# *What We Will Learn From FREEDOM and ISCHEMIA Trials?*

**Mun K. Hong, MD, FACC, FSCAI**

**Director, Cardiac Catheterization Laboratory**

**& Interventional Cardiology**

**St. Luke's-Roosevelt Hospital Center**

**New York, New York**

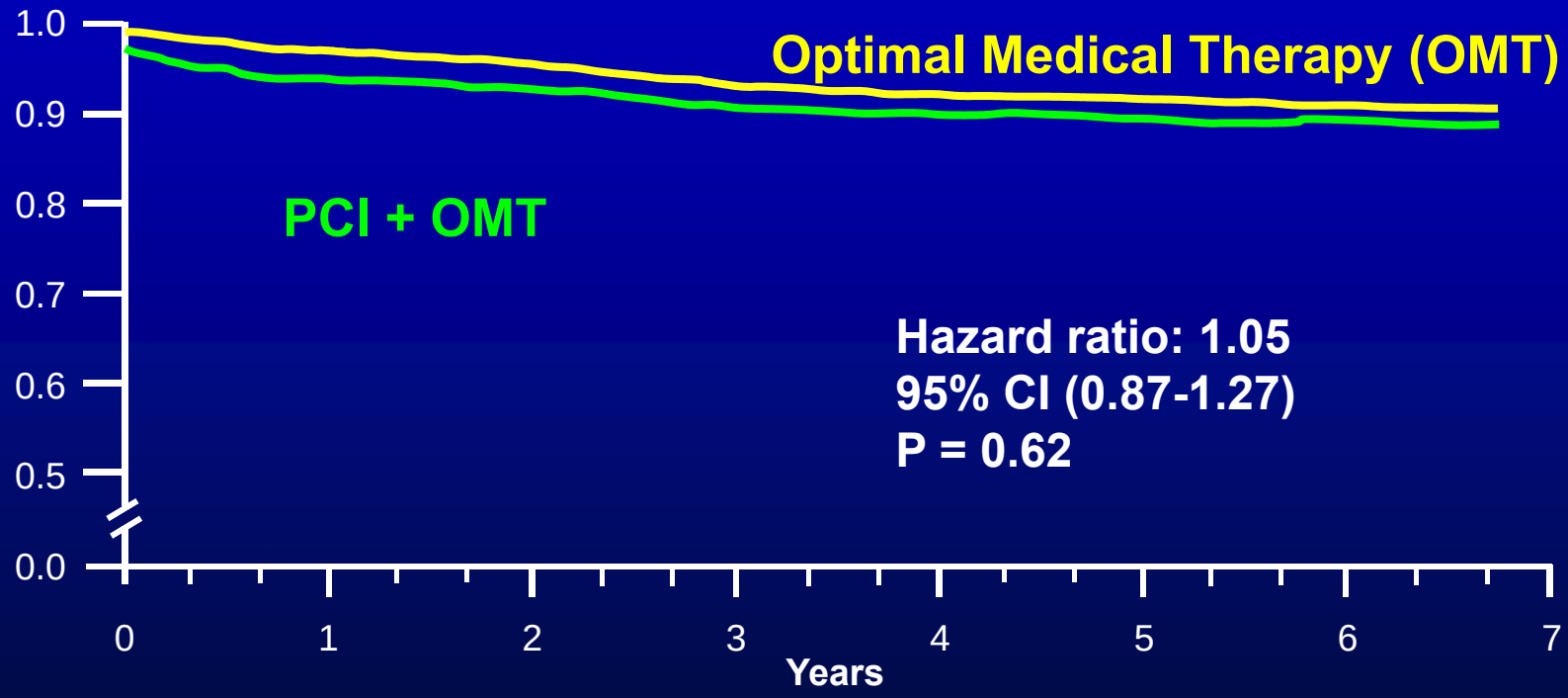
***What we would like to learn ≠***
***What we are likely to learn***

**Consequences =**
**More confusion and**
**reinforced biases**

# *ISCHEMIA TRIAL*

***International Study of Comparative Health Effectiveness with Medical and Invasive Approaches***

# *PCI did not reduce death or MI in Stable IHD Patients*




**Number at Risk**

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Medical Therapy | 1138 | 1017 | 959 | 834 | 638 | 408 | 192 | 30 |
| PCI | 1149 | 1013 | 952 | 833 | 637 | 417 | 200 | 35 |

Boden et al NEJM 2007

# *COURAGE Serial Nuclear Substudy: Outcomes in 105 Patients with Moderate-to-Severe Baseline Ischemia Who Returned for 2nd Study @ 6-18 months*

**A: PCI Reduces Ischemia Better than OMT Alone**

% of patients with mod-severe ischemia at baseline and significant reduction in ischemia at follow-up:

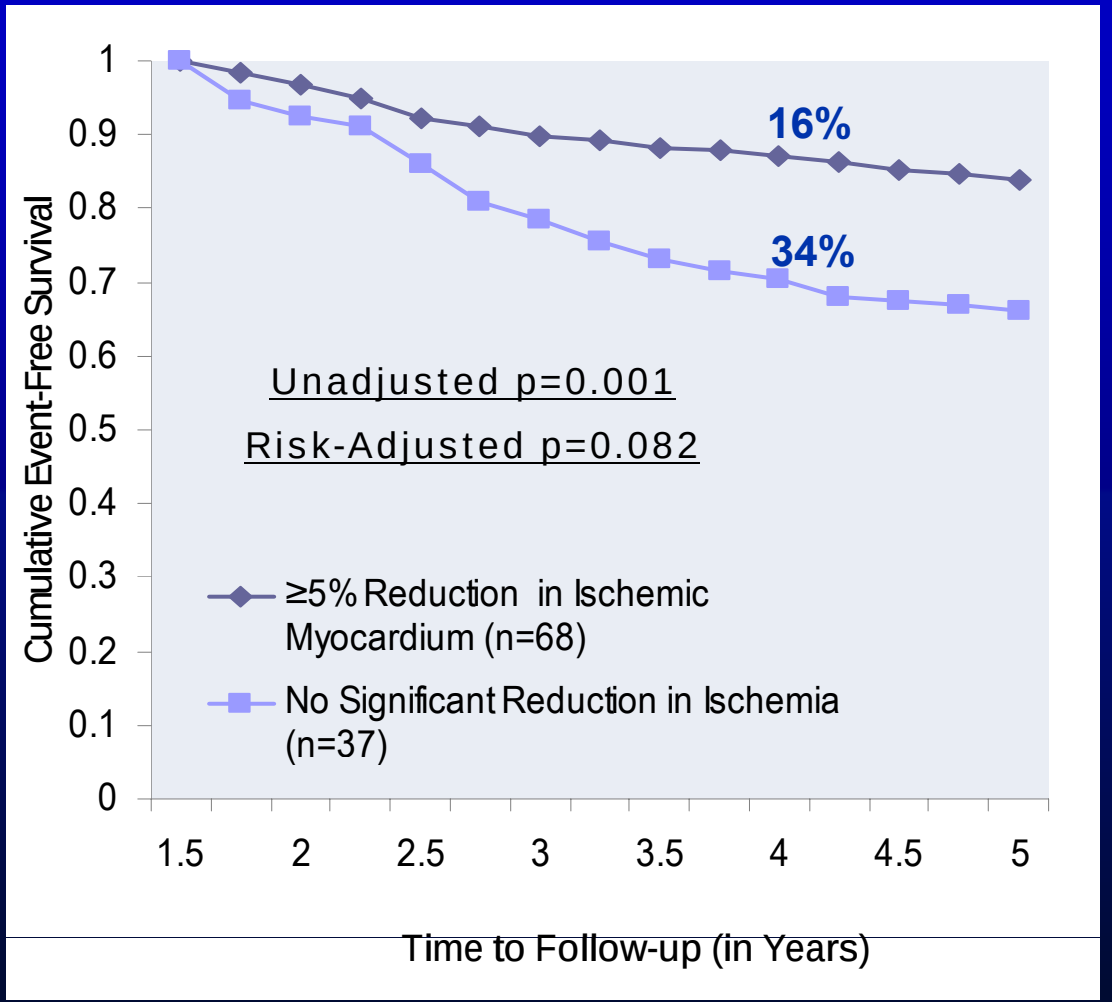
**PCI: 78%**

**OMT: 52% (*P*=0.007)**

**B: For Both Groups Combined, Ischemia Reduction Is Associated with Less Events**

Rate of death/MI over 3.5 years was 16% among patients with significant ischemia reduction compared with 34% without

**C: Does PCI Reduce Events?**

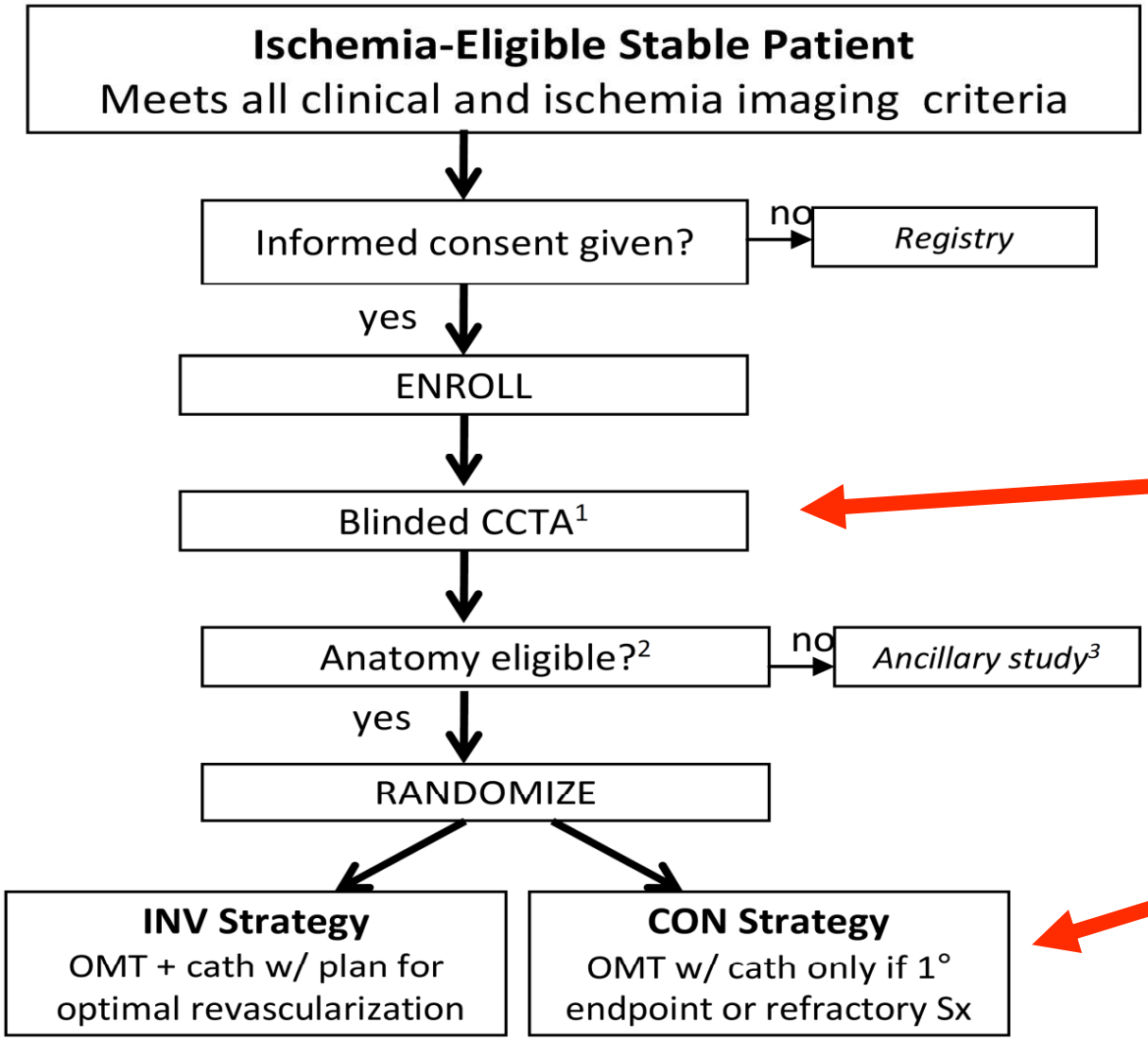



Shaw et al. *Circulation*. 2008;117:1283-1291.

# *ISCHEMIA TRIAL*

Chair- Judith Hochman, PI - David Maron
Co-PI's William Boden, Bruce Ferguson, Robert Harrington, Gregg Stone, David Williams

- **Patients: at least moderate ischemia, EF ≥35%**
- **Hypothesis: an initial invasive strategy of cath and optimal revascularization (PCI or CABG) + OMT is *superior* to a conservative strategy of OMT alone with cath reserved for OMT failure**
- **Composite Primary Endpoint: CV death, MI, or hospitalization for UA, resuscitated cardiac arrest, or heart failure (adjudicated)**
- **Secondary Aim—Major: test hypothesis that invasive strategy improves angina-related QOL compared with OMT alone**
- **Sample Size: 8,000**
- **Follow-up: average ~4 years**




[1] CCTA will not be performed in patients with eGFR<60 ml/min

[2] Exclude and register left main disease patients and <50% stenosis in all major epicardial coronary arteries

[3] Funding for this ancillary study will be sought via a separate application

# *Inclusion Criteria*

- **Men or women 21 years or older who fulfill one of the following ischemia eligibility criteria:**

| Nuclear Perfusion | Echo/CMR Wall Motion | CMR Perfusion |
|---|---|---|
| **≥10% myocardium** | **≥3/16 segments with stress-induced severe hypokinesis or akinesis** | **≥12.5% myocardium** |

# *Exclusion Criteria*

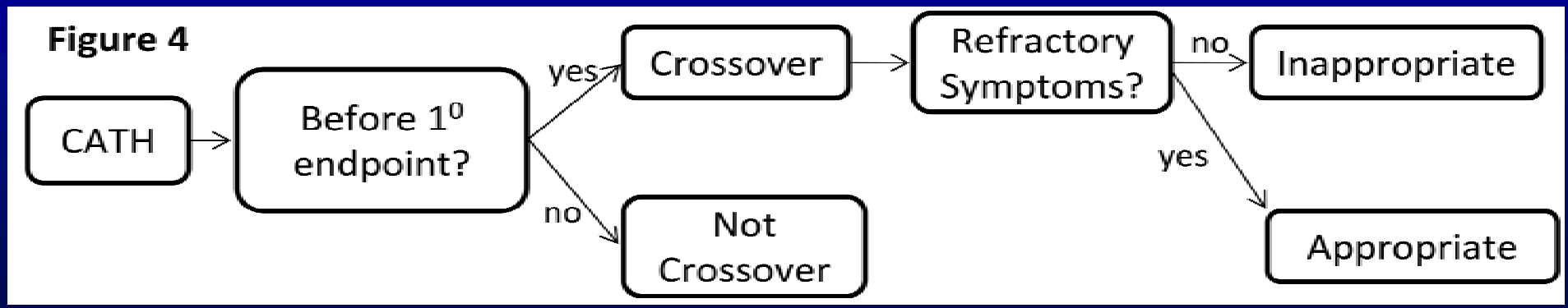
- Unprotected left main ≥50% on pre-randomization CCTA or prior cardiac catheterization
- LVEF<35%
- No obstructive CAD (defined as ≥50% stenosis) on pre-randomization CCTA or prior cardiac catheterization with the previous 12 months
- Unacceptable angina despite maximal medical therapy
- ACS with the previous 2 months
- PCI or CABG with the previous 12 months
- Sustained or symptomatic VT
- Stroke within the previous 6 months or ICH at any time
- Unsuitable for PCI or CABG based on prior known anatomy
- ASA, P2Y12 inhibitor, or heparin allergy
- Contrast allergy that cannot be adequately pre-medicated

# *Exclusion Criteria*

- NYHA class III-IV heart failure at entry or hospitalization for chronic heart failure within the last 6 months
- Non-ischemic cardiomyopathy/HCM
- Severe valvular disease or valvular disease likely to require surgery within 5 years
- Planned surgery within the next 12 months
- Life expectancy <5 years due to non-cardiovascular co-morbidity
- ESRD on dialysis or GFR<30ml/min
- Pregnancy
- Refusal to give informed consent
- Inability to cooperate with the protocol
- Physician refusal to allow patient to participate

# *Cath in Patients Randomized to CON*

- **Cath will be reserved only for patients who have ACS or whose symptoms are refractory to OMT**



***ACCURACY OF NON-INVASIVE STUDY?***

***CONFOUNDING BY CROSS-OVER?***

***EXCLUSION OF PATIENTS LIKELY TO BENEFIT FROM INVASIVE THERAPY?***

# *What will we learn from the ISCHEMIA trial?*

- **Initial invasive strategy for patients with stable ischemic heart disease does not appear to improve CV death, MI, or hospitalization for UA, resuscitated cardiac arrest, or heart failure.**
- **This study will likely confirm the COURAGE overall results, even with moderate to severe ischemic burden.**
- **The results will provide more armamentarium to further reduce referrals for invasive procedures.**

# *What do we want to learn from the ISCHEMIA trial?*

- **What is the best strategy to effectively treat patients with stable ischemic heart disease, considering all of the treatment options and risk/benefit?**
- **Which group benefits from the initial invasive strategy?**
- **When is the appropriate timing for “cross-over” for those patients initially managed with “optimal medical therapy”?**

# *FREEDOM TRIAL*

**Future REvascularization Evalution in patients with Diabetes mellitus: Optimal management of Multivessel disease**

# FREEDOM Trial

**Eligibility: DM patients with MV-CAD eligible for stent or surgery**
**Exclude: Patients with acute STEMI, cardiogenic shock**

Randomized 1:1

| MV-stenting<br>With Drug-eluting stents<br>N=1200 | CABG<br>With or without CPB<br>N=1200 |
|---|---|

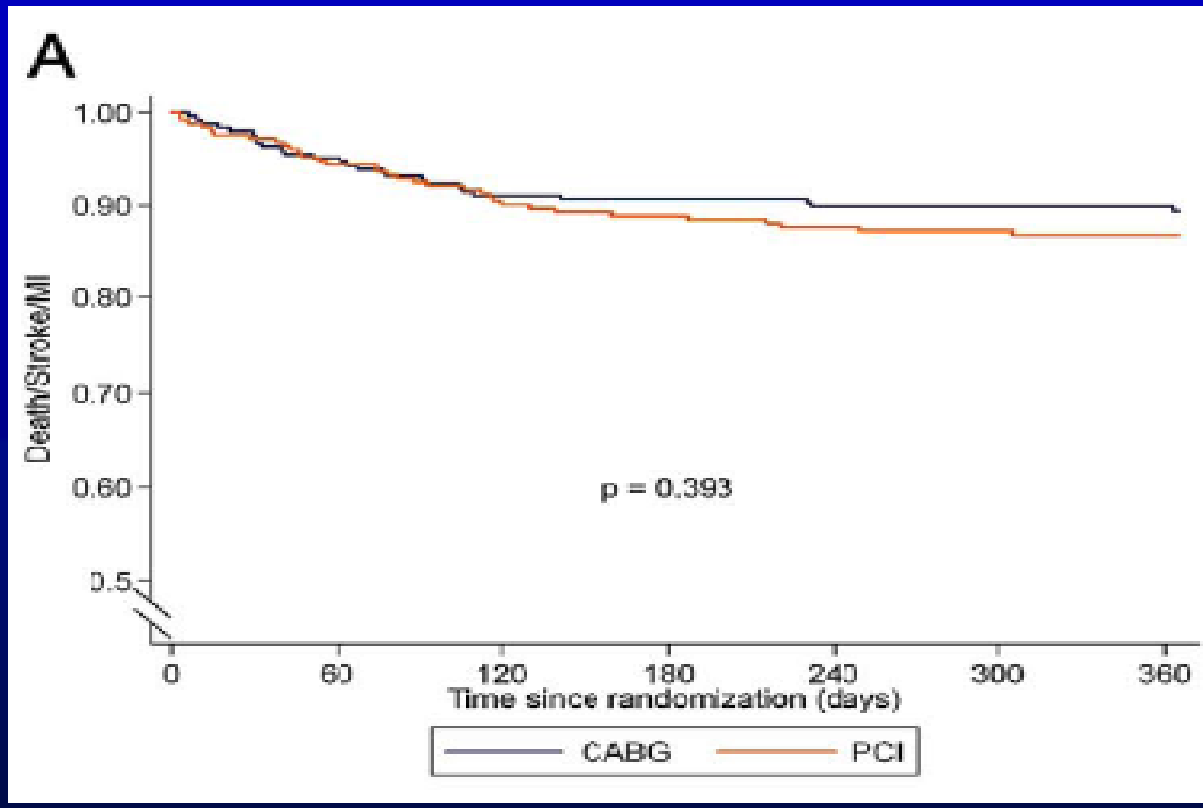
All concomitant Meds shown to be beneficial are encouraged, including:
clopidogrel, ACE inhibitors, ARBs, β-blockers, statins

PRIMARY: 3-year death, MI, stroke
SECONDARY: 12-month MACCE, 3-year Quality of Life

# *FREEDOM Trial: Superiority Trial*

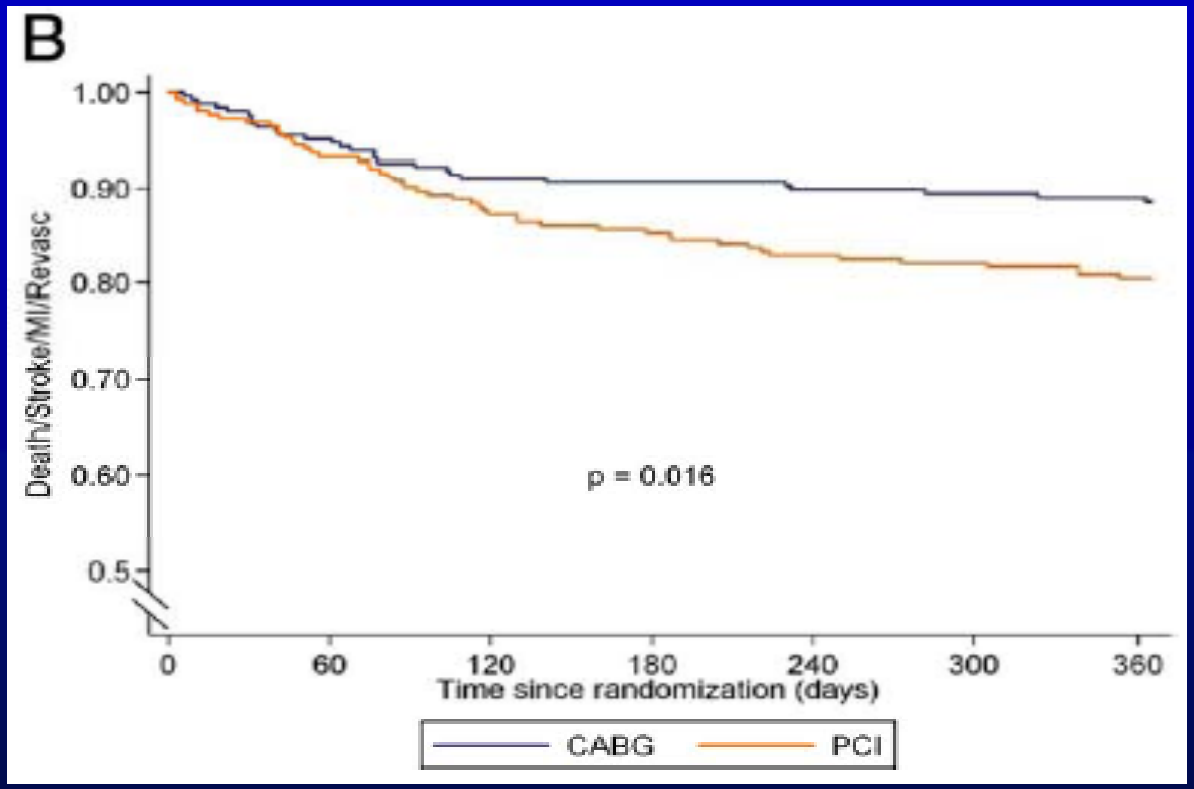
- **Primary outcome: Composite of**
  - **All cause mortality**
  - **Non-fatal MI**
  - **Stroke**

# *CARDia (Coronary Artery Revascularization in Diabetes) Trial*




*JACC 2010;55:432-40*

# *CARDia Trial*

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# *CARDia Trial*

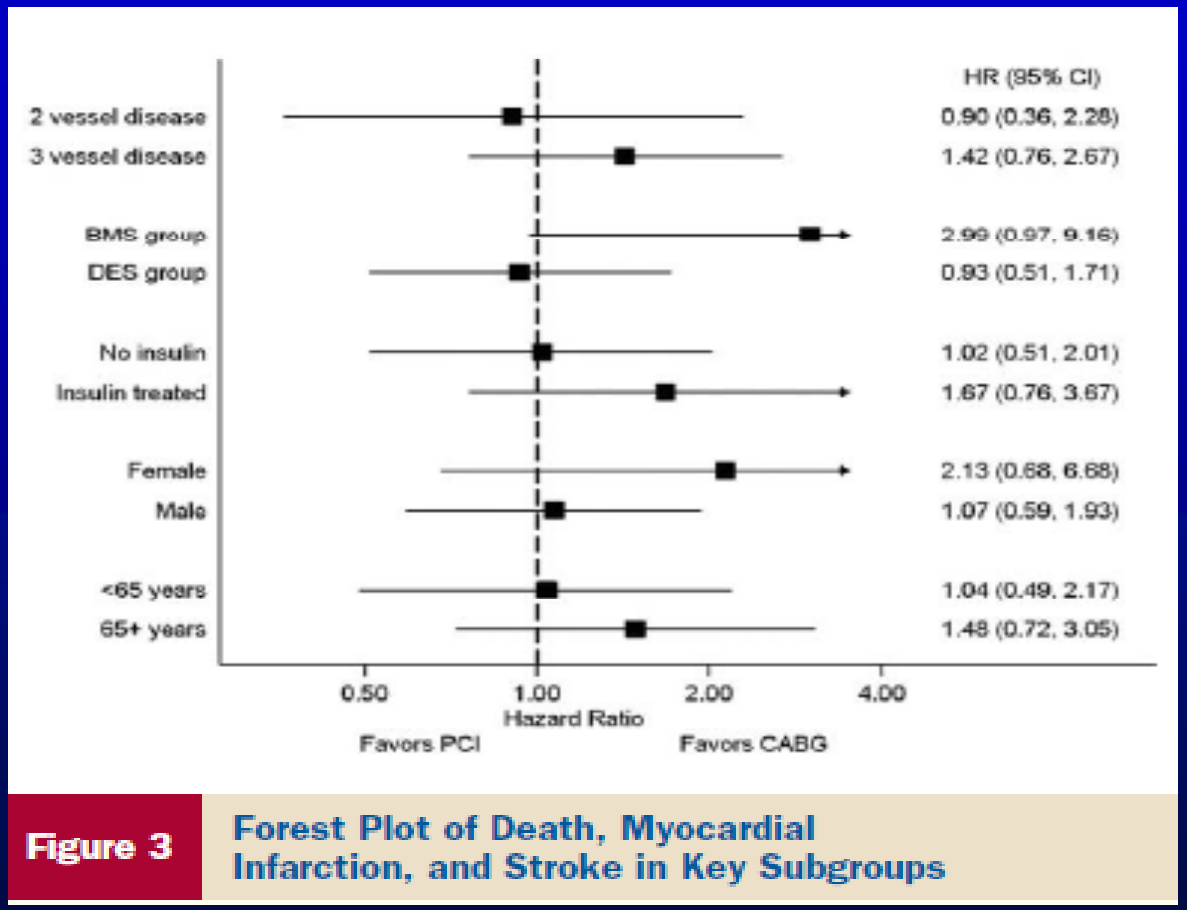


**Figure 3** Forest Plot of Death, Myocardial Infarction, and Stroke in Key Subgroups

***JACC 2010;55:432-40***

# *ARTS Trials: 5-Year Outcome in Diabetic Subgroup*

| | DES (N=159) | CABG (N=96) |
|---|---|---|
| MACCE | 40.5% | 23.4% |
| Mortality | 9.0% | 8.6% |
| MI | 40.5% | 23.4% |
| Repeat Revascularization | 33.2% | 10.7% |

*JACC Intervention 2011;1:317-323*

# *What will we learn from FREEDOM?*

- **DES treatment is similar to CABG regarding the composite endpoint of all-cause mortality, stroke, and non-fatal MI, thus disproving the superiority.**
- **But there will be greater need for repeat revascularization in the DES group.**
- **Consequence: Referring physicians will continue their preferred practice, with those believing in CABG refer more patients to CABG and those believing in percutaneous therapy continue to refer to the cath lab.**

# *What would we like to learn from FREEDOM?*

- **When is CABG preferred in diabetics?**
- **Which group benefits more from initial DES treatment strategy?**
- **What about hybrid revascularization?**

***If we knew what we were doing, it wouldn't be research.***

**Albert Einstein**