Non-Steroidal Anti-Inflammatory (NSAIDs) Treatment for Post- Operative Pericardial Effusion: The POPE Study

A Multicenter, Double-Blind, Randomized Trial

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on behalf of the French Society of Cardiology

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- No conflict of interest

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Post Operative Pericardial Effusions

- Frequent:
  - ✓ 50-80% of cardiac operated patients
- Asymptomatic
- Can convert into cardiac tamponade (CT):

  1 % of operated patients:

  ✓ 1/3: early CTs: day 1- day 7: intra-pericardial bleeding

  ✓ 2/3: late CTs: day 8 – day 30: mechanism: inflammation and bleeding

NSAIDs as a Treatment of Post Operative Pericardial Effusions: an Old Habit

- Prescribed in 40-77% of the patients[1] having an effusion

Although:

- Efficacy concerns:
  - ✓ no study has ever shown their efficacy for this condition
- Toxicity concerns:
  - ✓ multiplies by 1.5 to 2 the risk of myocardial infarction and acute heart failure
  - ✓ by 3 renal failure (x 6 If ACE-I co-administration)
  - ✓ by 4 gastrointestinal tract bleeding (x 8 if co-administration of a VKA or low dose aspirin).

(1) Tsang TS, Barnes ME, Hayes SN. et al. Mayo Clinic Experience 1979-1998. Chest 1999;116:322-331.

POPE Study

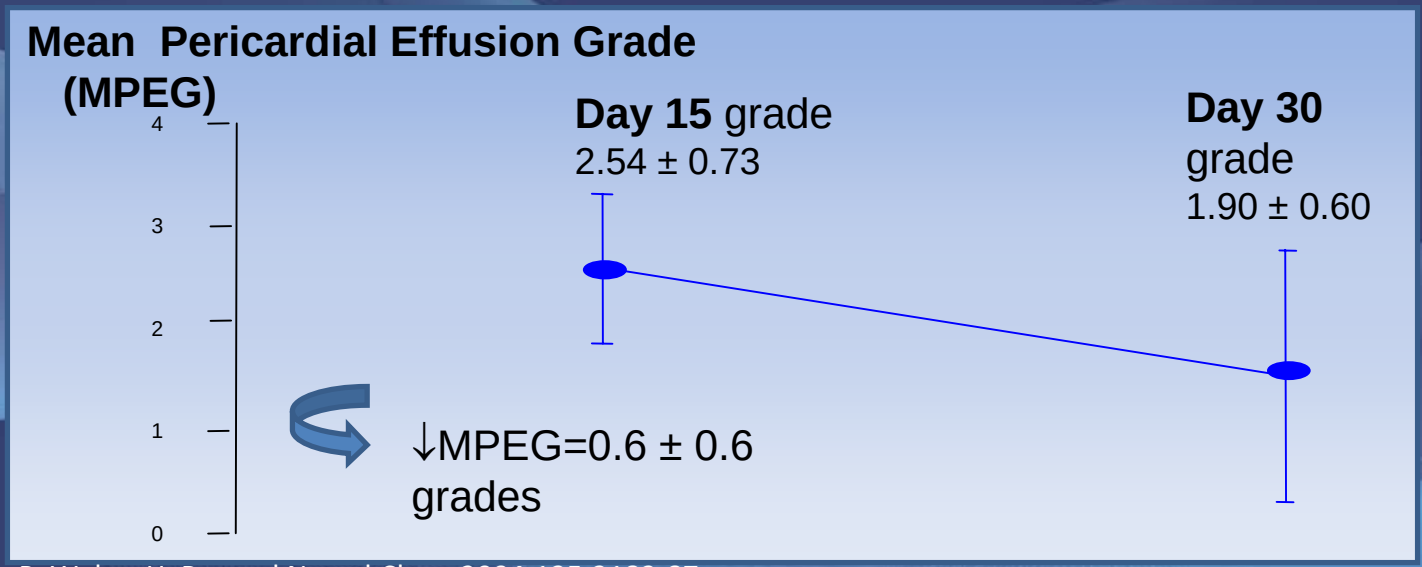
- **Objective**: to assess whether the NSAID diclofenac was effective in reducing post operative pericardial effusion volume.
- **Design**: multicenter, randomized, double-blind, placebo-controlled study
- **Setting**: five post operative cardiac rehabilitation centers (POCRC).
- **Patients**: 196 patients at high risk of tamponade
- **Treatment administration**: 14 days

Quantification and Spontaneous Evolution of Post Operative Pericardial Effusions

Echocardiographic classification

Grade at day 15	Loculated	Circumferential	Estimated Late CT risk at day 30[1]
0	0	0	0%
1 Small	< 10 mm	0	0%
2 Moderate	10-14 mm	< 10 mm	**7%**
3 Medium	15-19 mm	10 -14 mm	**15%**
4 large	≥ 20 mm	≥ 15 mm	**43%**

Spontaneous evolution



Meurin P, Weber H, Renaud N et al.Chest 2004;125:2182-87.

POPE Study: Methods (1)

- Inclusion criteria:
  - ✓Persistent pericardial effusion ≥ grade 2 on the echocardiography performed at admission in POCRC (8 to 30 days after surgery)
- Exclusion criteria:
  - ✓NSAID contra-indication (allergy, pregnancy, renal failure, evolutive gastro duodenal ulcer…)
  - ✓Cardiac transplantation or correction of congenital heart anomalies

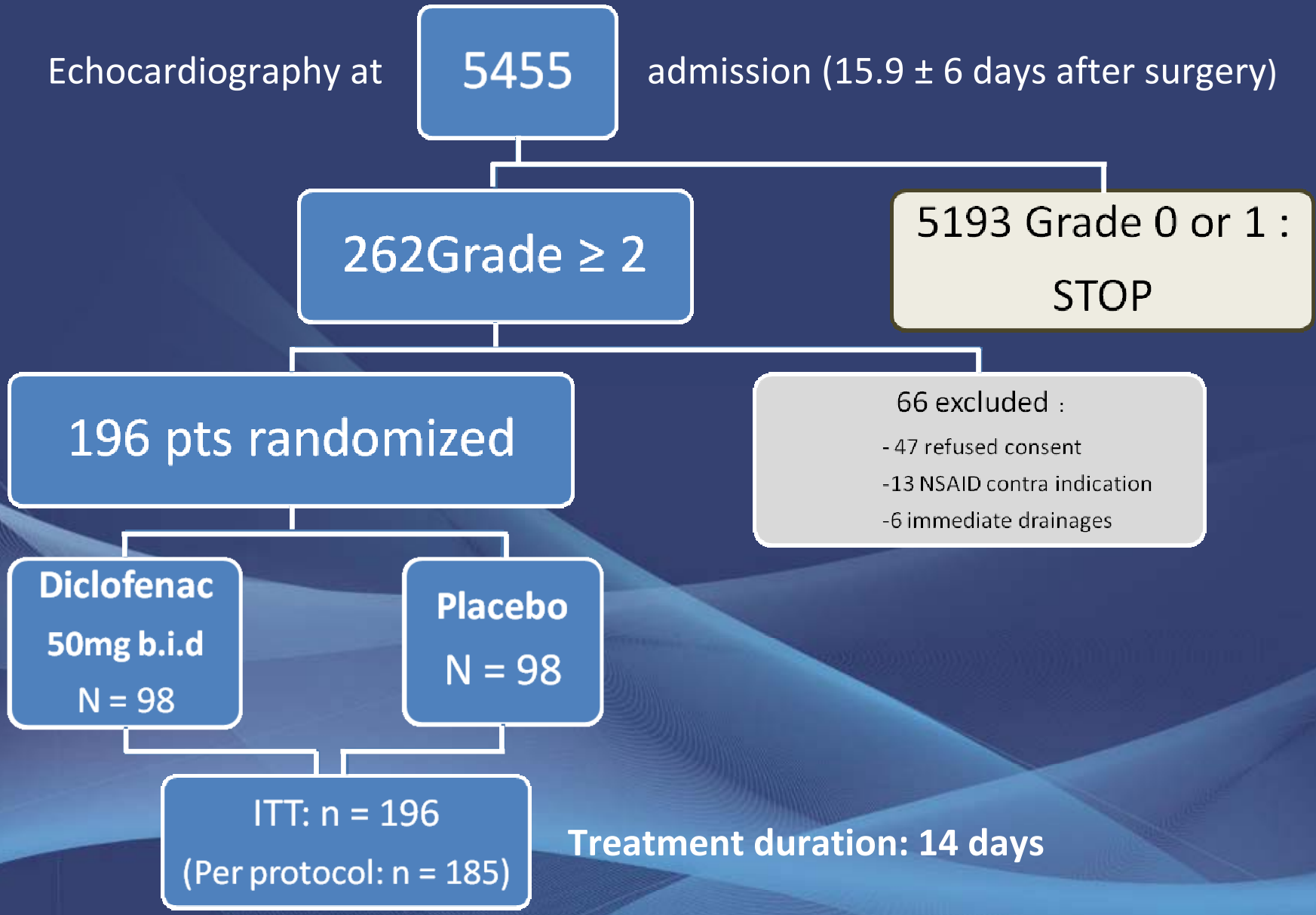
Methods (2): Primary Echographic Endpoint and Statistical Power

- Mean pericardial effusion grade (MPEG) decrease
  - ✓ Between the inclusion and the final echocardiographies
  - ✓ Expected to be of 0.6 grade in the placebo group

- Sample size assessment: 86 patients by group
  - ✓ 80% power to detect a supplementary reduction of 50% of the MPEG with diclofenac (versus placebo)
  - ✓ two-sided type 1 error of 5 %

Results

From January 2006 to January 2009



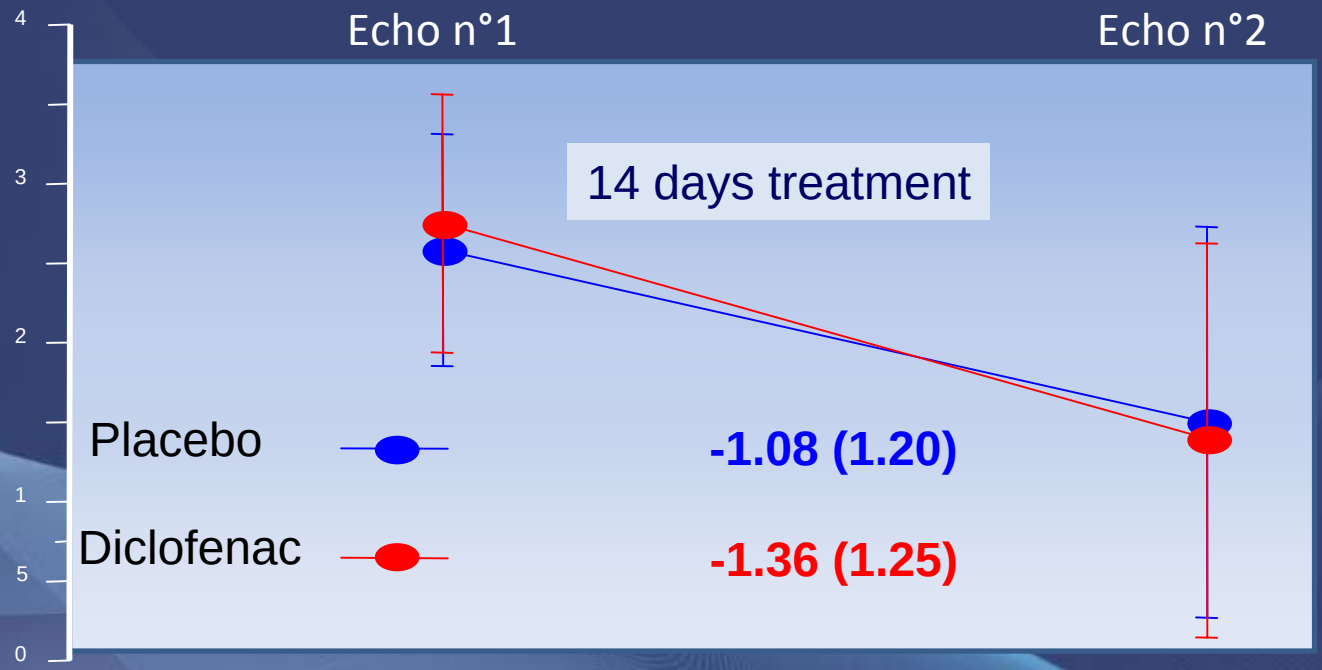
Baseline Characteristics

	Placebo Group (n = 98)	Diclofenac Group (n = 98)
Mean Age (SD), years	62.5 (12)	64.1 (11)
Male (%)	78%	82%
Surgery performed - CABG - Ao Valve Replacement - Mitral Valve Surgery - Root Aorta Surgery	 57% 32% 20% 8%	 60% 35% 11% 10%
Delay surgery-inclusion	15.9 (5.1)	15.9 (4.3)
Oral anticoagulants - INR at inclusion (SD)	43% 2.77 (1.12)	44% 2.51 (0.91)
Aspirin	75%	72%

POPE mean grade: MPEG	2.58 (0.73)	2.75 (0.81)
grade 2, n	55	47
grade 3, n	29	28
grade 4, n	14	23

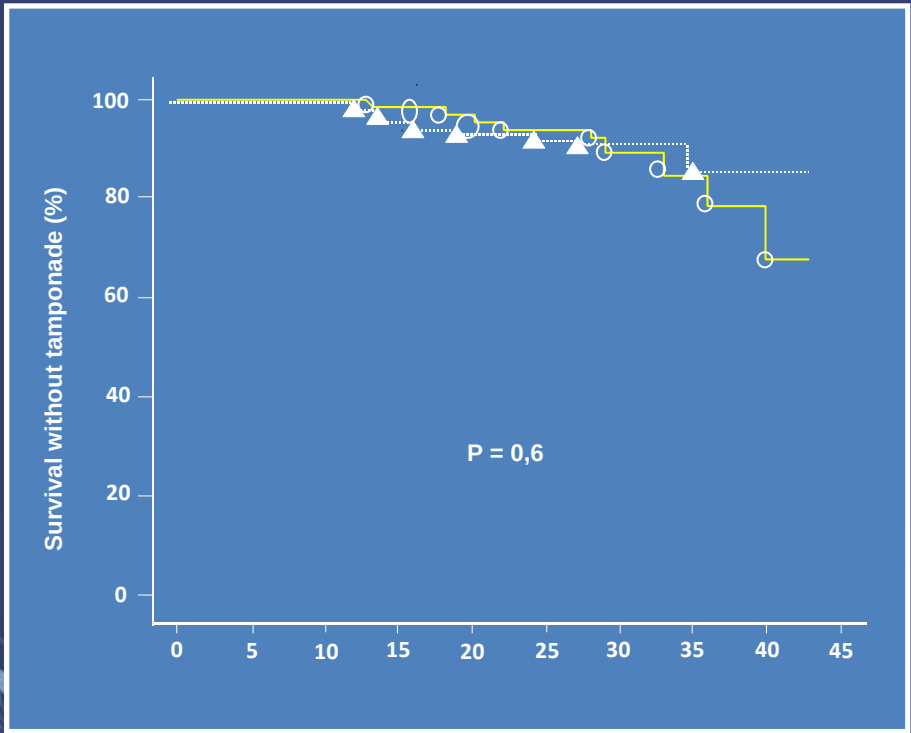
Primary Endpoint:
Mean Pericardial Effusion Grade Decrease

Surgery → Inclusion (Day 15.9 ± 6.4) → End of the study (Day 29.0 ± 7.0)



Grade	Placebo	Diclofenac	Mean (95% CI)	p
Initial	2.58 (0.73)	2.75 (0.81)		
Final	1.49 (1.22)	1.39 (1.20)		
Change	**-1.08 (1.20)**	**-1.36 (1.25)**	**0.28 (-0.63 to 0.06)**	**0.15**

Secondary Endpoints



placebo group

diclofenac group

Late Tamponades

n = 11 (11.2%)

n = 9 (9.2%)

	Placebo Group (n = 98)	Diclofenac Group (n = 98)	p
At least 1 grade decrease	**73 (74.4%)**	**71 (72.4%)**	0.7
Echo free space width (mm)	**-4. 8 (7.0)**	**-6.7 (7.4)**	0.07

Prespecified Sub-Groups Analysis

MPEG decrease (grades) in Patients	Placebo Group (n=98)	Diclofenac Group (n=98)	95% CI	p
With CRP level ≥ 30mg/l (n=90)	**-1.35 (1.26)**	**-1.64 (1.16)**	0.29 (-0.8 to 0.23)	**0.26**
Receiving an oral anticoagulant (n=85)	**-1.17 (1.37)**	**-1.56 (1.26)**	0.38(-0.96 to 0.18)	**0.18**
Per Protocol Analysis (n=185)	**-1.11 (SD 1.21)**	**-1.35 (SD 1.27)**	0.25 (-0.60 to 0.11)	**0.25**

Remarks

- High power of the sudy to assess NSAID effectiveness
  - ✓ Theoretical sample size: 172
    - included: 196
  - ✓ MPEG decrease expected : -0.6 grades
    - observed: -1.08 grade (SD 1.2)
- Study underpowered to test NSAID tolerance

Conclusion

- Patients with a moderate to large pericardial effusion 15 days after cardiac surgery are at high risk:
  - ✓ 10% pericardial drainages in the 2 following weeks
- NSAID administration is useless in this setting