Colchicine for Post-operative Pericardial Effusion: The Post-Operative Pericardial Effusion (POPE-2) Study.

A Multicenter, Double-blind, Randomized Trial

P. Meurin[1], S. Lelay-Kubas, B. Pierre, H. Pereira, B. Pavy,

MC. Iliou, JL. Bussiere, H. Weber , JP. Beugin, T. Farrokhi,

A.Bellemain-Appaix, L. Briota, JY. Tabet,

(1) Les Grands Prés, Villeneuve-Saint Denis. France

for the French Society of Cardiology.

Disclosures

- ✓ Concerning this study: no conflict of interest
  - All the authors/investigators worked for free
  - Main funding source: French Society of Cardiology
  - Mayoly-Spindler company provided the sudy's drug and placebo
- ✓ Other relationships with pharmaceutical companies:
  - Consultant for Servier
  - Research grant: Daïchi Sankyo

Background and Objectives

Post-Operative Pericardial Diseases

- ✓ Before post-op day 7: Phase 1
- Post-operative pericardial effusion (POPE): 50-80% patients
- Early tamponades: haemopericardium: 0.5 to 1% of the patients
- ✓ After post-op day 7: Phase 2
- Post pericardiotomy syndrom (PPS): COPPS-1[1] and **2** studies
- Persisting moderate to large POPE: POPE-1[2] and **2** studies

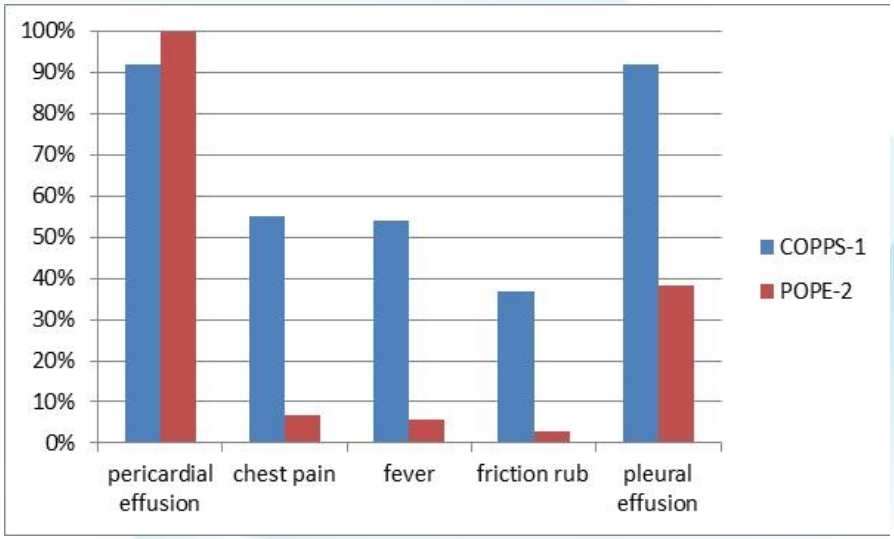
(1) Imazio M, (COPPS-1). Eur Heart J. 2010; 31:2749-54. (2) Meurin et al.POPE-1 Study. Ann Intern Med 2010; 152: 137-43

Post Operative Pericardial Diseases after day 7: PPS and POPES are very different

Symptoms :

PPS : yes

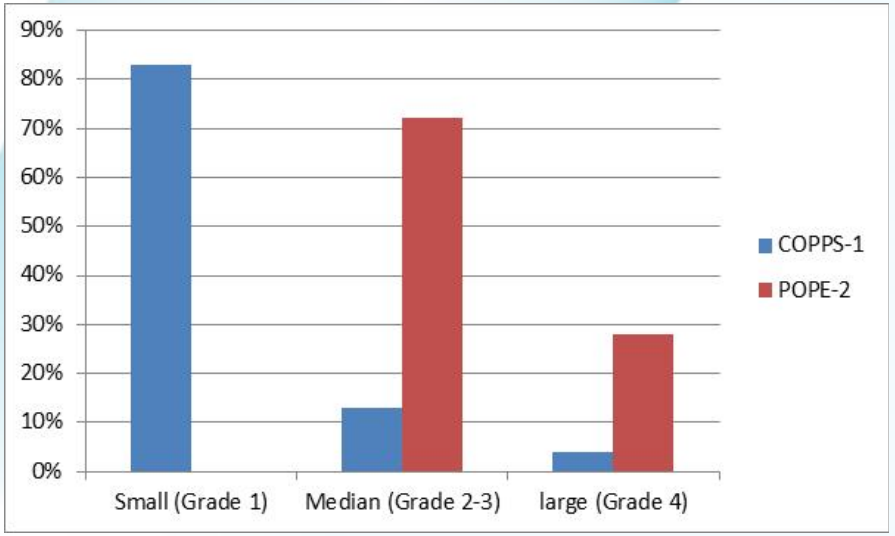
POPES ≈ no

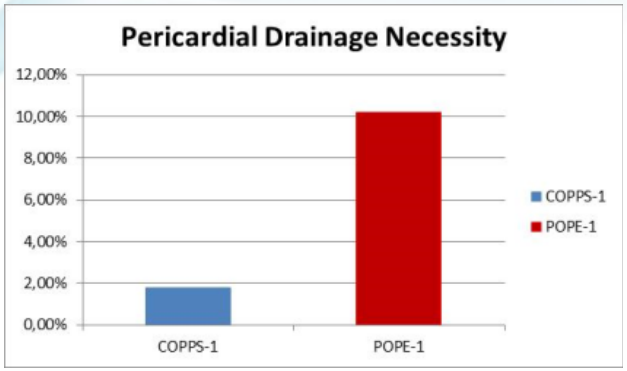


Effusions:

PPS ≈ no or small

POPES: yes, large





To sum-up:

- PPS: acute **Pericarditis,** but low Tamponade Risk
- POPES: **Effusion** initially asymptomatic, but high Tamponade Risk

(1) Meurin et al.POPE-1 Study. Ann Intern Med 2010.(2) Imazio et al.COPPS-1 Study. Eur Heart J 2010. (3) Imazio et al Am J Cardiol. 2011;108: 1183-7

Treatment of POPEs

- ✓ Non Steroidal Anti Inflammatory Drugs (NSAIDs) are useless[1]
- ✓ What about colchicine ?

- Very efficient to treat acute pericarditis[2]
  - (Add-on NSAID or aspirin)
- Efficient to prevent Post Pericardiotomy Syndrom[3]
- Efficient to treat post operative pericardial effusions ?

(1) Meurin et al. POPE-1 Study. Ann Intern Med 2010 ; (2) Imazio M; ICAP: A randomized trial of colchicine for acute pericarditis. N Engl J Med. 2013; 369:1522-8 ; (3) Imazio M, (COPPS-1): Eur Heart J. 2010.

POPE-2 **Study:** Methods

POPE-2 Study: methods (1)

- ✓ **Objective:** to assess whether colchicine was effective in reducing post operative pericardial effusion (POPE) volume.
- ✓ **Design:** multicenter, randomized, double-blind, placebo-controlled study
- ✓ **Setting:** Ten post operative cardiac rehabilitation centers (POCRC).
- ✓ **Patients:** 197 patients at high risk of tamponade
- ✓ **Treatment administration:** 14 days (colchicine or placebo)

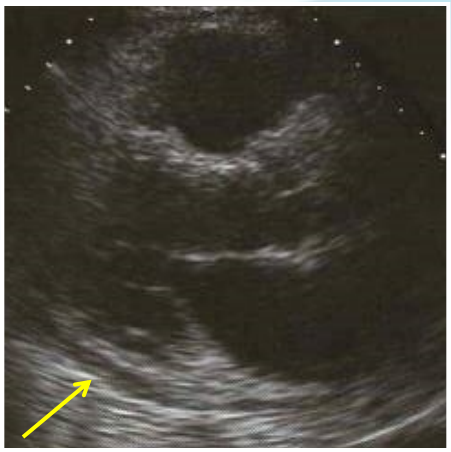
  - Pts ≥ 70kg: 2.0 mg for the first day followed by a maintenance dose of 1 mg daily
  - Pts <70 kg 1 mg per day without a loading dose

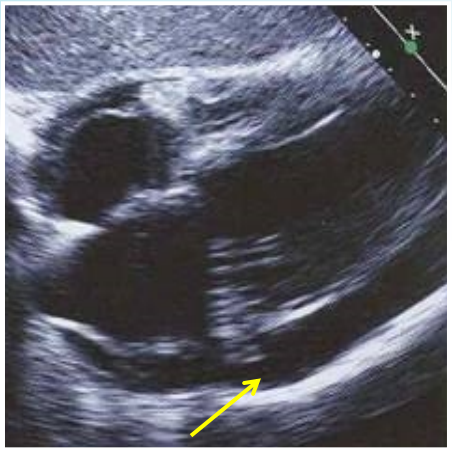
Methods (2)

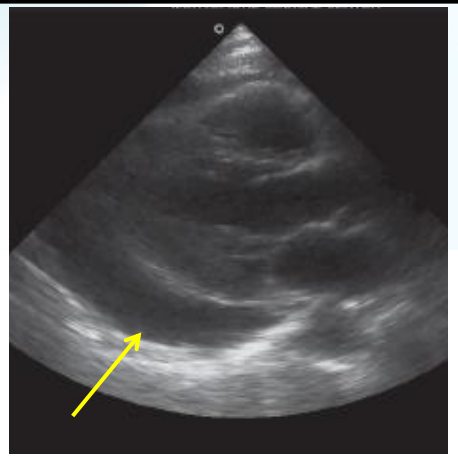
Quantification of POPEs: echocardiographic classification 1,2

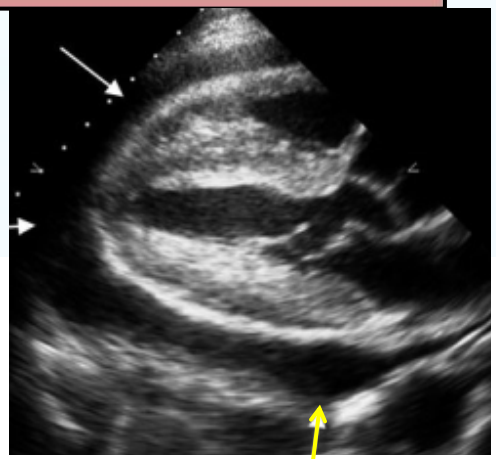
Grade at Day 15 (8-29)	Loculated	Circumferential	Estimated Late Tamponade Risk at Day 30
0	0	0	0
1- Small	< 10 mm	0	0
2-Moderate	10-14 mm	< 10 mm	2-7%
3-Medium	15-19 mm	10-14 mm	15%
4-Large	≥ 20 mm	≥ 15 mm	25-45%

≈ 10%









(1) Meurin P, Weber H, Renaud N et al. Chest 2004;125:2182-87. (2) Meurin et al. POPE-1 Study. Ann Intern Med 2010

POPE-2 Study: Methods (3)

✓ Inclusion criteria:

- Persistent pericardial effusion ≥ grade 2 on the echocardiography performed at admission in POCRC (8 to 30 days after surgery)

✓ Exclusion criteria:

- Colchicine contra-indication (allergy, pregnancy, renal failure, …)
- Cardiac transplantation or correction of congenital heart anomalies

Methods (4)

Quantification of POPEs Volume

Main endpoint:

Mean (echographic) Pericardial Effusion Grade (MPEG) evolution in the 2 groups (colchicine and placebo)

Example:

Determination of the Mean Pericardial Effusion Grade of a group of patients:

(Fictional) Group: 3 patients

Patient n°1: Grade **2** POPE

Patient n°2: Grade **3** POPE

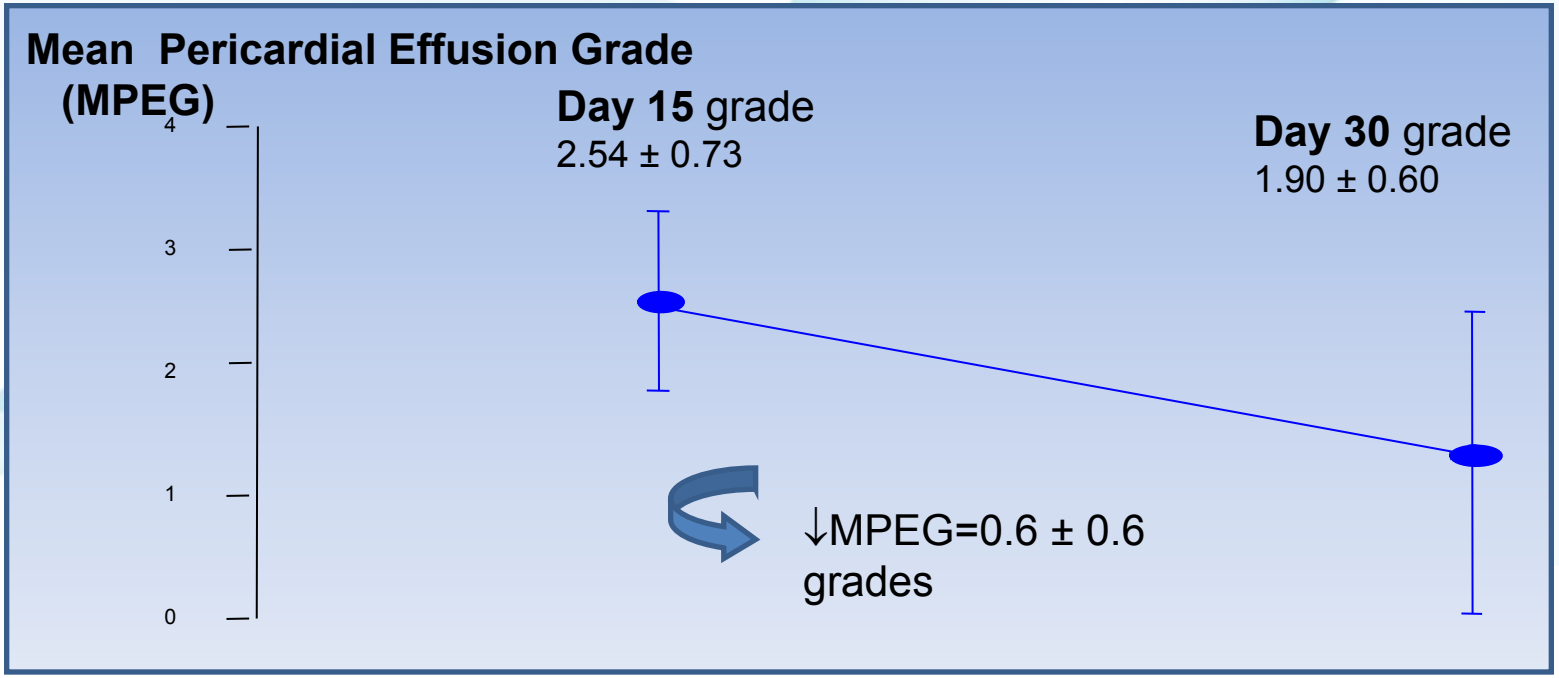
Patient n°3: Grade **4** POPE

Mean Pericardial Effusion Grade of this fictional Group= (2+3+4)/3= 3

Methods (5)

Spontaneous evolution of the Mean pericardial Effusion Grade: Data from a previous study1

Follow up of POPEs in 1277 consecutive patients



(1) Meurin P, Weber H, Renaud N et al. Chest 2004.

Methods (6):

Statistical Power

✓ Mean pericardial effusion grade (MPEG) decrease

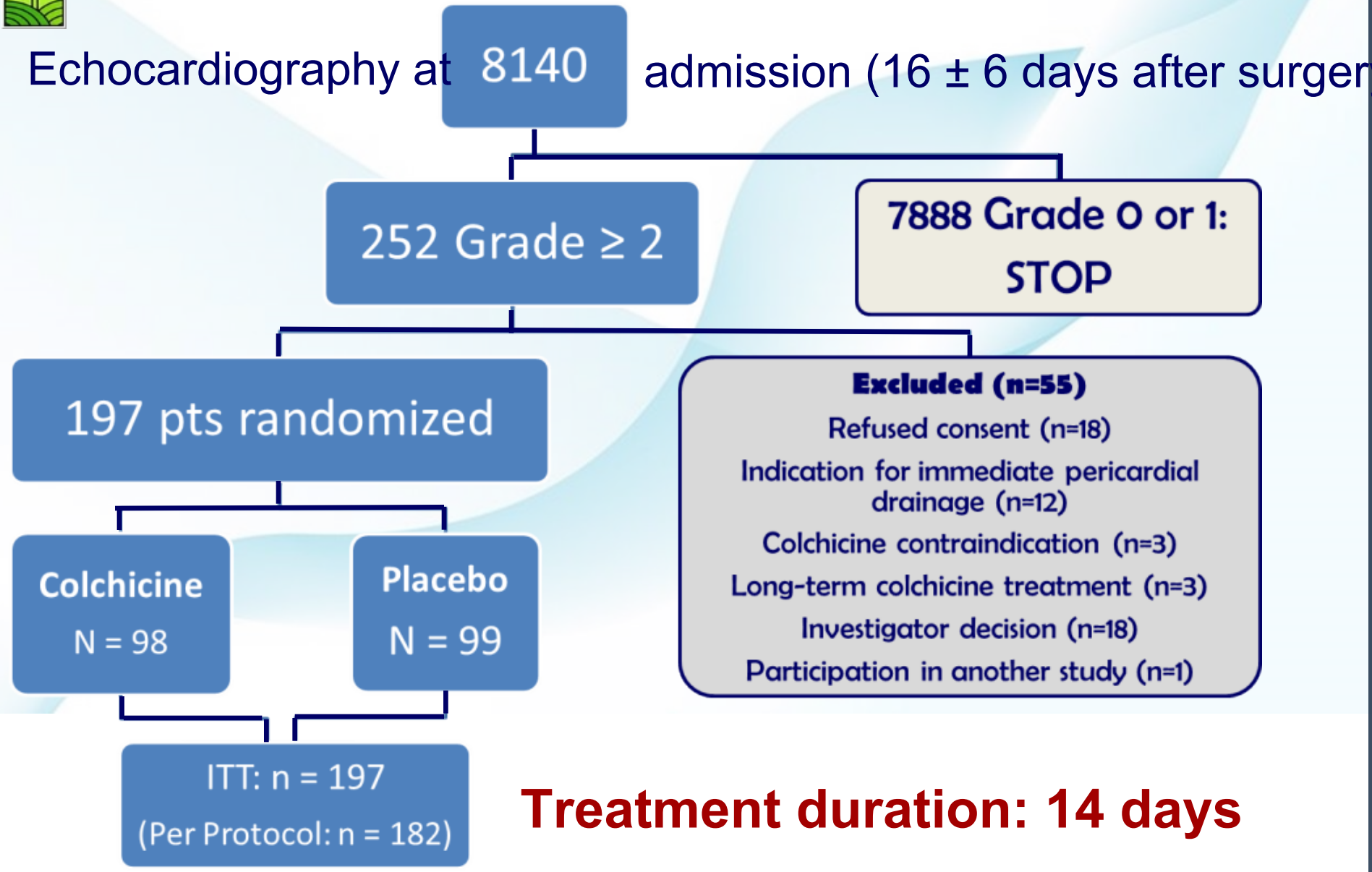
- Between the inclusion and the final echocardiographies
- Expected to be of 0.6 grades in the placebo group

✓ Sample size assessment: 86 patients per group

- 80% power to detect a supplementary reduction of 50% of the MPEG with colchicine (versus placebo)
- Two-sided type 1 error of 5 %

Results

From April 2011 to March 2013



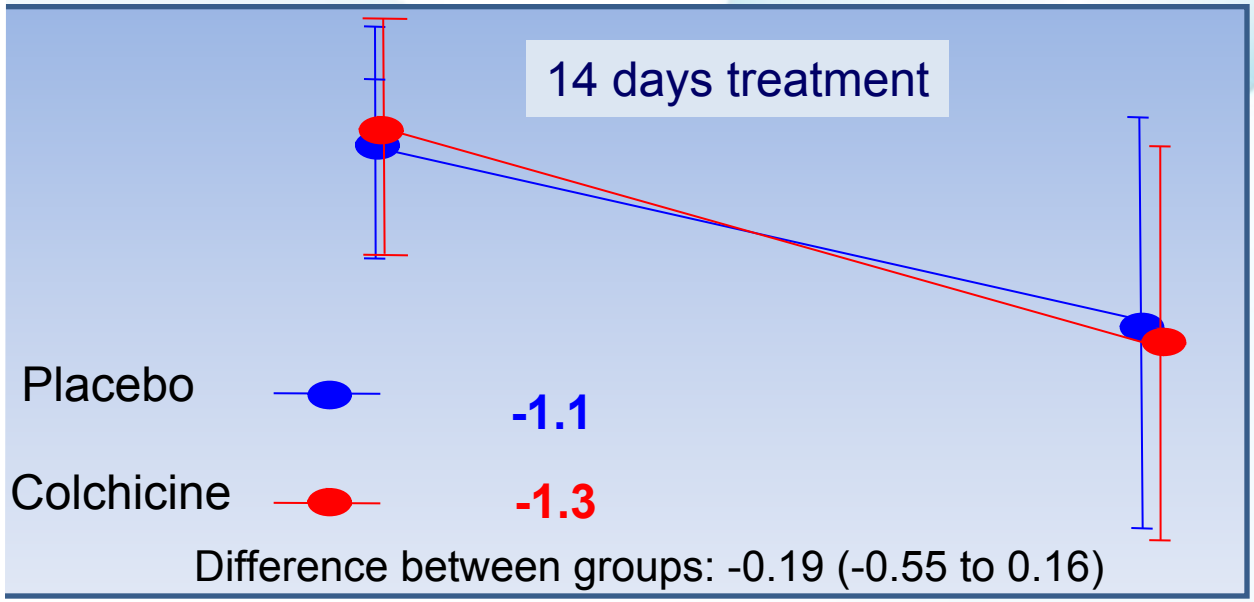
Treatment duration: 14 days

Baseline Characteristics

	Placebo Group (n = 99)	Colchicine Group (n = 98)
Mean Age (SD), years	65±10.	64±12
Male (%)	88 (89%)	82 (84%)
Surgery performed - CABG - Ao Valve Replacement - Mitral Valve Surgery - Root Aorta Surgery	52% 48% 39% 15%	59% 35% 27% 15%
Delay surgery-inclusion	16 ±5	16±5
Oral anticoagulants - INR at inclusion (SD)	51 % 2.4 ± 0,7	53 % 2.4 ± 0,79
POPE mean grade: MPEG	2.9 ± 0.8	3.0 ± 0.8
Grade 2	35%	27%
Grade 3	36%	43%
Grade 4	28%	28%

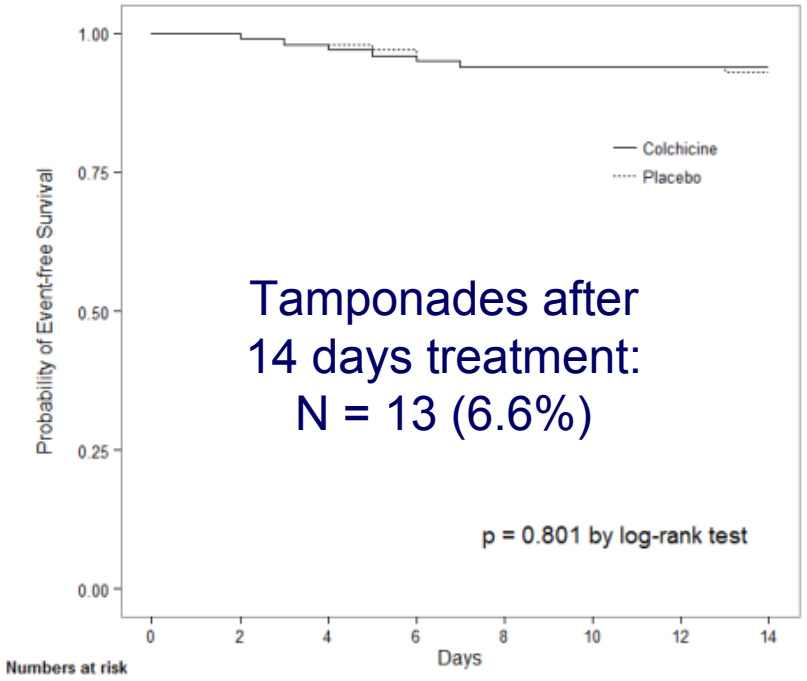
Primary Endpoint: Mean Pericardial Effusion Grade Decrease

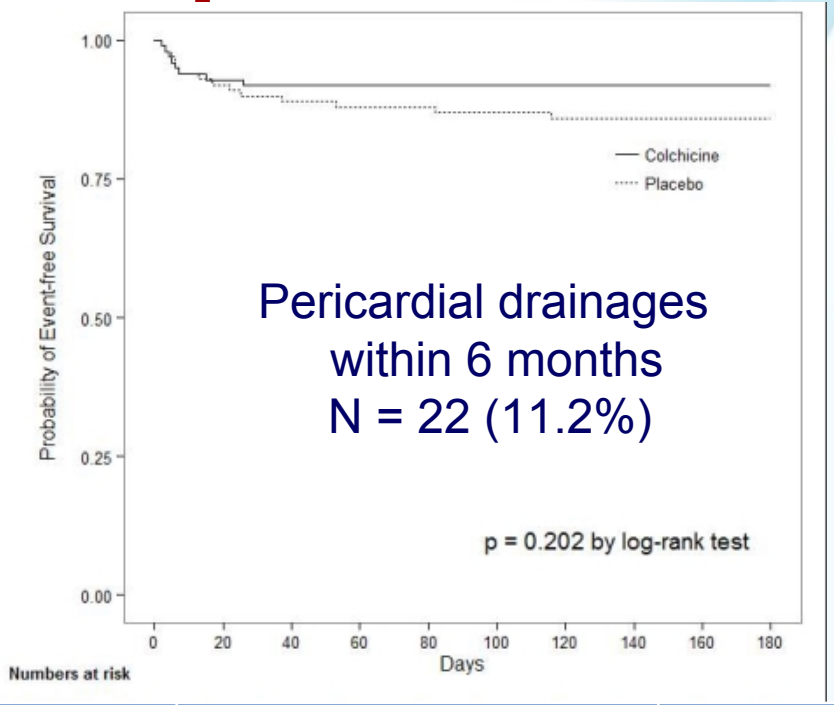
Surgery → Inclusion (Day 16 ± 5) → End of the study (*Day 29.0 ± 7.0*)



Grade	Placebo	Colchicine	Mean (95% CI)	p
	2.9±0.8	3.0±0.8		
	1.8±1.3	1.7±1.2		
	- 1.1±1.3	-1.3±1.3	-0.19 (-0.55 to 0.16)	0.23

Secondary Endpoints





	Placebo Group (n = 99)	Colchicine Group (n = 98)	p
Patients with at least 1 grade decrease	**67%**	**74%**	0,27
Reduction of the Echo free space width (mm)	**-4. 7 ± 6.9**	**-5.8 ± 6.1**	0.23
Atrial Fibrillation at the end of the study	**12%**	**15%**	0,51

Prespecified Sub-Groups Analysis

MPEG decrease (grades) in Patients	Placebo Group (n=99)	Colchicine Group (n=98)	95% CI	p
With CRP level ≥ 30mg/l (n=82)	-1.3±1.4	-1.4±1.4	-0.11 (-0.72 to 0.49)	0.81
Receiving an oral anticoagulant (n=102)	-0.9±1.3	-1.4±1.2	-0.48 (-0.99 to 0.02)	0.06
Per Protocol Analysis (n=182)	-1.1±1.3	-1.3±1.3	0.18 (-0.56 to 0.20)	0.28

Conclusion:

Moderate to large persisting (> 7 days) post operative pericardial effusion: What does this study add ?

1-

High risk patients: 11,5% reoperation within 6 months:

- 6,6 % tamponades in the 2 following weeks
- Another 5 % will require pericardial drainage within 6 months

2- Colchicine administration seems to be useless

[PS: NSAID administration seems to be useless (POPE-1

Thanks to

✓ POPE study investigators:

- **Les Grands Prés (CRCB):** A Ben Driss, R Dumaine, A Grosdemouge, P Meurin, N Renaud, JY Tabet, H Weber.
- **HopitalCorentin Celton**: MC Iliou. P Cristofini, Devaux N, Sissman J.
- **Hopital Bligny**: T Farrokhi, S Corone, S Hardy, C Randolph, V Beaslay.
- **IRIS**: B Pierre, JL Genoud, F Boucher, L Pacini, H Talpin.
- **Centre de Réadaptation Bois Gibert**: S Le Lay-kubas, C Voyer, C Monpère.
- **Centre Hospitalier Loire Vendée Océan:** B Pavy, A Tisseau.
- **Clinique de la Mitterie:** J De Monte, JP Beuvin, C Defrance, ME Lopes.
- **Centre Dieuleufit santé:** L Briota, R Brion, S Devaud, C Kugler-Chambron, R Auberger.
- **La Maison du Mineur**: A Bellemain-appaix, H Chevassus-Lescaut.
- **Clinique de châtillon**: JL Bussiere.

Patients

Back-up slide

✓ High power of the study to assess Colchicine effectiveness

- Theoretical sample size: 172
- Included: 197

✓ Study underpowered to test colchicine safety:

- 13 patients did not complete the study
  - 10 in the colchicine group:
    - ✓ Diarrhea (n = 7), constipation (n = 1), digestive haemorrhage (n = 1), leucopenia (n = 1)
  - 3 in the placebo group
    - ✓ Stroke (n = 1), constipation (n = 1), consentment withdrawal (n = 1)