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ORIGINAL ARTICLE

Use and safety of aprotinin in routine clinical practice

A European postauthorisation safety study conducted in patients undergoing cardiac surgery

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BACKGROUND Aprotinin has been used to reduce blood loss and blood product transfusions in patients at high risk of major blood loss during cardiac surgery. Approval by the European Medicines Agency (EMA) for its current indication is limited to patients at high risk of major blood loss undergoing isolated coronary artery bypass graft surgery (iCABG).

OBJECTIVE To report current real-world data on the use and certain endpoints related to the safety of aprotinin in adult patients.

DESIGN The Nordic aprotinin patient registry (NAPaR) received data from 83 European centres in a noninterventional, postauthorisation safety study (PASS) performed at the request of the EMA.

SETTING Cardiac surgical centres committed to enrolling patients in the NAPaR.

PATIENTS Patients receiving aprotinin agreeing to participate.

INTERVENTION The decision to administer aprotinin was made by the treating physicians.

MAIN OUTCOME MEASURES Aprotinin safety endpoints were in-hospital death, thrombo-embolic events (TEEs), specifically stroke, renal impairment, re-exploration for bleeding/tamponade.

RESULTS From 2016 to 2020, 5309 patients (male 71.5%; >75 years 18.9%) were treated with aprotinin; 1363 (25.7%) underwent iCABG and 3946 (74.3%) another procedure, including a surgical treatment for aortic dissection ($n = 660$, 16.7%); 54.5% of patients received the full-dose regimen. In-hospital mortality in iCABG patients was 1.3% (95% CI, 0.66 to 1.84%) vs. 8.3% (7.21 to 8.91%) in non-iCABG patients; incidence of TEEs and postoperative rise in creatinine level greater than 44 μmol l^{-1} 2.3% (1.48 to 3.07%) and 2.7% (1.79 to 3.49%) vs. 7.2% (6.20 to 7.79%) and 15.5% (13.84 to 16.06%); patients undergoing re-exploration for bleeding 1.4% (0.71 to 1.93%) vs. 3.0% (2.39 to 3.44%). Twelve cases of hypersensitivity/anaphylactic reaction (0.2%) were reported as Adverse Drug Reactions.

CONCLUSION The data in the NApaR indicated that in this patient population, at high risk of death or blood loss undergoing cardiac surgery, including complex cardiac surgeries other than iCABG, the incidence of adverse events is in line with data from current literature, where aprotinin was not used.

TRIAL REGISTRATION EU PAS register number: EUPAS11384.

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KEY POINTS

- Aprotinin therapy had become one of the principal interventions in Pillar two of the Patient Blood Management approach until its voluntary withdrawal from the market in 2007.
- Aprotinin has been re-introduced to the European market, and, as part of the re-instatement, its new marketing authorisation holder has established the NAPaR (Nordic Aprotinin Patient Registry).
- The NAPaR was aimed to collect real-world data on the use and certain endpoints associated with safety of aprotinin in each country where it was commercially available.
- Results from the NAPaR obtained from over 5000 patients at 83 sites in 9 European countries found that the occurrence of adverse events following the use of aprotinin in patients at high risk of death or blood loss undergoing cardiac surgery, including complex cardiac surgeries other than iCABG, is comparable to data from current literature where aprotinin was not used.

Introduction

Aprotinin is indicated for prophylactic use to reduce blood loss and blood product transfusions in adult patients who are at high risk of major blood loss undergoing isolated coronary artery bypass graft surgery (iCABG),[1,2] that is CABG not combined with other cardiovascular surgery. Aprotinin has a broad action on proteolytic enzymes, such as plasmin, trypsin and kallikrein.

The use of high-dose aprotinin for preventing bleeding, and consequently the need for blood transfusion after cardiac surgery was first reported in *The Lancet* in 1987.[3] This indication gained popularity in many countries and cardiac surgical centres over the subsequent 15 to 20 years. However, between 2006 and 2007, data from three observational studies and preliminary results from one randomised controlled trial suggested increased mortality in treated patients.[4–7] Two of the studies found an increased risk of renal events in patients treated with aprotinin compared with patients treated with lysine analogues.[4,6] Consequently, aprotinin was voluntarily removed from the market by the Marketing Authorisation Holder (MAH) in 2007,[8] and its European licence was formally suspended by the European Medicines Agency (EMA) in 2008.[9]

In 2010, the EMA, along with its independent expert advisory panel, revisited the totality of the data.[10] The reviewers noted discrepancies in the data analyses and their presentation.[11,12]

In 2012, the EMA recommended lifting the suspension on aprotinin.[10] In 2013, the Committee for Medicinal Products for Human Use (CHMP) concluded that aprotinin's benefit–risk ratio was positive for prophylactic use to reduce blood loss and blood transfusions in adult patients at high risk of major blood loss undergoing iCABG.[2] Aprotinin was re-introduced to the European market, with a new MAH (Nordic Pharma B.V., Hoofddorp, The Netherlands) from February 2016. As part of the reinstatement process, the EMA imposed on the MAH a requirement to build a patient registry to gather information on its use.[13,14]

This study aimed to monitor the pattern of use of aprotinin (Trasylol, Nordic Group B.V.), measure the incidence of safety outcomes and evaluate the adherence to and effectiveness of the risk minimisation measures described in the risk management plan (RMP) and the recommendations of the summary of product characteristics (SmPC).

To the best of the authors' knowledge, by presenting information captured in the NAPaR for adult patients, this article should provide first-time pivotal evidence on real-world use and safety of aprotinin in a large sample of patients undergoing cardiac surgery.

Methods

Study design and participants

The current study was a prospective, multicentre European noninterventional postauthorisation safety study (PASS) with active surveillance via a patient exposure registry. This is now the preferred method of the EMA to collect 'real world' information about safety of medicines rather than have comparator studies with contrived exclusion criteria. A PASS is defined as a noninterventional study carried out after a medicine has been authorised to obtain further information on its safety and to assess the effectiveness of risk-management measures. The Pharmacovigilance Risk Assessment Committee (PRAC) of the EMA specifically asked for data on three aspects of adherence to the SmPC.[1] These included: administration of a 1 ml test dose 10 min prior to administration of the loading dose; reports of allergic, hypersensitivity or anaphylactic reactions; adherence to the recommendation for anticoagulation control when using an activated coagulation time (ACT) during cardiopulmonary bypass. Specifically, if the ACT was used to monitor anticoagulation, a minimal celite-ACT of 750 s or kaolin-ACT of 480 s, independent of the effects of haemodilution and hypothermia, were recommended.

As part of the regulatory process, the EMA stipulated that the MAH could only deliver aprotinin to European cardiac surgical centres that agreed to supply data to the NAPaR. All participating cardiac surgery centres, therefore, committed to enrolling patients in the NAPaR.

Adult patients who agreed to participate and have their personal data entered in the anonymised database were

included in the NAPaR if they were exposed to aprotinin during any on-pump cardiac surgery performed at one of the participating centres. In Austria and Germany, according to the local legislation, only data on iCABG surgery could be collected. These countries almost universally used the half-dose regimen.

Patients were excluded if they did not fulfil the criteria of consent to enter data or evidence of exposure to aprotinin.

In each country, the study started on the date of commercial availability of aprotinin. The data lock point of the registry was 2 November 2020.

Ethics

The study was conducted in compliance with the Independent Ethics Committees/Institutional Review Boards (IEC/IRB) informed consent regulations, the Declaration of Helsinki and the Good Epidemiology and Good Pharmaco-epidemiology Practices (GEP/GPP) guidelines.

The present study, being a noninterventional PASS and with the EMA considering that there were no ethical issues raised by establishing a noninterventional registry, the study was not obligatorily declarable to relevant IECs/IRBs. However, the study protocol was submitted for approval to relevant IECs/IRBs in most countries and approvals obtained at national or local level depending on the country. According to local rules, before patients were included in the NAPaR, they could receive pertinent information about aprotinin (oral or written) and refuse data collection (oral).

All participating centres were encouraged to use aprotinin in compliance with the authorised indication of the drug. However, the centres were free to use the product for other indications.

A Drug Safety Monitoring Committee (DSMC) was established prior to the implementation of the NAPaR and met to examine the data at 6-month intervals. Data were independently collated and analysed under the guidance of the DSMC.

The protocol is available on the European Network of Centres for Pharmaco-epidemiology and Pharmacovigilance website (www.ENCePP.eu, EU PAS Register number: EUPAS11384).

Procedures

Patients were treated according to the routine clinical practice of the centres where they received surgery. The decision to prescribe aprotinin was made by their physicians according to clinical judgement.

According to the SmPC,[1] aprotinin administration is a four-step process: administration of an initial (test) dose at least 10 min prior to the loading dose (0.01 million kallikrein inhibitor units, MKIU); slow administration of a loading dose after induction of anaesthesia and prior to sternotomy (one or two MKIU for half- or full-dose regimens, respectively); priming of the pump of the heart–lung machine by a solution containing aprotinin (one or two MKIU for half-dose or full-dose regimens, respectively); constant infusion dose for the duration of the surgery (0.25 or 0.50 MKIU h^{-1} for half-dose and full-dose regimens, respectively). The total amount of aprotinin administered was not to exceed seven MKIU.

When activated clotting time (ACT) was chosen to monitor operative anticoagulation, the lowest occurring ACT value for each patient was recorded. The SmPC also allowed anticoagulation control using protamine titration or a fixed dose heparin protocol.[1]

Outcomes

Aprotinin safety was evaluated by: in-hospital death and distribution of primary cause of death; myocardial infarction, stroke or other reported thrombo-embolic events (TEEs); renal impairment based on acute kidney injury (AKI defined as pre-operative to postoperative rise in plasma creatinine level >44 μmol l^{-1} (0.5 mg dl^{-1}) or new renal replacement therapy (new RRT); any hypersensitivity or allergic response to aprotinin; and re-exploration for bleeding/tamponade. The change in plasma creatinine endpoint was used as it allowed regulators to compare results in NAPaR with prior publications suggesting renal injury.[4]

The European System for Cardiac Operative Risk Evaluation (EuroSCORE) II was completed before the procedure to evaluate the risk of postoperative death.[15] The Bleeding Risk Score (BRiSc) was used to stratify patients preoperatively into risk groups with markedly different rates of severe postoperative bleeding.[16] The BRiSc score is an additive score with five components (urgency of surgery; complexity of surgery; aortic valve disease yes/no; BMI less or more than 25 kg m^{-2}; and age more or less than 75 years).

Data collection

Data were collected during routine clinical practice and entered into an electronic web-based record form that could be accessed worldwide (Supplementary Material 1, http://links.lww.com/EJA/A717). The design of the NAPaR followed the template of the reports of the European Association for Cardio-Thoracic Surgery (EACTS),[17] with additional data assessment relevant for recording the use and monitoring the safety of aprotinin.

This registry was designed to collect uniform data on all patients exposed to aprotinin, and to match standard clinical practice.

The NAPaR prospectively captured information on the characteristics of the patients receiving aprotinin; the surgical procedure; the reasons and conditions of use of aprotinin and safety outcomes occurring during cardiac surgery, the next 24 h, the hospital stay and after discharge (Supplementary material 2, http://links.lww.com/EJA/A718).

Statistical analysis

There was no a priori calculation of power for this study because of its descriptive nature and the absence of comparative treatment groups.

Assuming that the incidence of iCABG would be observed in 50% of patients undergoing cardiac surgery and the exclusion rate around 25%, 5268 patients were to be included in the registry to obtain a 95% confidence interval (CI) with a maximal margin error of 1.56% (95% CI, 48.44 to 51.56%).

Data were analysed according to the procedure: iCABG vs. non-iCABG, and among non-iCABG according to: 're-do', defined as re-operation through a previous sternotomy; surgery in patients with active endocarditis; valve replacement and/or repair with or without CABG (hereafter labelled as valve surgery); aortic surgery without isolated aortic valve replacement and/or repair (hereafter labelled as aortic surgery) and surgical treatment for aortic dissection.

Quantitative variables are presented using the number of observed values, mean and standard deviation (SD). and qualitative variables using counts and percentages. If appropriate, the 95% CI was calculated using the Wald method. Statistical tests were applied, and *P* values calculated to explore potential association between study variables.

Statistical analyses were performed with the statistical software SAS (SAS Institute, Cary, North Carolina, USA), version 9.4. The significance threshold was set at 0.05 (two-sided).

Role of the funding source

The PRAC of the EMA imposed this PASS on the new MAH. They also validated the study protocol and reviewed collected data at regular intervals.

Nordic Group B.V. was involved in the study design, data analysis and interpretation, and appointed a professional agency in the writing of the article. However, this did not have any impact or influence on the selection of surgery centres that wished to participate, on the inclusion of patients and on the results and conclusions reported in this article.

All authors had full access to the data and had final responsibility for the decision to submit the article for publication.

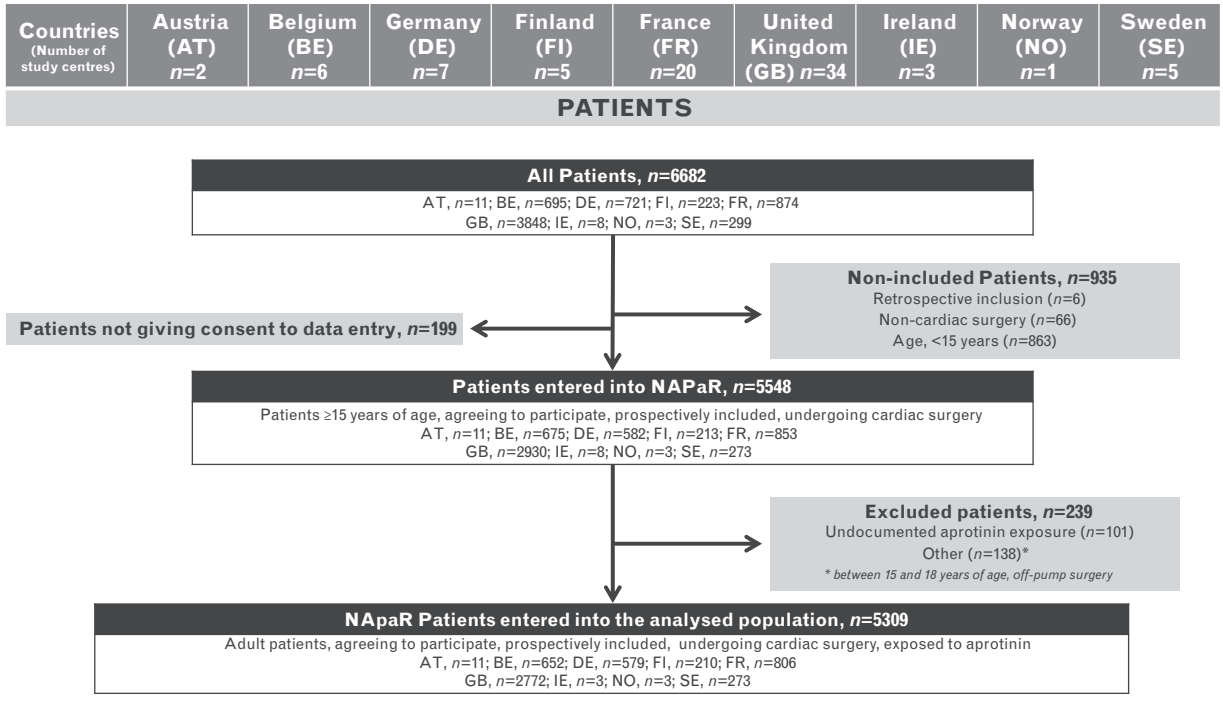
Results

Study oversight and participants

The study was conducted in 83 cardiac surgical centres in nine European countries (Fig. 1). The list of investigators is provided in Supplementary Material 3, http://links.lww.com/EJA/A719.

From 26 February 2016, to 31 August 2020, 6682 patients were identified for inclusion, among them 5309 patients constituted the study population (Fig. 1); 52.2% of patients were registered in cardiac surgery centres located

Fig. 1



Flow diagram of patient disposition.

Table 1 Main characteristics of adult patients exposed to aprotinin during isolated coronary artery bypass graft surgery or other procedures (on-pump surgery): postauthorisation safety study ($n = 5309$)

		iCABG $n = 1363$	NoniCABG $n = 3946$
Country	*n*	1363	3946
Austria	*n* (%)	9 (0.7%)	2 (0.1%)
Belgium	*n* (%)	17 (1.3%)	635 (16.1%)
Germany	*n* (%)	578 (42.4%)	1 (0.0%)
Finland	*n* (%)	31 (2.3%)	179 (4.5%)
France	*n* (%)	137 (10.1%)	669 (17.0%)
United Kingdom (UK)	*n* (%)	563 (41.3%)	2209 (56.0%)
Ireland	*n* (%)	0 (0%)	3 (0.1%)
Norway	*n* (%)	0 (0%)	3 (0.1%)
Sweden	*n* (%)	28 (2.1%)	245 (6.2%)
Sex	*n*	1363	3946
Male	*n* (%)	1127 (82.7%)	2670 (67.7%)
Female	*n* (%)	236 (17.3%)	1276 (32.3%)
Age (years)	*n*	1363	3946
Mean ± SD		66.4 ± 9.7	61.0 ± 15.9
Age (by classes) (years)	*n*	1363	3946
18–65	*n* (%)	563 (41.3%)	2001 (50.7%)
65–75	*n* (%)	520 (38.2%)	1222 (31.0%)
>75	*n* (%)	280 (20.5%)	723 (18.3%)
BMI (kg m^{-2})	*n*	1361	3930
Mean ±SD		28.6 ± 4.7	27.1 ± 5.7
BMI (by classes) (kg m^{-2})	*n*	1361	3930
<25	*n* (%)	315 (23.1%)	1530 (38.9%)
≥25	*n* (%)	1046 (76.9%)	2400 (61.1%)
Smoking history	*n*	395	2202
Never smoker	*n* (%)	180 (45.6%)	1117 (50.7%)
Former smoker	*n* (%)	139 (35.2%)	758 (34.4%)
Smoker	*n* (%)	76 (19.2%)	327 (14.9%)
Creatinine clearance (ml min^{-1})	*n*	1335	3908
Normal (>85)	*n* (%)	646 (48.4%)	1752 (44.8%)
Moderate decrease (50–85)	*n* (%)	545 (40.8%)	1500 (38.4%)
Severe decrease (<50)	*n* (%)	118 (8.8%)	559 (14.3%)
Dialysis[a]	*n* (%)	26 (2.0%)	97 (2.5%)
BRiSc (score)	*n*	1359	3367
Low (0)	*n* (%)	465 (34.2%)	85 (2.5%)
Moderate (1–2)	*n* (%)	858 (63.1%)	1916 (56.9%)
High (≥3)	*n* (%)	36 (2.7%)	1366 (40.6%)
EuroSCORE II	*n*	365	2111
Mean ± SD		4.6 ± 6.3	10.7 ± 12.7
Median [interquartile range, IQR]		2 [1 to 5]	6 [3 to 13]
Operation urgency	*n*	1361	3943
Elective	*n* (%)	798 (58.6%)	1961 (49.7%)
Urgent	*n* (%)	429 (31.5%)	1138 (28.9%)
Emergency	*n* (%)	128 (9.4%)	768 (19.5%)
Salvage	*n* (%)	6 (0.4%)	76 (1.9%)
Redo	*n*	1325	3367
No	*n* (%)	1256 (94.8%)	1780 (52.9%)
Yes	*n* (%)	69 (5.2%)	1587 (47.1%)
Bypass time (min)	*n*	1328	3645
Mean ± SD		83.1 ± 44.9	169.9 ± 88.5
Aprotinin regimen	*n*	1363	3946
Half dose	*n* (%)	713 (53.3%)	1673 (42.8%)
Full dose	*n* (%)	625 (46.7%)	2232 (57.2%)
Antiplatelet therapy	*n*	919	3371
0	*n* (%)	74 (8.1%)	1450 (72.7%)
1	*n* (%)	588 (64.0%)	741 (22.0%)
≥2	*n* (%)	257 (28.0%)	180 (5.3%)
Drugs with potential renal toxicity[b]	*N*	1327	3863
No	*n* (%)	917 (69.1%)	2267 (69.0%)
Yes	*n* (%)	378 (28.5%)	1134 (29.4%)
Not known	*n* (%)	32 (2.4%)	62 (1.6%)

ALD, aprotinin-loading dose; BMI, body mass index; BRiSc, pre-operative risk of excessive early postoperative bleeding; EuroSCORE II, predicted risk of in-hospital mortality; iCABG, isolated coronary artery bypass graft surgery; MKIU, million kallikrein inhibitor unit; *N* or *n*, number of patients; RRT, renal replacement therapy; SD, standard deviation. [a] Regardless of creatinine clearance. [b] Postoperative exposure.

in the United Kingdom. The mean rate of completion for main data was 87.8%.

Patients were mainly male (71.5%); 18.9% were older than 75 years of age, 65.1% overweight (BMI ≥25 kg m^{-2}), and 50.3% smokers/former smokers; 12.9% had pre-operative creatinine clearance less than 50 ml min^{-1}, indicating renal dysfunction. On the basis of BRiSc, 26.4% of patients were at high risk of bleeding. Their mean ± SD EuroSCORE II was 9.8 ± 12.2. The full-dose regimen was administered to 54.5% of the patients.

Surgical procedure and risk minimisation measures

One thousand three hundred and sixty-three patients (25.7%) underwent an iCABG (iCABG group) and 3946 patients (74.3%) underwent another surgical procedure (non-iCABG group). The proportion of patients who underwent iCABG greatly varied according to the country, ranging from 0% in Ireland ($n = 0/4$) and Norway ($n = 0/3$) to 99.8% in Germany ($n = 578/579$).

As compared with patients in the iCABG group, patients in the non-iCABG group were more frequently female and younger; they were less frequently overweight or smokers/former smokers; they presented more frequently with pre-operative renal dysfunction and less frequently received at least two antiplatelet therapies; they were at higher risk of excessive bleeding (BRiSc ≥3) and mortality (higher mean EuroSCORE II); they underwent redo more frequently (Table 1). In the non-iCABG group, aortic surgery was the most frequently reported procedure; 16.7% of patients underwent a surgical treatment for aortic dissection (Fig. 2). Mean bypass time was approximately twice longer in the non-iCABG than iCABG group (Table 1).

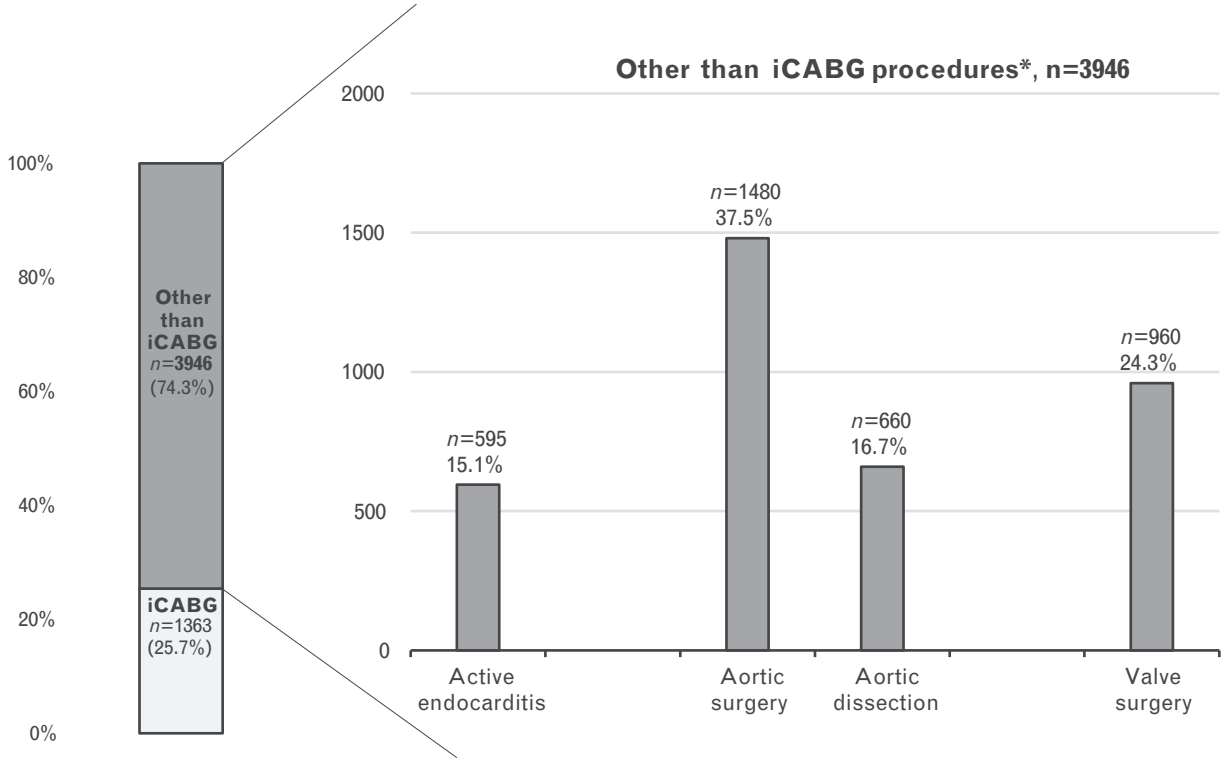
Regarding risk minimisation measures and compliance with SmPC, 94.6% of patients ($n = 4980/5267$) received a test dose of aprotinin and 98.3% ($n = 5195/5286$) were monitored for anticoagulation, mainly tested by the kaolin-ACT (77.7%, $n = 4106/5286$) or celite-ACT (2.0%, $n = 104/5286$). The minimal values for the 4106 patients who underwent kaolin-ACT were in accordance with the SmPC for 2539 (61.8%).

Mortality

Prior to discharge, 6.5% ($n = 335/5162$) of patients died. All deaths except 17 occurred in the non-iCABG group, resulting in statistically significantly higher mortality rate in this group ($P < 0.001$). In both groups, cardiac events were the primary cause of death (Table 2). In the non-iCABG group, mortality rate was heterogeneous among procedures ranging from 4.8% (valve surgery, $n = 45/940$) to 15.6% (aortic dissection, $n = 100/642$).

No deaths because of noncardiac TEE, haemorrhagic events, or neurologic causes were reported in the iCABG group. These factors were considered the main cause of death in, respectively, 5.4, 6.3 and 12% of patients from the non-iCABG group. Out of 38 deaths associated with

Fig. 2



Characteristics of nonisolated coronary artery bypass graft surgery procedures (postauthorisation safety study, $n = 3946$).

*Only four categories are detailed.

neurologic causes, 19 were reported in patients with aortic dissection. One death in the non-iCABG group was because of renal failure.

Thrombo-embolic events

5.9% of the patients ($n = 307/5166$) experienced at least one TEE, mainly stroke and permanent stroke, which were reported by 3.8% ($n = 196/5170$) and 2.4% ($n = 126/5170$) of patients, respectively. About one-third of these patients experienced at least one TEE ($n = 91/5166$, 1.8%), stroke ($n = 56/5170$, 1.1%), or permanent stroke ($n = 35/5170$, 0.7%) within the 24 h following the procedure.

The incidence of TEE, stroke and permanent stroke was always lower in the iCABG than non-iCABG group. The trend was significant or tended to be significant for permanent stroke regardless of the time of occurrence ($P < 0.001$ and $P = 0.054$) (Table 2).

The highest percentages of patients reporting at least one TEE, stroke or permanent stroke during the study were reported in patients with aortic dissection: 17.2% ($n = 111/644$), 13% ($n = 84/644$) and 9.5% ($n = 61/644$), respectively.

Renal events

After the procedure, 12.2% of patients ($n = 626/5125$) presented with AKI and 8.6% ($n = 433/5047$) underwent new RRT. AKI and new RRT occurred statistically significantly less frequently in the iCABG than non-iCABG group ($P < 0.001$ for both) (Table 2).

In the iCABG group, 2.7% of patients ($n = 36/1318$) had AKI and 1.7% ($n = 22/1300$) started new-RRT vs. 15.5% ($n = 590/3807$) and 11% ($n = 411/3747$) in the non-iCABG group (Table 2). Respectively, 25% ($n = 9/36$) and 34.9% ($n = 207/590$) of patients in iCABG and non-iCABG groups underwent new RRT.

Among patients with aortic dissection, 27.7% ($n = 175/633$) had AKI and 16.3% ($n = 103/633$) started new RRT; 36% ($n = 63/175$) of patients with AKI underwent new RRT.

Re-exploration for bleeding/tamponade

The absolute values for re-exploration follow the trend of other endpoints with lower incidence in the iCABG than non-CABG group: 2.1% ($n = 28/1322$) vs. 6.5% ($n = 249/3832$) for all re-explorations and 1.4% ($n = 18/1322$) vs. 3% ($n = 115/3832$) for re-explorations within the 24 h following surgery ($P < 0.001$ for both) (Table 2).

In patients with aortic dissection, the re-exploration rate was 10.6% ($n = 68/644$), 5% ($n = 32/644$) for re-exploration performed within the 24 h following surgery.

Table 2 Incidence of safety outcomes of interest in adult patients exposed to aprotinin during surgical procedure, according to the surgical procedure: postauthorisation safety study ($n = 5309$)

		iCABG $n = 1363$		Non-iCABG $n = 3946$
In-hospital mortality				
Death at discharge?	*n*	1317		3845
Yes	*n* (%)	17 (1.3%)		318 (8.3%)
	95% CI[a]	(0.66 to 1.84)		(7.21 to 8.91)
			P-value[†]: $P < 0.001$	
Primary cause	*n*	17		316
Cardiac events (excl. valvular)	*n* (%)	12 (70.6%)		126 (39.9%)
Neurological events	*n* (%)	0 (0.0%)		38 (12.0%)
Haemorrhagic events	*n* (%)	0 (0.0%)		20 (6.3%)
TEEs (other than cardiac)	*n* (%)	0 (0.0%)		17 (5.4%)
Infection	*n* (%)	1 (5.9%)		15 (4.8%)
Pulmonary	*n* (%)	1 (5.9%)		8 (2.5%)
Valvular	*n* (%)	0 (0.0%)		6 (1.9%)
Renal	*n* (%)	0 (0.0%)		1 (0.3%)
Other	*n* (%)	3 (17.6%)		85 (26.9%)
Thrombo-embolic events (TEEs)				
At least one TEE?	*n*	1324		3842
Yes	*n* (%)	31 (2.3%)		276 (7.2%)
	95% CI[a]	(1.48 to 3.07)		(6.20 to 7.79)
			P-value[†]: $P < 0.001$	
Myocardial infarction?	*n*	1324		3845
Yes	*n* (%)	12 (0.9%)		28 (0.7%)
	95% CI[a]	(0.38 to 1.38)		(0.45 to 0.97)
			P-value[†]: $P = 0.524$	
Stroke?	*n*	1324		3846
Yes	*n* (%)	16 (1.2%)		180 (4.7%)
	95% CI[a]	(0.60 to 1.75)		(3.91 to 5.21)
			P-value[†]: $P < 0.001$	
Permanent stroke?		1324		3846
Yes	*n* (%)	7 (0.5%)		119 (3.1%)
	95% CI[a]	(0.13 to 0.89)		(2.48 to 3.55)
			P-value[†]: $P < 0.001$	
At least one TEE in the 24 h?[a]	*n*	1324		3842
Yes	*n* (%)	17 (1.3%)		74 (1.9%)
	95% CI[a]	(0.66 to 1.84)		(1.45 to 2.30)
			P-value[†]: $P = 0.126$	
Myocardial infarction?	*n*	1324		3845
Yes	*n* (%)	7 (0.5%)		11 (0.3%)
	95% CI[a]	(0.13 to 0.89)		(0.11 to 0.44)
			P-value[†]: $P = 0.276$	
Stroke?	*n*	1324		3846
Yes	*n* (%)	9 (0.7%)		47 (1.2%)
	95% CI[a]	(0.23 to 1.09)		(0.85 to 1.53)
			P-value[†]: $P = 0.100$	
Permanent stroke?	*n*	1324		3846
Yes	*n* (%)	4 (0.3%)		31 (0.8%)
	95% CI[a]	(0.01 to 0.58)		(0.51 to 1.06)
			P-value[†]: $P = 0.054$	
Postoperative renal events				
AKI?	*n*	1318		3807
Yes	*n* (%)	36 (2.7%)		590 (15.5%)
	95% CI[a]	(1.79 to 3.49)		(13.84 to 16.06)
			P-value[†]: $P < 0.001$	
New RRT?	*n*	1300		3747
Yes	*n* (%)	22 (1.7%)		411 (11.0%)
	95% CI	(0.96% to 2.33%)		(9.70% to 11.60%)
			P value[†]: $P < 0.001$	
New RRT in AKI patients?	*n*	36		590
Yes	*n* (%)	9 (25.0%)		207 (35.1%)
	95% CI	(10.86% to 39.14%)		(31.23% to 38.94%)
			P-value[†]: $P = 0.217$	
Re-exploration for bleeding				
All ?	*n*	1322		3832
Yes	*n* (%)	28 (2.1%)		249 (6.5%)
	95% CI[a]	(1.34 to 2.89)		(5.72 to 7.28)
			P-value[†]: $P < 0.001$	
In the 24 h?	*n*	1322		3832
Yes	*n* (%)	18 (1.4%)		115 (3.0%)
	95% CI[a]	(0.74 to 1.99)		(2.46 to 3.54)
			P-value[†]: $P < 0.001$	

AKI, acute kidney injury: AKI was defined by pre-operative to postoperative rise in plasma creatinine level greater than 44 $\mu mol\,l^{-1}$ (0.5 $mg\,dl^{-1}$); CI, confidence interval; excl..: excluding; iCABG, isolated coronary artery bypass graft surgery; *n*, number of patients; RRT, renal replacement therapy; TEE, thrombo-embolic events. TEEs included stroke, myocardial infarction, or other TEEs. [a]Wald test for large sample. [†] χ^2.

Table 3 Comparison of safety outcomes for isolated coronary artery bypass graft surgery and acute aortic dissection: Nordic Aprotinin Patient Registry (NAPaR) vs. literature

iCABG Outcome	Source	Country	Ref	Date ref.	Patients (*n*)	*n* (%)
Mortality	NAPaR			Current	1317	17 (1.3)
	Non-NAPaR	Germany	19	2014	43 145	129 (2.99)
		France	20	2017	1249	300 (2.4)
		UK	21	2020	45 284	448 (0.99)
		Sweden	22	2020	2404	26 (1.1)
Permanent stroke	NAPaR			Current	1324	7 (0.5)
	Non-NAPaR	UK	23	2019	30 059	223 (0.6)
		UK	21	2020	14 098	131 (0.9)
		Sweden	24	2018	2404	25 (1.0)
New RRT	NAPaR			Current	1300	22 (1.7)
	Non-NAPaR	UK	23	2019	30 059	448 (1.5)
		UK	21	2020	14 098	188 (1.3)
		Sweden	22	2020	2404	29 (1.2)
Re-exploration for bleeding[a]	NAPaR			Current	1322	18 (1.4)
	Non-NAPaR	UK	23	2019	30 059	759 (2.52)
		Sweden	24	2018	2534	124 (4.9)
		Sweden	22	2020	2404	89 (3.7)
Acute aortic dissection **Outcome**	**Source**	**Country**	**Ref**	**Date**	**Patient (*n*)**	***n* (%)**
Mortality	NAPaR			Current	642	100 (15.2)
	Non-NAPaR	Germany	25	2016	2137	361 (16.9)
		UK	26	2017	5445	963 (17.7)
		USA	27	2020	7353	1250 (17.0)
		UK	21	2020	1263	223 (17.7)
		Sweden	22	2020	201	25 (12.4)
Permanent Stroke	NAPaR			Current	644	61 (9.5)
	Non-NAPaR	USA	27	2020	7353	956 (13.0)
		USA	28	2018	2982	325 (10.9)
		Germany	25	2016	2137	203 (9.5)
		Austria	29	2018	303	48 (15.8)
New RRT	NAPaR			Current	633	103 (16.3)
	Non-NAPaR	Austria	29	2018	303	83 (27.4)
		USA	28	2018	2982	496 (17.9)
		Sweden	22	2020	201	22 (14.1)
Re-Exploration for bleeding[a]	NAPaR			Current	644	32 (5.0)
	Non-NAPaR	Austria	29	2018	303	83 (27.4)
		Sweden	30	2017	256	35 (13.7)
		USA	28	2018	2982	260 (8.7)

No statistical difference (χ^2) between the NAPaR and combined non-NAPaR data for each category apart from re-exploration for bleeding. For re-exploration for bleeding, highly significant difference (χ^2, $P < 0.001$) for both iCABG and acute aortic dissection. iCABG, isolated coronary artery bypass graft surgery; NAPaR, Nordic Aprotinin Patient Registry; nRRT, new renal replacement therapy; UK, The United Kingdom; USA, The United States of America. [a]For bleeding/tamponade (within 24 h following procedure).

Anaphylactic/hypersensitivity reaction

In the iCABG group, four patients experienced an anaphylactic/hypersensitivity reaction and in the non-iCABG group a further eight patients.

Among the 12 patients (0.2%) who experienced an anaphylactic/hypersensitivity reaction, 10 reported the reaction shortly after the administration of the test dose. Other reactions occurred 15 min after administration of the bolus dose, which was administered 30 min after the test dose, in one patient, and during concomitant administration of aprotinin and gelatine in another patient. Five of these anaphylactic/hypersensitivity reactions were serious but not fatal. All patients recovered without sequelae.

Discussion

The creation of NAPaR was stipulated by European regulators as part of the risk management plan to allow aprotinin back onto the European market. Since the re-introduction of aprotinin treatment, NAPaR was implemented in cardiac surgical centres across European countries. In November 2020, the registry included data from 5309 adult patients exposed to aprotinin during cardiac surgery.

Firstly, the current study showed that approximately 75% of patients from NAPaR were exposed to aprotinin for procedures involving cardiac surgery other than iCABG. The procedures were mainly aortic surgery (including surgical treatment of aortic dissection), valve surgery (with/without CABG) or surgical treatment of patients with active endocarditis; re-do was frequent. These procedures are known to be longer and more complex than iCABG; therefore, increasing the risk of mortality.[18] Results from this study confirmed this higher risk. Moreover, the incidences of TEEs, AKI, or re-exploration for

bleeding/tamponade were higher in patients with non-iCABG than with iCABG, although these patients were younger, less frequently overweight and less frequently smokers or former smokers. The higher proportion of patients who underwent procedures other than iCABG, as compared with the findings of D'Agostino *et al.*[18] (74.3 vs. 56%), suggests that clinicians used aprotinin to fulfil a medical need in high risk cardiac surgeries.

Secondly, we observed that aprotinin was well tolerated. To confirm the absence of certain safety signals (mortality, permanent stroke, new renal replacement therapy and re-exploration for bleeding or tamponade), the data were compared with those in the last 10 years (Supplementary Material 4, http://links.lww.com/EJA/A72) for isolated CABG (Table 3a),[19–24] and surgical treatment of acute aortic dissection (Table 3b).[25–30] Data for patients with aortic dissection were chosen among patients in the non-iCABG as the indication for surgical treatment of aortic dissection is well defined and known to constitute high risk of complications. In the present study, the highest in-hospital mortality rate and incidence of TEEs was observed in patients with aortic dissection.

Regarding renal events, no consensus on the most appropriate definition of cardiac surgery-associated renal injury exists in the literature; over 35 criteria have been described to diagnose and manage renal injury. The criteria and incidence of renal events, therefore, markedly varies between studies, thus hindering comparisons. Following aprotinin exposure, there are major inconsistencies in the literature regarding the risk of renal impairment. Two observational studies suggested aprotinin may be nephrotoxic.[4,6] The first showed a highly significant detrimental effect of aprotinin on renal injury and failure,[4] and according to the second, there was a significant difference in the proportional rise in plasma creatinine between patients treated with aprotinin and those given epsilon-aminocaproic acid or no treatment.[6] Nevertheless, using the same data from the first study,[4] aprotinin was not mentioned as a risk factor for renal injury.[31] Moreover, in the study, which led to the precautionary suspension of aprotinin (BART study),[7] no difference in renal injury or failure occurrence was observed between aprotinin and lysine analogues. In the present study, 1.9% of the patients initiated RRT after iCABG vs. 1.2 to 1.5% in the literature (Table 3). However, as haemofiltration techniques are being used increasingly for nonrenal problems (e.g. acidosis, hyperkalaemia and fluid overload) and our data showed that only a small portion of patients with new-RRT had AKI, caution should be exercised when using new-RRT to evaluate renal injury.

The percentage of iCABG and non-iCABG patients who needed re-exploration for bleeding within the 24 h after surgery was far below that reported in the literature (Table 3). As re-exploration rate can be considered a marker for the effectiveness of aprotinin in limiting postoperative bleeding complications, this result shows the benefit of aprotinin.

Regarding compliance with SmPC and risk minimisation measures, results showed that they were usually followed by the specialists. Almost all patients had a test dose of aprotinin before treatment and were monitored for anticoagulation. However, minimal values for clotting time were in accordance with the SmPC in 60.7% of patients.

This study has several limitations. Its most obvious disadvantage is that there was no comparator group. However, as previously indicated, comparisons with prior publications were done to confirm the absence of safety signals. Secondly, most patients (52.2%) have been included from UK centres, leading to overrepresentation of British patients and clinical practice, whereas it is well known that the incidence and the risk of adverse outcomes vary widely between countries, cardiac centres and surgeons.[32,33] The UK overrepresentation was probably attributable to the fact that, during the suspension period, aprotinin local distribution to UK cardiac surgery centres had been continued through a limited access programme from the Medicines and Healthcare Products Regulatory Agency. Thirdly, whereas according to the study design, virtually all patients exposed to aprotinin were to be included in the NAPaR, data from patients treated for non-iCABG procedures were excluded from the study for regulatory reasons in Austria and Germany. Moreover, some patients were not included in the study (excluded or refused to consent to data collection) and data collection was not exhaustive, although completion rate was high.

This study had also strengths. Indeed, this registry represents recent real-world experience within a large-scale population over a 56-month period and includes more high-risk aprotinin-treated patients than those reported in the publications that questioned its safety.[4–7]

Conclusion

Using this large prospectively collected database, no signal of increased mortality, TEEs or renal injury was detected in patients exposed to aprotinin therapy for iCABG or other cardiac surgeries, including complex surgeries with high risk of death or blood loss.

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Presentation: the study protocol is available at: www.ENCePP.eu, EU PAS Register number: EUPAS11384.

Individual and tabulated data will be available on request from Nordic Group B.V. (info-nl@nordicpharma.com).

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