International Study of Comparative Health Effectiveness With Medical and Invasive Approaches - ISCHEMIA

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References

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The ISCHEMIA trial failed to show that routine invasive therapy was associated with a reduction in major adverse ischemic events compared with optimal medical therapy among stable patients with moderate ischemia.

Description:

The goal of the trial was to evaluate routine invasive therapy compared with optimal medical therapy among patients with stable ischemic heart disease and moderate to severe myocardial ischemia on noninvasive stress testing.

Study Design

- Randomized
- Parallel

Patients with stable ischemic heart disease and moderate to severe ischemia were randomized to routine invasive therapy (n = 2,588) versus medical therapy (n = 2,591).

In the routine invasive therapy group, subjects underwent coronary angiography and percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) as appropriate.

In the medical therapy groups, subjects underwent coronary angiography only for failure of medical therapy.

- Total number of enrollees: 5,179
- Duration of follow-up: 3.3 years
- Mean patient age: 64 years
- Percentage female: 23%
- Percentage with diabetes: 41%

Inclusion criteria:

- Patients >20 years of age
- Moderate to severe ischemia on noninvasive stress testing (nuclear ≥10% ischemia; echo ≥3 segments of ischemia; cardiac magnetic resonance ≥12% ischemia and/or ≥3 segments with ischemia; exercise treadmill test ≥1.5 mm ST depression in ≥2 leads or ≥2 mm ST depression in single lead at <7 METs with angina)

Exclusion criteria:

- ≥50% left main stenosis (from blinded computed tomography)
- Advanced chronic kidney disease (estimated glomerular filtration rate <30 ml/min)
- Recent myocardial infarction
- Left ventricular ejection fraction <35%
- Left main stenosis >50%
- Unacceptable angina at baseline
- New York Heart Association class III-IV heart failure
- Prior PCI or CABG within last year

Angina frequency at baseline:

- None, 34%
- Several times per month, 44%
- Daily/weekly, 22%

Other salient features/characteristics:

- Over the entire follow-up period, cardiac catheterization was performed in 96% of the invasive group vs. 28% of the medical therapy group
- Over the entire follow-up period, coronary revascularization was performed in 80% of the invasive group vs. 23% of the medical therapy group

Principal Findings:

The primary outcome of cardiovascular death, myocardial infarction, resuscitated cardiac arrest, or hospitalization for unstable angina or heart failure at 3.3 years occurred in 13.3% of the routine invasive group compared with 15.5% of the medical therapy group (p = 0.34). The findings were the same in multiple subgroups.

Invasive therapy was associated with harm (~2% absolute increase) within the first 6 months and benefit within 4 years (~2% absolute decrease).

Secondary outcomes:

- Cardiovascular death or myocardial infarction: 11.7% of the routine invasive group compared with 13.9% of the medical therapy group (p = 0.21)
- All-cause death: 6.4% of the routine invasive group compared with 6.5% of the medical therapy group (p = 0.67)
- Periprocedural myocardial infarction: (invasive/conservative hazard ratio [HR] 2.98, 95% confidence interval [CI] 1.87-4.74)
- Spontaneous myocardial infarction: (invasive/conservative HR 0.67, 95% CI 0.53-0.83)

<u>Myocardial infarction:</u>

- The primary definition of procedural myocardial infarction used creatine kinase-myocardial band (CK-MB) (>5 x upper reference limit [URL] for PCI and >10 x URL for CABG). Procedural myocardial infarction accounted for 20.1% of all myocardial infarctions.
- A spontaneous myocardial infarction was associated with a 2.4-fold increased hazard for all-cause mortality (p < 0.001) and a 3.4-fold increased hazard for

cardiovascular mortality compared with no myocardial infarction (p < 0.001).
- A procedural myocardial infarction was not associated with all-cause mortality (HR 1.14, 95% CI 0.42-3.08) or cardiovascular mortality compared with no myocardial infarction (HR 1.99, 95% CI 0.73-5.43).

Quality of life outcomes:

- Seattle Angina Questionnaire (SAQ) summary score at 3 months for invasive vs. conservative therapy:
  - 4.1 points (95% credible interval 3.2 to 5.0) overall
  - 8.5 points (95% credible interval 5.8 to 11.1) daily/weekly angina at baseline
  - 5.5 points (95% credible interval 4.3 to 6.9) monthly angina at baseline
  - 0.1 points (95% credible interval -1.2 to 1.4) no angina at baseline
- SAQ summary score at 12 months for invasive vs. conservative therapy:
  - 4.2 points (95% credible interval 3.3 to 5.1) overall
- SAQ summary score overall follow-up for invasive vs. conservative therapy:
  - 1.4 points (95% credible interval 0.2 to 2.5) overall
  - Among patients with more frequent angina at baseline (SAQ angina frequency score <80), those randomized to invasive therapy had a mean 3.7-point higher SAQ-summary score than conservative therapy (95% credible interval 1.6 to 5.8) with consistent effects across SAQ subscales.
  - Similar findings were observed for the Duke Activity Status Index (DASI). There was no difference overall for invasive vs. conservative therapy; however, for those with more frequent angina at baseline (SAQ angina frequency score <80) DASI score was 3.2 points higher (95% credible interval 0.6 to 5.7) for invasive vs. conservative therapy.
- Complete revascularization was associated with a greater improvement in angina-related quality of life than incomplete revascularization, especially among participants with baseline weekly/daily angina

Relationship of myocardial ischemia and coronary anatomy on 4-year clinical outcomes:

- There was no association between degree of ischemia and all-cause mortality (p for trend = 0.33). There was a weak association between degree of ischemia and myocardial infarction (p for trend = 0.04).
- There was an association between extent of coronary disease (modified Duke prognostic score) on all-cause mortality (p for trend < 0.001) and myocardial infarction (p for trend < 0.001).
- The invasive vs. conservative relationship on mortality was similar regardless of degree of ischemia (p for interaction = 0.56).

- The invasive vs. conservative relationship on myocardial infarction was similar regardless of degree of ischemia (p for interaction = 0.86).
- The invasive vs. conservative relationship on cardiovascular death or myocardial infarction was similar regardless of degree of ischemia (p for interaction = 0.86).
- The invasive vs. conservative relationship on mortality was similar regardless of extent of coronary disease (p for interaction = 0.89).
- The invasive vs. conservative relationship on myocardial infarction was similar regardless of extent of coronary disease (p for interaction = 0.49).
- The invasive vs. conservative relationship on cardiovascular death or myocardial infarction was similar regardless of extent of coronary disease (p for interaction = 0.33).

Relationship of diabetes on clinical outcomes:

- There was no difference in death or myocardial infarction between invasive vs. conservative strategies for participants with vs. without diabetes

Relationship of invasive vs. conservative treatment strategies on recurrent and total cardiovascular outcomes:

- There was no difference in invasive vs. conservative treatment strategies on prevention of net recurrent events or net total events

Relationship of heart failure on clinical outcomes:

- Among subjects with heart failure/left ventricular dysfunction, the cumulative incidence rate was 22.7 compared with 13.8 among those without heart failure/left ventricular dysfunction. Among those with heart failure/left ventricular dysfunction, invasive versus conservative therapy was associated with a lower rate of the primary outcome (17.2% vs. 29.3%). Among those without heart failure/left ventricular dysfunction, invasive therapy was not associated with benefit (13.0% vs. 14.6%; p-interaction = 0.055).

Relationship of complete revascularization on clinical outcomes:

- Among those randomized to invasive therapy, the effect of complete revascularization (anatomical assessment) vs. incomplete revascularization on the primary outcome (HR 0.79, p = 0.22)
- Among those randomized to invasive therapy, the effect of complete revascularization (functional assessment) vs. incomplete revascularization on the primary outcome (HR 0.96, p = 0.80)

Extended follow-up, median follow-up 5.7 years:

- All-cause mortality: 12.7% in the invasive group vs. 13.4% in the medical therapy group (p = 0.74)
- Cardiovascular mortality: 6.4% in the invasive group vs. 8.6% in the medical therapy group (p = 0.008)
- Noncardiovascular mortality: 4.4% in the invasive group vs. 5.6% in the medical therapy group (p = 0.016)

Health status in older adults:

- Difference in 1-year SAQ summary score: 4.90 at age 55, 3.48 at age 65, 2.13 at age 75 years (p for interaction = 0.008)
- Improvement in SAQ Angina Frequency was less dependent on age (p for interaction = 0.08)

Interpretation:

Among patients with stable ischemic heart disease and moderate to severe ischemia on noninvasive stress testing, routine invasive therapy failed to reduce major adverse cardiac events compared with optimal medical therapy. There was possible enhanced benefit for invasive compared with conservative therapy among those with heart failure/left ventricular dysfunction. There was also no benefit from invasive therapy regarding all-cause mortality or cardiovascular mortality/myocardial infarction. One-third of subjects reported no angina symptoms at baseline. There was a modest improvement in symptom benefit at 3 months, especially among those with daily/weekly angina, which persisted to 12 and 36 months. Routine invasive therapy was associated with harm at 6 months (increase in periprocedural myocardial infarctions) and associated with benefit at 4 years (reduction in spontaneous myocardial infarction). Procedural myocardial infarctions were not associated with an increase in all-cause or cardiovascular mortality, while spontaneous myocardial infarctions were associated with an increase in all-cause or cardiovascular mortality. These results do not apply to patients with current/recent acute coronary syndrome, highly symptomatic patients, left main stenosis, or left ventricular ejection fraction <35%.

Severe ischemia on stress testing was associated with myocardial infarction, while severe extent of coronary disease (modified Duke prognostic score) was associated with both mortality and myocardial infarction. However, the overall lack of benefit for invasive vs. conservative therapy was similar among those with severe ischemia on noninvasive testing and extensive coronary disease.