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

Per Anton Sirnes
MD, Ph.D  FESC
Private cardiology consultant, Moss, Norway
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?
New guidelines?

PUBLISHED: 2007: ACC/AHA Focus Update (of 2002 guideline) 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 different treatments 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.
Epidemiology of Chronic Stable Angina

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Women</th>
<th>Men</th>
</tr>
</thead>
<tbody>
<tr>
<td>45-55 y</td>
<td>0.5</td>
<td>3</td>
</tr>
<tr>
<td>65-75 y</td>
<td>10-15</td>
<td>10-20</td>
</tr>
</tbody>
</table>

Mortality: 1% pr year

Mycardial infarction 1-3% pr year
### Annual event rate from ESC 2006

<table>
<thead>
<tr>
<th>Condition</th>
<th>Event Rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>At least 20% coronary stenosis</td>
<td>3.5</td>
</tr>
<tr>
<td>Stable CAD</td>
<td>2.5</td>
</tr>
<tr>
<td>Stable angina</td>
<td>2.0</td>
</tr>
<tr>
<td>Stable CAD</td>
<td>1.5</td>
</tr>
<tr>
<td>Pre-existing vascular disease (88%), or DM, and one other risk factor, 55% angina</td>
<td>1.0</td>
</tr>
<tr>
<td>Stable angina, 60% angiographic CAD</td>
<td>0.5</td>
</tr>
<tr>
<td>Diabetes, with (70%) or without (30%) pre-existing vascular disease, and one other risk factor</td>
<td>0.0</td>
</tr>
</tbody>
</table>

#### Studies:
- **CAMELOT**: 2004
- **PEACE**: 2004
- **ACTION**: 2004
- **EUROPA**: 2003
- **HOPE**: 2000
- **IONA**: 2002
- **MICRO-HOPE**: 2000
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

A

Survival Free of Death from Any Cause and Myocardial Infarction

Hazard ratio, 1.05; 95% CI (0.87–1.27); P=0.62

No. at Risk
Medical therapy 1138 1017 959 834 638 408 192 30
PCI 1149 1013 952 833 637 417 200 35

B

Overall Survival

Hazard ratio, 0.87; 95% CI (0.65–1.16); P=0.38

No. at Risk
Medical therapy 1138 1073 1029 917 717 468 302 38
PCI 1149 1094 1051 929 733 488 312 44

C

Survival Free of ACS

Hazard ratio, 1.07; 95% CI (0.84–1.37); P=0.56

No. at Risk
Medical therapy 1138 1025 956 833 662 418 235 127
PCI 1149 1027 957 835 667 431 246 134

D

Survival Free of Myocardial Infarction

Hazard ratio, 1.13; 95% CI (0.89–1.43); P=0.33

No. at Risk
Medical therapy 1138 1019 962 834 638 409 192 120
PCI 1149 1015 954 833 637 418 200 134
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 Medical Rx in COURAGE

- Smoking: Cessation
- Fat: total <30% cal, sat. < 7% of cal
- Dietary cholesterol: <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 metop., 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%
Coronary Intervention for Persistent Occlusion after Myocardial Infarction

Hazard ratio, 1.16; 95% CI (0.92–1.45); P=0.20

Year after Enrollment

PCI group

Medicinal therapy group
BARI 2D

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

<table>
<thead>
<tr>
<th>REVASC</th>
<th>MEDICAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 Year surv %</td>
<td>88.3</td>
</tr>
<tr>
<td>No MACE %</td>
<td>77.2</td>
</tr>
</tbody>
</table>
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?

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Mortality</th>
<th>Symptoms</th>
<th>Reduce risk of MI</th>
<th>Cardiac Function</th>
<th>Arrhythmia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin</td>
<td>?+</td>
<td>0</td>
<td>+</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Statin</td>
<td>+</td>
<td>(?,?)</td>
<td>+</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Beta block</td>
<td>0</td>
<td>+</td>
<td>(+)</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Calc. antag</td>
<td>0</td>
<td>+</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Nitrates</td>
<td>0</td>
<td>+</td>
<td>0</td>
<td>(?,?)</td>
<td>0</td>
</tr>
<tr>
<td>ACE/ARB</td>
<td>+</td>
<td>(?,?)</td>
<td>+</td>
<td>+</td>
<td>(+)</td>
</tr>
<tr>
<td>PCI</td>
<td>0</td>
<td>+</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>CABG</td>
<td>(+)</td>
<td>+</td>
<td>(+)</td>
<td>(+)</td>
<td>0</td>
</tr>
</tbody>
</table>
Drugs to reduce mortality and MI

- **Antiplatelet**
  - Aspirin 75-160mg
  - 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

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Mortality</th>
<th>Symptoms</th>
<th>Reduce risk of MI</th>
<th>Cardiac Function</th>
<th>Arrhythmia</th>
</tr>
</thead>
<tbody>
<tr>
<td>EECP</td>
<td>0</td>
<td>+</td>
<td>0</td>
<td>+</td>
<td>0</td>
</tr>
<tr>
<td>SCS</td>
<td>0</td>
<td>+</td>
<td>0?</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Laser</td>
<td>0/-</td>
<td>(+)</td>
<td>0</td>
<td>-</td>
<td>0</td>
</tr>
<tr>
<td>Bone marrow cells</td>
<td>?</td>
<td>(+)</td>
<td>?</td>
<td>(+)</td>
<td>?</td>
</tr>
<tr>
<td>genVGF</td>
<td>?</td>
<td>?</td>
<td>?</td>
<td>(?+)</td>
<td>?</td>
</tr>
<tr>
<td>Ranolazine</td>
<td>0</td>
<td>+</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Ivabradine</td>
<td>0</td>
<td>+</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
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

% change

Rest HR Isch thresh Max W VO2 max

PCI EXERC

P< 0.05
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, hospital due to angina)

PCI: 21
Ex: 6

Exercise training: the "forgotten" alternative?

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

Ulrik Wisløff, PhD; Asbjørn Støylene, MD, PhD; Jan P. Loennechen, MD, PhD; Morten Bruvold, MSc; Øivind Rognmo, MSc; Per Magnus Haram, MD, PhD; Arnt Erik Tjønna, MSc; Jan Helgenud, 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; Øivind Ellingsen, MD, PhD; Terje Skjærpe, MD, PhD

- Randomized 27 pts (men age 75) with heart failure between intensive interval training and moderate continuous 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
- 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-dihydropyridine
  - Verapamil - long action preferably
    - Negative inotropic caution with BB and depr LV
  - Diltiazem
    - More safely to be combined with BB?
Confirmed long acting nifedipine as a safe drug with some effect on secondary 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 $I_{Kr}$ ($\uparrow$QT)
• Both $I_{na}$ and $I_{Kr}$ inhib. balances the arrhythmic 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 antiarrhythmic 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 placebo
- JAMA. 2007;297:1775–1783
## MERLIN TIMI-36 outcomes

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

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

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 efficacy or safety, and is much more expensive.
Yearly cost in € for old and new angina medications

€ pr year

atenolol
Metoprolol
amlodipine
Biosprolol
Carvedilol
ISDN
Nifedine GITS
ivabradine
Ranolazine
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 double blind
- significant 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 haemorrhage
Old drugs new application?

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

A Noman, D Ang, CC Lang and AD Struthers

*Heart* 2009;85;80
Other treatment modalities

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

Intramyoardial 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.


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

50 pts with chronic ischemia 25 inj BM, 25 placebo 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 underestimated
- Increasing evidence for EECP and SCS
- On the horizon: injection therapy??