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Updated 3/15/13
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Coronary Artery Disease: Revascularization (Teacher's Guide)

(40 minutes)

I. Objectives

- To review the evidence on whether percutaneous coronary intervention (PCI) offers any additional benefit to optimal medical therapy in stable coronary artery disease (CAD)

- To compare the efficacy of PCI versus coronary artery bypass grafting (CABG) in patients with multivessel disease

- To review the accepted indications for CABG in stable CAD

II. Case 1

A 58-year-old man with a history of type II diabetes, hyperlipidemia and a myocardial infarction 3 years ago presents to the emergency room for chest pain at rest lasting 20 minutes. On admission, his pulse is 97 bpm and BP = 157/63 mm Hg, and his exam is otherwise unremarkable. An EKG shows diffuse nonspecific ST/T wave changes. His chest radiograph is normal. The patient is admitted to the hospital, and he rules out for acute coronary syndrome (ACS) with negative serial cardiac enzymes. He is started on an aspirin, beta-blocker and nitroglycerin paste, and he remains free of chest pain. On an exercise treadmill test done the following morning, he develops 1 mm horizontal ST depressions. The patient achieves 7 METS before he has to stop because of fatigue.

Should this patient be referred for a coronary angiogram to evaluate for revascularization?

First, have team members vote on whether they would refer this patient for a coronary angiogram, and ask them to justify their answer.

Ask if this patient has a high, intermediate or low long-term risk of future cardiovascular events. His Duke treadmill score is +2, which places him in the intermediate risk category (5-8% mortality over the next four years). (See "Chest Pain: Diagnosis and Prognosis" module.)

Now ask one of the learners to review the methods of the COURAGE trial, which compared optimal medical therapy to optimal medical therapy plus PCI.[1]

Ask one of the learners to review the study's definition of "optimal medical therapy":[1]
- *Antiplatelet therapy*
- *Anti-ischemic therapy (beta-blocker, nitrates, amlodipine)*
- *Angiotensin-converting enzyme inhibitor or angiotensin-receptor blocker*
- *Aggressive lipid-lowering to an LDL goal of 60-85 mg/dL with a statin $\pm$ ezetimibe*
- *HDL-raising and triglyceride-lowering with exercise, niacin and/or fibrates.*

Now ask one of the learners to summarize the results of the COURAGE trial. The main findings were:
- *No difference in the composite or individual endpoints of death, nonfatal MI or stroke.*
- *Significant increase in the need for repeated revascularization in the optimal medical therapy group.*
- *Greater freedom from angina in the PCI group, especially in the first year.*

Ask learners if they are surprised that there was no decrease in the rate of MI or hospitalization for ACS in the PCI group, and whether they can explain this, pathophysiologically. One explanation is that while significant coronary artery stenoses ($\geq$ 70%) often cause angina, they are usually stable and less likely to rupture. Unstable plaques are often only mildly stenotic, but they are more likely to rupture and cause an ACS.

Ask the team whether the results of this study would apply to the patient in this case. Although he did have class IV angina on admission, it resolved with medical therapy, and he was able to achieve 7 METS on his ETT without recurrent chest pain. He did, however, have objective evidence of ischemia on his ETT, and assuming a coronary angiogram showed a stenotic lesion, this patient would have met inclusion criteria for this trial.

Now that you have reviewed the COURAGE trial, ask team members to vote again on whether they would refer this patient for coronary angiography to evaluate for possible PCI.

Emphasize that PCI was compared to optimal medical therapy, and that it may be necessary to be aggressive in medical treatment and risk factor modification in order to achieve results similar to revascularization. Note the high rates of adherence of participants in this trial.

When should patients generally be evaluated for possible revascularization?

Some of the exclusion criteria for the COURAGE trial include generally accepted indications for revascularization:[1]
- *Class IV angina refractory to medical treatment*
- *Markedly positive stress test (ST depression or hypotension in stage 1 [i.e., less than 5 METS])*
- *Refractory heart failure or cardiogenic shock*
- *Ejection fraction < 30%*
- *Revascularization within the last 6 months*

In addition, patients who developed worsening angina or worsening objective evidence of ischemia on optimal medical therapy during the trial were referred for revascularization.

Note that this trial should not be applied to patients have an acute coronary syndrome. In general, these patients benefit from early revascularization.

II. Case 2

A 61-year-old woman with hypertension and hyperlipidemia is seen in general medicine clinic. She complains of intermittent, stabbing chest pains unrelated to exertion for the past two months. She is currently taking metoprolol, enalapril, simvastatin and aspirin. Her exam is normal. Her baseline EKG shows left ventricular hypertrophy with strain, which is unchanged from a prior EKG. She undergoes a treadmill Sestamibi and stops at 4 METS because of chest pain. The nuclear medicine portion of the exam reveals two large areas of ischemia in the anterolateral and inferior walls. She is referred to the cardiologist, who performs a cardiac catheterization. The angiogram reveals a 90% proximal left anterior descending (LAD) stenosis, an 80% proximal left circumflex stenosis and an 80% mid-right coronary artery (RCA) stenosis. Her left ventricular ejection fraction is 50%.

Should this patient undergo revascularization? If so, should she undergo PCI or CABG?

Ask the team whether this patient would have been enrolled in the COURAGE trial. She meets one of the exclusion criteria (markedly positive stress test in stage 1 of the Bruce protocol), so the COURAGE trial is not applicable to her.[1] Most cardiologists would perform a coronary angiogram in anticipation of revascularization, though strictly speaking, there has never been an RCT comparing optimal medical therapy to PCI in high-risk CAD. There have also been no trials in the modern era comparing optimal medical therapy to CABG in stable CAD with a normal ejection fraction.

Ask your team to vote on whether they would recommend that this patient undergo PCI or CABG.

Now ask one of the learners to summarize the methods of the SYNTAX trial, which compared PCI with drug-eluting stents to CABG in patients with multivessel and/or left main disease.[2]

Ask another learner to summarize the results of the SYNTAX trial.[2] Key findings from this trial were:
- *Decrease in the primary endpoint of major cardiovascular or cerebrovascular events (MACCE), defined as death, MI, stroke or repeat revascularization, in the CABG group (12.4% CABG vs. 17.8% PCI).*
- *Most of this decrease was driven by the decrease in repeat revascularization in the CABG group (5.9% CABG vs. 13.5% PCI)*
- *Small increase in the risk of stroke in the CABG group (2.2% CABG vs. 0.6% PCI)*
- *No difference in the rates of death or MI*

Ask team members whether this study is applicable to the patient in Case 2. (It is.) Ask them to vote again on whether they would recommend PCI or CABG to this patient.

If this patient had type 2 diabetes, would this influence your decision about whether she should undergo PCI or CABG?

Diabetics are more likely than nondiabetics to undergo incomplete revascularization with PCI, which can increase the risk of adverse outcomes.

A meta-analysis of 10 RCTs comparing CABG to PCI in multivessel disease confirmed that there is no overall difference in mortality between the two treatments. However, a subgroup analysis found that CABG confers a survival benefit in patients with diabetes.[4]

The FREEDOM trial addressed the question of revascularization strategies in diabetics with multivessel disease. Ask one of your learners to review the methods of this trial.[3]

Now ask one of your learners to review the major results of this trial. CABG was associated with:
- *Decrease in MI (6.0% vs. 13.9% at 5 years)*
- *Decrease in death (10.9% vs. 16.3% at 5 years)*
- *Decrease in need for repeat revascularization (11.8% vs. 16.8% at 1 year)*
- *Increase in stroke (5.2% vs. 2.4%, with all of the excess in the perioperative period)*

Ask your learners to vote again on whether they would recommend PCI or CABG.

If this patient had an ejection fraction of only 30%, would that influence your decision on whether she should be revascularized? If so, should she undergo PCI or CABG?

There are no trials comparing PCI to optimal therapy or CABG in patients with low ejection fraction (EF). COURAGE excluded these patients, and only 5% of SYNTAX patients had a low EF.

Review the methods and results of the STICH trial, which compared medical therapy with CABG to medical therapy alone.[5] The key findings were:
- *Statistically non-significant trend towards decreased all-cause mortality in the CABG group at 5 years (41% medical therapy vs. 36% CABG)*
- *Trend towards decreased cardiovascular mortality in the CABG group at 5 years (33% medical therapy vs. 28% CABG)*

If one assumes the trend in decreased mortality is real, patients with a low EF who undergo CABG increase their short-term, 30-day mortality (ARI = 3%) in exchange for a modest reduction in 5-year mortality (ARR = 5%). Ask your learners whether they would consider the trade-off a reasonable one.

Emphasize that the bottom line in both of the above cases is to discuss all the treatment options with the patients, their pros and cons, and to involve them in the decision-making process.

III. Questions for Further Discussion

Should fractional flow reserve be measured to determine the appropriateness of revascularization with PCI?

The FFR is the ratio of maximum blood flow in a stenotic artery to maximum blood flow if the same artery were normal. For example, an FFR of 0.80 means that the maximum blood flow to the myocardial distribution of that artery reaches only 80% of what it would be if that artery were completely normal. A low FFR identifies a stenosis as having the potential to induce myocardial ischemia. FFR measurement is performed using a pressure transducer wire at the time of angiography.

The FAME-2 trial enrolled patients with stable CAD who had FFR measurements of their stenoses.[6] Patients who had an FFR > 0.80 did not undergo PCI and received optimal medical therapy only. Patients who had an FFR $\leq$ 0.80 were

randomized to PCI with optimal medical therapy vs. optimal medical therapy alone.

The randomized portion of the trial was stopped early because patients in the PCI group were less likely to require urgent revascularization than those receiving only optimal medical therapy (1.6% vs. 11.2%). There were no differences in the rates of MI or death. Patients in the registry who had an FFR > 0.80 did well with optimal medical therapy alone, with a 3% rate in the primary endpoint of death, MI or urgent revascularization at 7 months.

Ask your team members whether they think the FAME-2 strategy for managing stable CAD should supplant the strategy for optimal medical therapy outlined in COURAGE.

Some cardiologists argue that a high FFR can be used to reduce the number of unnecessary stents inserted, since a quarter of the patients in FAME-2 had an FFR > 0.80. However, even in patients with low FFRs, elective PCI reduces only the need for urgent revascularization, and not the rates of MI or death. Moreover, FFR measurement requires invasive coronary angiography and adds to the overall cost of the procedure.

IV. Key Articles

1. Boden W, *et al.* for the COURAGE Trial Research Group. Optimal medical therapy with or without PCI for stable coronary artery disease. *N Engl J Med* 2007; 356: 1503-16. FULL TEXT PDF

Methods

- Randomized, controlled trial of 2287 patients with stable CAD
- Inclusion criteria:
  -- $\geq$ 70% stenosis in $\geq$ 1 proximal coronary artery and objective evidence of myocardial ischemia OR
  -- $\geq$ 80% stenosis in $\geq$ 1 coronary artery without provocative testing
- Exclusion criteria:
  -- Persistent class IV angina
  -- Markedly positive stress test (substantial ST-depression or hypotension during stage 1 of Bruce protocol)
  -- Refractory heart failure or cardiogenic shock
  -- EF < 30%
  -- Recent revascularization, or coronary anatomy not suitable for PCI
- Randomized to PCI plus optimal medical therapy versus optimal medical therapy alone.
- Optimal medical therapy defined as:
  -- Aspirin or clopidogrel (patients received both if undergoing PCI)
  -- Anti-ischemic therapy with metoprolol, amlodipine and/or nitrates
  -- Lisinopril or losartan
  -- Aggressive lipid lowering of LDL to between 60-85 mg/dL, raising of HDL and lowering of triglycerides
- Primary outcome: Death or nonfatal MI

Results

- Baseline characteristics similar between the two groups
  -- 1/3 single-vessel disease, 2/3 multivessel disease
  -- Similar medical treatment in both groups, with high rates of adherence
- After a median follow-up of 4.6 years:
  -- No difference in the primary outcome of death or nonfatal MI (19% PCI vs. 18.5% medical therapy).
  -- No difference in secondary endpoints of death, nonfatal MI and stroke; hospitalization for acute coronary syndrome; MI alone; or death alone.
  -- Patients in the medical therapy group were more likely to undergo subsequent revascularization (21% PCI vs. 33% medical therapy), which was usually performed for angina unresponsive to maximal medical therapy or progressive ischemia on noninvasive testing.
  -- Patients in the PCI group were more likely to be free of angina than the medical therapy group at 1 year (66% PCI vs. 58% medical therapy), but

there was no difference by 5 years.
-- Subgroup analysis did not identify any subgroups that had a better outcome with PCI.

Limitations

- Referral bias may have led to the exclusion of patients with the most severe disease. (For example, may cardiologists would not refer a patient with a 99% ostial stenosis of the LAD to the study.)
- Trial was nonblinded, so increased improvement in angina in the PCI group might have been due in part to the placebo effect
- Most of the patients in the PCI group received bare-metal and not drug-eluting stents.
- High rates of adherence to aggressive medical therapy may limit generalizability of this study.
- 85% of the trial participants were male, limiting its applicability to women.

2. **Serruys P, *et al*. for the SYNTAX Investigators. Percutaneous coronary intervention versus coronary-artery bypass grafting for severe coronary artery disease. *N Engl J Med* 2009; 360: 961-72.** FULL TEXT PDF

Methods

- Randomized, controlled trial of PCI with paclitaxel-eluting stents vs. CABG
- Inclusion criteria:
  -- Three-vessel and/or left main disease, in which equivalent revascularization could be achieved with either PCI or CABG
  -- Stenoses had to be $\geq$ 50%, and patients had to have either angina or objective evidence of myocardial ischemia
- Exclusion criteria:
  -- Previous PCI or CABG
  -- Acute myocardial infarction
- Randomization stratified at each site according to presence or absence of left main disease and medically treated diabetes
- Primary clinical endpoint of major adverse cardiac or cerebrovascular events (MACCE): death, stroke, myocardial infarction or repeat revascularization at 12 months.
- SYNTAX scores, which measure the complexity of anatomical lesions, were calculated, and rates of MACCE were analyzed based on this score.

Results

- 1800 patients randomized
- In-hospital rates of MACCE were similar between the two groups
- At 12 months, incidence of MACCE lower in the CABG group (12.4%) than the PCI group (17.8%)

> -- ARR = 5.4%, NNT = 19

- Secondary endpoints:
  -- Higher rates of repeat revascularization in the PCI group (13.5%) than the CABG group (5.9%)
  -- Higher rates of stroke in the CABG group (2.2%) than the PCI group (0.6%)
  -- Similar rates of death and myocardial infarction
- Subgroup analysis:
  -- Rates of MACCE similar in CABG and PCI groups in patients with low SYNTAX score (*i.e.*, those with less complex lesions)
  -- Rates of MACCE higher in PCI groups in patients with intermediate to high SYNTAX scores (i.e., those with more complex lesions).
  -- In patients with left main disease, rates of MACCE similar between CABG and PCI groups.
  > -- Increased rate of revascularization in PCI group partially offset by increased rate of stroke in CABG group.

  -- In patients with three-vessel disease, without left main disease, the rate of MACCE was higher in the PCI group, driven mainly by the rate of repeat revascularization.

Limitations

- Overall rates of repeat revascularization in the PCI group were lower than those reported in other studies.
- Fewer patients in the CABG group than the PCI group were on clopidogrel. This would tend to reduce the benefit seen with CABG.
- The 12-month period of follow-up may be insufficient to detect long-term benefits, especially of CABG.
- Only 5% of patients enrolled had congestive heart failure, so the results may not be applicable to them.

3. **Farkouh M, *et al*. for the FREEDOM Trial Investigators. Strategies for multivessel revascularization in patients with diabetes. *N Engl J Med* 2012; 367: 2375-84.** ABSTRACT

Methods

- Randomized, controlled trial of drug-eluting stents vs. CABG in about 2,000 patients with diabetes and multivessel coronary artery disease, without left main stenosis or left ventricular dysfunction
- Both groups received optimal medical therapy, with cholesterol, blood pressure and diabetes control, and dual antiplatelet therapy in PCI patients.
- Primary outcome was composite of death, nonfatal MI and nonfatal stroke.

Results

- Primary outcome lower in the CABG group: 18.7% vs. 26.6% at 5 years
  -- ARR = 7.9%, NNT = 13
  -- Curves began to diverge at 2 years
- CABG also associated with:
  -- Reduction in MI (6.0% vs. 13.9% at 5 years)
  -- Reduction in mortality (10.9% vs. 16.3% at 5 years)
  -- Increase in stroke (5.2% vs. 2.4% at 5 years)
  -- Lower rates of revascularization (4.8% vs. 12.6% at 1 year)
- Benefit of CABG was consistent in all prespecified subgroups, including those with lower SYNTAX scores (i.e., less complex anatomy)

V. Reference Articles

4. Hlatky M, *et al.* Coronary artery bypass surgery compared with percutaneous coronary interventions for multivessel disease: a collaborative analysis of individual patient data from ten randomised trials. *Lancet* 2009; 373: 1190-7. ABSTRACT

Methods

- Meta-analysis of individual patient data from 10 RCTs (7812 patients) comparing CABG to PCI in patients with multivessel CAD
  -- 6 trials used balloon angioplasty without stenting in the PCI arm, while 4 trials used bare metal stents
- Primary outcome was all-cause long-term mortality
- Primary research question was whether survival after CABG or PCI was modified by the patient's baseline clinical characteristics

Results

- No overall difference in short-term (90 days) or long-term (5.9 years) mortality
  -- At 5.9 years, 15% of CABG patients died, compared to 16% of PCI patients (P = NS)
- Subgroups that showed a mortality benefit of CABG over PCI were:
  -- Diabetics: 23% in CABG group vs. 29% in PCI group
  -- Age > 65 yrs
- No significant difference in survival, based upon whether patients received balloon angioplasty or BMS.

Limitations

- Multiple subgroup analyses (at least 14) may have produced some significant findings by chance.
  -- Effect of age on response to treatment modality has not been reported in any previous RCTs.
- Did not analyze any trials that used drug-eluting stents

5. Velazquez E, _et al_. for the STICH Investigators. Coronary-artery bypass surgery in patients with left ventricular dysfunction. _N Engl J Med_ 2011; 364: 1607-16. FULL TEXT PDF

Methods

- Randomized, multicenter, non-blinded study comparing medical therapy to medical therapy plus CABG in 1212 patients with CAD and EF $\leq$ 35%.
- Patients excluded from study if they had a significant left main stenosis or class III or IV angina on medical therapy.
- Primary outcome of all-cause mortality at 5 years

Results

- 30-day mortality significantly higher in CABG group: 1% medical therapy vs. 4% CABG
- Intention-to-treat analysis found no difference in all-cause mortality at 5 years: 41% medical therapy vs. 36% CABG
- Per protocol and on treatment analysis did find significant reductions in all-cause mortality in the CABG group
- Trend towards decreased cardiovascular mortality in the CABG group: 33% medical therapy vs. 28% CABG
- Statistically significant reduction in combined endpoint of death or hospitalization for CV causes: 68% medical therapy vs. 58% CABG

Limitations

- Large number of cross-overs likely minimized the difference in mortality in the medical therapy and CABG groups.
- Very high rates of medical adherence in both groups, limiting the generalizability.

6. DeBruyne B, _et al_. Fractional flow reserve-guided PCI versus medical therapy in stable coronary artery disease. _N Engl J Med_ 2012; 367: 991-1001. ABSTRACT

Methods

- Inclusion criteria:
  -- Class I-III angina *or* class IV angina (since stabilized) *or* asymptomatic, with documented ischemia on noninvasive testing
  -- At least one coronary artery stenosis
- All patients underwent fractional flow reserve (FFR) measurement. Patients who had an FFR $\leq$ 0.80 were randomized to PCI with optimal medical therapy vs. optimal medical therapy alone
- Patients with an FFR > 0.80 did not undergo PCI, and were entered into a registry
- Primary composite endpoint: death, nonfatal MI or urgent revascularization
- Planned to randomized 1600 patients and follow them for 2 years

Results

- About 75% of patients had an FFR $\leq$ 0.80 and were randomized
- Study stopped early at about 7 months, after 888 patients were randomized, because of a significant reduction in the primary endpoint (4.3% PCI vs. 12.7% medical therapy)
- The difference in the primary endpoint was due to solely to a reduction in urgent revascularization. There was no difference in MI or death rates.
- Patients in the registry who had an FFR > 0.80 were low risk, with only 3% experiencing the primary endpoint

Limitations

- Symptomatic patients were not required to have documented ischemia to enter this trial. Many patients may have undergone unnecessary coronary angiography as a result.
- No formal stopping rules had been established. Trial was terminated because of the subjective endpoint of need for revascularization, not because of any difference in objective endpoints of MI or death.

VI. Resources

7. Patel M, *et al.* ACCF/SCAI/STS/AATS/AHA/ASNC/HFSA/SCCT 2012 Appropriate Use Criteria for Coronary Revascularization Focused Update. *J Am Coll Cardio*l 2012; 59: 857-81. FULL TEXT PDF

Practice guidelines rating revascularization as appropriate, uncertain or inappropriate in different clinical and angiographic scenarios.