ACRIN PA 4005: Multicenter Randomized Controlled Study of a Rapid 'Rule-out' Strategy Using CT Coronary Angiogram Versus Traditional Care for Low-Risk ED Patients with Potential ACS

Harold Litt MD-PhD
University of Pennsylvania
Philadelphia, PA

Disclosures and Funding

- Grant funding from Siemens Medical Solutions for unrelated CT projects
- This project is funded, in part, under a grant with the Pennsylvania Department of Health (SAP4100042725). The Department specifically disclaims responsibility for any analyses, interpretations or conclusions.
- Additional funding was obtained from the American College of Radiology Imaging Network (ACRIN) Foundation. The study was organized and coordinated by ACRIN, which receives funding from the National Cancer Institute (U01 CA079778 and U01 CA080098).

Introduction 1

- Patients presenting to EDs with symptoms of potential ACS are a diagnostic dilemma
  - Many admitted for “rule-out”, few will have a cardiac diagnosis
  - High cost to society, inefficient resource use
  - Biomarkers and decision rules can not exclude ACS with sufficient accuracy
- A negative cath means low event risk

Papanicolaou MN, et al. Am J Cardiol 1986;58:1181-1187.
Pitts WR, et al. Am J Cardiol. 1997;80:1086-1087.

Introduction 2

- Coronary CTA has high NPV for CAD
- Previous ED studies of CCTA have shown
  - Low event rate for pts with no or min disease
  - Efficiency compared to SPECT-MPI
  - Potential cost savings vs. SPECT-MPI
- No previous study had sufficient power to demonstrate acceptable safety endpoint
  - <1% rate of 30-day MACE for neg “rule-out”

Introduction 3

- Observational trials and single center RCT
  - ROMICAT 368 pts, 50% neg CT, no ACS
  - Hollander et. al, 568 pts, no MACE w/neg CT
  - Goldstein et. al, 197 pts, ↓LOS & cost, no MACE
- Multicenter RCT - CT-STAT
  - 699 pts at 16 sites – CT vs. SPECT-MPI
  - 54% reduction in time to diagnosis
  - 38% cost savings
  - MACE after negative test
    - 2/268 CT (0.75%, 95% CI 0.09-2.7%)
    - 1/266 SPECT-MPI (0.38%, 95% CI 0.01-2.1%)

Methods 1

- Multicenter RCT of CCTA based strategy vs. traditional care (2:1) at 5 sites
- Primary hypothesis
  - Patients without significant CAD by CCTA have <1% rate of 30-day cardiac death or MI
- Secondary aims – CCTA vs. trad care
  - ED discharge rate and length of stay
  - 30-day MACE and revascularization
  - 30-day resource utilization

Methods 2

- Eligibility criteria
  - >30 yrs, signs/symptoms of potential ACS
  - TIMI score 0-2, no acute ischemia on ECG
  - Need for admission or testing to exclude ACS
- Exclusion criteria
  - Clearly non-cardiac pain
  - Comorbidity requiring hospital admission
  - Normal cath or CCTA within previous year
  - Contraindications to CCTA
  - Post-randomization exclusions
    - CrCl < 60 or subject received PE protocol CT

Methods 3 - Testing

- 64 slice or greater CT
  - Noncontrast scan for calcium scoring
  - Contrast enhanced CCTA
  - Use of β-blockers and NTG per local protocol
  - All readers ACC/AHA level 3
    - Local interpretations for clinical decisions
    - In analysis, stenosis quantified
      - None, <50%, 50-69%, ≥70%
- Stress testing per local protocol
  - Imaging or not, choice of modality

Methods 4 – Follow-up

- 30-day direct patient contact
  - AMI, rehospitalization, revascularization
  - Cardiac testing, cardiology visits, med use
- Record review
  - All potential cardiac hospitalization
  - All potential MACE
  - If no direct patient contact
    - Including neighboring hospitals
- SSDI if no other survival information

Methods 5 – Outcomes and Definitions

- All MACE reviewed by adjudication cmte
- Significant CAD
  - ≥50% stenosis in LM, LAD, CX, RCA or 1st order branches
  - Study indeterminate if non-diagnostic segment and no significant CAD elsewhere
- ACS – AMI or confirmed unstable angina
  - Reversible ischemia or ≥ 70% stenosis at cath

Results 1

- 1392 subjects July 2009 – Nov 2011
  - 22 removed post-randomization (most CrCl)
  - 908 randomized to CCTA, 462 traditional care
  - Groups well matched, 60% black

Characteristic	CCTA (N=908)	Traditional Care (N=462)
Age, Mean +/- SD (Range)	49 +/- 8.9 (30-78)	50 +/- 9.5 (30-83)
Gender		
Male	443 (49%)	202 (44%)
Female	465 (51%)	260 (56%)
Ethnicity		
Hispanic/Latino	21 (2%)	11 (2%)
Not Hispanic/Latino	867 (95%)	439 (95%)
Unknown	20 (2%)	12 (3%)
Race[1]		
American Indian/Alaskan Native	5 (0.6%)	6 (1%)
Asian	11 (1%)	7 (2%)
Black/African American	525 (58%)	288 (62%)
Native Hawaiian/other Pacific Islander	2 (0.2%)	0
White	361 (40%)	162 (35%)
Unknown	9 (1%)	4 (0.9%)
Cardiac history and risk factors[1]		
Hypertension	463 (51%)	232 (50%)
Hypercholesterolemia	249 (27%)	118 (26%)
Family History of CAD	268 (30%)	126 (27%)
Diabetes Mellitus	130 (14%)	64 (14%)
Current Tobacco use	291 (32%)	156 (34%)
Cocaine use in last week	49 (5%)	20 (4%)
Myocardial infarction	10 (1%)	6 (1%)
Heart failure	10 (1%)	9 (2%)

Characteristic	CCTA (N=908)	Traditional Care (N=462)
Pulse at presentation		
>= 80 beats/minute	519 (57%)	250 (54%)
60 - 79 beats/minute	356 (40%)	197 (42%)
< 60 beats/minute	33 (4%)	15 (3%)
Presenting electrocardiogram		
Normal	584 (64%)	299 (65%)
Nonspecific	208 (23%)	111 (24%)
Early repolarization	24 (3%)	14 (3%)
Non-diagnostic	68 (7%)	24 (5%)
Ischemia known to be old	11 (1%)	6 (1%)
Ischemia not known to be old	10 (1%)	7 (2%)
ST Elevation consistent with AMI-old	2 (0.2%)	0
Other/Unknown	1 (0.1%)	1 (0.2%)
TIMI Risk Score		
0	461 (51%)	234 (51%)
1	325 (36%)	166 (36%)
2 or more	122 (13%)	62 (13%)

Results 2 – Index visit testing

	CCTA (N=908)	Traditional Care (N=462)
CCTA Performed	**N=767 (84%)**	**N=26 (6%)**
Maximal stenosis < 50%	640 (83%)	20 (77%)
Maximal stenosis 50-69%	52 (7%)	2 (8%)
Maximal stenosis ≥70%	28 (4%)	2 (8%)
Indeterminate/nondiagnostic	47 (6%)	2 (8%)
Stress testing (with or without imaging)	**N=124 (14%)**	**N=267 (58%)**
Normal	98 (79%)	245 (92%)
Reversible ischemia	15 (12%)	16 (6%)
Indeterminate/nondiagnostic	11 (9%)	6 (2%)
Cardiac catheterization performed	**N=37 (4%)**	**N=18 (4%)**
Maximal stenosis < 50%	9 (24%)	10 (56%)
Maximal stenosis ≥ 50%	28 (76%)	8 (44%)
No testing performed	**80 (9%)**	**167 (36%)**

- 16% didn't get CT
  - 7-33% across sites
  - Elevated HR (27%)
- Similar cath rate
  - CT higher pos rate
- No testing
  - 9% vs. 36%

Results 3 - Safety

- No 30-day MACE in 640 pts with neg CTA
  - 0% event rate, 95% CI 0–0.57%
- Secondary aims - 30-day CCTA vs. trad

Outcome	Coronary CTA (N=908)	Traditional Care (N=462)	% Difference ** (95% CI)
Cardiovascular Events			
Death	0	0	0
AMI *	10 (1%)	5 (1%)	0.02% (-5.6, 5.7)
Composite Death & AMI	10 (1%)	5 (1%)	0.02% (-5.6, 5.7)
Revascularization	24/893 (2.7%)	6/457 (1.3%)	1.4% (-4.3, 7.0)

- One serious AE in each arm
  - Bradycardia related to meds for HR control

Results 4 – Efficiency

- CCTA more often discharged from ED
  - 50% vs. 23% (95% CI 21.4-33.2)
- LOS shorter
  - Overall CCTA vs. trad care: 18 vs. 25 hrs*
  - Negative testing: 12 vs. 25 hrs*
  - Per protocol (had CCTA or stress testing)
    - Overall 15 vs. 26 hrs*
    - Negative CCTA or stress (trad care) 12 vs. 25 hrs*

  *p<0.001
- More CCTA pts diagnosed with CAD
  - 9.0 vs. 3.5% (95% CI 0-11.2)

Results 6 – Resource Utilization

- No significant differences in 30-day resource utilization (CCTA vs. trad care)

Use of Resources	CCTA-based (%)	Traditional Care (%)	95% CI for Difference
Catheterization	5.1	4.2	-4.8 to 6.6
Revascularization	2.7	1.3	-4.3 to 7.0
Repeat ED visit	8.0	7.5	-5.2 to 6.2
Re-hospitalization	3.1	2.4	-4.9 to 6.4
Cardiologist visit	7.1	3.8	-2.4 to 9.0

- We are obtaining 1 year follow-up

Discussion 1

- CCTA-based strategy safe and efficient
  - Upper limit of CI for 30-day MACE < 1%
  - Increased rate of ED discharge, shorter LOS
  - Fewer negative caths, more CAD diagnoses
- Previous trials results similar but
  - Observational or no comparison arm
  - RCTs not large enough to demonstrate acceptable safety
  - Wider range of trad care in our trial
  - “Real world” management and disposition

Discussion 2 - Limitations

- Comparative RCT needs ~50,000 subjects
  - Low event rate in population studies
  - Study powered for conservative safety goal
- Need for any testing in these patients
  - Enrolled only those needing admission/testing
  - Still 9% vs. 36% didn't get tested
- Low to intermediate risk only
  - Can't extrapolate to higher risk groups

Discussion 3 – CT Limitations

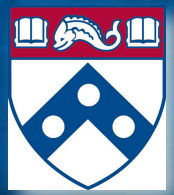
- Radiation exposure – tracked in study
  - Very technology dependent
  - Most CCTA now lower dose than SPECT-MPI
- 16% randomized to CCTA didn't get it
  - Elevated HR most common cause (27%)
  - Very technology dependent, ↓ over time
- More diagnosed with incidental CAD
  - Better prevention or more testing?

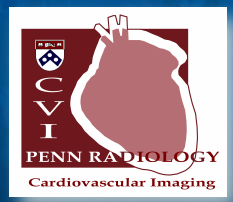
Conclusions

- CCTA as first test for low-intermediate risk pts presenting to EDs with potential ACS
- Safety
- Efficiency
  - Increased ED discharge rates
  - Reduced length of stay
- Long term follow-up needed
  - Resource utilization
  - Effects of CAD diagnosis on outcomes

Acknowledgements 1

- Hospital of the University of Pennsylvania
  - Site Investigators: Judd E. Hollander, MD, Harold I. Litt, MD, PhD
  - Research Coordinators: Emily Barrows, Jeffrey Le, Shannon Marcoon, Julie Pitts, RN, Scott Steingall, RT
- Penn State University Medical Center at Hershey
  - Site Investigators: James M. Leaming, MD, Harjit Singh, MD, Michelle A. Fischer, MD, Steven Ettinger, MD, Carlos Jamis-Dow, MD, Kevin Moser, PhD
  - Research Coordinators: Swati Shah, Kevin Gardner, RN, Russell Dicristina, Susan Oskorus
- Penn Presbyterian Medical Center
  - Site Investigators: Laurence Gavin, MD, Anna Marie Chang, MD
  - Research Coordinators: Christopher Decker, Michael Green, Katie O'Conor, Angela Roach, Kristy Walsh, Max Wayne





Acknowledgements 2

- Wake Forest University
  - Site Investigators: J. Jeffrey Carr, MD, MSc, Daniel W. Entrikin, MD, Kim Askew, MD, James W. Hoekstra, MD, Simon Mahler, MD, Chadwick D. Miller, MD, MS
  - Research Coordinators: Denise Boyles, Stephanie Bradshaw, Mark Collin, Erin Harper, Lisa Hinshaw, MS, Jane Kilkenny, Megan Koonts, Lori Triplett, RN
- University of Pittsburgh Medical Center
  - Site Investigators: Charissa B. Pacella, MD, Joan M. Lacomis, MD and Christopher R. Deible, MD, PhD
  - Research Coordinators: Sara Vandruff, Barbara Early, Tina Vita, Dawn McBride
- Brown University: Biostatistical/research design
  - Constantine Gatsonis, PhD, Brad Snyder, MS, Sanaa Boudhar, MS, Patricia Fox, MS and Erin Greco, MS

Acknowledgements 3

- Data Safety Monitoring Board
  - David Bluemke, MD, PhD (Chair), National Institute of Health; Todd A. Alonzo, PhD, University of Southern California; Jon F. Merz, MBA, JD, PhD, University of Pennsylvania; Herbert Y. Kressel, MD, Beth Israel Deaconess Medical Center.
- Adjudication Committee
  - W. Frank Peacock, MD, Cleveland Clinic; Robert Hendel, MD, University of Miami
- ACRIN Data Management, Regulatory Compliance and Administration
  - Cynthia Olson, Roberta Clune, Victoria Shoyelu, Bola Shodunke, Kim Brown, Cynthia Price, Patricia Blair, Martha Heckel, Mary Kelly, Charles Apgar, Mitchell Schnall MD, PhD