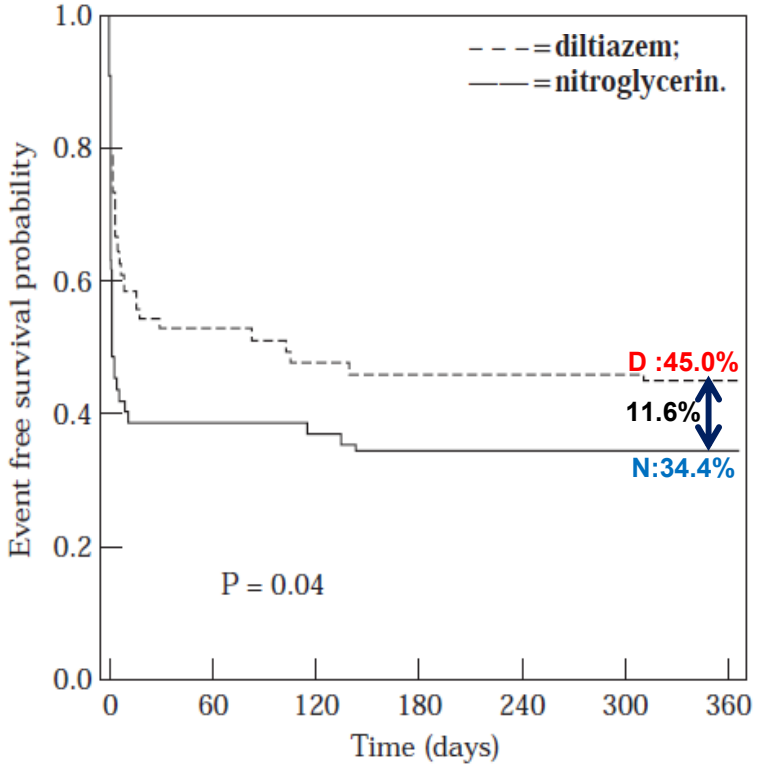
Eur Heart J. (1998) 19, 1208–1213.

Long-term follow-up after early intervention with intravenous diltiazem or intravenous nitroglycerin for unstable angina pectoris

Ischemic end-point free survival during one month follow-up.



Ischemic end-point free survival during one year follow-up.



Eur Heart J. (1998) 19, 1208–1213.

Long-term follow-up after early intervention with intravenous diltiazem or intravenous nitroglycerin for unstable angina pectoris

The number of primary end–point events one year after initial hospitalization

	Nitroglycerin	Diltiazem	
Number of patients	61	60	
First 48 hours			
Death	0	0	
Myocardial infarction	15	8	ns
PTCA	3	2	ns
CABG	0	0	
Refractory angina	18	8	$P<0{\cdot}05$
Composite end-point	25	13	$P=0{\cdot}03$
48 h — one year follow-up			
Death	2	3	ns
Myocardial infarction	5	7	ns
Non-scheduled CABG	7	13	ns
Non-scheduled PTCA	16	9	ns
Unstable angina	30	21	ns
Composite end-point	27	24	ns

Eur Heart J. (1998) 19, 1208–1213.

The Role of Diltiazem
: Myocardial Infarction

Diltiazem in acute myocardial infarction treated with thrombolytic agents: a randomized placebo -controlled trial (INTERCEPT)

Objective

•To study the effect of diltiazem in acute myocardial infarction treated with thrombolytic agents

Countries

•UK, Belgium, Netherlands, Denmark (61centers)

Subject

Acute myocardial infarcti on treated with thromboly tic agents n=874

Design

•Prospective randomized double-blind parallel sequential trial

Primary Endpoint

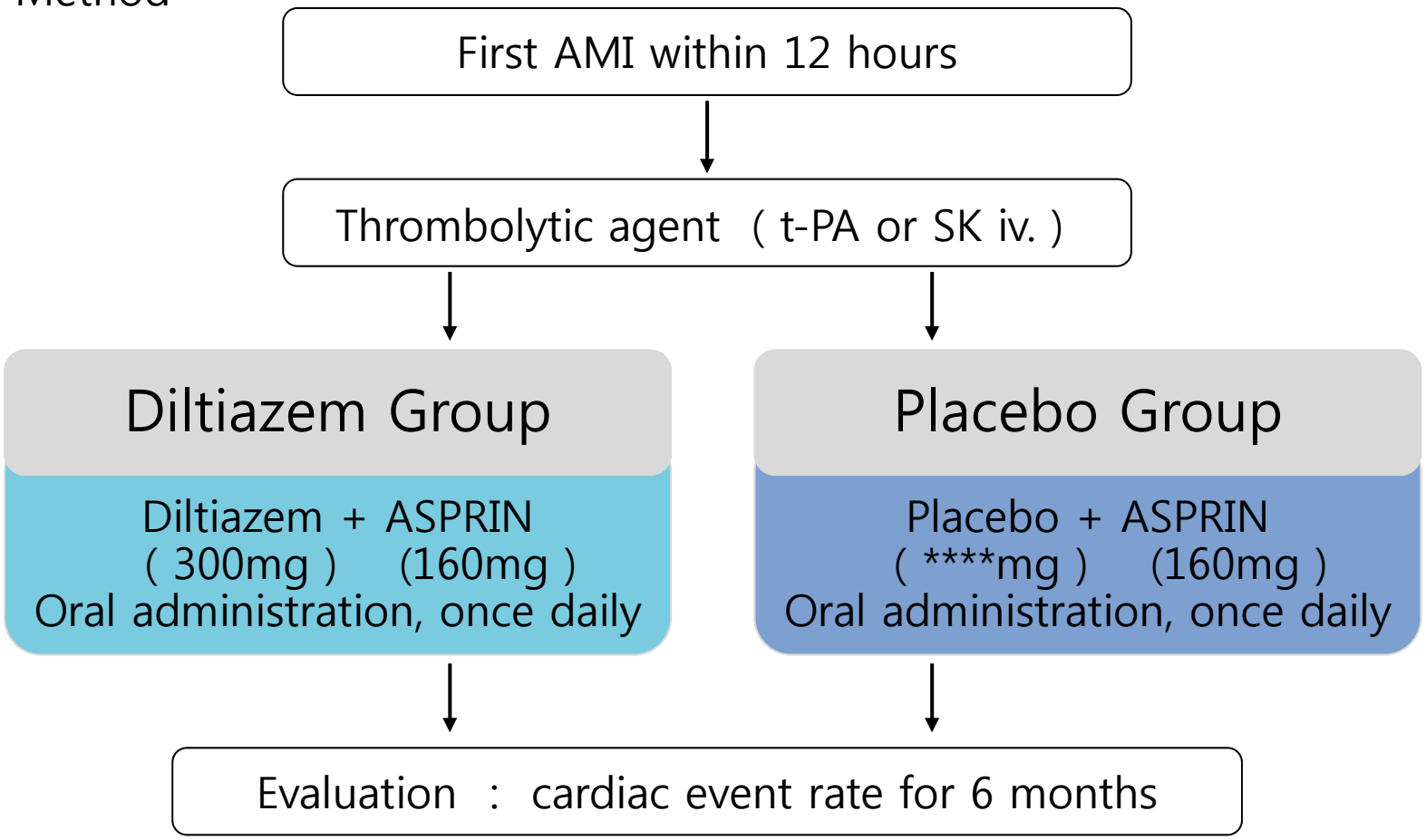
Cardiac death, non-fatal reinfarction, refractory ischemia

Method

•After acute myocardial infarction treated with thrombolytic agent (t-PA or SK intravenous injection) within 12 hours
- Placebo group(n=444): Placebo + Aspirin 160mg
- Diltiazem group(n=430) : Diltiazem 300mg + Aspirin 160mg

Diltiazem in acute MI treated with thrombolytic agents : a randomized placebo-controlled trial (INTERCEPT)

- Method



The Lancet 2000;355,1951-1956

Diltiazem in acute MI treated with thrombolytic agents : a randomized placebo-controlled trial (INTERCEPT)

Diltiazem showed a 21% reduction of the primary endpoint (NS), and significantly reduced non-fatal cardiac events (p=0.05)

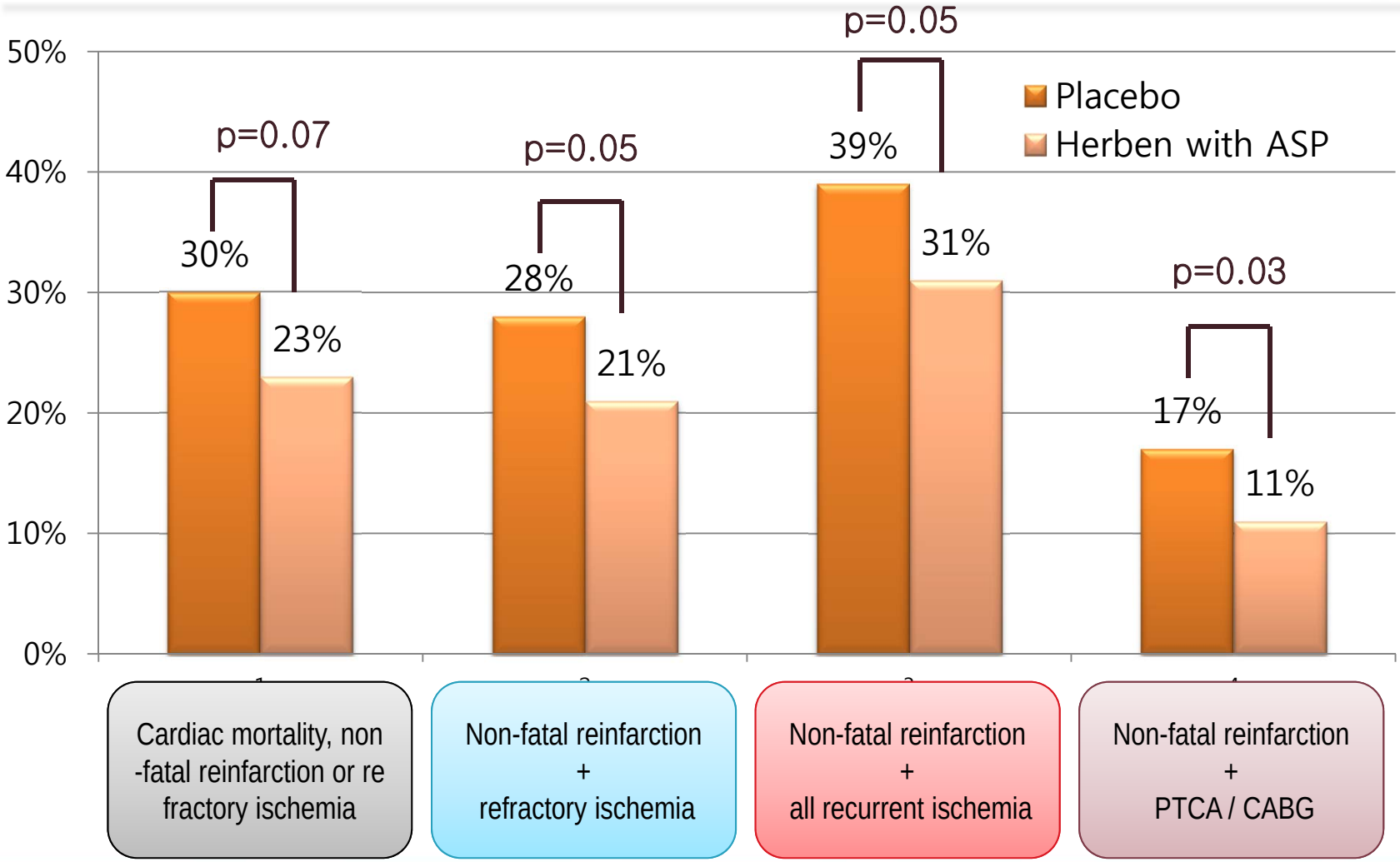
	Diltiazem group (n=430)	Placebo group (n=444)	Reduction rate	P-values
Cardiac death	7	6	—	NS
Reinfarction	16	22	26%	NS
Reischemia	74	103	26%	NS
Primary endpoint (Total of the above)	97	131	21%	P = 0.07
Non-fatal cardiac event (reinfarction+reischemia)	90	125	24%	P = 0.05

Diltiazem showed a 22% significant reduction of electrocardiographic evidence of ischemia (p=0.05)、 and a 42% significant reduction of myocardial revascularization therapy (p=0.03)

	Diltiazem group (n=430)	Placebo group (n=444)	Reduction rate	P-values
Electrocardiographic evidence of ischemia	116	153	22%	P = 0.05
Revascularisation therapy (PTCA、CABG)	30	53	42%	P=0.03

The Lancet 2000;355,1951-1956

Diltiazem in acute MI treated with thrombolytic agents : a randomized placebo-controlled trial (INTERCEPT)



The Lancet 2000;355,1951-1956

Diltiazem in acute MI treated with thrombolytic agents : a randomized placebo-controlled trial (INTERCEPT)

Diltiazem did not reduce cumulative occurrence of car diac death, non-fatal reinfarction, or refractory ischemi a during a 6-month follow-up, but

reduce all composite endpoints of non-fatal cardiac ev ents, especially the need for myocardial revascularizati on

Comparison of Beta Blockers and CCBs on Myocardial Infarction in Japanese Subjects

The Japanes beta-blockers and Calcium Antagonists Myocardial Infarction (JBCMI) Investigator

• Background

The efficacy of beta blockers in managing patients with post-acute myocardial infarction (AMI) was established based on randomized controlled trials predating the era of modern therapy in Western populations. We compared the effects of beta blockers on cardiovascular events with those of calcium antagonists in Japanese post-AMI patients on modern reperfusion therapy by performing a multicenter, prospective, randomized, open-blind end point study.

• Method

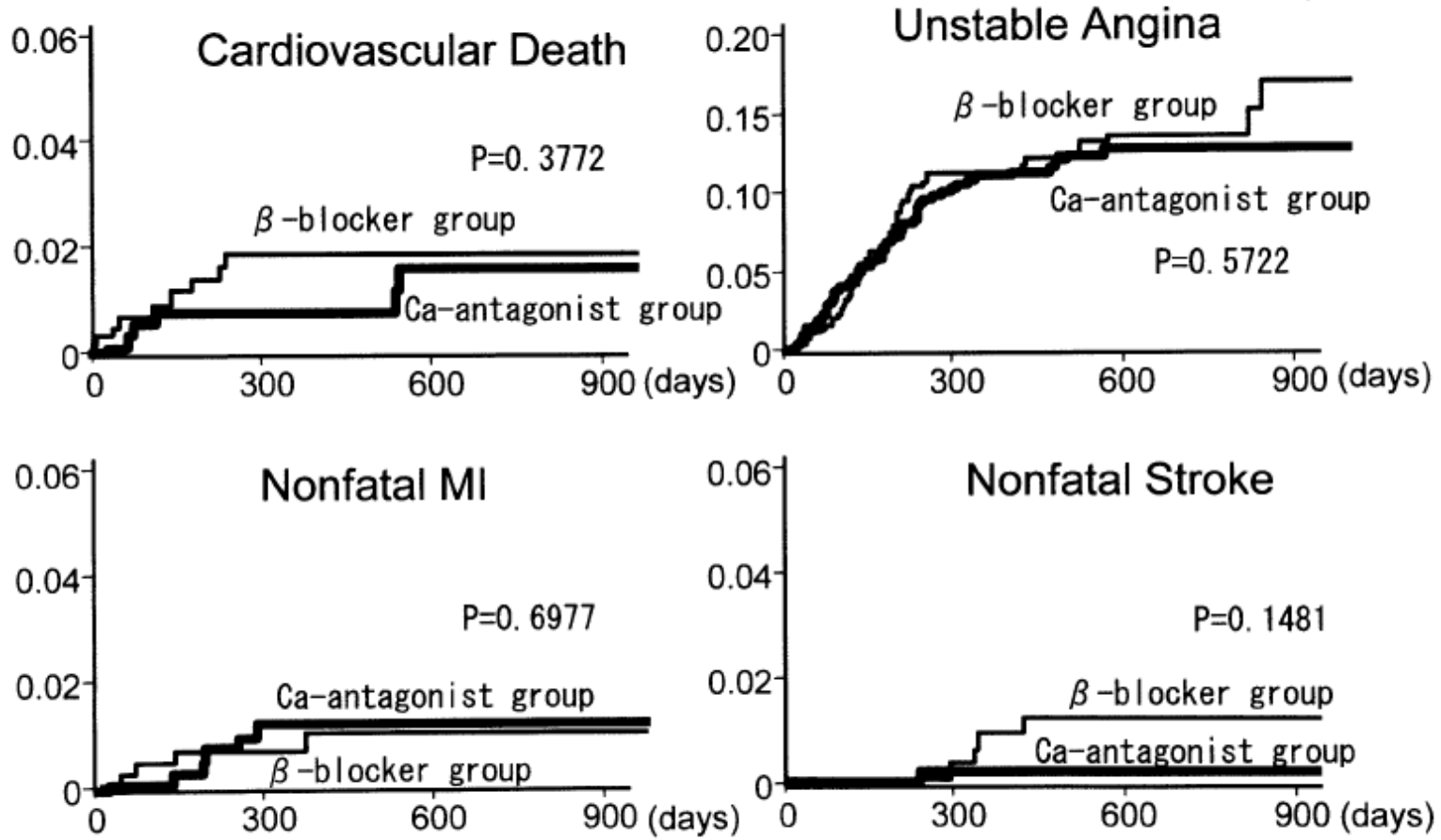
1,090 patients were assigned to the beta-blocker group(n=545) & calcium antagonist group(n=545). The mean follow-up period was 455 days. There was no significant difference in the incidence of cardiovascular death (1.7% vs 1.1%), reinfarction (0.9% vs 1.3%), uncontrolled unstable angina (11.0% vs 10.6%), and nonfatal stroke (0.7% vs 0.2%) between the 2 groups. However, the incidences of heart failure and coronary spasm were significantly higher in the beta-blocker group than in the calcium antagonist group. (4.2% vs 1.1%, p = 0.001; 1.2% vs 0.2%, p = 0.027, respectively).

• **Result**

Cardiovascular event rate is substantially lower in Japanese post-AMI patients receiving modern therapy than in those reported in the West, and that there are no significant differences in the cardiovascular event rate between the beta-blocker and calcium antagonist groups.

Am J Cardiol. 2004;93:969–973

Comparison of the Effects of Beta Blockers and CCBs on Myocardial Infarction in Japanese Subjects



Subjects: 1090 Japanese post-AMI patients

Methods: 545 patients were assigned to the beta-blocker group and 545 patients to the calcium antagonist.

Am J Cardiol. 2004;93:969–973

Intravenous Diltiazem in Acute Myocardial Infarction

Diltiazem as Adjunctive Therapy to Activase (DATA) Trial

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GUY PELLETIER, MD, FACC, PIERRE DE GUISE, MD, MARTIN JUNEAU, MD
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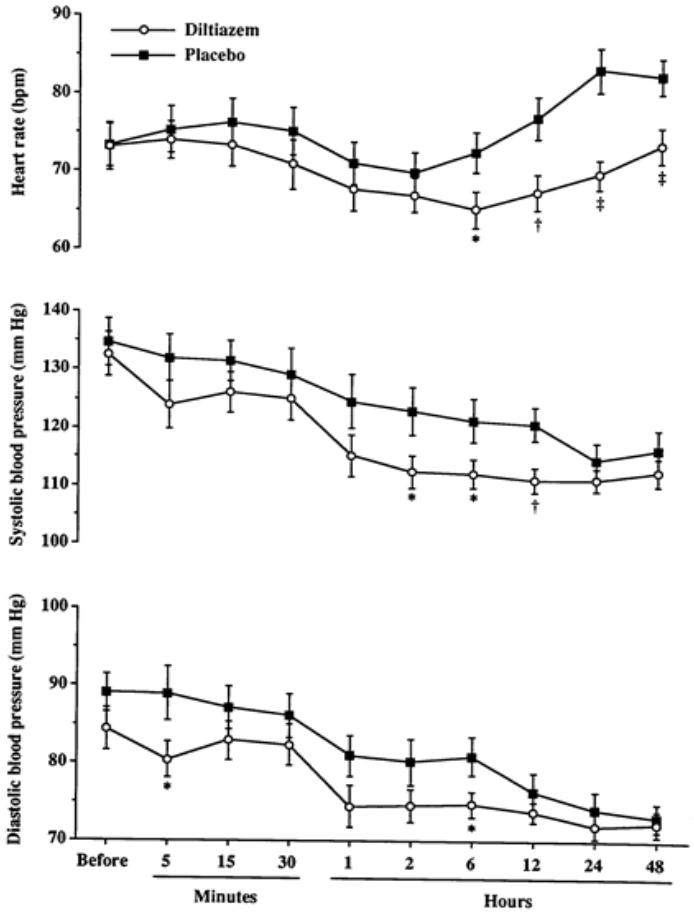
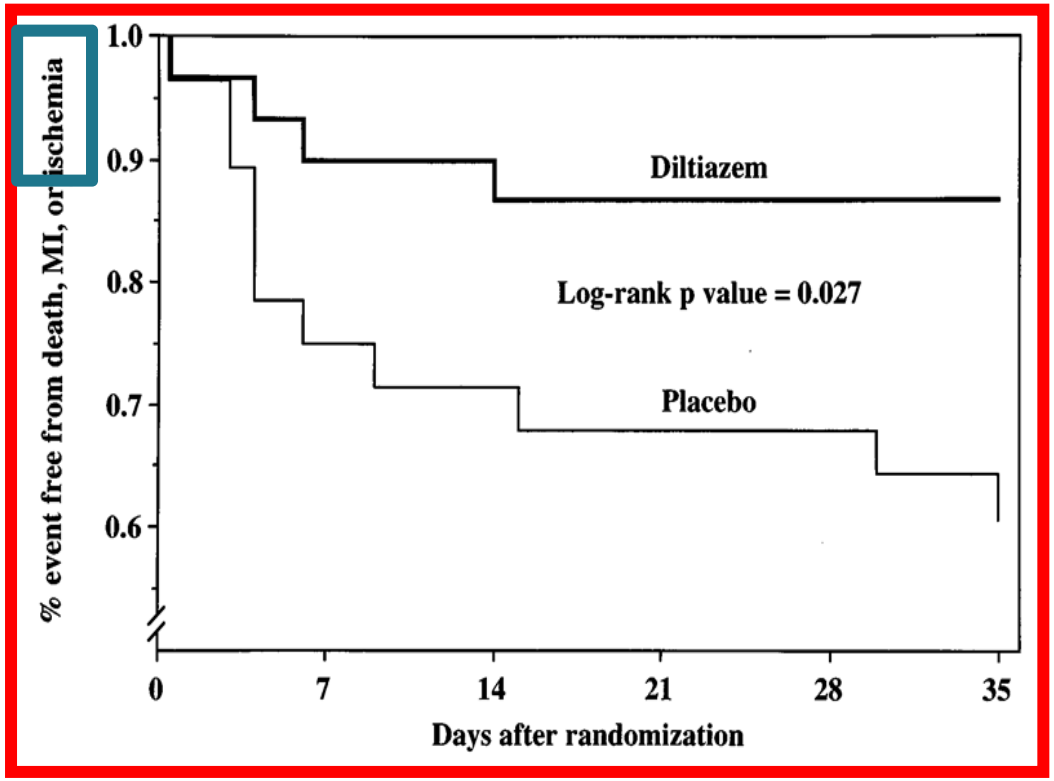
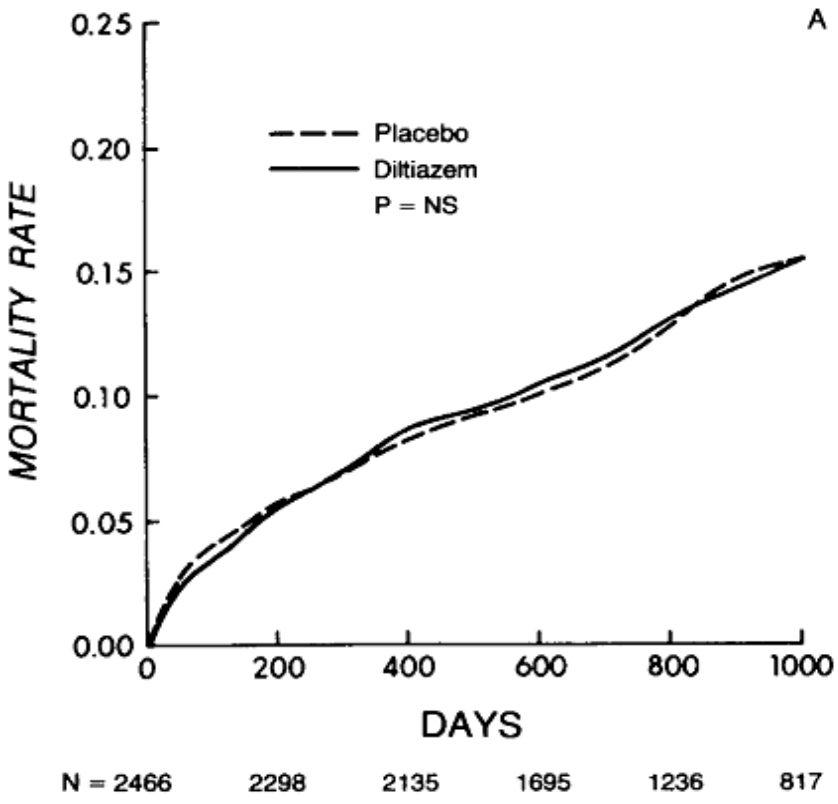
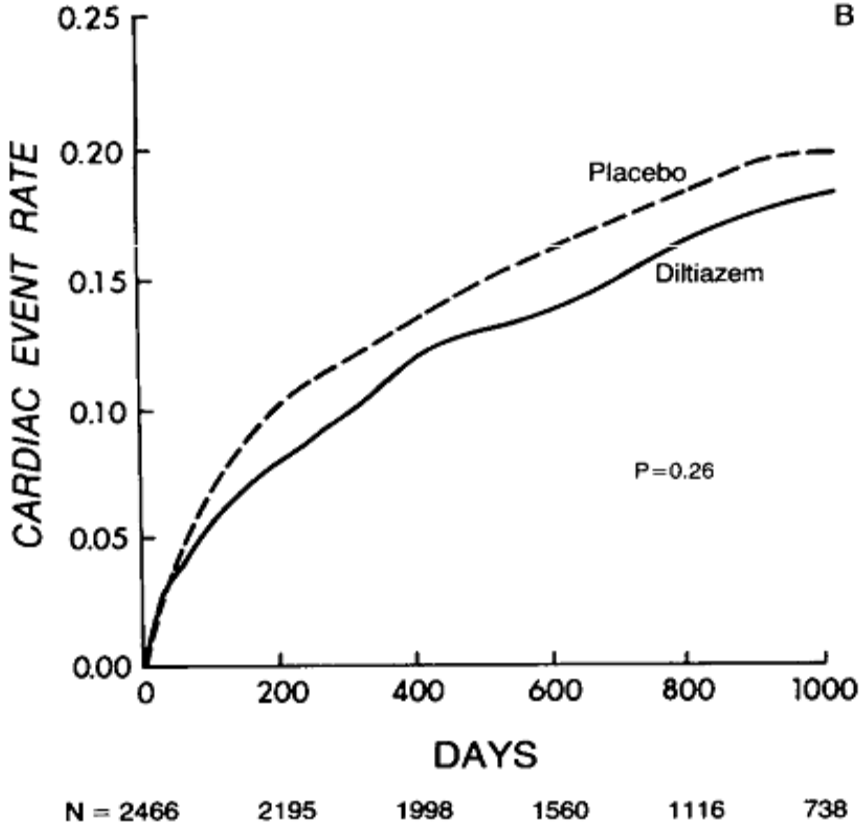




J Am Coll Cardiol 1998;32:620-8

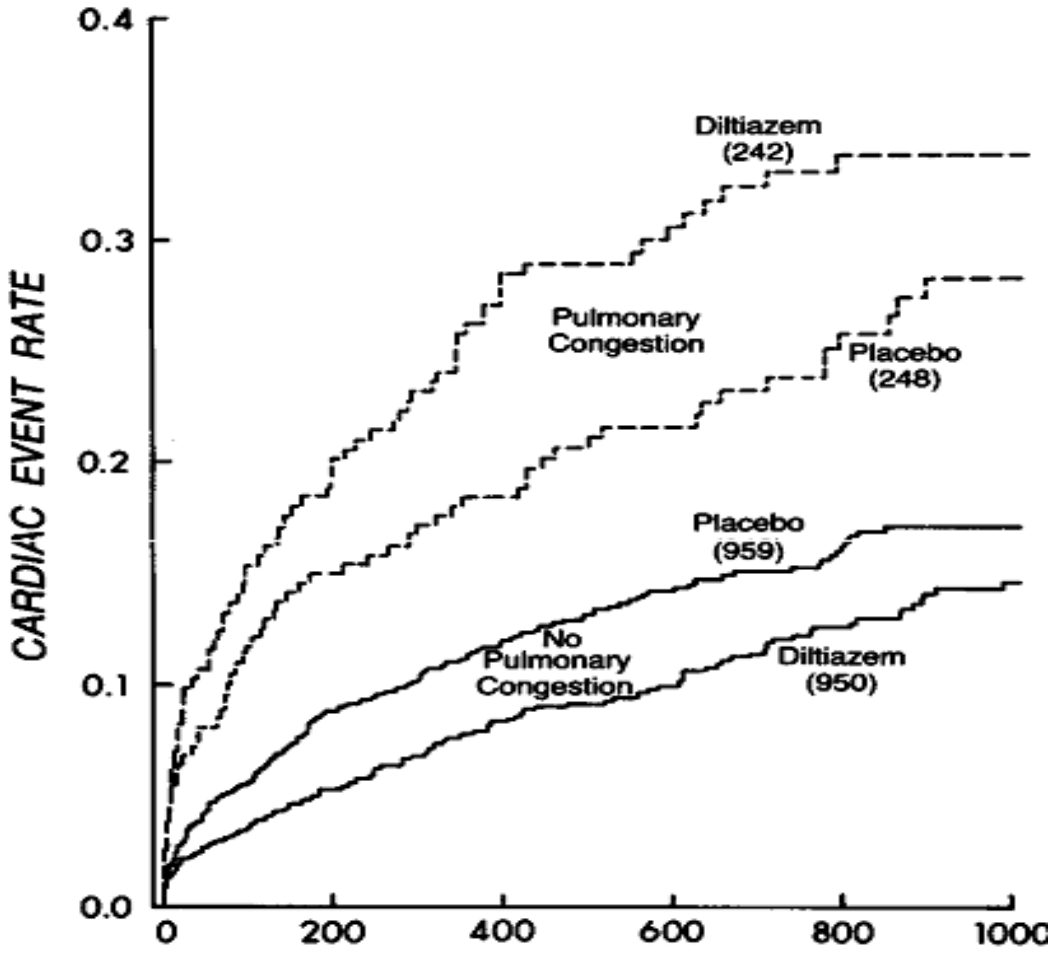
MDPIT study
no efficacy on mortality and cardiac event
2466 AMI patients, diltiazem 240mg/d





NEJM 1988;319:385-92

Bidirectional effect on AMI by pulmonary congestion and LVEF



NEJM 1988;319:385-92

ACC/AHA 2007 Guidelines for the Management of Patients With Unstable Angina/Non-ST-Elevation MI

In summary, definitive evidence for a benefit of CCBs in UA/NSTEMI is predominantly limited to symptom control.

For immediate-release nifedipine, an increase in serious events is suggested when administered early without a beta blocker.

The heart rate-lowering CCB drugs (verapamil and **diltiazem**) can be administered early to patients with UA/NSTEMI without HF without overall harm and with trends toward a benefit.

Therefore, when **beta blockers cannot be used**, and in the **absence of clinically significant LV dysfunction**, heart rate-slowing CCBs are preferred.

ACC/AHA 2007 Guidelines for the Management of Patients With Unstable Angina/Non-ST-Elevation MI

Class I

1. Calcium channel blockers are recommended for ischemic symptoms when beta blockers are not successful. *(Level of Evidence: B)*
2. Calcium channel blockers are recommended for ischemic symptoms when beta blockers are contraindicated or cause unacceptable side effects. *(Level of Evidence: C)*

Conclusion

Diltiazem

did not reduce the hard endpoints,

however,

reduce ischemia and may replace beta-blocker in

specific circumstances.

Diltiazem

is effective in patients with hypertension

stable angina, unstable angina and myocardial infarction