Chronic stable angina: What is the status of the ESC Guidelines? What is current optimal non-interventional treatment?

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Guidelines on chronic stable angina

European Heart Journal
doi:10.1093/eurheartj/ehl002

ESC Guidelines

Guidelines on the management of stable angina pectoris: full text‡

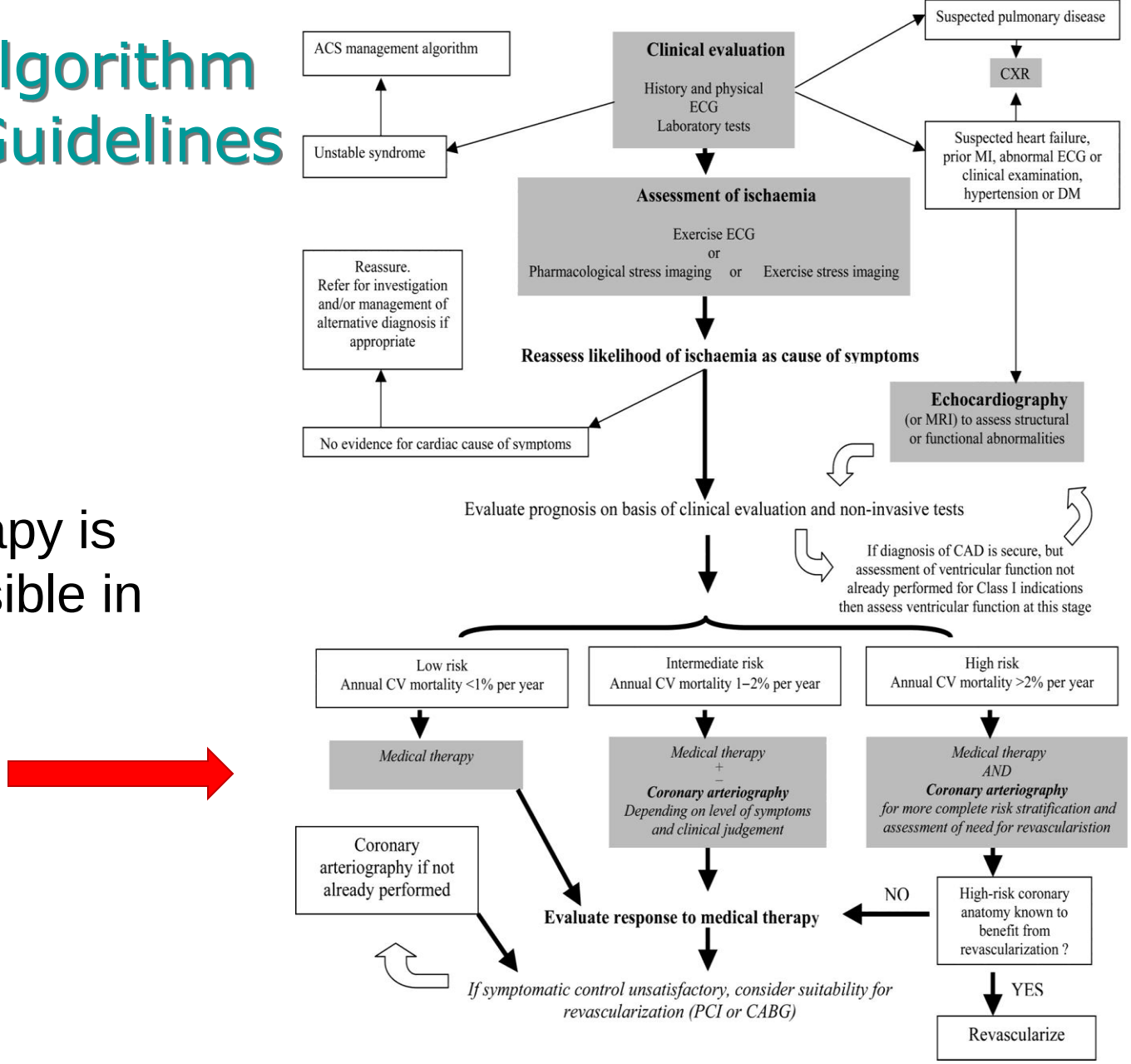
The Task Force on the Management of Stable Angina Pectoris of the European Society of Cardiology

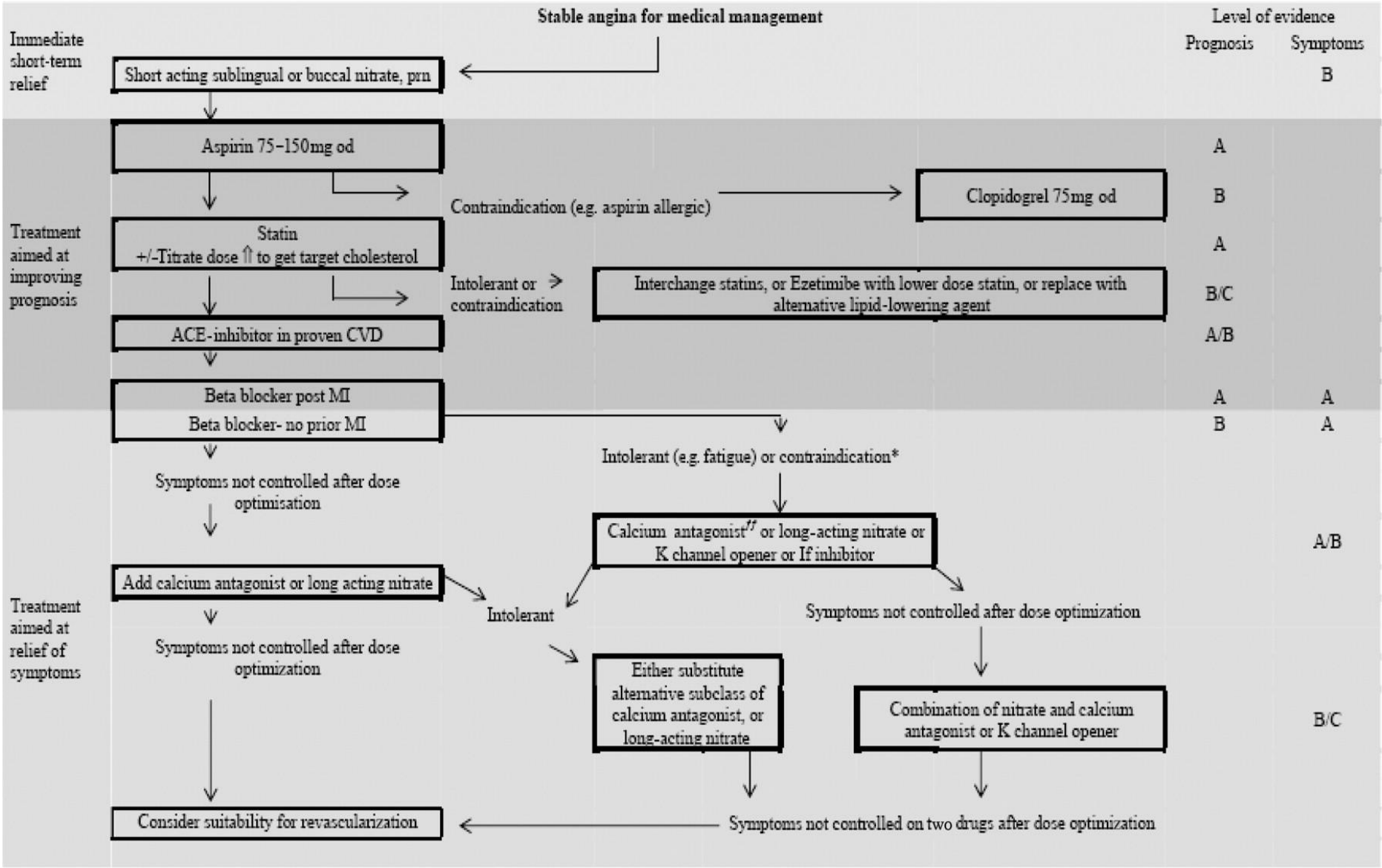
Authors/Task Force Members, Kim Fox, Chairperson, London (UK)*, Maria Angeles Alonso Garcia, Madrid (Spain), Diego Ardissino, Parma (Italy), Pawel Buszman, Katowice (Poland), Paolo G. Camici, London (UK), Filippo Crea, Roma (Italy), Caroline Daly, London (UK), Guy De Backer, Ghent (Belgium), Paul Hjemdahl, Stockholm (Sweden), José Lopez-Sendon, Madrid (Spain), Jean Marco, Toulouse (France), João Morais, Leiria (Portugal), John Pepper, London (UK), Udo Sechtem, Stuttgart (Germany), Maarten Simoons, Rotterdam (The Netherlands), Kristian Thygesen, Aarhus (Denmark)

ESC/CPG: June 2006
Eur. Heart Journal
2006;27:1341
63 pages and 643 ref,
Online on:www.escardio.org
Fulltext, pocket version Slide set

Treatment algorithm from 2006 Guidelines

What kind of medical therapy is the best possible in 2009?




Stable angina for medical management
Level of evidence
Prognosis
Symptoms
Immediate short-term relief
Short acting sublingual or buccal nitrate, prn
B
Treatment aimed at improving prognosis
Aspirin 75–150mg od
A
Contraindication (e.g. aspirin allergic)
Clopidogrel 75mg od
B
Statin
+/-Titrate dose ⇑ to get target cholesterol
A
Intolerant or contraindication
Interchange statins, or Ezetimibe with lower dose statin, or replace with alternative lipid-lowering agent
B/C
ACE-inhibitor in proven CVD
A/B
Beta blocker post MI
Beta blocker- no prior MI
A
A
B
A
Intolerant (e.g. fatigue) or contraindication*
Symptoms not controlled after dose optimisation
Calcium antagonist†† or long-acting nitrate or K channel opener or If inhibitor
A/B
Add calcium antagonist or long acting nitrate
Treatment aimed at relief of symptoms
Intolerant
Symptoms not controlled after dose optimization
Symptoms not controlled after dose optimization
Either substitute alternative subclass of calcium antagonist, or long-acting nitrate
Combination of nitrate and calcium antagonist or K channel opener
B/C
Consider suitability for revascularization
Symptoms not controlled on two drugs after dose optimization

New guidelines?

PUBLISHED: 2007: ACC/AHA Focus Update (of 2002 guidel) on chronic angina

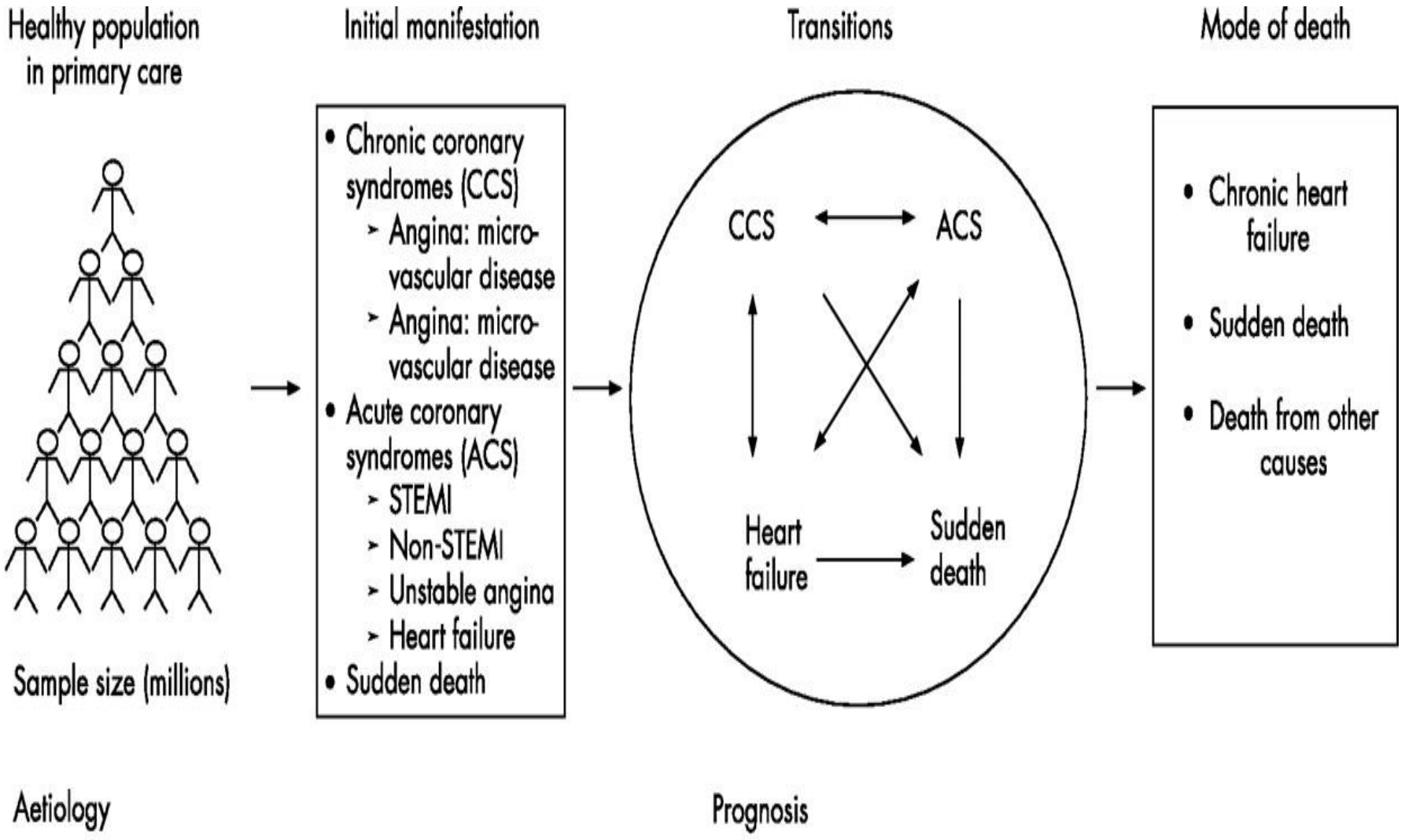
FUTURE ?

- 2007 NICE requested by UK dep of Health to prepare new angina guidelines. anticipated publ. 2011
- ESC/CPG: Guidelines on Myocardial Revascularization (2010-11)
- ESC/CPG: Guideline on Management of Dyslipidemias (2010-11)
- ESC/CPG: revision of chronic angina guidelines ????

Important studies published since the publication of ESC angina guidelines in June 2006

- Dec 2006: Coronary Intervention for Persistent Occlusion after Myocardial Infarction (OAT)
- Dec 2006: Initial Strategy of Intensive Medical Therapy Is Comparable to That of Coronary Revascularization for Suppression of Scintigraphic Ischemia in High- Risk But Stable Survivors of Acute Myocardial Infarction (INSPIRE)
- April 2007: Optimal Medical Therapy with or without PCI for stable coronary disease (COURAGE)
- June 2009: A Randomized Trial of Therapies for Type 2 Diabetes and Coronary Artery Disease (BARI 2D)
- Further studies on new medications: ivabradine, ranolazine
- Further studies in non –pharmacological treatment
  - EECP. SCS, Laser revascularization, Gene therapy,
- Very few randomized studies comparing diff treatment in the last 3 years

Figure 5 Understanding the aetiology and prognosis of coronary heart disease with large population studies resolving different phenotypic symptoms and their temporal relationships. STEMI, ST elevation myocardial infarction.



Timmis, A. D et al. Heart 2007;93:786-791

Epidemiology of Chronic Stable Angina

Prevalence %

	45-55 y	65-75 y
Women	0,5	10-15
Men	3	10-20

Mortality: 1% pr year

Mycardial infarction 1-3% pr year

Annual event rate from ESC 2006

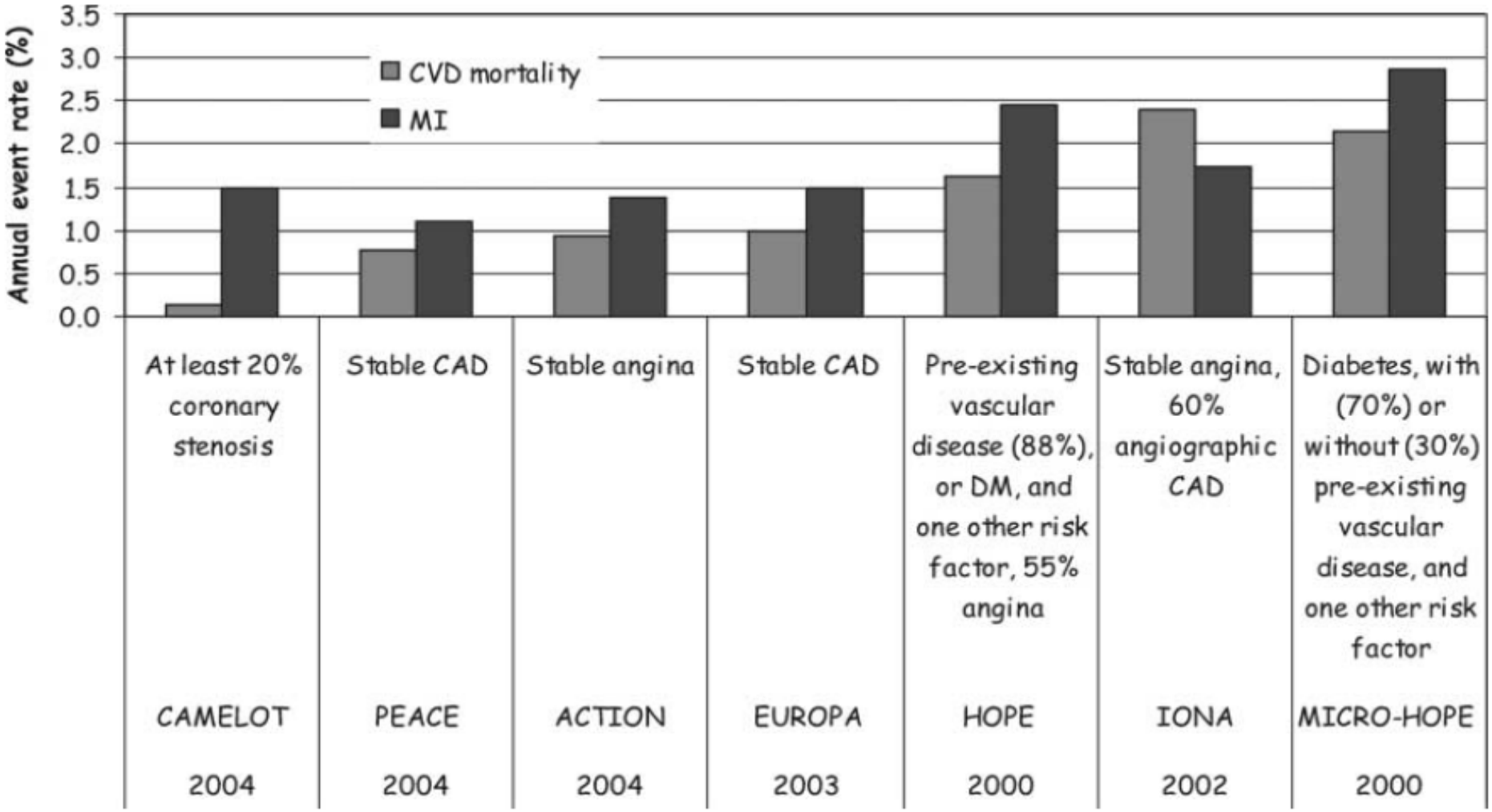
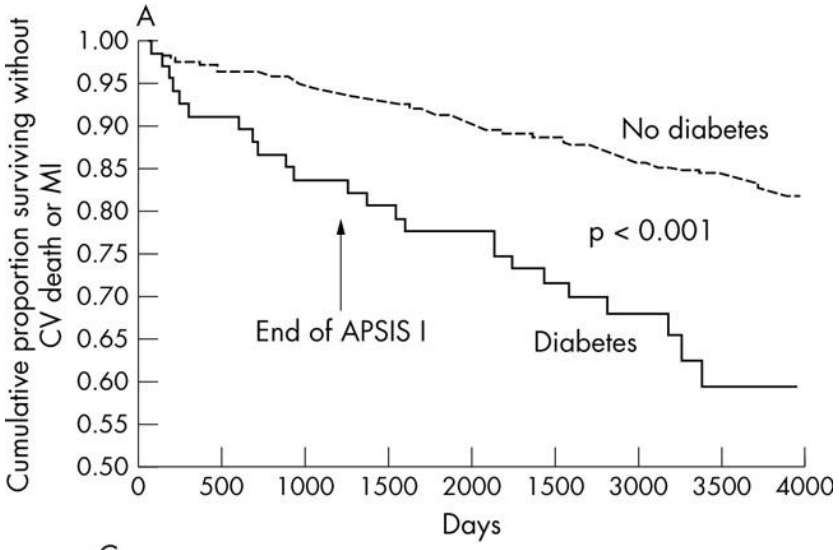
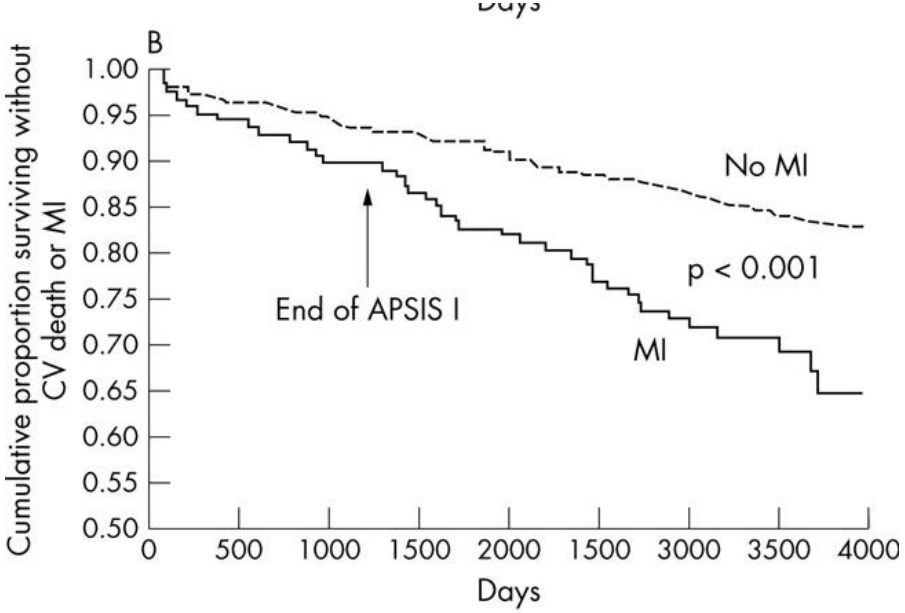
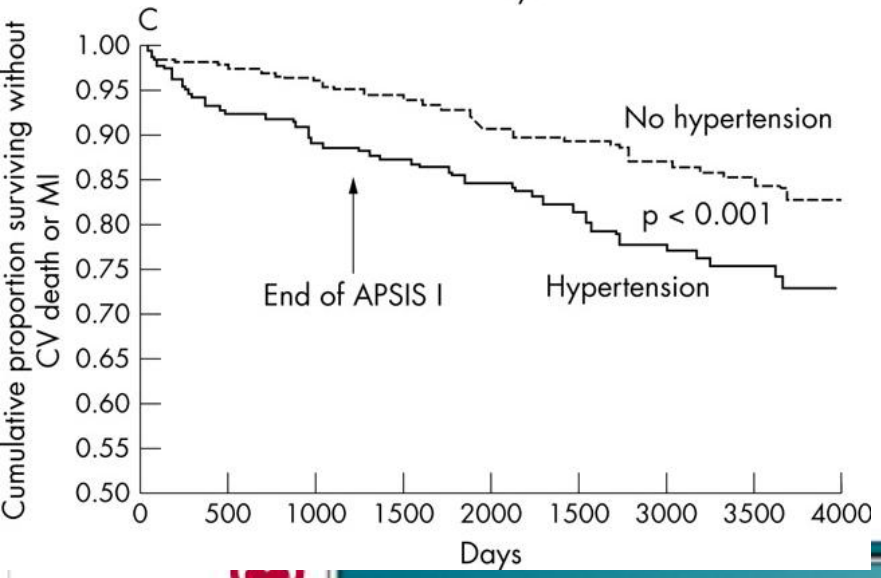


Figure 2 Kaplan-Meier plots illustrating the influence of (A) diabetes mellitus, (B) previous MI, and (C) a history of hypertension on the risk of CV death or MI. All three risk indicators were significantly ($p < 0.001$) associated with an adverse outcome. Diabetes was the risk indicator providing the greatest separation between subgroups.







Hjemdahl, P et al. Heart 2006;92:177-182

Objectives in Chronic Stable Angina

- Reduce the risk of death and myocardial infarction
- Improve Quality of Life: i.e. reduce angina symptoms

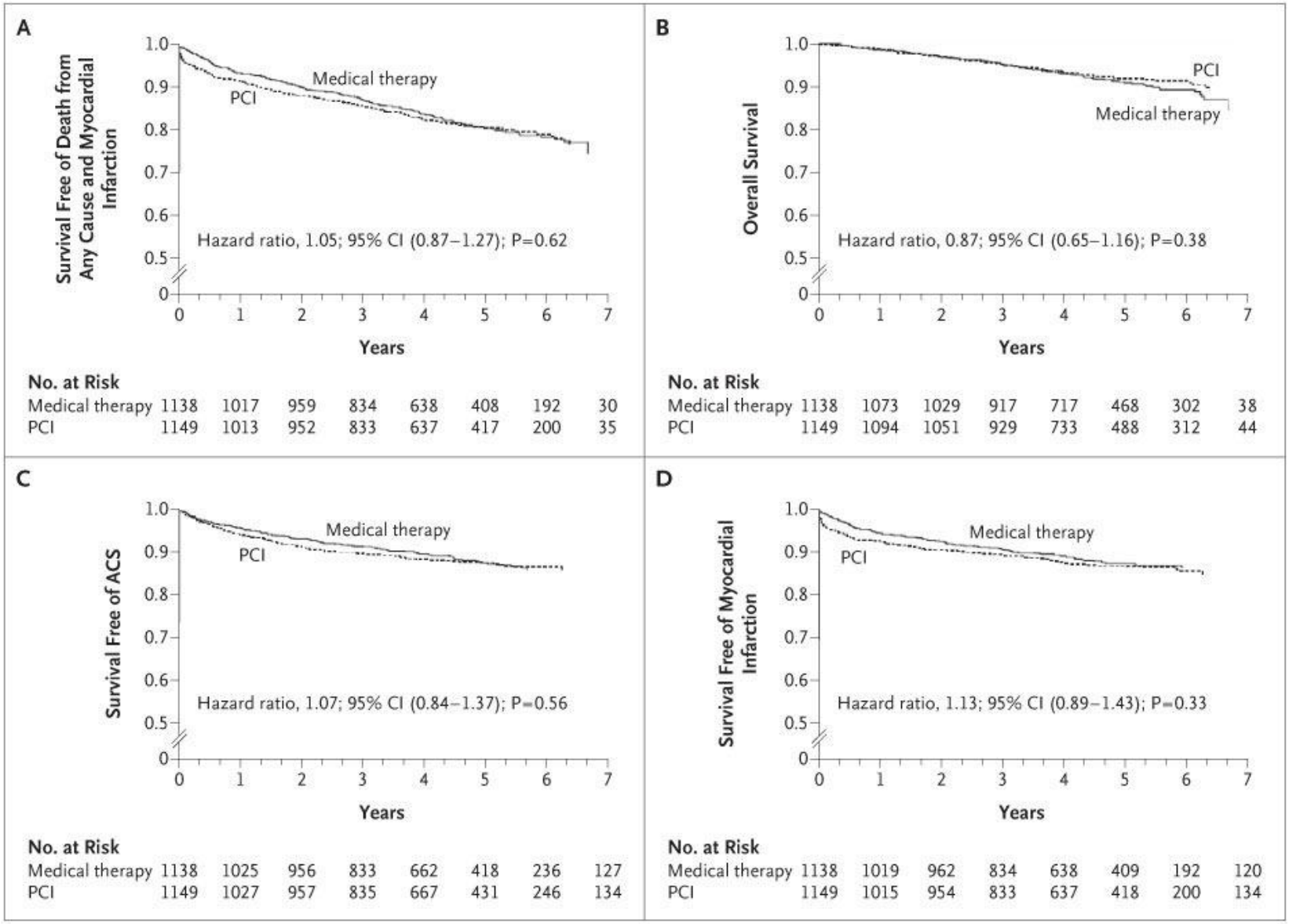
Goals of treatment in chronic angina

- Relief or decrease of angina and ischemia
- Prevention of progression of disease
- Prevention of complications of disease including
  - Myocardial infarction
  - Worsening of left ventricular function
  - Development of congestive heart failure
  - Cardiovascular death
  - Sudden cardiac death
  - Arrhythmias

Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) study

- 70% stenosis + evidence of myocardial ischemia;
- or >80% stenosis and classic angina.
- 35000 screened 6.4% enrolled
- Exclusion: LMC, EF<30% (35% if 3VD), marked ischemia
- Both arms: intensive control of lipids, blood pressure, and blood glucose and counseling on lifestyle factors, such as nutrition, exercise, and smoking

COURAGE NEJM. 2007;356:1503-1516



CORAGE population

- 2287 pts 62±10y. 85% male
- 58% CCS class II/III
- 34% Diabetes
- 66% Hypertension
- 69% 2 or 3 vessel disease
- 34 % Prox LAD
- Mean EF 61%

Optimal Medi cal Rx in COURAGE

- Smoking: Cessetion
- Fat : total <30% cal , sat. < 7% of cal
- Dietary cholest: <300mg/day
- Lipids: LDL < 1.55-2.2, HDL >1.0 TG<1.7
  - Simvastatin up to 80mg than add ezet. Fibrate niacin is needed
- Physical activity: 30-45min 5/week
- BMI goal <25 or at least 10% w.loss
- Diabetes: HbA1c < 7%
- Blood Pressure < 138/85 (<130/85 if dia or renal)
- Anti-platelet: ASA (81-325) or clodpiogrel
- Anti-ischemic: long-acting metopr., amlodip., isosorb . Alone or in combination as needed
- Post MI: β-block . Lisinopr, or losart. if EF<40% or ant MI

Therapy in COURAGE – medical Rx at 5y

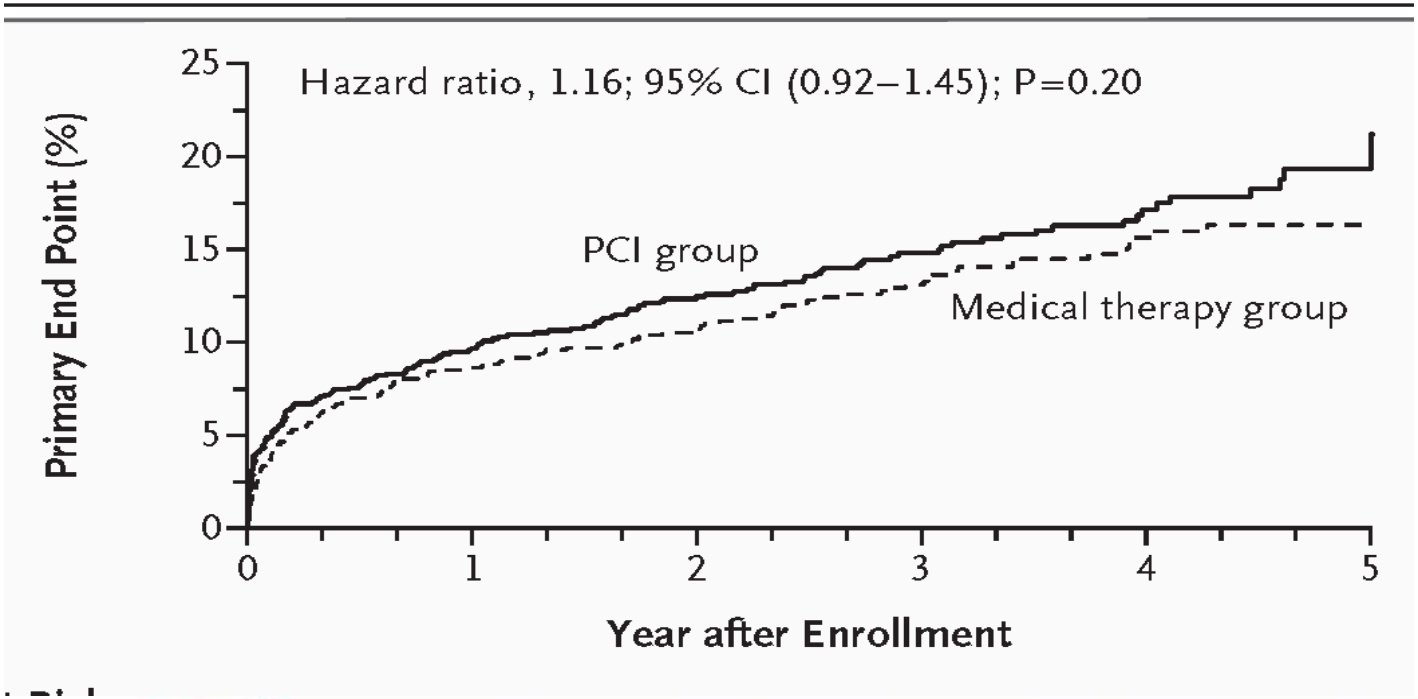
• BP	122/70 (5y)
• Total chol. /LDL/HDL	3.6 /1.9 /1.1
• Smoking	20%
• ACE /ARB	72%
• Statin	93%
• Other antilipid	54%
• Aspirin	94%
• Betablocker	86%
• Calcium Ch blocker	52%
• Nitrates	57%

OAT study: opening chronic occlusion post AMI vs medical Rx

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 DECEMBER 7, 2006 VOL. 355 NO. 23

Coronary Intervention for Persistent Occlusion after Myocardial Infarction



BARI 2D
(N.Eng.J Med Volume 360:2503-2515 June 11, 2009)

2368 pts with chronic angina and DIA

1605 PCI intended stratum
763 CABG intended stratum

Randomized to revasc. or intensive medical Rx in each stratum

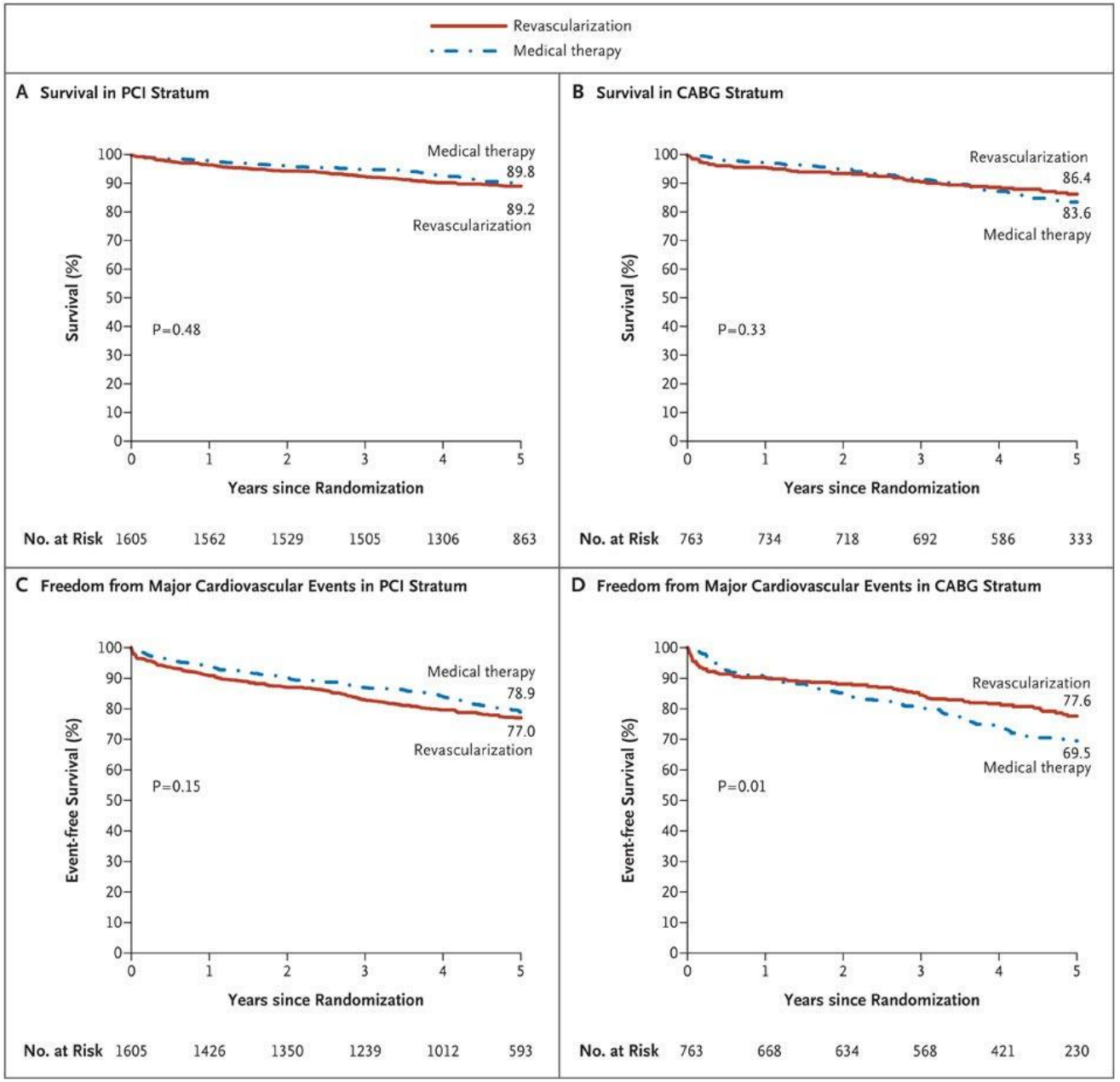
	REVASC	MEDICAL
5 Year surv %	88.3	87,8
No MACE %	77.2	75.9

BARI 2D

Revascs or medical Rx gave equal at 5 y

CABG group less MACE than Medical

42% Medical crossed over to revasc



Boden: editorial NEJM;

"The BARI 2D results replicate the principal finding of COURAGE trial that an **initial strategy of PCI provides no incremental clinical benefit over intensive medical therapy, in patients with both diabetes and coronary disease"**

"BARI 2D shows that for many patients with both diabetes and coronary disease,
optimal medical therapy rather than any intervention is an excellent first-line strategy, particularly for those with less severe disease"

Is there a downside of coronary interventions?

Interventional Cardiology

Detection of Coronary Microembolization by Doppler Ultrasound in Patients With Stable Angina Pectoris Undergoing Elective Percutaneous Coronary Interventions

Philipp Bahrmann, Gerald S. Werner, Gerd Heusch, Markus Ferrari, Tudor C. Poerner, Andreas Voss and Hans R. Figulla

Circulation 2007;115;600-608; originally published online Jan 29, 2007;
DOI: 10.1161/CIRCULATIONAHA.106.660779

What do the different Rx do?

Therapy	Mortality	Symptoms	Reduce risk of MI	Cardiac Function	Arrhythmia
Aspirin	?+	0	+	0	0
Statin	+	(?+)	+	0	0
Beta block	o	+	(+)	+	+
Calc.antag	o	+	0	0	0
Nitrates	o	+	0	(?+)	0
ACE/ARB	+	(?)	+	+	(+)
PCI	o	+	0	0	0
CABG	(+)	+	(+)	(+)	0

Drugs to reduce mortality and MI

- Antiplatelet
  - Aspirin 75-160mg

  or (and??)
  - Clopidogrel 75mg
- Lipid lowering
  - Statins (aggressive ? LDL < 2)
  - Other lipid agents? (ezetamibe? Niacin?
- ACE/ARB as a general vascular protective drug??

Some newer treatment modalities

Therapy	Mortality	Symptoms	Reduce risk of MI	Cardiac Function	Arrhythmia
EECP	0	+	0	+	0
SCS	0	+	0?	0	0
Laser	0/-	(+)	0	-	0
Bone mar cells	?	(+)	?	(+)	?
genVGF	?	?	?	(?+)	?
Ranolazine	0	+	0	0	0
Ivabradine	0	+	0	0	0

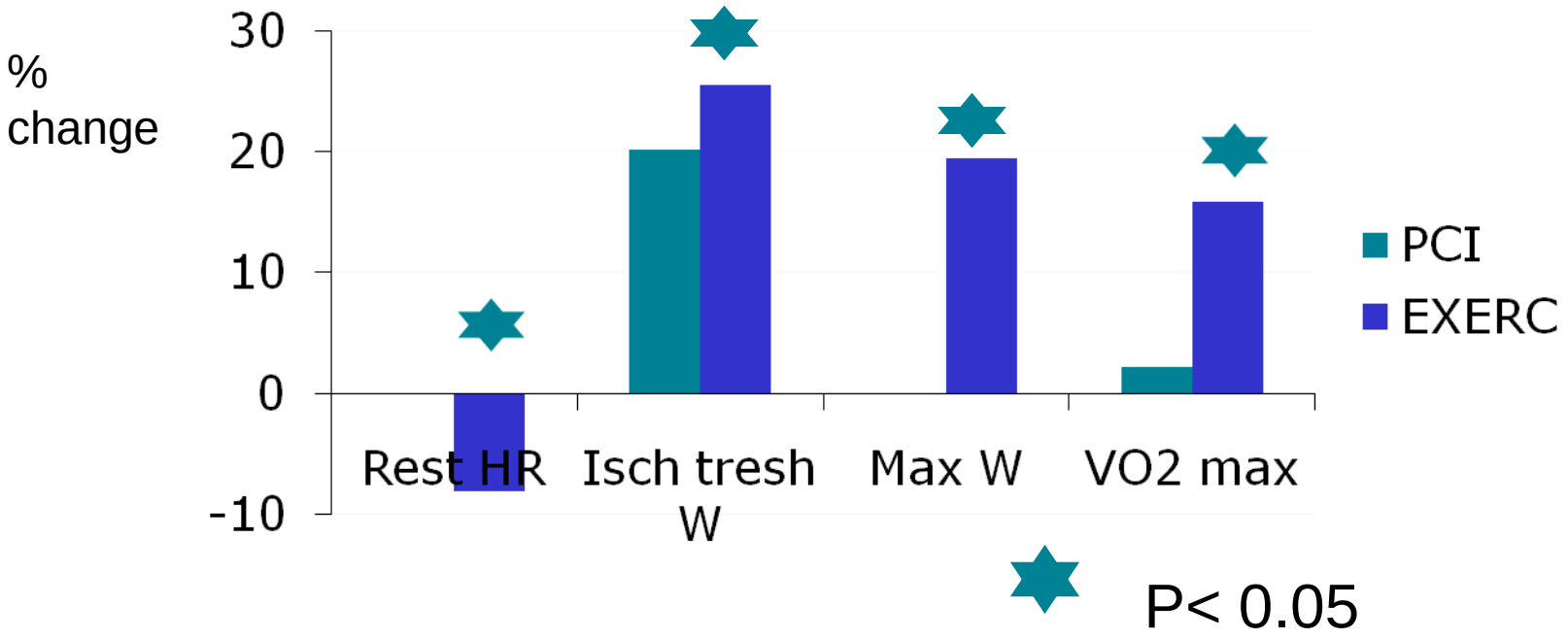
Physical activity as a real treatment option in angina

Reiner Hambrecht et al from Leipzig
Circulation 2004,109:1371

- 100 pts random to PCI or active training
- Mean age 62
- 23% diabetics
- 80% on ACEI
- 76% on statins ,
- 87% on betablocker
- 98% on aspirin
- 1/2/3 VD 58/27/15 % 20 % LAD
- EF 61%
- 46 % previous MI

PCI vs Exercise training Hambrecht et al

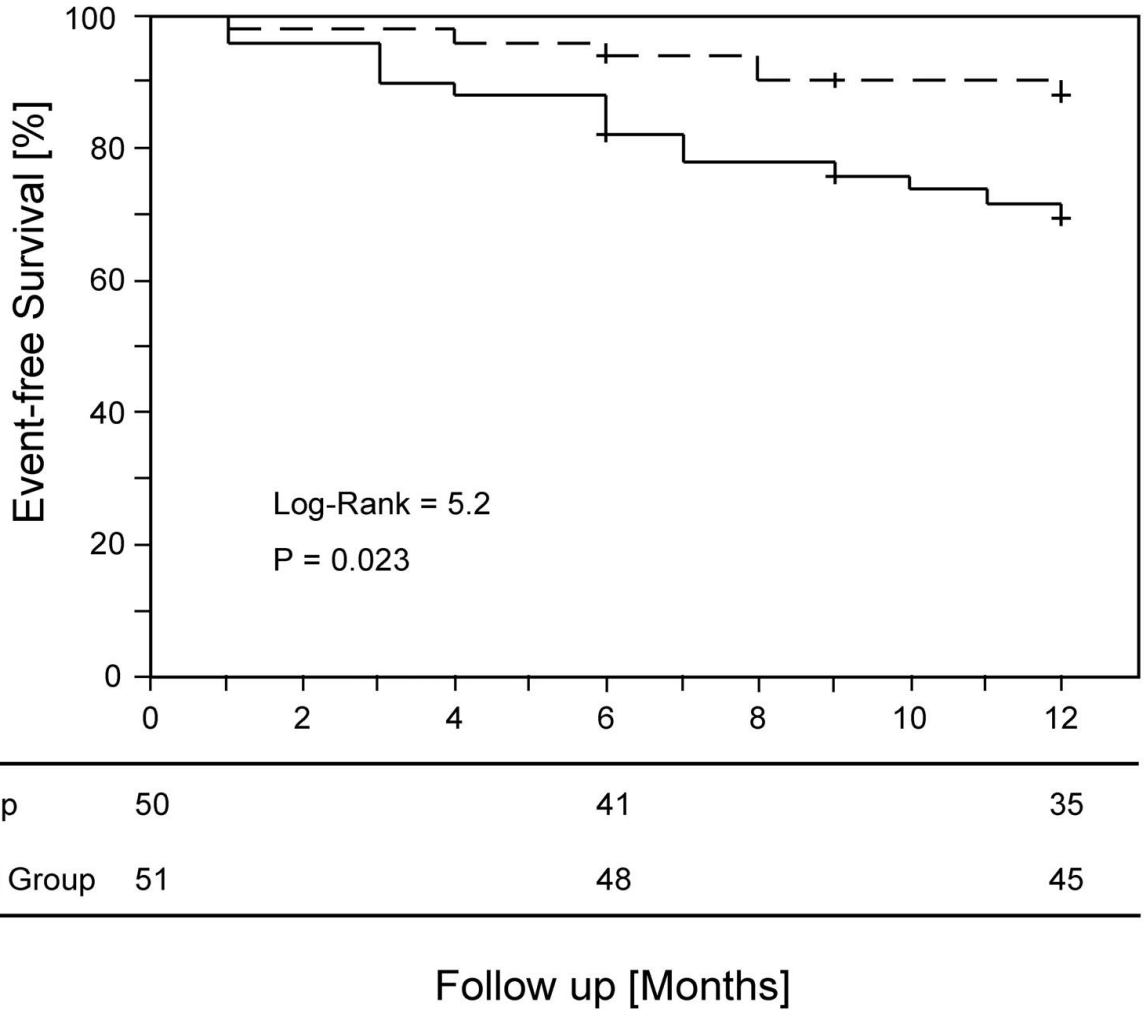
- 1997 – 2001 only BMS
- In hospital bicycle exerc 10min 6 times daily for 14 days
- Home training bic 20min daily and group training 60m weekly



Event-free survival after 12 months was significantly superior in exercise training group versus PCI group (P=0.023 by log-rank test)

Any ischemic event
(MACE, hosptil due to angina

PCI: 21
Ex: 6



Patients at Risk			
PTCA/Stent Group	50	41	35
Exercise Training Group	51	48	45

Hambrecht, R. et al. Circulation 2004;109:1371-1378

Exercise training: the ”forgotten” alternative?

Exercise Physiology

Superior Cardiovascular Effect of Aerobic Interval Training Versus Moderate Continuous Training in Heart Failure Patients

A Randomized Study

Ulrik Wisløff, PhD; Asbjørn Støylen, MD, PhD; Jan P. Loennechen, MD, PhD; Morten Bruvold, MSc; Øivind Rognmo, MSc; Per Magnus Haram, MD, PhD; Arnt Erik Tjønna, MSc; Jan Helgerud, PhD; Stig A. Slørdahl, MD, PhD; Sang Jun Lee, PhD; Vibeke Videm, MD, PhD; Anja Bye, MSc; Godfrey L. Smith, PhD; Sonia M. Najjar, PhD; Øyvind Ellingsen, MD, PhD; Terje Skjærpe, MD, PhD

(*Circulation. 2007;115:3086-3094.*)

- Randomized 27 pts (mena age 75) with heart failure between intensive interval training and moderate continous training
- EF : moderate no change Intens: 28% to 38%
- prBNP down 40% with intensive training
- Improve mitoch function (biopsy) only with intens train

Exercise training

- Study wanted!!
- Sponsor (Nike??)
- Intensive interval training vs. ordinary training advice for chronic stable angina??

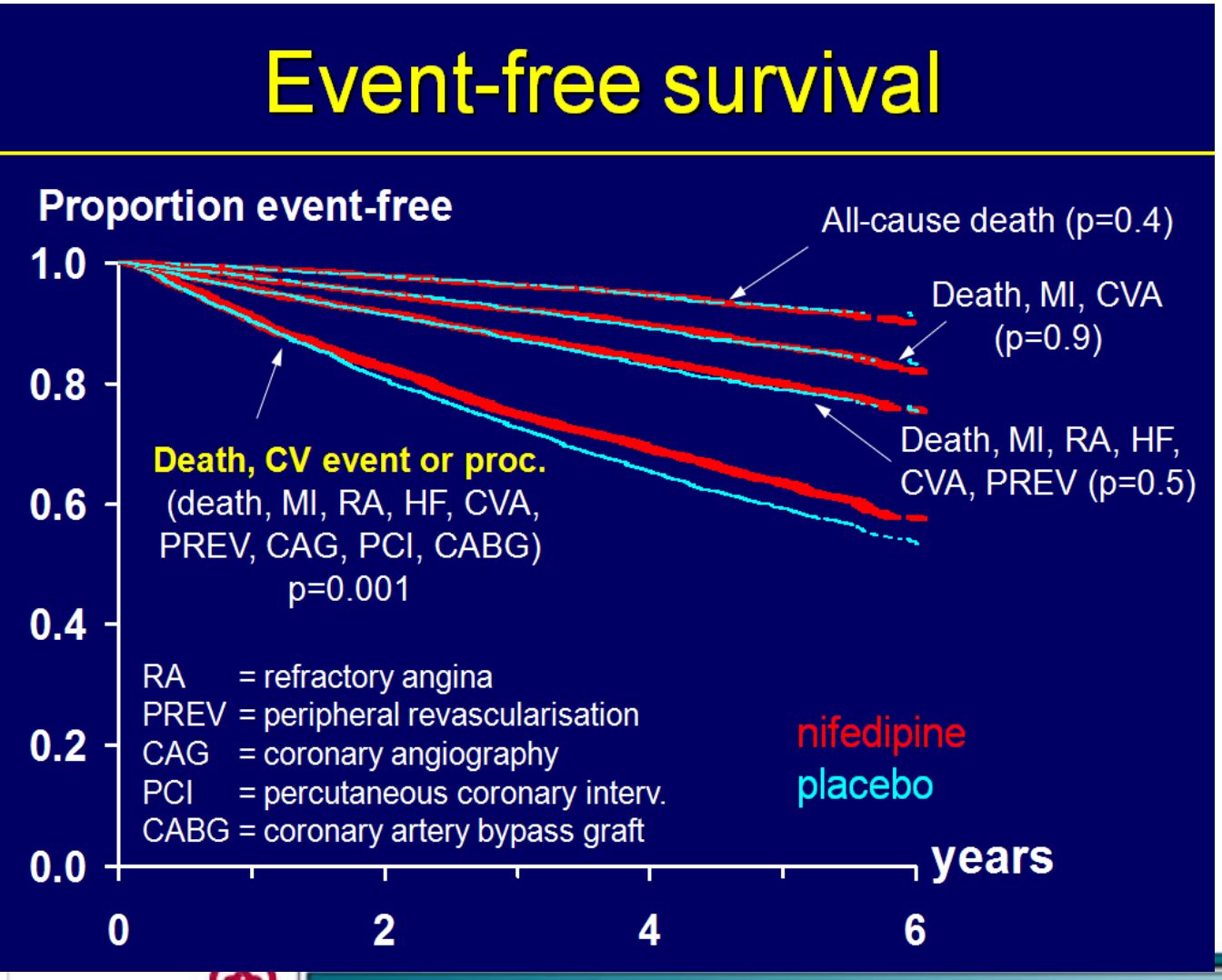
Beta adrenergic blockers

- Reduce heart rate, and oxygen consumption
- Always indicated in post AMI and heart failure
- Never proven to reduce mortality in angina pts without previous MI or CHF
- Many BB have negative metabolic effects
  - dyslipidemia, diabetogenic, weight gain, increase central aortic pressure pressure
- Metoprolol – long acting preferably
- Atenolol (should it still be used??)
- Bisoprolol - most B1 selective BB
- Carvedilol - metabolic neutral

Calcium antagonist

- Not proven to reduce death or MI
- Safety well documented in several trials
- Dihydropyridine
  - Nifedipine GITS - ACTION study
  - Amplodipine
  - (lercanidipine?)
- Non- dihydroyridine
  - Verapamil – long action preferabely
    - Negative inotropic caution with BB and depr LV
  - Diltiazem
    - More safely to be combined with BB?

ACTION STUDY



Confirmed long acting nifedipine as a safe drug with some eff on sec endpoints

Long acting nitrates

- Not proven to reduce death or MI
- Symptomatic effect
- Need to individualize dosage
  - Initial headache
  - Can often be increase to 100-200mg in suitable patients
- Tolerance problem - asymmetric dosage
- Dermal patch – effective for some

Any new kids on the block??

ivabradine
ronalazine
Nicorandil
fasudil

Ranolazine

- Inhibits late I_{Na} current
- Reduce Ca^{++} and Na^{+} overload
- In high conc. Inhibits I_{Kr} (↑QT)
- Both I_{na} and I_{Kr} inhib. balances the arrhytmic potential
- Decrease QTc in some longQT syndr
- Increase efficiency of oxygen use
- (inhibit fatty acid oxyd?)

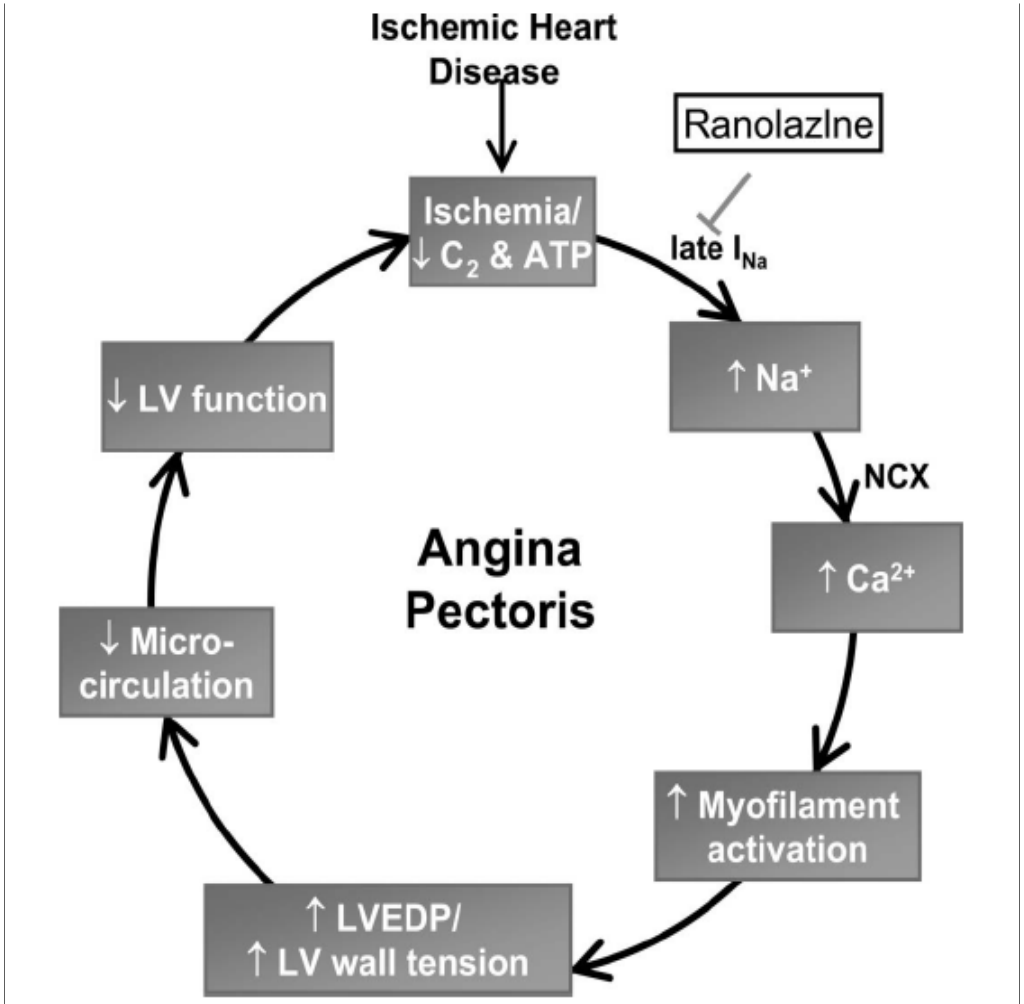


FIGURE 4. Scheme for the pathophysiology of myocardial ischemia and the role of late I_{Na} inhibition with ranolazine.

Ranolazine

- Metabolic agent
- No effect on HR or BP
- Some antiarrhytmic action (?)
- No increase in torsade
- Improve diastolic function (?)
- Improved glycemic control
- Improves angina symptoms and exercise tolerance in several randomized trials
- Safe in long term trials

MERLIN TIMI-36

Metabolic Efficiency With Ranolazine for Less Ischemia in Non ST-Elevation Acute Coronary Syndrome

- 6560 patients with ACS
- Multi-center study
- Long term Rx ranolazine vs plac
- JAMA. 2007;297:1775–1783
- Circulation. 2007;116:1647–1652.

Ranolazine

MERLIN TIMI-36 outcomes

End point	Ranolazine (%)	Placebo (%)	HR (95% CI)	p
Primary end point	21.8	23.5	0.92 (0.83–1.02)	0.11
CV death/MI/ recurrent ischemia	18.7	19.2	0.96 (0.86–1.08)	0.50
CV death/MI	10.4	10.5	0.99 (0.85–1.15)	0.87
Recurrent ischemia	13.9	16.1	0.87 (0.76–0.99)	0.03

Morro DA et al. *JAMA* 2007; 297:1775-1783.

Ranolazine

- Approved in the USA 2006
- UScomp CV therapeutics.
- 2008 EMEA marketing authorization (co-mark w Roche)
- Expensive - 150€ /month.
- Side effects: G-I, asthenia, dizziness
- ↑ QT -clinically rel?
- no ↑ mortality
- no ↑ in torsade
- CYP3A4 dependent – (drug interactions)

Ivabradine

- Lowers heart rate by ↓ rate of spontaneous diastolic depolarization through I_f current inhibition in SA node
- Produced by French company Servier
- On the marked in several Europ countries
- 2,5-7,5 mg twice daily
- Improve angina symptoms and Ex cap.
- Several randomized studies both against placebo, amlod, BB and on top of BB
- Safe in long-term studies also in reduced LV (Beutiful study)

Beautiful study results

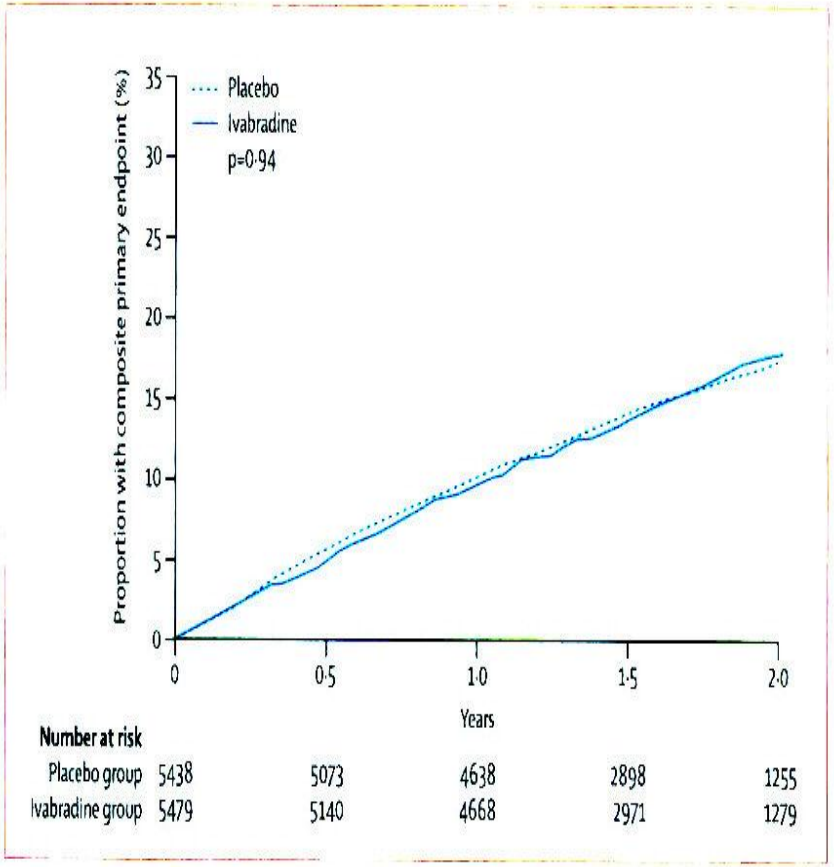


Figure 3: Kaplan–Meier time-to-event plot, by treatment group for composite primary endpoint in the total study population

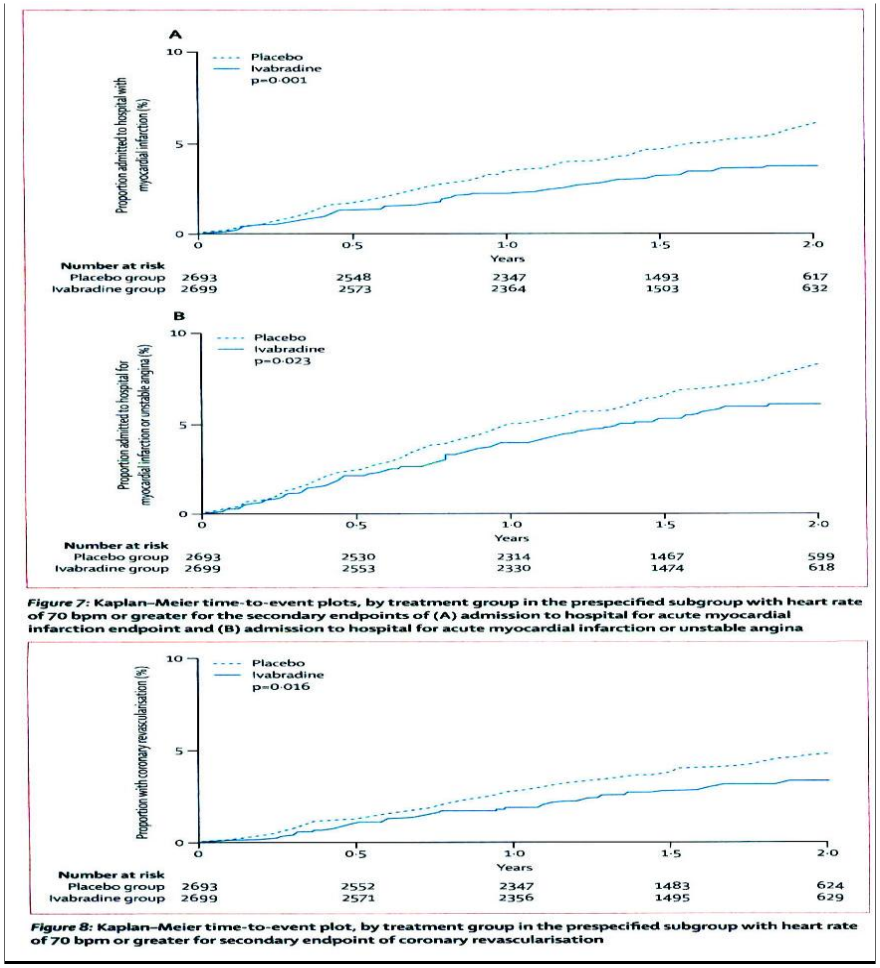


Figure 7: Kaplan–Meier time-to-event plots, by treatment group in the prespecified subgroup with heart rate of 70 bpm or greater for the secondary endpoints of (A) admission to hospital for acute myocardial infarction endpoint and (B) admission to hospital for acute myocardial infarction or unstable angina

Figure 8: Kaplan–Meier time-to-event plot, by treatment group in the prespecified subgroup with heart rate of 70 bpm or greater for secondary endpoint of coronary revascularisation

All patients

Heart rate >70

Ivabradine

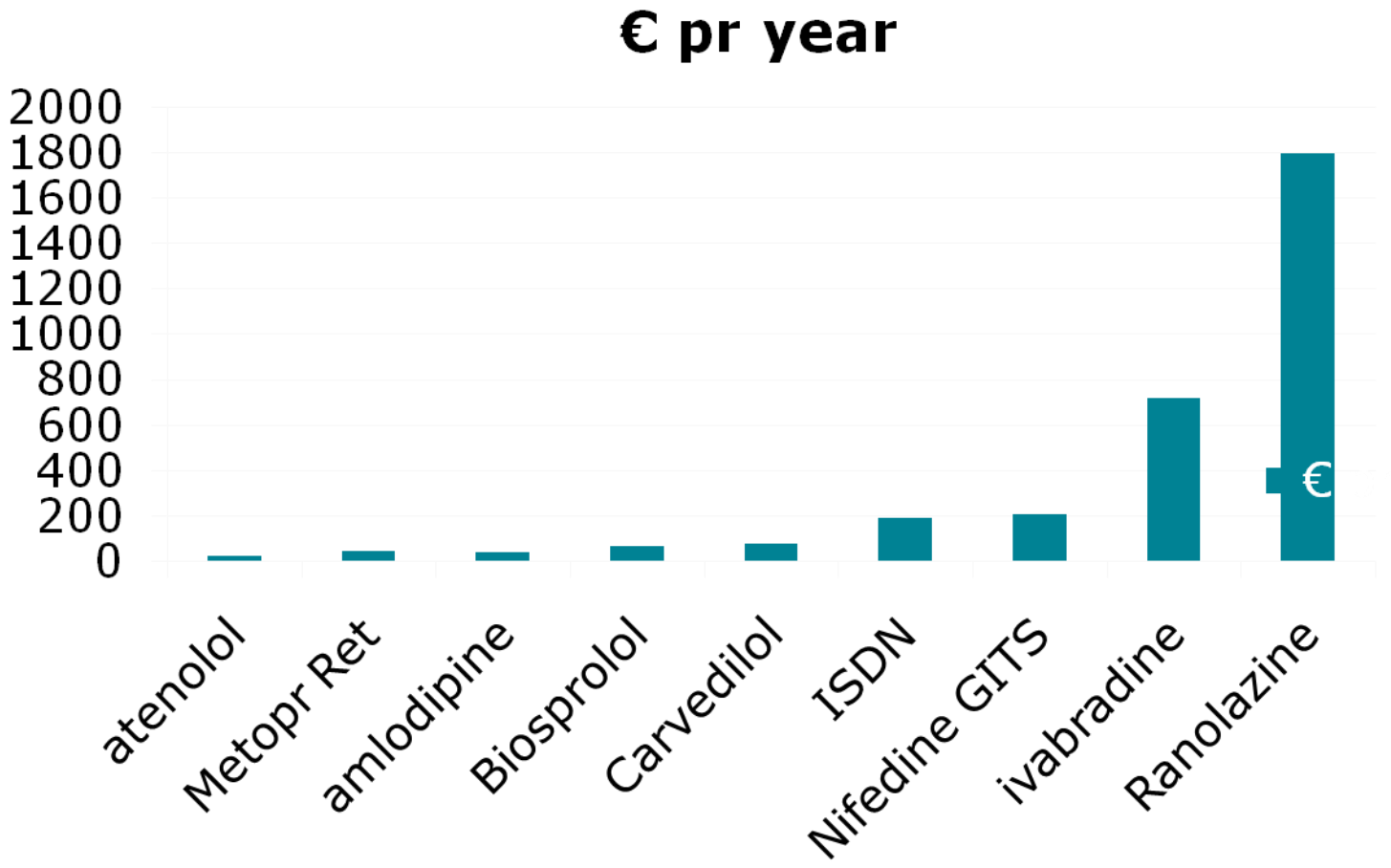
- Best effect if HR > 70 despite BB?
- Side eff: slight visual disturbance
- Bradycardia
- CYP3A4 dependent
- Caution in comb with QT prol. drugs
- € 50-75 / month

NICE recommendation

- People who are intolerant of beta-blockers should be treated with a rate-limiting calcium channel blocker, long-acting nitrate or nicorandil before ivabradine is considered.

- This is because ivabradine has not demonstrated advantages over these drugs in terms of effcacy or safety, and is much more expensive.

Yearly cost in € for old and new angina medications



Nicorandil

- Potassium channel activator
- IONA trial publ 2002 (Lancet 2002 Apr 13;359(9314):1269-75
- reduced the primary end point by 17 percent (13 versus 15.5 for placebo, hazard ratio 0.83, 95% CI 0.72-0.97).
- Very limited use in Europe
- arterial and venous dilator
- improves coronary blood flow due to potassium channel opening and nitrate-like effect.

Fasudil

- vasodilator
- inhibitor of Rho kinase
- JACC 2005 ;46(10):1803-11
- 84 pts doubl blind
- signif greater time to ≥1 mm ST segment depression at both peak (172 versus 44 sec with placebo) and trough (93 versus 24 sec)
- no difference in time to angina, frequency of angina or nitro use
- Also investigated in PAH and subarch haemmorrage

Old drugs new application ?

HEART

High-dose allopurinol prolongs time to exercise-induced ischaemia in chronic stable angina

A Noman, D Ang, CC Lang and AD Struthers

Heart 2009;95;80

Other treatment modalities

- EECP and Spinal Cord Stimulation (SCS)
  - Increasing evidence from randomized studies
- Laser revascularization
  - No new studies
  - Some effect on angina
  - Some negative effect on LV performance
- Newest option: Grow new vessels

Bone Marrow injection

JAMA®

Online article and related content current as of May 19, 2009.

Intramyocardial Bone Marrow Cell Injection for Chronic Myocardial Ischemia: A Randomized Controlled Trial

Jan van Ramshorst; Jeroen J. Bax; Saskia L. M. A. Beeres; et al.

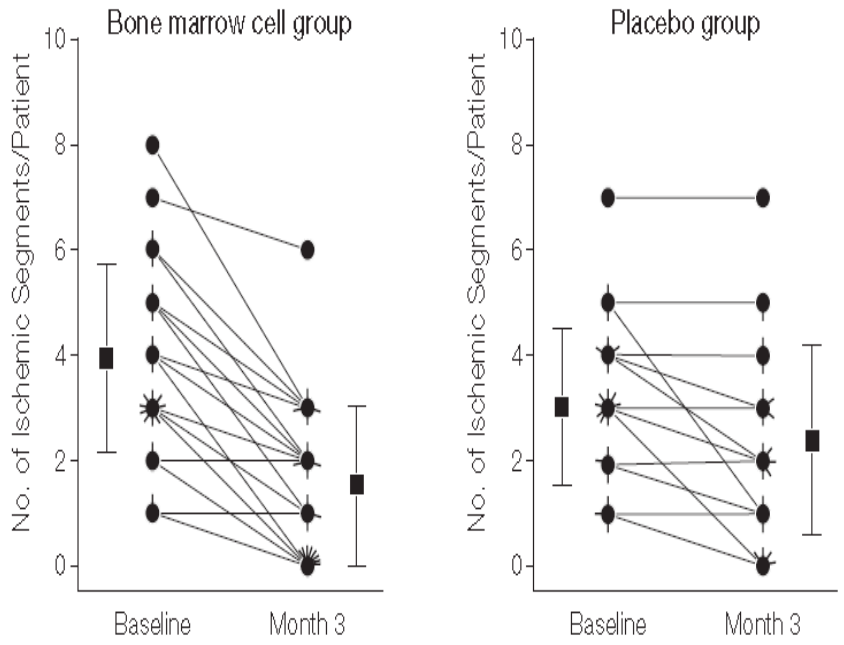
JAMA. 2009;301(19):1997-2004 (doi:10.1001/jama.2009.685)

http://jama.ama-assn.org/cgi/content/full/301/19/1997

50 pts with chronic ischemia 25 inj BM, 25 placeb inj
Intramyoardial injection of ischemic regions
SPEC, echho, Seatle Angina Quest

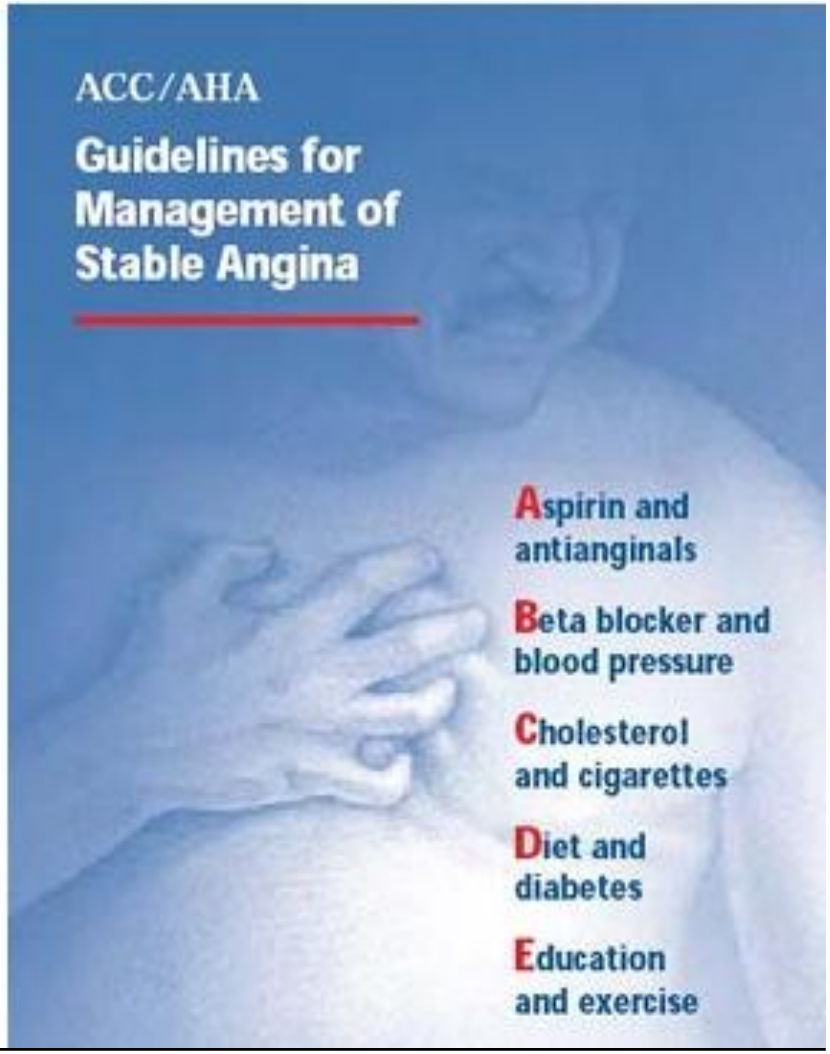
Bone Marrow Injection

Figure 2. Improvements in Segments With Inducible Myocardial Ischemia as Assessed by SPECT



3 months follow up
signif decrease in CCS angina class and increase QL score
3% increase in MR EF

Conclusion: chronic angina



- The Old Truths still hold
- We must always do what we can to achieve the goals with more aggressive conventional therapy
- Some new promising drugs (ranolazin and ivabradine) for difficult cases
- Exercise always underused and understimated
- Increasing evidence for EECP and SCS
- On the horizon: injection therapy ??