Treatment Options for Angina

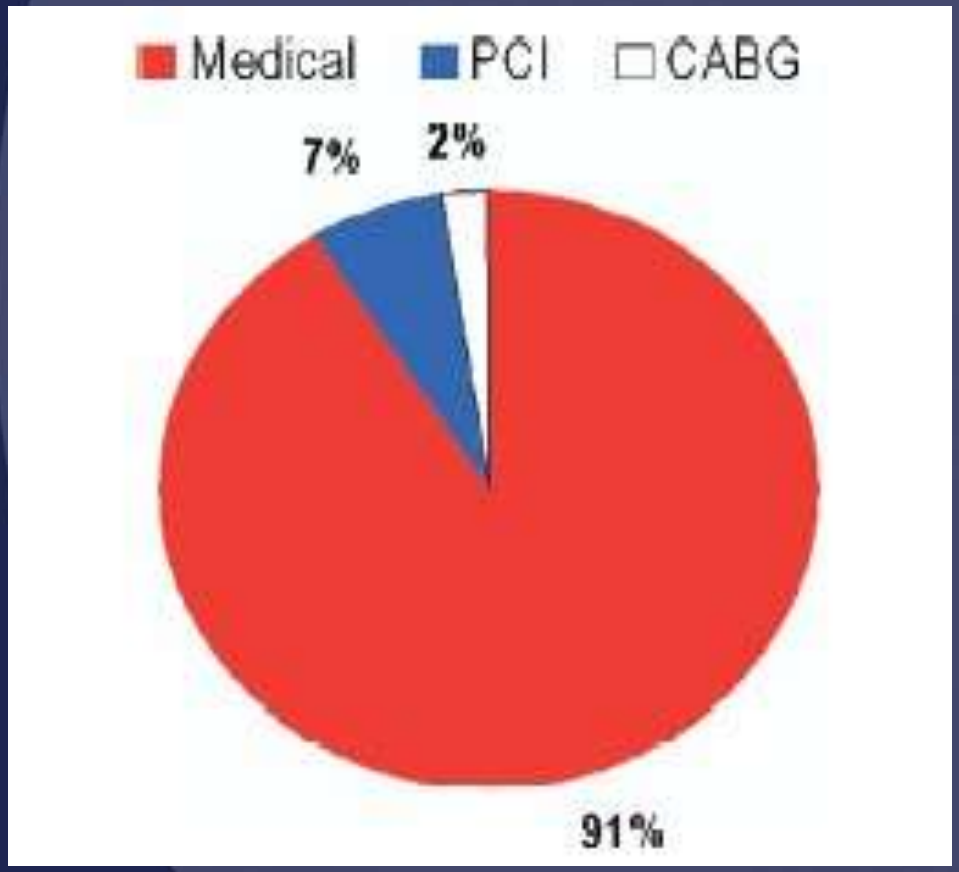
Interventional Cardiology Perspective

Michael A. Robertson, M.D.

10/30/10

Community Heart and Vascular

Prevalence of CAD in USA



- 15 million Americans with CAD
- 2 million diagnostic catheterizations
- 1 million PCI's
  - 60% USA
  - 10% acute MI
  - 30% stable angina
- 350,000 CABG

Kereiakes et al, JACC 2007;50;1598-1603

OMT vs. PCI

- Aggressive optimal medical therapy
- Provisional percutaneous intervention for refractory, recurrent or worsening angina

Aggressive optimal medical therapy

Upfront percutaneous intervention

PROVISIONAL PCI vs. UPFRONT PCI

PROVISIONAL PCI vs. UPFRONT PCI

- **OUTCOMES OF INTEREST**
  - Death
  - Myocardial infarction and/or ACS
  - Relief of angina

Table 2 Main Characteristics of the Trials

Trial	Year of Most Recent Publication	Enrollment Period	Total No. of Patients	Mean Age (yrs)	Women (%)	Previous MI (%)	Protocol Revascularizations in PCI Group (%) Total (CABG)	Use of Stents in PCI Group (%)	Nonprotocol Revascularizations in Medical Group (%) Total (CABG)	Length of Follow-Up (Months)
Sievers et al. (29)	1993	NR	88	56	NR	55	100 (0)	0	20 (5)	24
ACME 1 (19)	1997	1987–1990	227	60	0	34	96 (0)	0	41 (11)	60
ACME 2 (19)	1997	1987–1990	101	60	0	45	100 (0)	0	40 (30)	60
ACIP (17)	1997	1991–1993	558	62	14	40	89 (41)	0	29 (22)	24
Dakik et al. (16)	1998	1995–1996	44	54	41	100	100 (0)	29	9 (9)	12
AVERT (28)	1999	1995–1996	341	58	16	42	94 (0)	28	12 (1)	20
MASS (23)	1999	1988–1991	144	65	42	0	100 (0)	0	17 (11)	60
Bech et al. (14)	2001	NR	181	61	36	25	100 (0)	46	7 (0)	24
ALKK (32)	2003	1994–1997	300	57	13	100	93 (0)	16	24 (NR)	52
RITA 2 (21)	2003	1992–1996	1,018	58	18	47	93 (0)	8	35 (12)	84
TIME (27)	2004	1996–2000	301	80	42	47	71 (20)	44	42 (NR)	48
Hambrecht et al. (20)	2004	1997–2001	101	60	0	46	100 (0)	100	6 (0)	12
DANAMI (24)	2006	1990–1994	1,008	57	18	100	82 (29)	0	20 (NR)	28
INSPIRE (25)	2006	1999–2002	205	64	24	100	67 (26)	39	26 (10)	60
MASS II (30)	2006	1995–2000	408	60	32	46	95 (0)	68	24 (15)	60
SWISSI II (18)	2007	1991–1997	201	55	12	100	100 (0)	0	44 (NR)	122
COURAGE (15)	2007	1991–2004	2,287	61	15	38	96 (0)	90	31 (7)	54

Schomig et al. JACC 2008; 52; 894-904

Table 1 Summaries of Trials Comparing Medical Therapy Versus PCI for Stable Coronary Artery Disease Patients

Trial (Ref. #)	STENTS	Mortality and MI	Angina Relief	QOL	Repeat Revascularization
RITA-2 (7)	8%	No difference	PCI	PCI	PCI
ACME (8)	0%	No difference	PCI	PCI	PCI
ACME-2 (16)	0%	No difference	PCI	PCI	NA
MASS (9)	0%	No difference	PCI	NA	No difference
MASS-II (11)	68%	No difference	PCI	PCI	No difference
AVERT (10)	28%	No difference	PCI	PCI	No difference
TIME*	44%	No difference	PCI	PCI	PCI
COURAGE (12)	90%	No difference	No difference !!!	PCI	PCI

*TIME Investigators. Lancet 2001;358:951–7.
MI = myocardial infarction; NA = not available; PCI = percutaneous coronary intervention; QOL = quality of life.

Kereiakes et al, JACC 2007;50;1598-1603

Problems with Clinical applicability of the OMT vs. PCI randomized trials

- Enrollment in “strategy trials” is typically difficult and prolonged
  - Declared target endpoints are rarely achieved
- Stable CADDz has a slowly progressive course and therefore outcomes in such trials need to be assessed over a long period of time, delaying answers to proposed research questions

- Revascularization approaches and medical therapies evolve and become more refined over time
  - Hard to interpret findings with “moving therapeutic targets”
- Is there truly a way to get rid of treatment bias when patients are enrolled/randomized after angiography

THE COURAGE TRIAL

- Enrolled 2287 patients with stable angina
  - 80% had CCS Class 0, 1, or II symptoms
  - Only 20% had CCS Class III symptoms
  - EF 60%.

- Randomization occurred **AFTER** coronary angiography
  - Stenosis of at least 70% in at least one proximal epicardial coronary artery and objective evidence of myocardial ischemia
  - Stenosis of at least 80% and classic angina without provocative testing
  - Approximately 30% had proximal LAD disease
  - Approximately 40% had two vessel CADdz
  - Approximately 30% had three vessel CADdz

Boden et al. NEJM; 356; 15; 1503-1516

THE COURAGE TRIAL

- Excluded Class IV angina (persistent), markedly abnormal ETT in stage I, cardiogenic shock of persistent CHF, EF less than 30%, revascularization in last six months of coronary anatomy not suitable for PCI

- Primary endpoint: A composite of death from any cause and nonfatal myocardial infarction

- Secondary endpoints
  - Composite of death, MI, CVA, hospitalization for USA
  - CCS angina class in follow-up
  - QOL, use of resources, cost-effectiveness

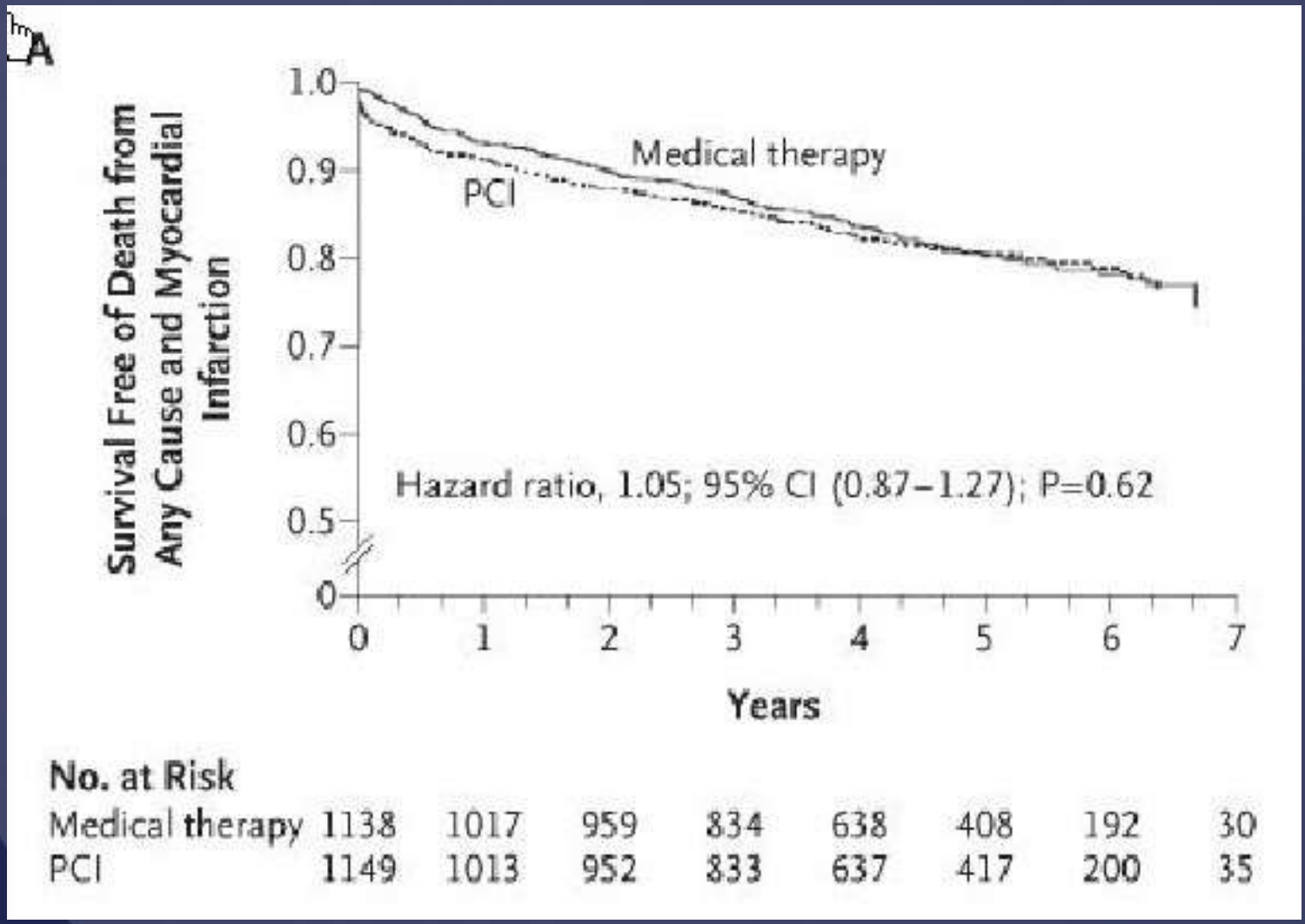
Boden et al. NEJM; 356; 15; 1503-1516

OPTIMAL MEDICAL THERAPY IN COURAGE

- Compliance with medical therapy was extraordinary (?unrealistic?)
  - At one-year, three-year, and five-year follow-up compliance was:
  - Aspirin: 94-95% throughout
  - Beta-blocker: 85%-89% throughout
  - Statin: 92-95% throughout
- This level of compliance is in contrast to CRUSADE registry
  - 46% compliance with beta-blocker alone
  - 36% compliance with beta-blocker plus Aspirin
  - 21% compliance with beta-blocker, Aspirin, and lipid-lowering

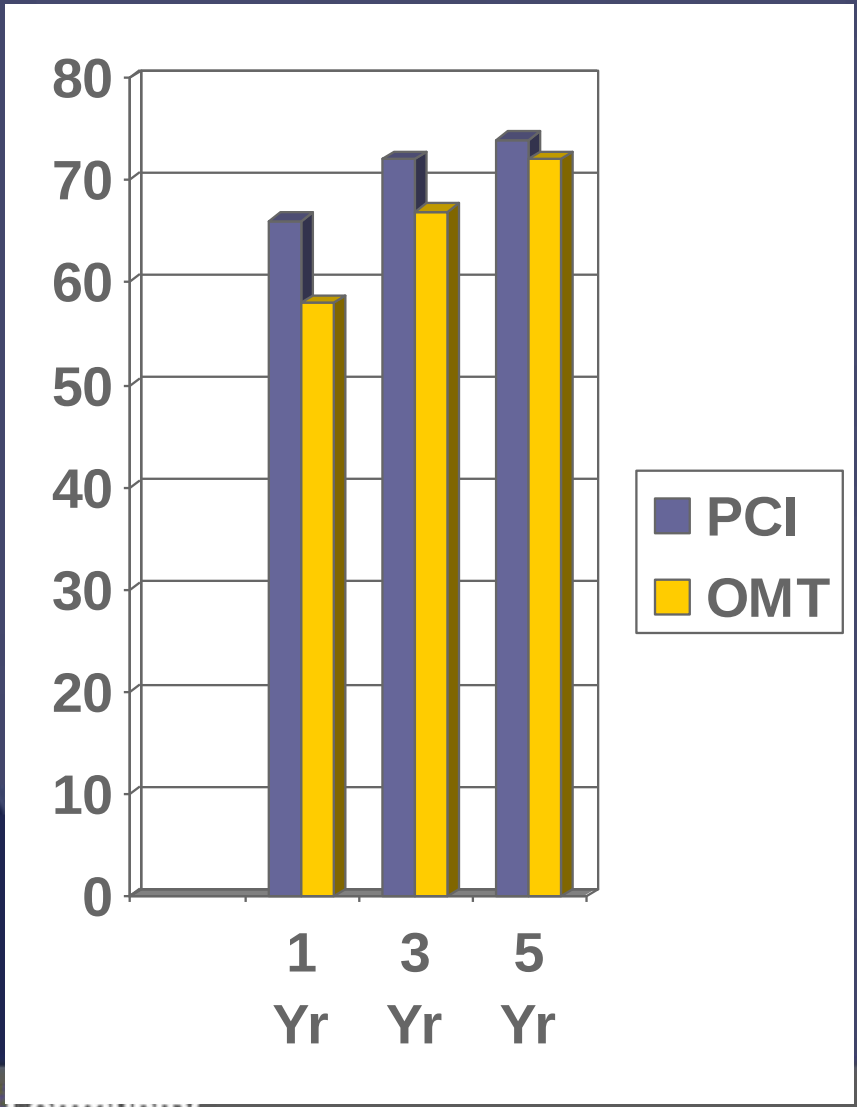
Boden et al. NEJM; 356; 15; 1503-1516

COURAGE Results



Boden et al. NEJM; 356; 15; 1503-1516

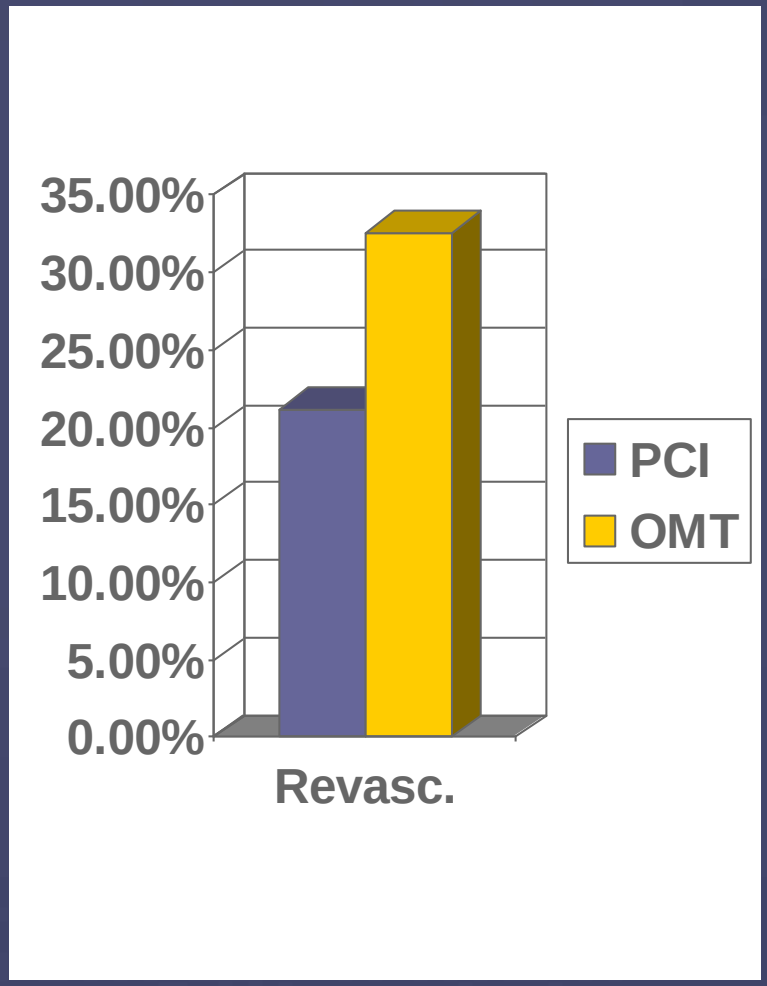
Angina-free existence in COURAGE



1 Yr. (p<0.001) ARR 8%
3 Yr. (p=0.02) ARR 5%
5 Yr. (p=NS)

Boden et al. NEJM; 356; 15; 1503-1516

Need for Revascularization in COURAGE



(21.1% PCI vs. 32.6% OMT)
p<0.001

Boden et al. NEJM; 356; 15; 1503-1516

Critique of COURAGE

- This was a low risk population (cardiac mortality 0.4%/year)
- Patient's were randomized AFTER coronary angiography (no way to exclude a bias towards exclusion of those with severe and/or complex stenosis)
- Although there was no overall difference in mortality and myocardial infarction
  - Are there subsets where there could be an advantage,
    - particularly in DES era (only 2.7% treated with DES)
    - With initial complete revascularization (although 70% of patients assigned to PCI had $\geq$ 2-vessel disease, only 36% received > 1 stent)

Kereiakes et al, JACC 2007;50;1598-1603

Critique of COURAGE

- Even in BMS era, there was reduction in angina and improvement in QOL with PCI. In COURAGE in particular this was seen:
  - Despite incomplete initial revascularization strategies
  - Despite phenomenal (?unrealistic?) compliance with medical therapies, which is dramatically higher than registry data for “real-world” compliance
- There is very likely to be better effect and more prolonged angina relief in DES era (median time to revascularization in the PCI cohort in COURAGE was 10 months)

Kereiakes et al, JACC 2007;50;1598-1603

MASS II Ten Year Results

- 611 patients at a single institution (Sao Paulo, Brazil) with multivessel CADdz and felt to have anatomy appropriate for either CABG or multivessel PCI
- 78-86% had Class II or III angina
- Randomized to CABG, PCI, or OMT
- 89-93% of patients had proximal LAD stenosis
- 58-59% had three vessel disease
- Normal LVEF
- 23-36% diabetics

Hueb et al. Circulation 2010: 122; 949-957

MASS II Ten Year Results

Table 2. Major Adverse Cardiac Events at 10-Year Follow-Up

	PCI	MT	CABG	*P* (Log-Rank)
Primary end points	42.4	59.1	33.0	<0.001
Overall mortality	24.1	31.0	25.1	0.089
Cardiac death	14.3	20.7	10.8	0.019
Additional intervention	41.9	39.4	7.4	0.001
AMI	13.3	20.7	10.3	0.010
CVA	5.4	6.9	8.4	0.550

AMI indicates acute MI; CVA, cerebrovascular accident.
Values are percentages.

Hueb et al. Circulation 2010: 122; 949-957

MASS II Ten Year Results

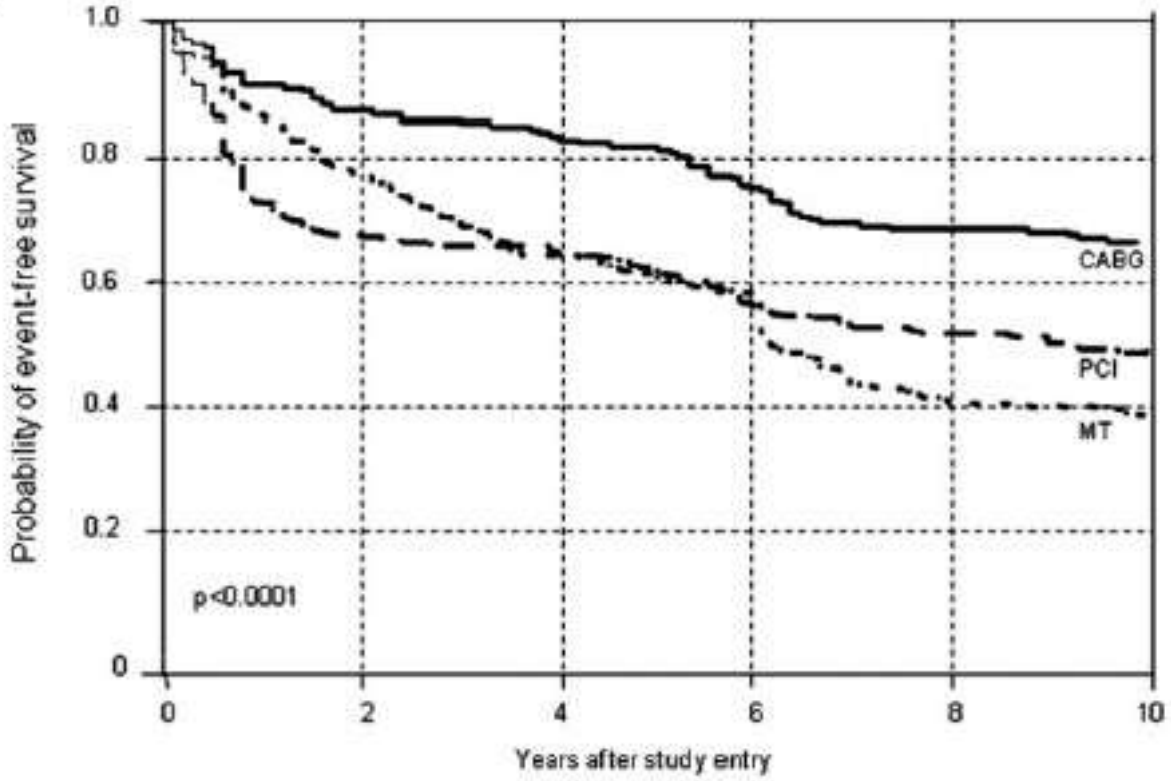


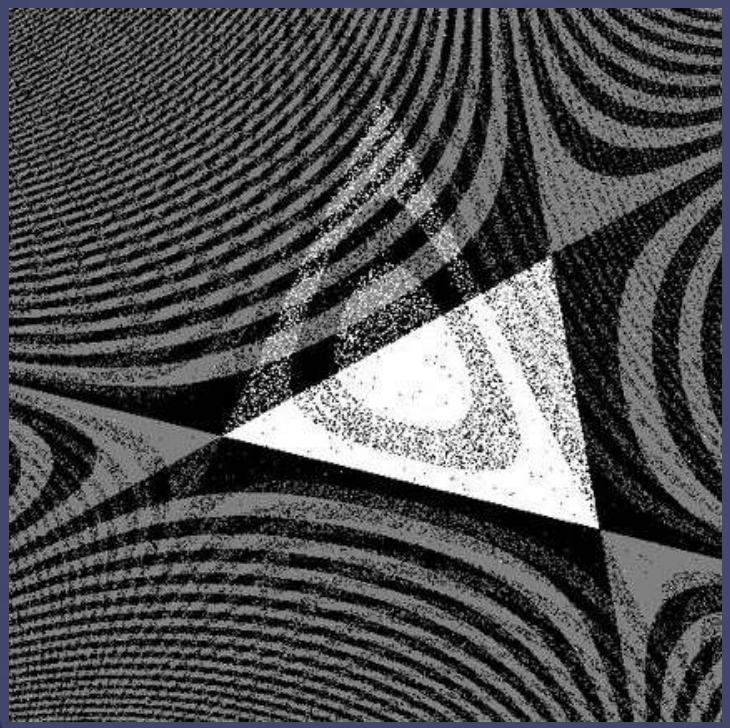
Figure 1. Probability of event-free survival (free of overall mortality, unstable angina that required revascularization, or Q-wave MI) among patients in the MT, CABG, and PCI treatment groups.

Hueb et al. Circulation 2010: 122; 949-957

Why Appropriateness Criteria?

- Ongoing effort by ACCF and partners to assist clinicians in caring for patients
- ACC/AHA guidelines provide a foundation for summarizing evidence-based cardiovascular care
  - Paucity of large randomized clinical trials assessing the value of technology for specific patients
  - Guidelines often provide no recommendation or a Level C recommendation (expert opinion)
- There remains tremendous variability in utilization of cardiovascular procedures (over- or under-use?)
- Appropriateness criteria have more detailed and complex clinical scenarios than guidelines
- Provide a framework for examining variability in utilization among practices/regions
- Hopefully guides more efficient and equitable allocation of health care resources and lead to better patient outcomes

OMT vs. PCI



ACCF Appropriateness Criteria for Coronary Revascularization

-- Writing group assembled 180 common clinical scenarios

-- Over 4000 scenarios would be necessary to account for the majority of important clinical factors and all permutations of these variable

"Almost nothing in medicine is black or white. The majority of decisions are shades of gray"

Appropriateness Criteria for Coronary Revascularization

- Clinical Presentation (ACS, stable angina, etc)
- Severity of angina (CCS Class I, II, III, IV)
- Extent of ischemia on non-invasive testing and the presence or absence of other prognostic features such as CHF, depressed LVEF or diabetes
- Extent of medical therapy
- Extent of anatomic disease (1-, 2-, 3-vessel disease, with or without proximal LAD or left main coronary disease)

Patel et al. JACC 2009; 53; 530-553

High Risk Findings on Noninvasive Study							CCS Class III or IV Angina					
Symptoms Med. Rx							Stress Test Med. Rx					
Class III or IV Max Rx	A	A	A	A	A		High Risk Max Rx	A	A	A	A	A
Class I or II Max Rx	A	A	A	A	A		High Risk No/min Rx	A	A	A	A	A
Asymptomatic Max Rx	U	A	A	A	A		Int. Risk Max Rx	A	A	A	A	A
Class III or IV No/min Rx	A	A	A	A	A		Int. Risk No/min Rx	U	U	A	A	A
Class I or II No/min Rx	U	A	A	A	A		Low Risk Max Rx	U	A	A	A	A
Asymptomatic No/min Rx	U	U	A	A	A		Low Risk No/min Rx	I	U	A	A	A
Coronary Anatomy	CTO of 1 vz.; no other disease	1-2 vz. disease; no Prox. LAD	1 vz. disease of Prox. LAD	2 vz. disease with Prox. LAD	3 vz. disease; no Left Main		**Coronary Anatomy**	CTO of 1 vz.; no other disease	1-2 vz. disease; no Prox. LAD	1 vz. disease of Prox. LAD	2 vz. disease with Prox. LAD	3 vz. disease; no Left Main

Figure 4. Appropriateness Ratings by High-Risk Findings on Noninvasive Imaging Study and CCS Class III or IV Angina (Patients Without Prior Bypass Surgery)

Patel et al. JACC 2009; 53; 530-553

Intermediate Risk Findings on Noninvasive Study							CCS Class I or II Angina					
Symptoms **Med. Rx**							**Stress Test Med. Rx**					
Class III or IV Max Rx	A	A	A	A	A		High Risk Max Rx	A	A	A	A	A
Class I or II Max Rx	U	A	A	A	A		High Risk No/min Rx	U	A	A	A	A
Asymptomatic Max Rx	U	U	U	U	A		Int. Risk Max Rx	U	A	A	A	A
Class III or IV No/min Rx	U	U	A	A	A		Int. Risk No/min Rx	U	U	U	A	A
Class I or II No/min Rx	U	U	U	A	A		Low Risk Max Rx	U	U	A	A	A
Asymptomatic No/min Rx	I	I	U	U	A		Low Risk No/min Rx	I	I	U	U	U
Coronary Anatomy	CTO of 1 vz.; no other disease	1-2 vz. disease; no Prox. LAD	1 vz. disease of Prox. LAD	2 vz. disease with Prox. LAD	3 vz. disease; no Left Main		**Coronary Anatomy**	CTO of 1 vz.; no other disease	1-2 vz. disease; no Prox. LAD	1 vz. disease of Prox. LAD	2 vz. disease with Prox. LAD	3 vz. disease; no Left Main

Figure 3. Appropriateness Ratings by Intermediate-Risk Findings on Noninvasive Imaging Study and CCS Class I or II Angina (Patients Without Prior Bypass Surgery)

Patel et al. JACC 2009; 53; 530-553

Low Risk Findings on Noninvasive Study							Asymptomatic					
Symptoms **Med. Rx**							**Stress Test Med. Rx**					
Class III or IV Max Rx	U	A	A	A	A		High Risk Max Rx	U	A	A	A	A
Class I or II Max Rx	U	U	A	A	A		High Risk No/min Rx	U	U	A	A	A
Asymptomatic Max Rx	I	I	U	U	U		Int. Risk Max Rx	U	U	U	U	A
Class III or IV No/min Rx	I	U	A	A	A		Int. Risk No/min Rx	I	I	U	U	A
Class I or II No/min Rx	I	I	U	U	U		Low Risk Max Rx	I	I	U	U	U
Asymptomatic No/min Rx	I	I	U	U	U		Low Risk No/min Rx	I	I	U	U	U
Coronary Anatomy	CTO of 1 vz.; no other disease	1-2 vz. disease; no Prox. LAD	1 vz. disease of Prox. LAD	2 vz. disease with Prox. LAD	3 vz. disease; no Left Main		**Coronary Anatomy**	CTO of 1 vz.; no other disease	1-2 vz. disease; no Prox. LAD	1 vz. disease of Prox. LAD	2 vz. disease with Prox. LAD	3 vz. disease; no Left Main

Figure 2. Appropriateness Ratings by Low-Risk Findings on Noninvasive Imaging Study and Asymptomatic (Patients Without Prior Bypass Surgery)

Patel et al. JACC 2009; 53; 530-553

- “Appropriateness criteria “are not intended to diminish the acknowledged difficulty or uncertainty of clinical decision-making and cannot act as substitutes for sound clinical judgment and practice experience.”

Frederick A. Masoudi, MD, MSPH, FACC
Moderator, Coronary Revascularization Technical Panel

Ralph G. Brindis, MD, MPH, FACC, FSCAI
Chair, Appropriateness Criteria Task Force