



**HAL**  
open science

# Cost Analysis of Aprotinin Reintroduction in French Cardiac Surgery Centres: A Real-World Data-Based Analysis

Pascal Colson, Jean-Luc Fellahi, Philippe Gaudard, Sophie Provenchère,  
Bertrand Rozec

► **To cite this version:**

Pascal Colson, Jean-Luc Fellahi, Philippe Gaudard, Sophie Provenchère, Bertrand Rozec. Cost Analysis of Aprotinin Reintroduction in French Cardiac Surgery Centres: A Real-World Data-Based Analysis. *Advances in Therapy*, In press, 10.1007/s12325-023-02464-7 . hal-04014514

**HAL Id: hal-04014514**

**<https://hal.science/hal-04014514>**

Submitted on 4 Mar 2023

**HAL** is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

# Cost Analysis of Aprotinin Reintroduction in French Cardiac Surgery Centres: A Real-World Data-Based Analysis

Pascal Colson<sup>1,2</sup> ; Jean-Luc Fellahi <sup>3,4</sup> ; Philippe Gaudard <sup>1,5</sup> ; Sophie Provenchère <sup>6,7</sup> ; Bertrand Rozec <sup>8,9</sup>; from the ARCOTHOVA Group

1 Department of Anesthesiology and Critical Care Medicine, Arnaud de Villeneuve Hospital, CHU Montpellier, 371 avenue du doyen Gaston Giraud, 34295 Montpellier, France

2 Montpellier University, INSERM, CNRS, Institut de Génomique Fonctionnelle, Montpellier, France

3 Department of Anesthesiology and Critical Care Medicine, Louis Pradel Hospital, Hospices Civils de Lyon, 59 Boulevard Pinel, 69500 Lyon, France

4 Laboratoire CarMeN, Inserm U1060, Université Claude Bernard Lyon 1, Lyon, France

5 University of Montpellier, PhyMedExp, INSERM, CNRS, Montpellier, France

6 Department of Anesthesiology and Critical Care Medicine, AP-HP, Bichat-Claude-Bernard Hospital, Paris, France

6 Department of Anesthesiology and Critical Care Medicine, AP-HP, Bichat-Claude-Bernard Hospital, Paris, France

7 INSERM Clinical Investigation Center 007, Paris, France

8 Service d'Anesthésie-Reanimation, hôpital Laënnec, Centre Hospitalier Universitaire, 44093 Nantes, France

9 Institut du Thorax, Institut National de la Santé et de la Recherche Médicale (INSERM), Centre National de la Recherche Scientifique (CNRS), Université de Nantes, 44093 Nantes, France

**e-mail:** p-colson@chu-montpellier.fr

## **Keywords:**

Budget impact; France; Cardiac surgery; ICU stay; Aprotinin; Tranexamic acid.

# ABSTRACT

## Introduction:

The European Medicines Agency restored aprotinin (APR) use for preventing blood loss in patients undergoing isolated coronary artery bypass graft (iCABG) in 2016 but requested the collection of patient and surgery data in a registry (NAPaR). The aim of this analysis was to evaluate the impact of APR reintroduction in France on the main hospital costs (operating room, transfusion and intensive unit stay) compared to the current use of tranexamic acid (TXA), which was the only antifibrinolytic available before APR reinstatement.

## Methods:

A multicenter before-after post-hoc analysis to compare APR and TXA was carried out in four French university hospitals. APR use followed the ARCOTHOVA (French Association of Cardiothoracic and Vascular Anesthetists) protocol, which had framed three main indications in 2018. Data from 236 APR patients were retrieved from the NAPaR (N = 874); 223 TXA patients were retrospectively retrieved from each center database and matched to APR patients upon indication classes. Budget impact was evaluated using both direct costs associated with antifibrinolytics and transfusion products (within the first 48 h) and other costs such as surgery duration and ICU stay.

## Results:

The 459 collected patients were distributed as: 17% on-label; 83% off-label. Mean cost per patient until ICU discharge tended to be lower in the APR group versus the TXA group, which resulted in an estimated gross saving of €3136 per patient. These savings concerned operating room and transfusion costs but were mainly driven by reduced ICU stays. When extrapolated to the whole French NAPaR population, the total savings of the therapeutic switch was estimated at around €3 million.

## Conclusion:

The budget impact projected that using APR according to ARCOTHOVA protocol resulted in decreased requirement for transfusion and complications related to surgery. Both were associated with substantial cost savings from the hospital's perspective compared with exclusive use of TXA.

# INTRODUCTION

Perioperative bleeding is a major concern in cardiac surgery as it is associated with the risks of exposure to allogeneic blood transfusion, prolonged lengths of hospital stay and increased mortality [1–5]. The definition of a patient at high risk of bleeding or autologous transfusion involves multiple factors including the patient's ability to initiate and sustain adequate haemostasis and the characteristics of surgery. These factors are used as key criteria in a broad range of predictive scores [6–9]. Nonetheless, the incidence of allogeneic blood exposure remains high even when a restrictive transfusion strategy is applied, approximately 50% [10, 11].

Overall awareness of the need to reduce exposure to blood product is supported by international guidelines on patient blood management (PBM) [12–14]. Among the intraoperative strategies of PBM, antifibrinolytic therapy is recommended to reduce bleeding and transfusions of blood products and reoperations for bleeding (Class I, Level A) [13]. Antifibrinolytics are a class of haemostatic agents used to prevent excessive blood loss associated with degradation of intravascular fibrin clots by action of plasmin [15]. The lysine analogues epsilon aminocaproic acid (EACA, also referred as aminocaproic acid, not available in France) and tranexamic acid (TXA) specifically inhibit the conversion of plasminogen to plasmin. APR, a naturally occurring polypeptide, is an inhibitor of serine proteases. It has a broad range of targets such as plasmin, trypsin and kallikrein [15]. Concerns regarding APR safety in cardiac surgery arose in 2005 and culminated in 2008 with the publication of the BART study [16]. Following BART results, APR was withdrawn from the market at the request of various National health authorities and the EMA. However, further analysis reported several problems with the way the BART study was conducted, which cast doubt on the previous conclusions. Moreover, overall data available showed that APR's benefits are greater than its risks in restricted indications [17]. Therefore, the EMA lifted the suspension of APR from the market in 2012 [17].

The debate on APR withdrawal/reinstatement spread confusion among clinicians regarding its role and place. To clarify the situation, the European Society of Anaesthesiology set up a task force to assess the current evidence and provide a summarised definition of high-risk patients for whom APR might be beneficial [18]. This expert opinion to target APR indication was followed by national expert groups such as Aprotinin-ARCOTHOVA experts [19]. Besides, a European post-authorisation marketing authorisation safety study was part of the risk minimisation measures associated with APR's lifting of suspension. This Nordic Aprotinin Patient Registry (NAPaR) was established to collect real-world data on APR use and investigate specific safety concerns in the patient population not included in the current indication. This registry was expected to record information on virtually all patients exposed to Nordic Aprotinin.

The impact of APR on the economic burden of bleeding and transfusion started to be investigated before the product withdrawal [20–23]. After years of absence, the expectation regarding the benefits of APR was no longer restricted to its clinical efficacy but also to its cost efficiency. Also, very few APR data were available after its reinstatement in cardiac units. Therefore, to assess the overall financial impact of APR reinstatement, four teaching hospital centres pooled their anonymised data to develop a budget impact model (BIM) comparing the costs associated with surgery, bleeding, transfusion and ICU stay for 1:1 matched patients treated with TXA or APR.

## METHODS

This is a multicentre retrospective analysis using real-world databases from French academic hospitals, selected on the basis they had performed at least 50 adult (age  $\geq$  18 years) cardiac surgery cases under APR between December 2018 (first patient in) and December 2020 (interim database lock). APR use followed the three indication groups defined by the French Society of Anaesthesiologists in Thoracic and Cardiac Surgery (ARCOTHOVA: Anesthésie-Réanimation Coeur-Thorax-Vaisseaux) [19]:

- Indication 1: isolated coronary artery bypass graft under cardiopulmonary bypass (iCABG) with bleeding risk [ongoing active antiplatelet therapy or previous sternotomy (redo)]
- Indication 2: High-risk cardiac surgery other than iCABG in patients with at least three of the TRUST SCORE risk factors [6] including age  $\geq 75$  years, complex surgery with or without aortic repair or replacement, cardiac transplant, non-elective surgery, platelet impairment and BMI  $< 25$ .
- Indication 3: High-risk cardiac surgery other than those defined in indications 1 and 2 including redo (except iCABG), infectious endocarditis, aortic dissection or mechanical heart device.

Patients in APR groups were retrieved from the French NAPaR registry (EU PAS register number: EUPAS11384). They defined the proportion of patients in the three indication groups. To compare patients treated with APR to those treated with TXA, APR and TXA patients were matched following their bleeding risk according to the three indication groups.

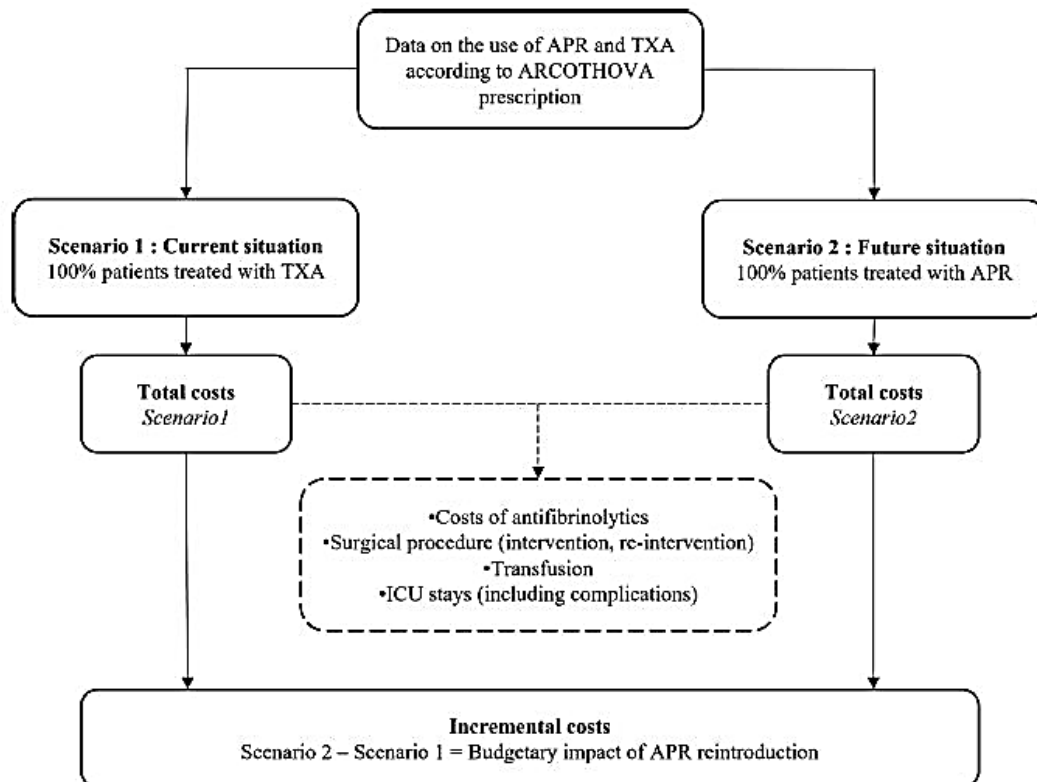
Patients in the TXA group were retrieved from the pharmacy and services database of each institution, where data from patients treated by TXA are routinely collected for accounting. From the lists of these patients, matching was used to recruit patients in the study according to the three indications, with similar proportions in each indication for APR group. To obtain matching as close as possible to 1:1, TXA patients were retrospectively collected over a longer period from May 2016 to October 2019. All anonymised data were then transferred and centralised for analysis by our statistician partner CEMKA.

As data were retrospectively analysed, the use of antifibrinolytics followed routine practice. Unlike TXA, APR benefits from a standardized protocol published by ARCOTHOVA: half-dose regimen (patient's loading dose,  $1.10^6$ KIU; pump priming,  $1.10^6$ KIU; continuous infusion,  $0.25.10^6$  KIU/h), a dose regimen that was advised in 2018 by the representative cardiac anaesthetist group in France (ARCOTHOVA).

The main objectives were to compare the costs associated with the patient journey in cardiac surgery departments according to the selected prophylactic antifibrinolytics and to assess the overall budget impact of APR reintroduction from the hospital perspective. The secondary objectives were to characterize patients exposed to APR following ARCOTHOVA prescription criteria, quantify the use of hospital resources in a patient journey and assess the cost of a patient journey according to ARCOTHOVA indications.

Only the data needed for the matching process (i.e., ARCOTHOVA criteria: type of surgery, platelet impairment, redo, age  $\geq 75$  years, BMI  $< 25$ , complex surgery, aortic surgery, endocarditis, transplant, emergency, etc.) and for the cost analysis [number of antifibrinolytics, time in the operating room (OR) for the main surgery and, when applicable, for the reoperation for bleeding, number of transfusion products, intensive care unit (ICU) length of stay and postoperative survival) were available in pooled databases.

As the main registry contributors provided the sample used in this model, the sample is assumed to be representative and no sample size was determined prior to the analysis.



**Fig. 1 Scenario assessed in the budget impact model**

Direct costs were analysed in euros (€) from the hospital perspective including antifibrinolytic use, length of surgical procedure (operation and possible reoperation), need for blood product transfusion and ICU stay. When carried out, reinterventions were included in length of surgery. Any other complications, regardless of the type, that occurred during a hospital stay and were managed in ICU were included in ICU stay costs to avoid duplication. As the ICU stay depended on postoperative complications, including acute renal failure, low cardiac output syndrome, pulmonary dysfunction, thromboembolic events, sepsis complications and others, the length of the ICU stay was considered a surrogate of a composite outcome, which would have included each above-mentioned complication.

In addition, a cardiac complication following cardiac surgery was counted as an extension of the ICU stay instead of a new hospitalisation. These above-mentioned costs were collected from the public databases of the French Ministry of Health and the Agency for Hospital Information as well as published unit value from the French official journal. Hospital costs were analysed using the 2019 basis and were inflated to those of 2021 (Supplementary materials, Table S1). It was assumed that the inflation rate for 2021 was equivalent to that of 2020 for medical services. Patients deceased during the hospital stay including the OR or ICU were excluded from the cost analysis. The total population was therefore analysed to estimate resource utilization during the hospital stay.

A budget impact model (Fig. 1) was developed in Microsoft<sup>R</sup> Excel<sup>R</sup> (Microsoft 365 MSO V.2203) to compare the costs associated with the use of APR versus TXA in patients undergoing high risk of bleeding cardiac surgery from the hospital perspective in France. The model compared the difference in overall cost between two scenarios for the management of patients in the population of interest:

- A scenario WITHOUT aprotinin (Scenario 1): treatment with TXA, which was considered as the standard antifibrinolytic therapy for cardiac surgery to prevent major bleeding.
- A scenario WITH aprotinin (Scenario 2): the expected changes in patient management if APR were to completely replace TXA (full substitution hypothesis).

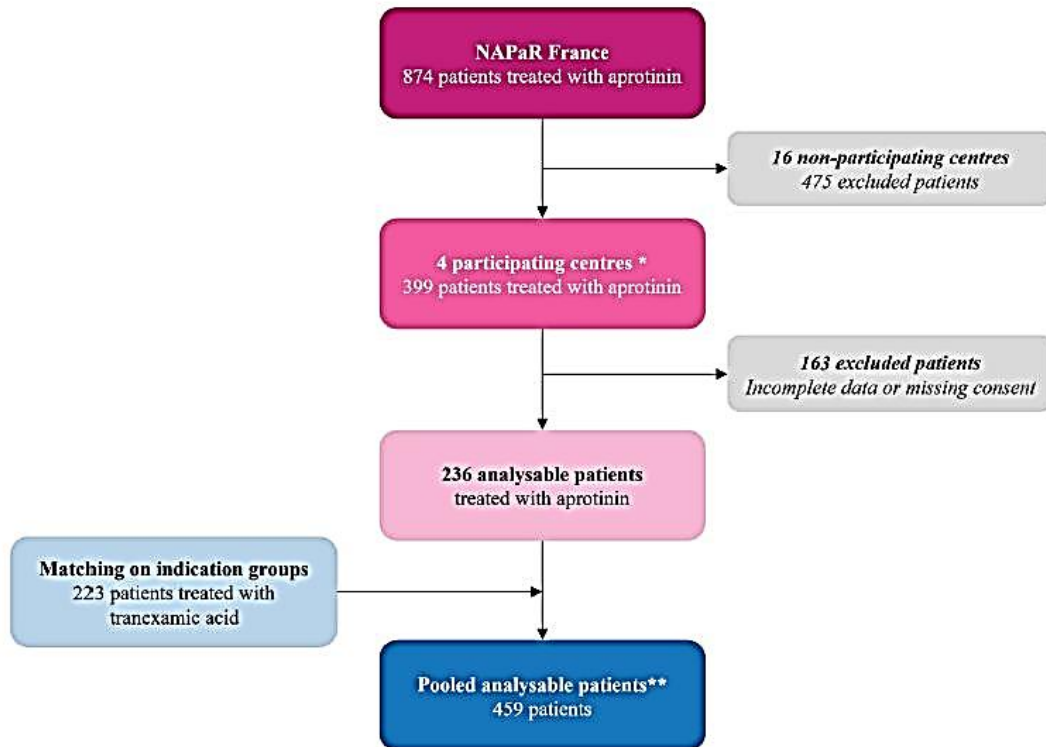
We assumed that the distribution of patients among the three indications was strictly equivalent in the two scenarios (scenario with aprotinin and scenario without aprotinin). The budget impact represented the cost difference between these two scenarios. One-way sensitivity analyses were performed by changing the base case parameters of the model and a variability of  $\pm 20\%$  of the central value was assumed to be a reasonably wide range as approved by the leading clinical experts. The modelling of clinical pathways and the identification of healthcare resource utilization were developed in collaboration with all four authors, each referent for the NAPaR in their health institutions.

The statistical analysis was performed using SAS<sup>R</sup> V9.4 software (North Carolina, USA). Quantitative and qualitative variables were undergoing high risk of bleeding cardiac surgery from the hospital perspective in France. The model compared the difference in overall cost between two scenarios for the management of patients in the population of interest:

- A scenario WITHOUT aprotinin (Scenario 1): treatment with TXA, which was considered as the standard antifibrinolytic therapy for cardiac surgery to prevent major bleeding.
- A scenario WITH aprotinin (Scenario 2): the expected changes in patient management if APR were to completely replace TXA (full substitution hypothesis).

We assumed that the distribution of patients among the three indications was strictly equivalent in the two scenarios (scenario with aprotinin and scenario without aprotinin). The budget impact represented the cost difference between these two scenarios. One-way sensitivity analyses were performed by changing the base case parameters of the model and a variability of  $\pm 20\%$  of the central value was assumed to be a reasonably wide range as approved by the leading clinical experts. The modelling of clinical pathways and the identification of healthcare resource utilization were developed in collaboration with all four authors, each referent for the NAPaR in their health institutions.

The statistical analysis was performed using SAS<sup>R</sup>V9.4 software (North Carolina, USA). Quantitative and qualitative variables were described for each group and for the total population. Quantitative variables were expressed as mean  $\pm$  standard deviation (SD), median, or range and qualitative variables as percentages. A subgroup analysis was conducted to compare the two treatment arms according to the three ARCOTHOVA indication groups using the chisquare test for qualitative variables, and t test or analysis of variance was performed for quantitative variables when the distribution was close to normal (Shapiro-Wilk test not significant). Otherwise, Wilcoxon's non-parametric test was used. The association between "antifibrinolytic treatment" and "indication" was assessed by the chi-square test to ensure that the three ARCOTHOVA indications were distributed similarly between the two treatment arms.



**Fig. 2 Flow chart illustrating the assessed population.**

\*Participating centres (APR patients): Bichat-Claude Bernard Hospital, Paris: 139; Laennec Hospital, Nantes: 109; Arnaud de Villeneuve Hospital, Montpellier: 87; Louis Pradel Hospital, Lyon: 64. \*\*In the pooled data set, centres were anonymised prior to analysis. Patient distribution was as follows: centre 1: 50 (APR) and 49 (TXA); centre 2: 64 (APR) and 64 (TXA); centre 3: 35 (APR) and 35 (TXA); centre 4: 87 (APR) and 75 (TXA)

## RESULTS

Of the 874 APR patients recorded in the French NAPaR between December 2018 and December 2020, 399 patients were treated in the 4 participating centres including Public Assistance Hospitals of Paris (Bichat-Claude Bernard), University Hospital of Nantes (Laennec), University Hospital of Montpellier (Arnaud de Villeneuve) and University Hospital of Lyon (Louis Pradel). Since 163 patients had missing data and were excluded, the 236 remaining patients (60%) defined the APR group. These patients were retrospectively matched to 223 TXA patients who underwent similar high risk cardiac surgeries between May 2016 and October 2019. A total of 459 adult patients were enrolled in the study (Fig. 2).

Patients' characteristics were not statistically different between the APR and tranexamic groups (Table 1).



**Table 1** Baseline patient characteristics

	Aprotinin	Tranexamic acid	Total	<i>p</i> value
<i>n</i> (%)	236 (51.4)	223 (48.6)	459 (100)	
Patients' characteristics				
Age range <sup>c</sup>	<i>N</i> = 186	<i>N</i> = 174	<i>N</i> = 360	0.90 <sup>b</sup>
< 30	9 (3.8)	8 (3.6)	17 (3.7)	
[30:45]	24 (10.2)	19 (8.5)	43 (9.4)	
[46:75]	131 (55.5)	123 (55.2)	254 (55.3)	
> 75	22 (9.3)	24 (10.8)	46 (10.0)	
BMI	<i>N</i> = 183	<i>N</i> = 139	<i>N</i> = 322	
	25.8 [5.1]	25.9 [5.1]	25.8 [5.1]	0.85 <sup>a</sup>
BMI < 25	<i>N</i> = 233	<i>N</i> = 223	<i>N</i> = 456	0.46 <sup>b</sup>
	106 (44.9%)	110 (49.3%)	216 (47.1%)	
Bleeding factors				
Redo	<i>N</i> = 236	<i>N</i> = 159	<i>N</i> = 395	0.08 <sup>b</sup>
	91 (38.6%)	47 (21.1%)	138 (30.1%)	
Endocarditis	55 (23.3%)	41 (18.4%)	96(20.9%)	0.23 <sup>b</sup>
DAPT	41 (17.4%)	55 (24.7%)	96 (20.9%)	0.07 <sup>b</sup>
Emergency	<i>N</i> = 235	<i>N</i> = 223	<i>N</i> = 458	0.26 <sup>b</sup>
	130 (55.1%)	147 (65.9%)	277 (60.4%)	
Indication				
iCABG	37 (15.7%)	41 (18.4%)	78 (17.0%)	0.30 <sup>b</sup>
Bleeding risk factors ≥ 3	34 (14.4%)	41 (18.4%)	75 (16.3%)	
Other high-risk surgery	165 (69.9%)	141 (63.2%)	306 (66.7%)	
Bleeding				
	<i>N</i> = 235	<i>N</i> = 221	<i>N</i> = 456	0.73 <sup>b</sup>
	228 (96.6%)	216 (96.9%)	444 (96.7%)	
24-h postoperative (ml)	<i>N</i> = 228	<i>N</i> = 153	<i>N</i> = 445	
	759 [724]	721 [594]	741 [663]	0.21 <sup>a</sup>
Death				
At ICU discharge	25 (10.6%)	23 (10.3%)	48 (10.5%)	1 <sup>b</sup>

Data are expressed as mean [SD], or *N* (%)

SD standard deviation; BMI body mass index; DAPT dual antiplatelet therapy; iCABG isolated coronary artery bypass graft with cardiopulmonary bypass; ICU intensive care unit

<sup>a</sup>Wilcoxon test

<sup>b</sup>Chi-square test

<sup>c</sup>Kruskal-Wallis test by indications, performed separately in each treatment group

## Resource Utilisation

When considering the two groups, irrespective of the three indications, there were no statistical differences in any of the mean resource utilizations except for the antifibrinolytic used between the APR and TXA groups. More than half of the analysed patients (53%) were transfused with an average of 2.4 units of RBC. Overall transfusion rate for other blood-derived products was around 39% for both fresh frozen plasma (FFP) and platelets and 32%

for fibrinogen. The mean duration of surgery was 105 min. Ten per cent of patients underwent a reoperation for bleeding with a mean OR time around 105 min. The average length of ICU stay for the analysed population was 8 days.

Table 2 describes resource utilization according to the three groups' indications. Reoperation was significantly more frequent for the TXA group compared with the APR group (24% vs. 6%,  $p<0.0001$ ) in indication 2.

There were some statistical differences regarding blood product transfusion and fibrinogen administration when comparing per indication:

– In indication 1, TXA patients were more likely to receive RBC than APR patients (26.8% vs. 16.2%,  $p<0.001$ ). The reverse is observed for fibrinogen administration with a higher transfusion rate in the APR group (16.2%) than TXA group (9.8%) ( $p<0.001$ ).

– In indication 2, TXA patients were more likely to receive RBC, FFP transfusion and fibrinogen administration than APR patients (68.3%, 51.2%, 41.5% vs. 55.9%, 47.1%, 29.4% respectively,  $p<0.001$ ). The reverse is observed for platelet transfusion, which was statistically higher in the APR group compared to the TXA arm (55.9% vs. 39.0%,  $p<0.001$ ).

– In indication 3, APR patients were more likely to receive RBC, FFP transfusion and platelets than TXA patients (60.6%, 49.7% and 42.4% vs. 56.7%, 42.6% and 37.6%, respectively,  $p<0.001$ ). TXA patients received more fibrinogen administration than APR patients (39.7% vs. 32.8%,  $p<0.0001$ ).

## **Cost Analysis**

Independently of the indication, the mean cost per patient was estimated at €20,997 for the APR group compared to €24,133 in the TXA group. It included the following costs: antifibrinolytics, surgical procedure, transfusions and ICU stay (Supplementary materials, Table S2). The main resource use was driven by ICU stays.

When focusing on the three groups of indications (Table 3), the total mean cost was higher with TXA compared to APR except for indication 1. Total mean cost was always driven by ICU stays, independently of the indication, and increased substantially for indication 2 in TXA patients.

## **Budget Impact**

The distribution of the 874 NAPaR patients (December 2018–December 2020) was 137 patients (15.7%) undergoing iCABG (indication 1), 126 patients (14.4%) with at least three risk factors undergoing high-risk cardiac surgery other than iCABG (indication 2) and 611 (69.9%) undergoing other high-risk surgical procedures (indication 3) (Supplementary materials, Table S3). The budget impact of APR reintroduction was calculated for this entire group of NAPaR patients ( $N = 874$ ).

**Table 2** Resource utilization by treatment arm and indications

		Indication 1 iCABG	Indication 2 bleeding risk factors $\geq 3$	Indication 3 other high-risk cardiac surgery	<i>p</i> value
<i>N</i>	<i>TXA</i>	41	41	141	
	<i>APR</i>	37	34	165	
Surgery time, min <sup>a</sup>	<i>TXA</i>	218 [67]	302.4 [134]	308 [121]	< 0.001 <sup>b</sup>
	<i>APR</i>	213 [58]	310 [133]	304 [129]	< 0.001 <sup>b</sup>
Reoperation <sup>a</sup>	<i>TXA</i>	2 (4.9)	10 (24.4)	14 (9.9)	< 0.001 <sup>c</sup>
	<i>APR</i>	2 (5.4)	2 (5.9)	17 (10.3)	
Reoperation time, min	<i>TXA</i>	94 [16]	105 [34]	112 [62]	0.042 <sup>b</sup>
	<i>APR</i>	71 [27]	75 [36]	108 [62]	0.168 <sup>b</sup>
Antifibrinolytic, units	<i>TXA</i>	5.04 [0.9]	6.0 [3]	5.6 [2.3]	0.299 <sup>b</sup>
	<i>APR</i>	6.2 [0.9]	6.7 [1.2]	6.4 [1.8]	0.262 <sup>b</sup>
RBC <sup>a</sup>	<i>TXA</i>	11 (26.8)	28 (68.3)	80 (56.7)	< 0.001 <sup>c</sup>
	<i>APR</i>	6 (16.2)	19 (55.9)	100 (60.6)	
RBC, units	<i>TXA</i>	2.09 [0.8]	5.8 [5.2]	4.7 [3.9]	0.023 <sup>b</sup>
	<i>APR</i>	2 [0.9]	4.9 [3.7]	4.5 [4.9]	0.095 <sup>b</sup>
Fresh frozen plasma <sup>a</sup>	<i>TXA</i>	1 (2.4)	21 (51.2)	60 (42.6)	< 0.001 <sup>b</sup>
	<i>APR</i>	1 (2.7)	16 (47.1)	82 (49.7)	
Fresh frozen plasma, units	<i>TXA</i>	2 [NA]	6.5 [5.4]	6.4 [8.2]	0.459 <sup>b</sup>
	<i>APR</i>	1 [NA]	5.9 [4.5]	5.7 [5.3]	0.219 <sup>b</sup>
Platelet transfusion <sup>a</sup>	<i>TXA</i>	10 (24.4)	16 (39.0)	53 (37.6)	< 0.001 <sup>c</sup>
	<i>APR</i>	9 (24.3)	19 (55.9)	70 (42.4)	
Platelet, units	<i>TXA</i>	1.1 [0.3]	2.6 [1.7]	1.9 [1.3]	0.007 <sup>b</sup>
	<i>APR</i>	1.1 [0.3]	2.0 [1.7]	1.9 [1.4]	0.128 <sup>b</sup>
Fibrinogen transfusion <sup>a</sup>	<i>TXA</i>	4 (9.8)	17 (41.5)	56 (39.7)	< 0.001 <sup>c</sup>
	<i>APR</i>	6 (16.2)	10 (29.4)	54 (32.8)	
Fibrinogen, g	<i>TXA</i>	2.6 [1.0]	4.4 [2.6]	4.5 [2.0]	0.069 <sup>b</sup>
	<i>APR</i>	2.7 [0.5]	3.5 [1.2]	4.2 [3.3]	0.490 <sup>b</sup>
ICU length of stay, days	<i>TXA</i>	3.0 [1.9]	14.9 [20.0]	8.9 [12.1]	< 0.001 <sup>b</sup>
	<i>APR</i>	5.1 [5.6]	8.5 [10.9]	7.2 [7.8]	0.204 <sup>b</sup>

Data are expressed as mean [SD], or *N* (%)

*TXA* tranexamic acid, *APR* aprotinin; *RBC* red blood cells; *ICU* intensive care unit; *iCABG* isolated Coronary artery bypass graft; *NA* not applicable

<sup>a</sup>Significant difference between treatments by indication at the 0.05 threshold

<sup>b</sup>Chi-square test with the treatment  $\times$  indication interaction variable

<sup>c</sup>Kruskal-Wallis test by indications, performed separately in each treatment group

**Table 3** Costs of resource utilization by treatment arm in three groups of indications per patient

	Aprotinin				Tranexamic acid			
	Indication	Indication	Indication	All	Indication	Indication	Indication	All
	1	2	3	indications	1	2	3	indications
Antifibrinolytics	€500	€500	€500	€500	€4	€5	€4	€4
Surgical procedure	€2 628	€3812	€3822	€3 634	€2694	€3977	€3862	€3696
Transfusions	€786	€2427	€3091	€2 958	€620	€3973	€3010	€3113
ICU stay	€9 969	€16,622	€14,228	€13 905	€5 927	€29,201	17,427	€17,320
<b>Total</b>	<b>€13 883</b>	<b>€23 361</b>	<b>21 641</b>	<b>€20 997</b>	<b>€9 244</b>	<b>€37 155</b>	<b>€24 302</b>	<b>€24,133</b>

ICU intensive care unit

**Table 4** Budget impact associated with 2 years of aprotinin use in France

	Indication 1	Indication 2	Indication 3	All indications
Antifibrinolytics	€67,995	€62,397	€303,221	€433,613
Surgical procedure	– €9090	– €20,812	– €24,598	– €54,500
Transfusions	€22,828	– €246,906	€49,663	– €1,74,415
ICU stay	€553,944	– €1,583,923	– €1,954,648	– €2984 627
<b>Total</b>	<b>€635,677</b>	<b>– €1,789,244</b>	<b>– €1,626,362</b>	<b>– €2,779 929</b>

Scenario 2 (aprotinin arm)—scenario 1 (tranexamic acid arm) for 874 patients. In orange cells, the differential is positive (cost in TXA < APR), and in green cells the differential is negative (cost in TXA > APR)

ICU intensive care unit

## Base Case Analysis

Total costs of patients on APR undergoing cardiac surgery (scenario 2) according to NAPaR profiles were estimated to be approximately €18 million, whereas the costs for TXA patients (scenario 1) were estimated at €21 million. The budget impact of APR use, which was calculated as the difference in the total cost between the two scenarios (scenario 2 – scenario1), was estimated to a net saving of around €3 million over 2 years. Furthermore, over the same period, savings were achieved for surgical procedures, transfusions and ICU stay (Table 4). The total substitution of TXA for APR resulted in a net expenditure of approximately €433 K in antifibrinolytics. All other resources benefited from net savings: €54 K in costs associated with surgical procedures, €174 K in transfusions and €2984 K in ICU stay.

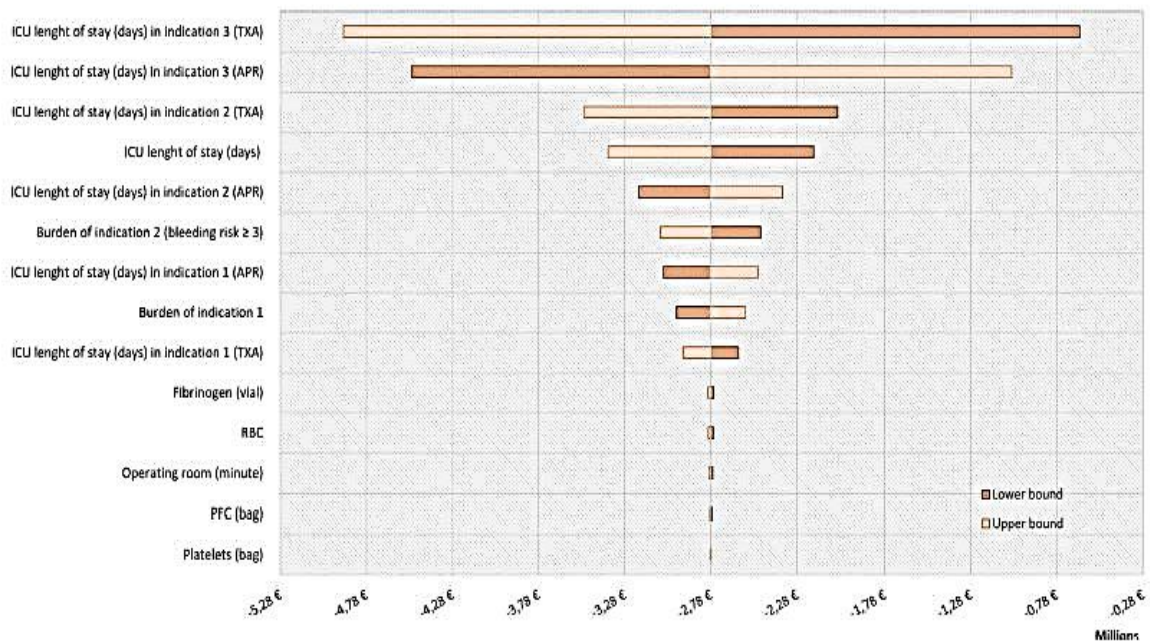
When considering the budget impact for each indication separately, the use of APR resulted in net savings for patients managed in indications 2 and 3, whereas in indication 1 a net saving was only observed for surgical procedure (Table 4).

## Sensitivity Analysis

A one-way sensitivity analysis was performed by changing the base case values of several parameters of interest of the model; the results are presented using a tornado diagram in Fig. 3. The results showed that all input variables led to direct changes in the net budget impact. All conditions being equal, the analysis showed a greater sensitivity for the budget impact of the length of stay in ICU, the daily cost of stay in ICU and the distribution of patients in each indication group. Therefore, the reintroduction and use of APR result in net savings (ranging from €0.65 million to €4.9 million) compared to TXA for all the parameters variations simulated.

## DISCUSSION

Comparing the costs associated with the patient journey in cardiac surgery departments according to the used prophylactic antifibrinolytics, we observed that APR reintroduction induced a reduction of the overall budget compared to the current use of TXA. Although there is an additional charge in the antifibrinolytics, the total savings from ICU stay and transfusion products compensated the initial additional costs.



**Fig. 3 One-way sensitivity analysis: difference in the budget-impact between APR and TXA settings.**

Central value: base case budget-impact cost saving of €2.78 million. One-way sensitivity analysis: difference in budget impact according to a variability of  $\pm 20\%$  for variable such as ICU length of stay, indication distribution, need for transfusion and surgery duration.

Several studies have been performed on the economic impact of APR before its withdrawal [20–24]. These studies were based on cost analyses similar to our study since all included at least the drug cost, blood product costs, length of stay and utilization of resources of operating room (including reoperation) and ICU stay. However, these studies varied on other associated

factors like staff grades, staff availability, long-term complications after ICU and surgery cases with a majority of low-risk surgery [20–24]. Nevertheless, they demonstrated that, though APR increased costs due to drug acquisition as well as the cost of administration, its use led to the utilization of fewer resources than with placebo. Our study tends to actualize the economic impact of APR on the following key points: first, expenses were updated with current resource costs; second, the study compared APR to another antifibrinolytic drug, TXA; third, various conditions of bleeding risk were studied with three distinct indications.

Owing to the updated resource costs, we observed that APR introduction was associated with a lower budget impact compared to TXA provided administration followed specific indications. Resource costs were mainly driven by ICU stays, then by surgical procedures and transfusions (66%, 17% and 14% versus 72%, 15% and 13%, respectively, for APR versus TXA), far above antifibrinolytics' weight in average hospital expenditure per patients (2% versus 0.02% for APR versus TXA).

However, the budget impact varied drastically with the indication.

For indication 1, 17% of patients included in the study underwent iCABG surgery. In our model, APR use compared to TXA had only a moderate reduction in surgical procedure costs (- 2.3%), which did not compensate for the increased costs on other resource utilization (+ 50%). The results seem at odds with former studies on CABG surgery [21–24]. However, perioperative cost had been shown not to be significantly different between full-dose or half-dose APR and placebo for primary CABG surgery [21]; cost savings were previously described in cases of repeated CABG surgery due to reduced complication costs, particularly with the full-dose regimen [21]. We cannot exclude that the use of half-dose APR had limited cost savings in our series. Robinson et al. [23], who have developed an operational model to evaluate the influence of APR use on waiting lists and time, demonstrated that APR indirectly decreased costs by reducing waiting lists as well as by reducing morbidity and mortality associated with waiting time. We observed longer reoperation times for TXA patients than for APR patients, for which the consequences on the waiting list were not evaluated. However, the incidence of reoperation (around 5%) was small, and the cost saving was probably very limited [23].

Practitioners have purposefully decided to administer APR in high-bleeding-risk patients, due to either patients' conditions (indication 2) or complex surgery cases (indication 3). The low proportion of patients in the on-label group (indication 1) might appear unconventional but it was following practitioners' empirical experience of a favourable risk-benefit ratio beyond CABG surgery. Repeated data had suggested that APR might have clinical advantages over TXA in high-risk patients [24–26]. These studies, along with clinical experience, helped to forge a strong opinion in the cardiac anaesthesiologist community in favour of APR use in cases at higher risk than iCABG. The common feeling was quite well represented in the consensus statement issued by the European Society of Anaesthesiologists task force in 2015 [18]. In the NAPaR, which reports real-life data from 83 European centres, APR was used mostly in surgical procedures other than iCABG (74.3% of surgery cases) [27].

Indication 2 concerned a small group of patients (16.3%) but a substantial reduction (37%) in costs associated with resource utilization was observed with APR compared to TXA, mainly due to transfusions and ICU stays (reduction by 39% and 43%, respectively). The results suggested that indication 2 defined by patient's risk was quite appropriate for APR administration as it contributed to the biggest reduction in our budget impact model (Table 4).

These financial benefits answered, at least partly, the ESA task force's question about the place that APR might hold nowadays [18].

The biggest group of patients was included in indication 3 (66.7%). Overall reduction in cost resources was rather modest (11%) mainly because of reduction in resource costs for ICU stay (18%). Considering the larger number of patients, the results on the budget impact model were nevertheless quite important with overall savings estimated around the same as for indication 2 (€1.626 K versus €1.789 K).

The more significant change in the budget impact model in indication 2 and 3 compared to TXA is related to ICU stays. The ICU stays were influenced by incidence of complications like low cardiac output syndrome, acute renal failure, stroke or other thrombo-embolic events. Details on postoperative outcomes were not collected in the study because extra costs related to the treatment of complications were supposedly covered by daily ICU costs. It was assumed that prolonged stay in ICU was related to complicated postoperative follow-up. The reduction in ICU stay with APR is puzzling considering the small reduction in bleeding and small differences in transfusion or fibrinogen administration compared to TXA, which can hardly explain the prolonged stay. The reduction of ICU stay has been barely described in previous studies [28] and might be related to other mechanisms than preventing bleeding and transfusion [29]. Interestingly, the higher ICU costs for TXA patients were mainly due to those patients who stayed [2 weeks in the ICU (data not shown). Further studies are required to confirm this observation and eventually to establish the causality of APR effect on ICU stay.

### **Strengths and Limitations**

Our study had several limitations. First, the results observed reflect the practice in France and may not apply to other healthcare systems. Second, our cohort was retrospective and heterogeneous with recruitment of various indications, and we used a non-standardised protocol for TXA administration, with the inherent limitation of a before-and-after design.

Third, the matching process based on APR indication definition might not fully exclude residual confounding. However, since all consecutive potential participants were screened over the study period, the cohort reflected real world antifibrinolytic exposure. Moreover, the sensitivity analysis seemed to confirm the primary result. Fourth, costs were calculated with official prices (fixed by the national health regulatory authorities), which could be slightly different in each institution after negotiation with the manufacturer. However, the negotiated prices concerned only blood products with a limited impact on the overall costs. Finally, the small recruitment for indications 1 and 2 may preclude definitive conclusions.

Strengths of our study included its careful design that limited missing data. In addition, patients' recruitment was based on consecutive cases, which reflected real-life activity. Lastly, it involved a comparison of APR to the current antifibrinolytic competitor.

# CONCLUSION

The present budget impact analysis projected that the re-introduction and use of APR tend to reduce the requirement for transfusion and ICU stay in patients undergoing high-risk cardiac surgery and therefore leads to substantial cost savings from the hospital's perspective compared with exclusive use of TXA.

## ACKNOWLEDGEMENTS

The authors thank the contract research organisation CEMKA France for performing the statistical analysis.

### **Funding.**

Sponsorship for this study and the journal's Rapid Service Fee and Open Access fees were funded by Nordic Pharma.

### **Authorship.**

All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole and have given their approval for this version to be published.

### **Author Contributions.**

Pascal Colson, Jean-Luc Fellahi, Philippe Gaudard, Sophie Provenchère, Bertrand Rozec: concept and planning of the work described; acquisition, analysis and interpretation of the data; Pascal Colson, Jean-Luc Fellahi, Philippe Gaudard, Sophie Provenchère, Bertrand Rozec: drafting and/or critical revision of the manuscript and approved the final submitted version of the manuscript.

### **Disclosures.**

Pascal Colson is a consultant for Nordic Pharma. Jean-Luc Fellahi is a consultant for Nordic Pharma. Philippe Gaudard is a consultant for Nordic Pharma. Sophie Provenchère is a consultant for Nordic Pharma. Bertrand Rozec is a consultant for Nordic Pharma. Compliance with Ethics Guidelines. As required by French regulations, the real-life data from the NAPaR study were approved by the French data protection authority (CNIL) and the French ethics committee on January 16, 2018. Due to the use of a pooled anonymized data set, no ethics approval for this study was needed.

### **Data Availability.**

The data are available from CEMKA, Bourg-la-Reine, France.



### *Why carry out this study?*

Despite technical advances, coronary revascularisation is still a surgical procedure associated with a significant risk of bleeding and blood products transfusion

After being withdrawn from the market in 2008, aprotinin market authorisation was reinstated in France in 2018. One of the risk minimisation measures was to monitor the use of this specialty through a post-authorisation safety study: NAPaR

The aim of the present study was to evaluate the budget impact of reintroducing aprotinin versus tranexamic acid in French cardiac surgery centres based on real-world data from the NAPaR

### *What was learned from the study?*

Aprotinin reintroduction followed ARCOTHOVA prescription, which means that besides isolated coronary artery bypass surgery, aprotinin could also be used in high-bleeding-risk patients undergoing cardiac surgery carrying a high bleeding risk

When compared to tranexamic acid, 2 years of aprotinin use was associated with substantial cost savings (around €3 million when generalized to the 874 patients included in the NAPaR)

Savings were mainly driven by the cost of stays in the intensive care unit

## REFERENCES

1. Paone G, Likosky DS, Brewer R, et al. Transfusion of 1 and 2 units of red blood cells is associated with increased morbidity and mortality. *Ann Thorac Surg.* 2014;97:87–93.
2. Koch CG, Li L, Duncan AI, et al. Morbidity and mortality risk associated with red blood cell and blood-component transfusion in isolated coronary artery bypass grafting. *Crit Care Med.* 2006;34: 1608–16.
3. Vlot EA, Verwijmeren L, van de Garde EMW, Kloppenburg GTL, van Dongen EPA, Noordzij PG. Intra-operative red blood cell transfusion and mortality after cardiac surgery. *BMC Anesthesiol.* 2019;4(19):65.
4. D'Agostino RS, Jacobs JP, Badhwar V, et al. The society of thoracic surgeons adult cardiac surgery database: 2019 update on outcomes and quality. *Ann Thorac Surg.* 2019;107:24–32.
5. Colson PH, Gaudard P, Meunier C, Seguret F. Impact of red blood cell transfusion on in-hospital mortality of isolated coronary artery bypass graft surgery. A retrospective observational study of french nationwide 3-year cohort. *Ann Surg.* 2022. <https://doi.org/10.1097/SLA.0000000000005488>.
6. Alghamdi AA, Davis A, Brister S, Corey P, Logan A. Development and validation of Transfusion Risk Understanding Scoring Tool (TRUST) to stratify cardiac surgery patients according to their blood transfusion needs. *Transfusion (Paris).* 2006;46: 1120–9.
7. Vuylsteke A, Pagel C, Gerrard C, et al. The Papworth Bleeding Risk Score: a stratification scheme for identifying cardiac surgery patients at risk of excessive early postoperative bleeding. *Eur J Cardio-Thorac Surg.* 2011;39:924–30.
8. Goudie R, Sterne JAC, Verheyden V, Bhabra M, Ranucci M, Murphy GJ. Risk scores to facilitate preoperative prediction of transfusion and large volume blood transfusion associated with adult cardiac surgery. *Br J Anaesth.* 2015;114:757–66.
9. Klein AA, Collier T, Yeates J, et al. The ACTA PORTscore for predicting perioperative risk of blood transfusion for adult cardiac surgery. *Br J Anaesth.* 2017;119:394–401.
10. Murphy GJ, Pike K, Rogers CA, for the TITRe2 Investigator, et al. Liberal or restrictive transfusion after cardiac surgery. *N Engl J Med.* 2015;372: 997–1008.
11. Mazer CD, Whitlock RP, Fergusson DA, for the TRICS Investigators and Perioperative Anesthesia Clinical Trials Group, et al. Restrictive or liberal redcell transfusion for cardiac surgery. *N Engl J Med.* 2017;377:2133–44.
12. The Society of Thoracic Surgeons Blood Conservation Guideline Task Force, Ferraris VA, Ferraris SP, Saha SP, et al. The Society of Thoracic Surgeons Blood Conservation Guideline Task Force. Perioperative blood transfusion and blood conservation in cardiac surgery: the Society of Thoracic Surgeons and The Society of Cardiovascular Anesthesiologists clinical practice guideline. *Ann Thorac Surg.* 2007;83:S27-86.

13. Pagano D, Milojevic M, Meesters MI, et al. 2017 EACTS/EACTA guidelines on patient blood management for adult cardiac surgery. *Eur J Cardiothorac Surg*. 2018;53:79–111.
14. Raphael J, Mazer CD, Subramani S, et al. Society of cardiovascular anesthesiologists clinical practice improvement advisory for management of perioperative bleeding and hemostasis in cardiac surgery patients. *Anesth Analg*. 2019;129:1209–21.
15. Koster A, Faraoni D, Levy JH. Antifibrinolytic therapy for cardiac surgery: an update. *Anesthesiology*. 2015;123:214–21.
16. Fergusson DA, Herbert PC, Mazer CD, et al. BART investigators: a comparison of aprotinin and lysine analogues in high-risk cardiac surgery. *N Engl J Med*. 2008;358:2319–31.
17. European Medicines Agency. Assessment report Antifibrinolytics containing aprotinin, aminocaproic acid and tranexamic acid aprotinin [Internet]. 2013. [http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Referrals\\_document/Antifibrinolytic\\_medicines/WC500153601.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Referrals_document/Antifibrinolytic_medicines/WC500153601.pdf). Accessed 15 May 2018.
18. The European Society of Anaesthesiology task force reports on the place of aprotinin in clinical anaesthesia. Aprotinin: is it time to reconsider? *Eur J Anaesthesiol*. 2015;32(9):591–5. <https://doi.org/10.1097/EJA.0000000000000284>
19. Amour J, Cholley B, Colson P, et al. L'ordonnance type du groupe de travail Aprotinine-ARCOTHOVA [Internet]. Arcothova. 2020. <http://www.arcothova.com/recommandations/>. Accessed 14 Apr 2020.
20. Ray MJ, Brown KF, Burrows CA, O'Brien MF. Economic evaluation of high-dose and low-dose aprotinin therapy during cardiopulmonary bypass. *Ann Thorac Surg*. 1999;68:940–5.
21. Smith PK, Datta SK, Muhlbaier LH, Samsa G, Nadel A, Lipscomb J. Cost analysis of aprotinin for coronary artery bypass patients: analysis of the randomized trials. *Ann Thorac Surg*. 2004;77:635–42.
22. Meyerson SL, Smith PK. Medical and economic impact of aprotinin use in adult cardiac surgery. *Transfus Altern Transfus Med*. 2004;6:17–21.
23. Robinson D, Bliss E. A model of the direct and indirect effects of aprotinin administration on the overall costs of coronary revascularization surgery in a university teaching hospital cardiothoracic unit. *Clin Ther*. 2002;24:1677–89.
24. Karkouti K, Wijeyesundera DN, Yau TM, et al. The risk-benefit profile of aprotinin versus tranexamic acid in cardiac surgery. *Anesth Analg*. 2010;110: 21–9.
25. Sander M, Spies CD, Martiny V, et al. Mortality associated with administration of high-dose tranexamic acid and aprotinin in primary openheart procedures: a retrospective analysis. *Crit Care*. 2010;14:R148.

26. Walkden GJ, Verheyden V, Goudie R, Murphy GJ. Increased perioperativemortality following aprotinin withdrawal: a real-world analysis of blood management strategies in adult cardiac surgery. *Int Care Med.* 2013;39:1808–17.
27. De Hert S, Ouattara A, Royston D, van der Linden J, Zacharowski K. Use and safety of aprotinin in routine clinical practice. A European postauthorisation safety study conducted in patients undergoing cardiac surgery. *Eur J Anaesthesiol.* 2020;37:1–10.
28. Deloge E, Amour J, Provenche`re S, Rozec B, Scherrer B, Ouattara A. Aprotinin vs tranexamic acid in isolated coronary artery bypass surgery. A multicentre observational study. *Eur Journal Anaesthesiol.* 2017;34(5):280–7.
29. McEvoy M, Reeves ST, Reves JG, Spinale FG. Aprotinin in cardiac surgery: a review of conventional and novel mechanisms of action. *Anesth Analg.* 2007;105:949–62.