Journal Club

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COPE

Imazio M, Bobbio M, Cecchi E, Demarie D, Demichelis B, Pomari F, Moratti M, Gaschino G, Giammaria M, Ghisio A, Belli R, Trinchero R. Colchicine in addition to conventional therapy for acute pericarditis: results of the COlchicine for acute PEricarditis (COPE) trial. Circulation. 2005 Sep 27;112(13):2012-6.

COPE

Colchicine in addition to conventional therapy for acute pericarditis

- Background
  - Colchicine typically used in treatment of recurrent pericarditis
  - 19 patient French study using colchicine 1st line showed recurrence rate of 10.5% at 5 months
  - Pericarditis will be complicated by recurrence in 5-50% of cases
  - 1st episode usually viral/infectious; Recurrence is more often an autoimmune process

Methods

- Prospective, Randomized, Open label
- 2 Sites
- All patients had clinical and echo followup at 48 and 72 hours, 10 days, 1 month, 6 months, 1 year then yearly

Subjects

- Consecutive patients with 1st episode of acute pericarditis
  - At least 2 of the following
    - Typical chest pain
    - Pericardial friction rub
    - Widespreasd ST segment elevation on EKG
  - Idiopathic, viral, autoimmune, post-pericardiotomy, connective tissue
  - Age >=18 years
- Exclusion criteria
  - TB, neoplastic, or purulent pericarditis
  - Liver disease or transaminases >1.5x normal
  - Creatinine >2.5
  - Myopathy or CK >upper normal limit
  - Blood dyscrasia or GI disease
  - Pregnant women or women not using contraception
  - Hypersensitivity to colchicine or current treatment with colchicine

Treatment

- Conventional
  - ASA 800mg q6-8h for 7-10 days with tapering over 3-4 weeks
- Experimental
  - ASA as above
  - Colchicine 1-2mg day 1 then 0.5-1mg qd for 3 months
- Steroid therapy reserved for patients unable to take ASA

End Points

- Primary
  - Recurrence rate
    - Recurrence defined as either continued activity or recurrence after initial diagnosis of pericarditis
    - Recurrent pain + 1 or more
      - Fever, pericardial friction rub, EKG changes, echo evidence of pericardial effusion, leukocytosis, elevated ESR or CRP
  - Incessent type – unable to wean treatment without recurrence in 1st 6 weeks
  - Intermittant type – Symptom free interval more than 6 weeks
- Secondary – persistence of symptoms at 72 hours
- Remission – free of symptoms, with no further EKG, clinical or echo signs
- Failure – Persistence of fever, effusion worsening, general illness lasting >7 days

How are end points counted?

- A single patient can have multiple recurrences
  - Patient has pericarditis and cannot be weaned from ASA
    - Incessent type, counts as a recurrence
  - Patient has pericarditis and symptoms resolve for 6 weeks, then recur
    - Intermittent type, counts as a recurrence
  - Patient has pericarditis, and symptoms resolve for 6 weeks, but then recurs, and unable to wean meds
    - 1 or 2 recurrences?

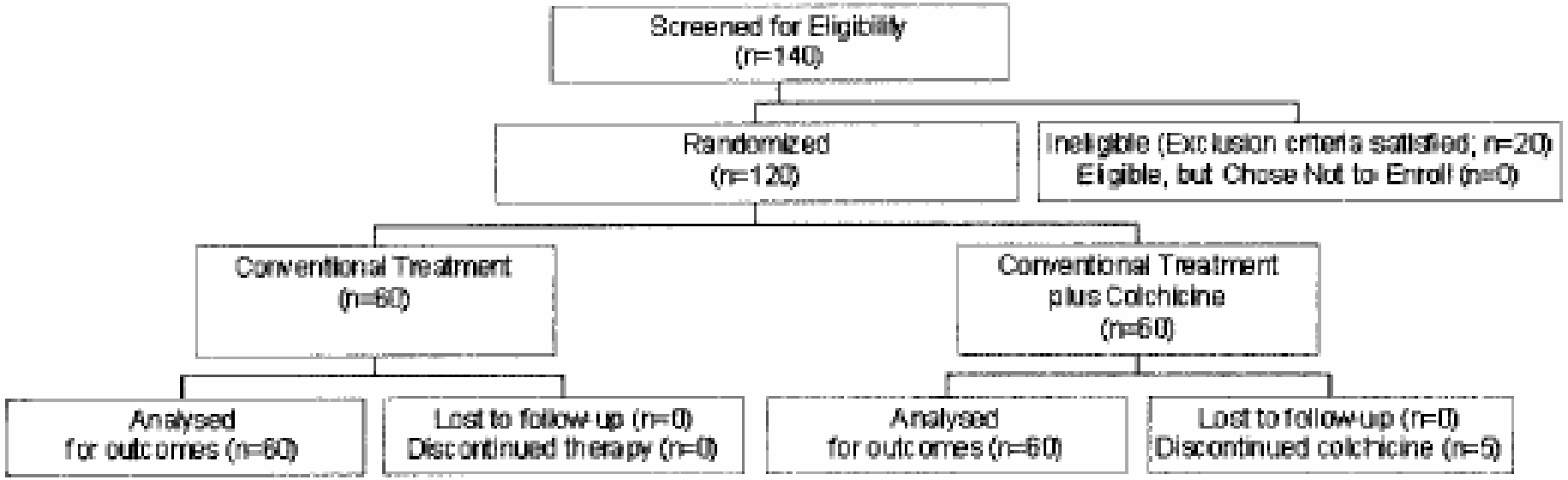


TABLE 1. Baseline Clinical Characteristics of Randomized Patients

Feature	Group I: No Colchicine (n=60)	Group II: Colchicine (n=60)	P
Age, y	57.2±19.6	56.5±18.2	NS
Male gender	26 (43.3)	28 (46.7)	NS
Pericarditic chest pain	60 (100.0)	60 (100.0)	NS
Pericardial rub	19 (31.7)	21 (35.0)	NS
ST-segment elevation	53 (88.3)	52 (86.7)	NS
Pericardial effusion	38 (63.3)	41 (68.3)	NS
Cardiac tamponade	1 (1.6)	1 (1.6)	NS
Idiopathic pericarditis	51 (85.0)	50 (83.3)	NS
Autoimmune causes*	9 (15.0)	10 (16.7)	NS

Values are n (%) or mean±SD.

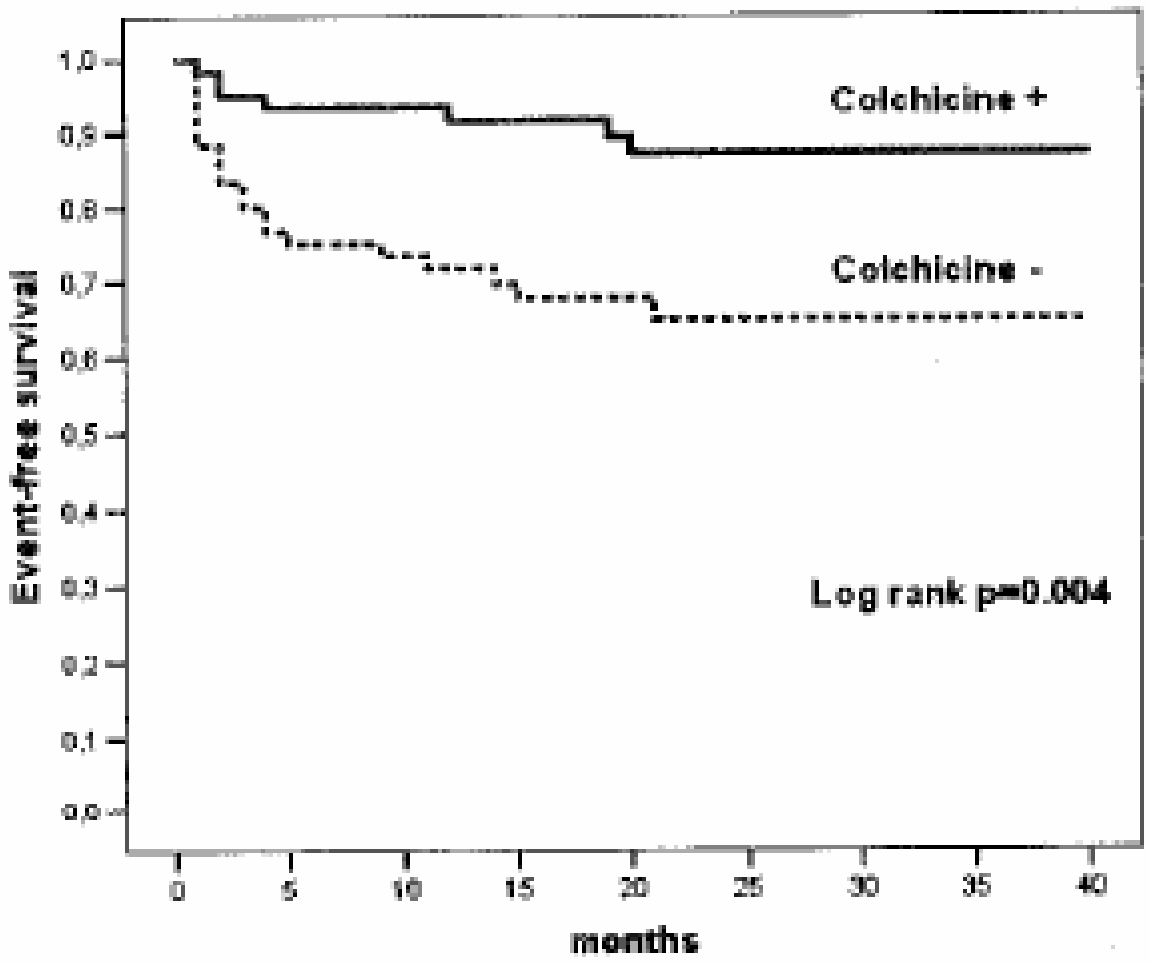
*Autoimmune causes include connective tissue diseases and postpericardiotomy syndromes.

TABLE 2. Follow-Up Data of Randomized Patients

Feature	Group I: No Colchicine (n=60)	Group II: Colchicine (n=60)	*P*
Mean follow-up, mo	23.7±8.8	24.2±8.7	NS
Corticosteroid use,* n (%)	10 (16.6)	9 (15.0)	NS
Recurrence, n (%)	20 (33.3)	7 (11.7)	0.009
Recurrence rate at 18 mo, %	32.3	10.7	0.004†
Symptom persistence at 72 h, n (%)	22 (36.7)	7 (11.7)	0.003
Side effects, n (%)	4 (6.7)	5 (8.3)	NS
Severe adverse effects, n (%)	0 (0.0)	0 (0.0)	NS
Cardiac tamponade, n (%)	0 (0.0)	0 (0.0)	NS
Constrictive pericarditis, n (%)	0 (0.0)	0 (0.0)	NS

*Steroid prescribed for the index attack because of aspirin contraindications or intolerance.

†*P* value from log-rank test.



Patients at risk:

Colchicine+ 60	58	52	45	39	33	14	8
Colchicine- 60	45	44	32	24	18	11	7

Figure 2. Kaplan-Meier event-free survival curves according to treatment groups (see text for details).

TABLE 3. Baseline Clinical Features of Patients With and Without Recurrences During Follow-Up

Feature	Patients With Recurrence (n=27)	Patients Without Recurrence (n=93)	P
Age, y	57.3±18.8	56.7±18.9	NS
Female gender	19 (70.4)	47 (50.5)	NS
Pericardial effusion	20 (74.1)	59 (63.4)	NS
Severe pericardial effusion	5 (18.5)	5 (5.4)	NS
Cardiac tamponade	1 (3.7)	1 (1.1)	NS
Idiopathic etiology	21 (77.8)	80 (86.0)	NS
Autoimmune causes*	6 (22.2)	13 (14.0)	NS
Corticosteroid use†	9 (33.3)	10 (10.7)	0.011
Colchicine use	7 (3.7)	53 (56.9)	<0.001

Values are n (%) or mean±SD.

*Autoimmune causes include connective tissue diseases and postpericardiotomy syndromes.

†Steroid prescribed for the index attack because of aspirin contraindications or intolerance.

Subgroup analysis

	Recurrance at 18 months
ASA (N=50)	23.5%
ASA + Colchicine (N=51)	8.8%
Prednisone (N=10)	86.7%
Prednisone + Colchicine (N=9)	11.1%

Stats

- Power calculation
  - Beta error (False negative)
    - Erroneously accepting null hypothesis/failure to detect a difference
    - Occurs when sample size is too low
  - Used estimates of recurrence rates seen in prior trials (including observational)
  - Beta set at 80% - 80% chance of seeing a difference of predetermined magnitude if such a difference exists
  - Estimated recurrence of 10.5% with colchicine, 32.5% with control
  - Need 60 patients in each arm to have 80% power

http://members.aol.com/johnp71/proppowr.html

Stats

- Alpha error
  - Erroneously rejecting the null hypothesis (False Positive)
  - Predetermined, typically set at $p<0.05$
  - 5% possibility that the results arose from chance alone

Stats

- T test
  - Used for continuous variables
    - BP, age, HR, EF
  - Calculation involves means, standard deviations
  - http://graphpad.com/quickcalcs/ttest1.cfm?Format=SD
- Chi Square
  - Used for categorical variables
  - Flexible, can be set up a number of ways
  - Fischer exact test is a specific chi square test used for a 2x2 table
  - Calculation involves expected frequencies
  - http://graphpad.com/quickcalcs/contingency1.cfm

What is the significance of these numbers?

	Yellow	Red
Men	30	70
Women	45	55

http://graphpad.com/quickcalcs/contingency1.cfm

Lets Look at That Again

On Treatment Followup at 18 months

	Recurrence	No Recurrence	
ASA	11.75 23.5%	38.25 76.5%	50
ASA + Colchicine	4.5 8.8%	46.5 91.2%	51
	16.25	84.75	101

http://graphpad.com/quickcalcs/contingency1.cfm

High Res CT coronary angiography

Mollet NR, Cademartiri F, van Mieghem CA, Runza G, McFadden EP, Baks T, Serruys PW, Krestin GP, de Feyter PJ. High-resolution spiral computed tomography coronary angiography in patients referred for diagnostic conventional coronary angiography. Circulation. 2005 Oct 11;112(15):2318-23. Epub 2005 Oct 3.

Patients

- 70 consecutive patients referred for coronary angiography
  - Sinus rhythm
  - Can hold breath for 15 seconds
  - No prior PCI or CABG
- 18 patients excluded due to
  - Logistics of doing CT in conjunction with cath (9)
  - Arrhythmia (4)
  - Renal dysfunction (4)
  - Contrast allergy (1)
- 1 Patient's data could not be analyzed
- 51 Patients ultimately included

Patient Preparation

- Patients with HR >70 received 100mg metoprolol
  - Unless CHF or AV block
  - 73% received metoprolol
- Patients with HR >80 received 1mg lorazepam
  - 31% received lorazapam

Scan Protocol

- 64 slice CT Scanner (Siemans)
- Radiation exposure for angiography 15.2-21.4 mSv
  - Compare to 16 slice calcium scoring 1.3-1.7 mSv
- 100 mL contrast injected at 5 mL/s
- EKG gating for image reconstruction
- Mean scan time 13 seconds

Quantitative coronary angiography

- 17 segments
- Classification
  - Normal
  - Nonsignificant disease (<50% stenosis)
  - Significant stenosis

CT Image Interpretation

- Scans read by independent radiologist and cardiologist
- Calcium scores calculated (Agatston score)
- Lesions classified as significant or insignificant
- 69% analyzed with 1 data set, 27% with 2, 4% with 3 data sets
- Good image quality in 90% of patients

Statistics

- Compared QCA to CT coronary angiogram
- Segment by segment
- Vessel by vessel
- Patient by patient

TABLE 1. Patient Characteristics

Symptoms	
Atypical chest pain	6 (12)
Stable angina pectoris	32 (63)
Unstable angina pectoris	3 (6)
Non–ST-segment elevation myocardial infarction	11 (22)
Risk factors	
Hypertension	17 (33)
Hypercholesterolemia	36 (71)
Diabetes mellitus	7 (14)
Smoking	15 (29)
Family history of acute coronary syndrome	13 (26)
Obese (body mass index $\geq$30 kg/m^2)	14 (28)
Calcium score, median (interquartile range)*	231 (15–736)
Conventional angiography	
Absence of coronary artery disease	7 (13)
Nonsignificant disease	6 (12)
Single-vessel disease	16 (31)
Multivessel disease	23 (45)

n=52. Values are n (%) unless otherwise indicated.
*Agatston score.

TABLE 2. Diagnostic Performance and Predictive Value of 64-Slice CT Coronary Angiography for the Detection of ≥50% Stenoses on QCA

	n	Sensitivity, %	Specificity, %	PPV, %	NPV, %	+LR	−LR
Segment-based analysis							
All segments	725	99 (94–98)	95 (93–96)	76 (67–89)	100 (99–100)	20.81	0.01
Proximal segments	204	100 (89–100)	97 (93–98)	83 (67–97)	100 (97–100)	29.00	0.00
Mid segments	142	97 (83–99)	94 (88–97)	81 (63–96)	99 (94–99)	15.47	0.04
Distal segments	121	100 (68–100)	97 (92–99)	73 (39–98)	100 (96–100)	37.67	0.00
Side branches	258	100 (87–100)	94 (90–96)	65 (48–85)	100 (98–100)	16.57	0.00
LM	51	100 (21–100)	100 (93–100)	100 (92–100)	100 (2–100)	∞	0.00
LAD	230	97 (85–100)	92 (88–95)	69 (53–86)	99 (96–99)	12.68	0.03
LCx	235	100 (88–100)	97 (94–99)	83 (66–97)	100 (98–100)	34.33	0.00
RCA	209	100 (89–100)	95 (91–97)	77 (60–95)	100 (97–100)	19.89	0.00
Patient-based analysis							
All segments	51	100 (91–100)	92 (67–99)	97 (86–99)	100 (73–100)	13.00	0.00

PPV indicates positive predictive value; NPV, negative predictive value; +LR, positive likelihood ratio; −LR, negative likelihood ratio; LM, left main coronary artery; LCx, circumflex coronary artery; and RCA, right coronary artery. For segment-based analysis, analysis of 725 segments visualized on the conventional angiogram and classified according to a 17-segment modified AHA classification was performed. Segments were further classified on the basis of their location within the coronary tree (proximal, mid, or distal segments of the main coronary artery arteries or side branches) and their location within a single vessel (LM, LAD, LCx, or RCA). For patient-based analysis, analysis of 51 patients was performed. Values in parentheses represent 95% CIs.

Segment by Segment analysis

- 725 segments analyzed out of potential total 867 (83.6%)
  - 102 segments not visualized due to absence of ramus intermedius or hypoplastic vessels
  - 40 segments not visualized due to proximal occlusions or poorly filled distal vessels
  - 17 segments * 51 patients = 867
- Interobserver kappa 0.73
- Intraobserver kappa 0.79

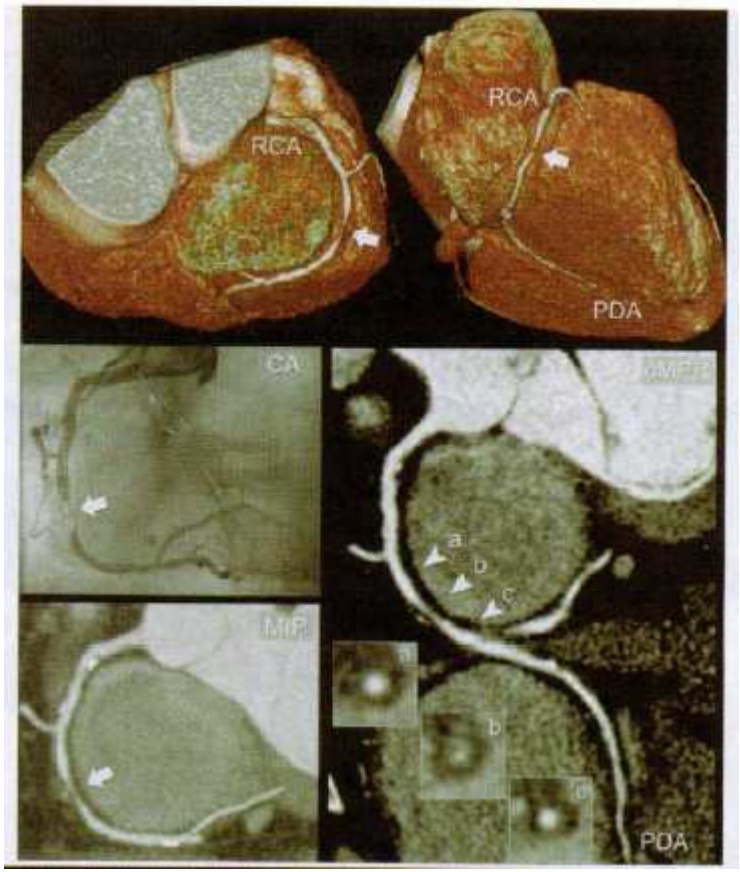
What they don't show in the table Segment by Segment

- 1 mid LAD stenosis (52%) missed by CT
- 30 insignificant lesions by QCA (8 normal, 22 insignificant stenoses) classified as significant by CT
  - 83% of these segments calcified

- Random selection of single segment per patient
  - Sensitivity13/13 for significant disease, specificity 36/38

What they don't show in the table

- Vessel by Vessel
  - 1 diseased LAD classified as nonsignificant by CT
- Patient by Patient
  - 1 Patient with luminal irregularity by QCA classified as having disease by QCA
  - 7 patients with single vessel disease (QCA) classified as multivessel disease by CT
  - 12 normal patients correctly identified by CT
  - 38 patients with significant CAD identified correctly by CT



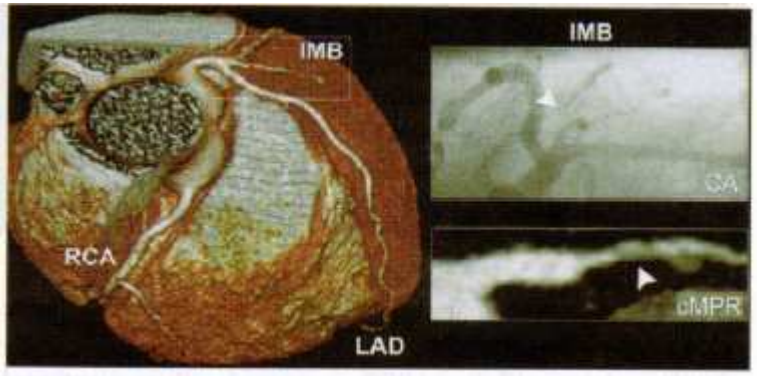


Figure 1. a, CT coronary angiogram and corresponding conventional angiogram of the right coronary artery (RCA) in a patient presenting with stable angina pectoris and a calcium (Agatston) score of 79. The arrow indicates a significant lesion located at the mid RCA. Cross-sectional CT images show a large noncalcific plaque (b) and a normal coronary lumen proximal and distal to the lesion (a, c). Note that the volume-rendered images (colored images) provide an excellent anatomic overview of the coronary arteries but should not be used to score the presence and degree of coronary stenoses. b, Volume-rendered CT image (colored image) providing an overview of the coronary anatomy and showing a small (lumen diameter, 1.5 mm) intermediate branch (IMB). A detailed curved multiplanar reconstructed (cMPR) CT image reveals the presence of a significant stenosis (arrowhead) located at the proximal IMB, which was confirmed on the conventional angiogram (CA). The patient was correctly classified as having 2-vessel disease on the CT scan. MIP indicates maximum-intensity projection; PDA, posterior descending coronary artery; coronary artery; RCA, right coronary artery.

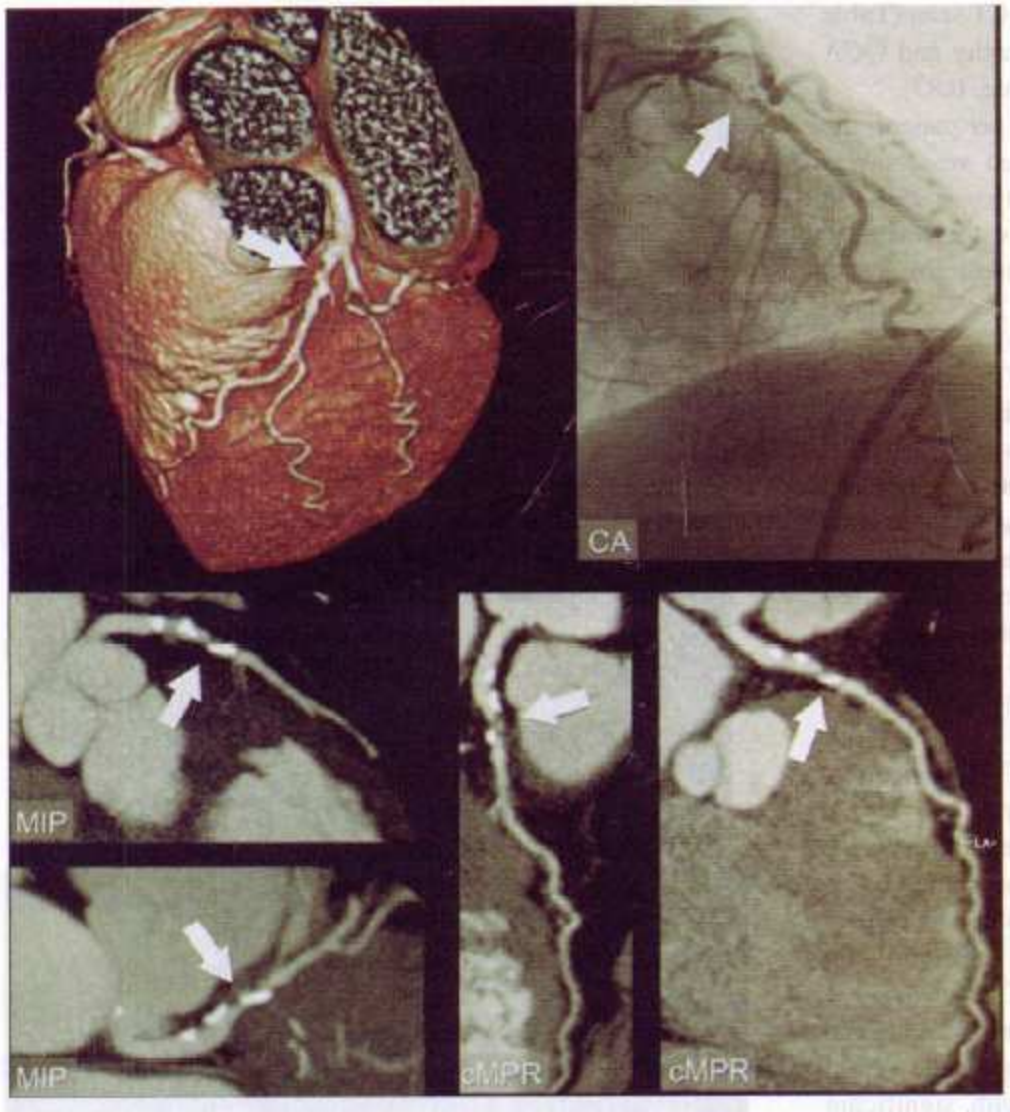


Figure 2. Volume-rendered CT image (colored image) providing an overview of the coronary anatomy and suggesting a significant stenosis of the proximal LAD (indicated by the arrow). More detailed analysis using different CT postprocessing techniques (maximum-intensity projections [MIP] and curved multiplanar reconstructions [cMPR]) confirms the presence of a significant stenosis, which corresponds with the conventional angiogram (CA).

Issues raised in the editorial

- Segmentation
  - Artificially creates more data points
  - Ignores connectivity of vascular tree
- Missing segments
  - Assume normal?
  - Invalid test?
  - Probability of disease extrapolated from other segments or vessels?
  - Probability of disease estimated from clinical risk factors?

Issues raised in the editorial

- Verification bias
  - Referral of only positive tests to cath
    - Exposes true and false positives
    - True and false negatives hard to estimate
  - Also consider underlying prevalence of disease
    - Current study has 75% prevalence of CAD
- Efficacy (controlled) and effectiveness (uncontrolled)

What if I flipped a coin? Segment analysis

	Disease	No Disease	
Heads (+)	47	315	362
Tails (-)	47	315	362
	94	631	725

- Sensitivity
  - 47/(47+ 47) = 50%
- Specificity
  - 315/(315 + 315) = 50%
- PPV
  - 47/(315 + 47) = 12%
- NPV
  - 315/(315 + 47) = 87%
- Overall Prevalence
  - 94/725 = 13%
- Low prevalence = High NPV

- CT PPV for all segments = 76%

Remember, only 83.6% of all segments visualized!

What if I flipped a coin? Patient analysis

	Disease	No Disease	
Heads (+)	19.5	6	25.5
Tails (-)	19.5	6	25.5
	39	12	51

- Sensitivity
  - 19.5/(39) = 50%
- Specificity
  - 6/(12) = 50%
- PPV
  - 19.5/(19.5+6) = 76%
- NPV
  - 6/(19.5 + 6) = 24%
- Overall Prevalence
  - 39/51 = 76%
- High Prevalence = High PPV