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Nonsteroidal Anti-inflammatory Drug Treatment for Postoperative Pericardial Effusion

A Multicenter Randomized, Double-Blind Trial

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Background: The incidence of asymptomatic pericardial effusion is high after cardiac surgery. Nonsteroidal anti-inflammatory drugs (NSAIDs) are widely prescribed in this setting, but no study has assessed their efficacy.

Objective: To assess whether the NSAID diclofenac is effective in reducing postoperative pericardial effusion volume.

Design: Multicenter randomized, double-blind, placebo-controlled study. (Clinical trials.gov registration number: NCT00247052)

Setting: 5 postoperative cardiac rehabilitation centers.

Patients: 196 patients at high risk for tamponade because of moderate to large persistent pericardial effusion (grade 2, 3, or 4 on a scale of 0 to 4, as measured by echocardiography) more than 7 days after cardiac surgery.

Intervention: Random assignment at each site in blocks of 4 to diclofenac, 50 mg, or placebo twice daily for 14 days.

Measurements: The main end point was change in effusion grade after 14 days of treatment. Secondary end points included frequency of late cardiac tamponade.

Results: The initial mean pericardial effusion grade was 2.58 (SD, 0.73) for the placebo group and 2.75 (SD, 0.81) for the diclofenac group. The 2 groups showed similar mean decreases from baseline after treatment (−1.08 grades [SD, 1.20] for the placebo group vs. −1.36 (SD, 1.25) for the diclofenac group). The mean difference between groups was −0.28 grade (95% CI, −0.63 to 0.06 grade; $P = 0.105$). Eleven cases of late cardiac tamponade occurred in the placebo group and 9 in the diclofenac group ($P = 0.64$). These differences persisted after adjustment for grade of pericardial effusion at baseline, treatment site, and type of surgery.

Limitation: The sample was not large enough to find small beneficial effects of diclofenac or assess the cardiovascular tolerance of diclofenac.

Conclusion: In patients with pericardial effusion after cardiac surgery, diclofenac neither reduced the size of the effusions nor prevented late cardiac tamponade.

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* For a list of all study investigators, see the **Appendix** (available at www.annals.org).

Clinically insignificant pericardial effusion is common after heart surgery, with an incidence of 50% to 85% a few days after surgery (1, 2). Cardiac tamponade occurs in about 1% to 2% of patients who have cardiac surgery and may develop slowly without clear-cut clinical signs. Most tamponade occurs more than 7 days after surgery (3, 4), which is a concern because patients often have already been discharged from the hospital by that time.

In our previous study (5), 22% of 1277 patients had pericardial effusion 20 days after cardiac surgery. The most powerful predictor of late cardiac tamponade was the size of the effusion. During follow-up, none of the patients with no effusion or a small effusion experienced late cardiac tamponade, but tamponade developed in 11% of patients with larger pericardial effusions.

Nonsteroidal anti-inflammatory drugs (NSAIDs) are widely used to reduce the size of asymptomatic postoperative pericardial effusions: for example, in 77% of the patients in one large study (3). Although no study has ever shown the efficacy of NSAIDs for this condition, guidelines and reviews (6–8) suggest that they be used. Because patients who have recently had heart surgery are fragile, it is important to understand the balance of risks and benefits for this treatment. Although NSAIDs are usually given for only a short time to patients with pericardial effusions, they can cause serious adverse effects, such as myocardial infarction and acute heart failure (9, 10), acute renal failure (11, 12), and upper gastrointestinal tract bleeding or perforation (13, 14), in other settings and types of patients.

We conducted a multicenter prospective, double-blind, randomized, controlled study that compared the efficacy of diclofenac and placebo in reducing the size of

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Context

Pericardial effusion is common after cardiac surgery, and it can progress to cardiac tamponade. Most physicians prescribe a nonsteroidal anti-inflammatory drug (NSAID) if pericardial effusion is detected, because inflammation is thought to be the cause, especially when the effusion is present 7 or more days after surgery. Expert recommendations and clinical guidelines encourage this practice, but no studies have found NSAIDs to be effective for this purpose.

Contribution

The researchers randomly allocated 196 patients with moderate to large pericardial effusions more than 7 days after cardiac surgery to receive either placebo or 50 mg of diclofenac twice daily for 14 days. The effusions decreased by about the same amount in both groups, and about the same number of patients in both groups developed cardiac tamponade.

Caution

The study did not have enough patients to detect small beneficial effects from diclofenac.

Implication

Physicians should stop prescribing NSAIDs for postoperative pericardial effusion because these agents have no or only small beneficial effects.

—The Editors

postoperative pericardial effusions in patients with effusions that persisted more than 7 days after heart surgery.

METHODS

Patients

Between 1 February 2006 and 15 December 2008, we screened all patients with recent cardiac surgery who were admitted to 5 French cardiac rehabilitation centers where patients routinely stay up to 30 days after their surgery. Patients were eligible for this study if they were 18 years or older and had pericardial effusion grade 2 or larger, corresponding to a loculated effusion larger than 10 mm or a circumferential effusion of any size (**Table 1**), on the first transthoracic echocardiography they received more than 7 days after surgery. We excluded patients who did not give written consent to participate; were pregnant or allergic to diclofenac; had a gastroduodenal ulcer, recent gastrointestinal hemorrhage, or renal failure, defined as a serum creatinine level of 170 μmol/L or greater (≥19.2 mg/L); received any NSAID on a long-term basis; had heart transplantation or correction of congenital heart anomalies; had cardiac surgery more than 30 days before their first transthoracic echocardiography; or had pericardial effusion that required drainage.

Study Design

On the day of admission, we administered the first transthoracic echocardiography and a standard set of laboratory tests and randomly assigned patients at each site in blocks of 4 to receive diclofenac, 50 mg, or placebo twice daily for 14 days. We repackaged the diclofenac and placebo so that they seemed to be identical red capsules in identical boxes. We prescribed treatment to prevent gastric and duodenal ulcers to all patients, but not all patients received the same treatment. We administered a second transthoracic echocardiography and another set of laboratory tests 14 days after treatment was started, or earlier if we suspected tamponade. We gave low-dose aspirin to patients who had coronary artery bypass graft (CABG) surgery and oral vitamin K antagonists to patients who had valvular replacement or repair.

An independent company (CLINACT, Paris, France) audited each patient file for complete data collection and the presence of information about adverse events and informed consent. Another independent company that is allowed to manage the pharmaceutical process for clinical trials (CLIPA-CRID Pharma, Saint-Gély-du-Fesc, France; French Health Product Safety Agency Authorization MM0902) determined that the diclofenac used in the study was bioequivalent to commercial diclofenac; generated the random assignment schedule; and controlled the manufacturing, packaging, and distribution of study drugs. The clinical trial ethics committee of Pitié-Salpêtrière Hospital (Paris, France) approved the protocol, and all participants provided written informed consent to participate before random assignment.

Study End Points

The primary end point was the mean change from baseline in the grade of pericardial effusion after 14 days of treatment. Secondary end points included frequency of cardiac tamponade; number of patients with at least a 1-grade decrease in their effusion; and mean change in the width of the effusion, measured in millimeters. We contacted patients' cardiologists to determine whether patients needed pericardial drainage after 14 days. Although our study was underpowered to assess the safety of diclofenac, we monitored patients for adverse drug effects with daily physical examinations and by measuring creatinine and hemoglobin in the blood.

Table 1. **Width of Echo-Free Space Between the Pericardium and Myocardium, Used to Determine the PE Grade**

PE Grade	Loculated PE, *mm*	Circumferential PE, *mm*
0	–	–
1 (minimal)	0–9	–
2 (moderate)	10–14	1–9
3 (medium)	15–19	10–14
4 (large)	≥20	≥15

PE = pericardial effusion.

Echocardiographic Variables

We administered M-mode, cross-sectional, and Doppler transthoracic echocardiography by using a standard echocardiographic technique with parasternal (long axis and short axis), apical (4 chambers and 2 chambers), and subcostal projections. We created pulsed and continuous Doppler echocardiograms of the mitral, aortic, and tricuspid flows from the apical views. We visualized pericardial effusion during diastole as an echo-free space around the heart that could be circumferential or loculated along the right or left cardiac cavities, and we measured the effusion width at the place where the volume was largest. Two operators jointly performed each examination. We measured interobserver variability on 50 echocardiograms and found interobserver agreement coefficients of 85% to 90% and κ values of 0.80 to 0.85 for effusion grade.

We diagnosed cardiac tamponade clinically by examining patients for hypotension, pulsus paradoxus, tachycardia, dyspnea, oliguria, and signs of right heart failure, and we diagnosed cardiac tamponade echocardiographically by looking for pericardial effusion, right atrial collapse, right ventricular collapse, left ventricular collapse, distention of the inferior vena cava with blunted inspiratory response, swinging of the heart in the pericardial space, and large respiratory fluctuations in mitral or tricuspid flows (6).

Statistical Analysis

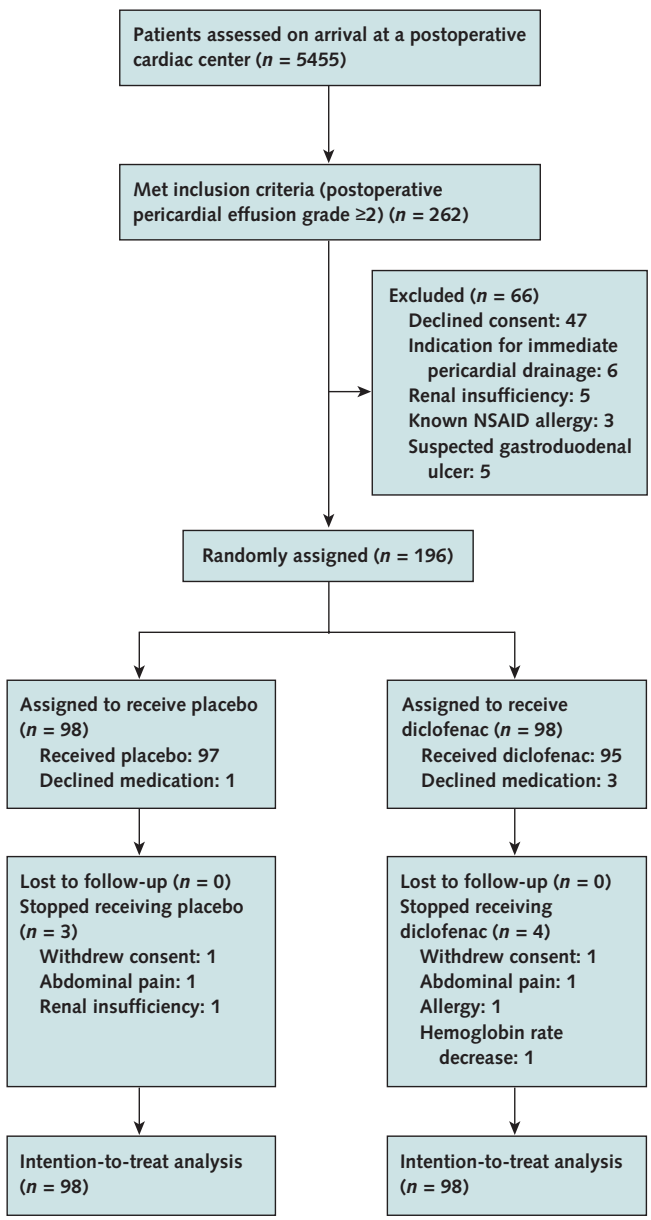
We determined the sample size by assuming that the decrease in mean pericardial effusion grade would be 0.6 grade in the control group, which is the value we found in our previous study (5). We calculated that we would need 172 patients (86 in each group) for 80% power to detect an additional 50% decrease in the diclofenac group, which corresponded to a total decrease of 0.9 grade, with a 2-sided, type I error of 5%.

We conducted prespecified analyses according to the intention-to-treat principle. We used the Mann–Whitney U test to compare the difference between treatment groups in the decrease of pericardial effusion grade from baseline to 14 days. We used the same test to compare differences between treatment groups for the change in pericardial width and the change in pericardial effusion grade for 2 prespecified subgroups: patients with a C-reactive protein level of at least 285.6 nmol/L (≥30 mg/L) and patients receiving a vitamin K antagonist. We used the Cochran–Mantel–Haenszel test, stratified by baseline pericardial effusion grade, to compare the difference between treatment groups in the number of patients with at least a 1-grade decrease and the number of cases of tamponade. In additional analyses, we assessed change in pericardial width and tamponade occurrence by using mixed-effect models, with site fitted as a random effect and baseline grade, type of surgery, and treatment fitted as fixed effects. Adjusting for the same factors, we also used ordered logistic regression to study the relationship for the decrease from baseline to 14 days of the grade for pericardial effusion. We considered a P value less than 0.050 to be statistically significant. We used R, version 2.5 (R Foundation for Statistical Computing, Vienna, Austria), for all analyses.

Role of the Funding Source

The French Society of Cardiology and Association Chirurgicale pour le Développement et l'Amélioration des Techniques de Dépistage et de Traitement des Maladies Cardiovasculaires provided funding for this study. The funding sources had no role in the design, conduct, and analysis of the study or in the decision to submit the manuscript for publication.

Figure. **Study flow diagram.**



NSAID = nonsteroidal anti-inflammatory drug.

Table 2. **Baseline Patient Characteristics**

Characteristic	Placebo Group (n = 98)	Diclofenac Group (n = 98)
Mean age (SD), *y*	62.5 (12)	64.1 (11)
Men, *n*	76	80
Mean body mass index (SD), kg/m^2	26 (3.8)	25.9 (3.8)
History of hypertension, *n*	49	53
History of diabetes, *n*	19	18
Atrial fibrillation, *n*	16	16
Surgery performed, *n**		
Coronary artery bypass graft	56	59
Mean grafts per procedure (SD)	3.1 (1.3)	3.2 (1.3)
Mean internal thoracic artery implants per procedure (SD)	1.6 (0.7)	1.7 (0.6)
Valve replacement		
Aortic valve	31	34
Mechanical	14	16
Bioprosthesis	17	18
Mitral valve	6	0
Mechanical	4	–
Bioprosthesis	2	–
Mitral valve repair	14	11
Aortic aneurysm replacement	8	10
Mean time from surgery to enrollment (SD), *d*	15.9 (5.1)	15.9 (4.3)
Baseline echocardiographic characteristics		
Mean left ventricular ejection fraction (SD), *%*	58.9 (8.2)	56.6 (8.1)
Mean pericardial effusion grade (SD)	2.6 (0.7)	2.8 (0.8)
Grade 2, *n*	55	47
Grade 3, *n*	29	28
Grade 4, *n*	14	23
Pericardial effusion localization, *n*		
Right atrial and ventricular wall	17	26
Left atrial and ventricular wall	50	45
Circumferential	31	27
Mean pericardial effusion width (SD), *mm*	12.8 (4.1)	14.4 (5)
Baseline biological variables		
Mean hemoglobin level (SD), *g/L*	6.65 (0.80)	6.65 (0.68)
Mean creatinine level (SD)		
μmol/L	91.6 (23.2)	93.7 (21.1)
mg/L	10.3 (0.1)	10.6 (2.4)
Mean INR in patients treated with vitamin K antagonists (SD)	2.77 (1.12)	2.51 (0.91)
Mean C-reactive protein level (SD)		
mg/L	41.8 (35.7)	38.9 (39.4)
nmol/L	397.9 (339.8)	370.3 (375.1)
Medication use, *n*		
Vitamin K antagonists	41	44
Aspirin	74	71
Mean dosage (SD), *mg/d*	111 (13)	117 (54)
Statin	67	70
β-Blocker	62	60
Amiodarone	26	27
Diuretic	21	20
Colchicine	2	2
ACE inhibitor	47	60

ACE = angiotensin-converting enzyme; INR = international normalized ratio.
* Patients could have more than 1 type of surgery.

RESULTS

Study Population

During the study period, we screened 5455 patients and found 262 with pericardial effusion large enough to be included (**Figure**). We excluded 66 patients for various reasons and enrolled 196 in the study, 98 in each treatment group. We enrolled 121 patients at 1 cardiac rehabilitation center and 34, 28, 12, and 11 patients at the other 4 centers. Three patients in the diclofenac group and 1 patient in the placebo group withdrew consent and did not receive study medication. Four other patients in the diclofenac group and 3 in the placebo group stopped therapy because of new symptoms, changes in laboratory results, or late withdrawal of consent. However, we obtained baseline and follow-up echocardiograms and laboratory tests in all patients who enrolled in the study. We did baseline transthoracic echocardiography a mean of 15.9 days (SD, 6.4) after surgery, and patients received study medications for a mean of 12.8 days (SD, 3.2). One patient in each group had pericardial drainage in the early postoperative period before being enrolled in the study.

At baseline, the 2 groups did not differ in clinical characteristics, type of surgery, or use of medication for other conditions (**Table 2**). The mean age was about 63 years, and 80% of the patients were male. **Table 2** describes the types of surgery; 33 patients had combined surgery (17 had CABG and aortic valve replacement, 5 had CABG and mitral valve replacement or repair, 9 had aortic valve replacement and ascending aorta replacement, and 2 had aortic valve replacement and mitral valve repair). The mean of the grades of pericardial effusion was 2.58 (SD, 0.73) for the placebo group and 2.75 (SD, 0.81) for the diclofenac group. One hundred two patients had grade 2 effusions, 57 had grade 3 effusions, and 37 had grade 4 effusions. The mean width of the pericardial effusion was 13.6 mm (SD 4.6). A total of 85 patients were receiving a vitamin K antagonist (mean international normalized ratio, 2.64), and 146 were receiving an antithrombotic agent (aspirin in 145 patients and clopidogrel in 1 patient). All patients received a gastroprotective agent (esomeprazole, 50.5%; pantoprazole, 30.1%; and omeprazole, 19.4%).

Study End Points and Events

The mean change in grade for pericardial effusion from baseline to 14 days (our primary end point) was −1.08 grades (SD, 1.20) for the placebo group and −1.36 grades (SD, 1.25) for the diclofenac group (mean difference between groups, −0.28 grade [95% CI, −0.63 to 0.06 grade]; $P = 0.11$) (**Table 3**).

Diclofenac therapy did not modify any of the secondary end points. The frequency of tamponade was 11.2% in the placebo group and 9.2% in the diclofenac group ($P = 0.49$) (**Table 4**). The mean change in the width of the effusion was −4.8 mm (SD, 7.0) in the placebo group and −6.7 mm (SD, 7.4) in the diclofenac group (mean difference between groups, −1.92 mm [CI, −3.91 to 0.69 mm]; $P = 0.07$) (**Appendix Table 1**). In the placebo group, 74.4% of patients had a grade decrease of 1 or more, versus 72.4% in the diclofenac group ($P = 0.845$) (**Appendix Table 2**). Diclofenac therapy did not affect the mean change in grade for pericardial effusion from baseline

Table 3. **PE Grade Over Time**

Time Point	Mean PE Grade (SD)		Mean Difference (95% CI)	*P* Value	Adjusted Mean Difference (95% CI)*	*P* Value
	Placebo Group	Diclofenac Group				
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)	0.105	−0.21 (−0.54 to 0.12)	0.22

PE = pericardial effusion.
* Adjusted for baseline PE grade, type of surgery, and site. Site was modeled as a random effect.

to 14 days in either of our 2 prespecified subgroups (**Appendix Table 3**).

Our per-protocol analysis corroborated our intention-to-treat analysis. For the 185 patients who received the experimental treatment for at least 80% of the observation time, the mean change in pericardial effusion grade from baseline was −1.11 grades (SD, 1.21) for the 94 patients in the placebo group versus −1.35 grades (SD, 1.27) for the 91 patients in the diclofenac group (mean difference between groups, −0.25 grade [CI, −0.60 to 0.11 grade]; $P = 0.25$).

Using a proportional odds logistic regression model to examine the effect of treatment on pericardial effusion grade, we calculated an odds ratio for treatment of 0.71 (CI, 0.43 to 1.19) after adjusting for baseline grade, site, and type of surgery.

Twenty patients (10.2%) required pericardial drainage a mean of 8.2 days (SD, 6.5) after inclusion (22.5 days [SD, 8.7] after surgery): 13 for clinical tamponade and 7 for echocardiography-determined pretamponade. The incidence of late cardiac tamponade was higher with higher grades of pericardial effusion at baseline: 2.9% for grade 2, 14% for grade 3, and 24.3% for grade 4 ($P < 0.001$) (**Table 4**). All patients with late cardiac tamponade had surgical pericardiotomy. No patients died.

In April 2009, 4 months after the last patient enrolled, we had information about poststudy pericardial drainage procedures for 195 patients. One patient in the placebo group required 2 pericardial drainages, one at postoperative day 33 (during the study) and the other at postoperative day 50. One patient in the diclofenac group had pericardial drainage at postoperative day 100 for a large, persistent, noncompressive pericardial effusion.

Three patients in the placebo group did not complete the study because of renal insufficiency (1 patient), abdominal pain (1 patient), or withdrawal of consent after 6 days of treatment (1 patient). Four patients in the diclofenac group did not complete the study because of cutaneous allergy (1 patient), hemoglobin level decrease with normal gastric endoscopy (1 patient), abdominal pain (1 patient), or withdrawal of consent after 10 days of treatment (1 patient). No patients had recognized gastrointestinal hemorrhage. The mean increase in serum creatinine level was 2.4 μmol/L (SD, 14.3) (0.027 mg/dL [SD, 0.162]) in the placebo group versus 3.1 μmol/L (SD, 18.3) (0.035 mg/dL [SD, 0.207]) in the diclofenac group ($P = 0.77$). The mean increase in hemoglobin level was 0.46 mmol/L (SD, 0.62) in the placebo group versus 0.170 mmol/L (SD, 0.63) in the diclofenac group ($P = 0.002$), which is consistent with subclinical gastrointestinal bleeding in patients receiving diclofenac.

Discussion

In this trial, which we believe is the first to assess the effectiveness of an NSAID to treat postoperative pericardial effusion, the use of diclofenac, 100 mg/d, did not significantly reduce the size of pericardial effusions or the risk for late cardiac tamponade. Moreover, this study confirms that

Table 4. **Frequency of Cardiac Tamponade, by Baseline PE Grade and Treatment Group***

Baseline PE Grade	Patients With Tamponade, *n/n* (%)†		Total, *n/n* (%)†	Adjusted Odds Ratio (95% CI)‡
	Placebo Group	Diclofenac Group		
2	1/55 (1.8)	2/47 (4.2)	3/102 (2.9)	2.4 (0.21 to 27.41)
3	7/29 (24.1)	1/28 (3.6)	8/57 (14.0)	0.11 (0.01 to 0.96)
4	3/14 (21.4)	6/23 (26.1)	9/37 (24.3)	1.30 (0.27 to 6.32)
Total	11/98 (11.2)	9/98 (9.2)	20/196 (10.2)	0.60 (0.22 to 1.62)

PE = pericardial effusion.
* For each grade, our logistic regression model included treatment, site (random effect), and surgery. Our logistic regression analysis of the treatment effect for all patients included treatment, site (random effect), baseline grade ($P < 0.001$), and type of surgery. We also examined the interaction between treatment and baseline grade, which was not significant.
† Number of patients with tamponade among all patients in the group with that PE grade.
‡ Adjusted for baseline PE grade, site, and type of surgery.

moderate to large pericardial effusion (grade 2, 3, or 4) occuring 7 to 30 days after cardiac surgery is a severe condition because 10.2% of these patients required surgical pericardiocentesis in the 14 days after they enrolled in the study.

Therapy with NSAIDs has been considered useful for postoperative pericardial effusions that persist after the first postoperative week. Pericardial effusions and tamponades that occur early after surgery are usually related to surgical bleeding; however, late effusions and tamponades (which are much more frequent) have multiple causal mechanisms, and inflammation seems to play a part. For example, the liquid of some of these late effusions is lemon-yellow, and late tamponade occurs more often in patients with the postpericardiotomy syndrome, an inflammatory disease that occurs in 15% to 20% of patients after cardiac surgery and may include fever, friction rubs, chest pain, pleuritis, and pericardial effusion (15). Therefore, use of an NSAID to treat late postoperative pericardial effusions seems logical, and it is common in daily practice (up to 77% of patients in several surveys [1, 3, 5]).

If the NSAID were found to be ineffective, continuing its use would be pointless and potentially dangerous, particularly because use of NSAIDs after cardiac surgery raises concerns. Patients who have valvular surgery routinely receive oral anticoagulants, and the combination of these agents with an NSAID could provoke gastrointestinal hemorrhage. Also, patients with coronary artery disease routinely receive an angiotensin-converting enzyme inhibitor, which can promote renal insufficiency in combination with an NSAID. In addition, use of an NSAID after CABG could promote atherothrombotic complications. For example, selective cyclooxygenase-2 inhibitors and nonselective NSAIDs are suspected to increase cardiovascular risk and, in particular, risk for death or re-infarction in patients with coronary artery disease (9). The use of cyclooxygenase-2 inhibitors immediately after CABG is also associated with increased incidence of cardiovascular events (16).

We chose diclofenac for this study because it is widely used and seems not to antagonize the irreversible platelet inhibition induced by aspirin (17), which is usually prescribed for these patients (74% of patients received low-dose aspirin in our study). We administered the drug after postoperative day 7 because early postoperative pericardial effusions and tamponades are less frequent than late ones and do not seem to be preventable by an NSAID. Because late effusions and tamponades occur between postoperative days 7 and 30 in more than 95% of the cases, we did not include patients who were past postoperative day 30.

Although postoperative pericardial effusion is frequent and potentially severe, few randomized, controlled trials have examined treatment for this condition. Aspirin (18) and diclofenac (19) were tested in clinical trials that examined prevention, not treatment, but these trials had so few patients that meaningful conclusions were not possible. Colchicine is being tested in an ongoing trial of prevention (15).

Our finding that diclofenac was no more effective than placebo could be explained if inflammation is not the predominant mechanism for most postoperative pericardial effusions. Furthermore, the ineffectiveness of diclofenac therapy for patients with a C-reactive protein level of at least 285.6 nmol/L suggests that no noninvasive test can separate inflammatory and hemorrhagic effusions. Therefore, we believe that prescribing an NSAID to treat an asymptomatic postoperative pericardial effusion should no longer be advised.

The main limitation of our study is that it was underpowered to detect small beneficial effects from diclofenac or to evaluate adverse clinical events from the drug, because only 95 patients received the drug.

In conclusion, diclofenac therapy did not seem to have a significant effect on the evolution of moderate to severe pericardial effusion that persists more than 7 days after cardiac surgery.

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Reproducible Research Statement: *Study protocol, statistical code, and data set:* Available from Dr. Meurin (e-mail, philippemeurin@hotmail.com).

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Appendix Table 1. **PE Width Over Time**

Time Point	Mean PE Width (SD), *mm*		Mean Difference (95% CI)	*P* Value	Adjusted Mean Difference (95% CI)*	*P* Value†
	Placebo Group	Diclofenac Group				
Initial	12.8 (4.1)	14.4 (5.0)				
Final	7.9 (6.7)	7.6 (7.8)				
Change	−4.8 (7.0)	−6.7 (7.4)	−1.92 (−3.91 to 0.69)	0.071	−1.93 (−3.97 to 0.11)	0.064

PE = pericardial effusion.
* Adjusted for baseline PE grade, site, and type of surgery. Site was modeled as a random effect.
† *P* value for interaction between subgroup and treatment. We adjusted the model for baseline PE grade, site, and type of surgery.

Appendix Table 2. **Baseline and End-of-Treatment PE Grade***

Baseline PE Grade	End-of-Treatment PE Grade					
	0	1	2	3	4	Total
Placebo group						
2	11	31	9	3	1	55
3	7	5	8	1	8	29
4	1	4	5	1	3	14
Total	19	40	22	5	12	98
Diclofenac group						
2	16	17	12	0	2	47
3	7	9	5	6	1	28
4	5	4	6	2	6	23
Total	28	30	23	8	9	98

PE = pericardial effusion.
* Shaded areas represent a decrease of at least 1 grade.

Appendix Table 3. **Change in Pericardial Effusion Grade in Prespecified Subgroups**

Value	Placebo Group (n = 98)		Diclofenac Group (n = 98)		Mean Difference (95% CI)	Adjusted Difference (95% CI)*	P Value for Interaction
	Patients, n	Mean Change (SD)	Patients, n	Mean Change (SD)			
C-reactive protein level†							
≥30 mg/L (≥285.6 nmol/L)	45	−1.38 (1.25)	41	−1.63 (1.18)	−0.26 (−0.77 to 0.26)	−0.11 (−0.61 to 0.39)	0.60
<30 mg/L (<285.6 nmol/L)	50	−0.82 (1.08)	56	−1.16 (1.29)	−0.34 (−0.79 to 0.11)	−0.29 (−0.74 to 0.16)	
Vitamin K antagonist use							
Yes	42	−1.12 (1.40)	43	−1.56 (1.26)	−0.44 (−1.0 to 0.13)	−0.50 (−1.04 to 0.04)	0.155
No	56	−1.05 (1.03)	55	−1.22 (1.24)	−0.16 (−0.59 to 0.27)	−0.01 (−0.43 to 0.42)	

* Adjusted for baseline pericardial effusion grade, site, and type of surgery.
† C-reactive protein levels were missing for 4 patients.