Direct oral anticoagulants (DOACs) and cholesterol crystal embolisms

Introduction

The direct oral anticoagulants (DOACs) dabigatran Pradaxa®, rivaroxaban Xarelto®, apixaban Eliquis® and edoxaban Lixiana®, are indicated for *the treatment of venous thrombo-embolisms and prophylaxis of venous and arterial thrombo-embolisms.* Dabigatran directly inhibits thrombin. Apixaban, edoxaban and rivaroxaban inhibits the coagulation factor Xa. Dabigatran and rivaroxaban were granted marketing authorization in the Netherlands in 2008, apixaban in 2011 and edoxaban in 2015 [1-4].

Cholesterol crystal embolization (also referred to as cholesterol embolization syndrome, atheromatous embolization or atheroembolism), refers to cholesterol crystals originating from an atheromatous core of an atherosclerotic plaque in a large artery, embolizing to a distant medium or small artery, leading to mechanical obstruction and inflammation resulting in end organ damage. Usually several small emboli (microemboli) are released over time. The possible end organ damage includes renal failure, skin manifestations like the blue toe syndrome or small cerebral infarctions. The inflammatory response may lead to fever and hypereosiniophilia. The diagnostic hallmark is a biopsy showing intravascular cholesterol crystals. Cholesterol crystal embolization may occur spontaneously or after arterial or other surgical interventions. Thrombolytic and anticoagulant treatment is also associated with cholesterol crystal embolization, but it is still uncertain whether this is an independent risk factor [5,6].

Reports

DOACs
From 18 February 2013 to 27 June 2017 the Netherlands Pharmacovigilance Centre Lareb received two reports of cholesterol crystal embolism associated with the use of a DOAC.

Report 150073
This non-serious spontaneous report from a specialist doctor concerns a male aged 71 years and older, with cholesterol crystal emboli following administration of rivaroxaban for atrial fibrillation with a latency of five weeks after start. The patient is recovering. Concomitant medications were sitagliptine, glimepiride, amlodipine and atorvastatin.

Report 241583
This serious spontaneous report from a specialist doctor concerns a male aged 71 years and older, with aggravated renal failure and blue toe syndrome based on cholesterol crystal emboli (proven by skin biopsy), following administration of dabigatran and edoxaban (the patient started dabigatran, but this was switched to edoxaban) for atrial fibrillation, with a latency of about a week for dabigatran and two days for edoxaban after start. The drug dabigatran had already been withdrawn, edoxaban was also withdrawn. The patient has not recovered. Concomitant medications were pantoprazole, ezetimibe, metoprolol, losartan and rosuvastatin.

Other antithrombotic drugs

From 15 November 2004 to 27 June 2017 the Netherlands Pharmacovigilance Centre Lareb received two reports of the Lower Level Term (LLT) cholesterol crystal embolism associated with the use of other antithrombotic drugs excluding the DOACs.

One of the reports (case 47050) was based on a scientific manuscript [7], concerned tenecteplase used for the indication acute myocardial infarction, where the cholesterol embolization syndrome occurred with no reported latency.
The other report (case 209467) concerned atleplase used for the indication cerebral infarction, where the reaction cholesterol crystal embolisms occurred eleven days after start.

Other sources of information

SmPC
The Dutch SmPC of dabigatran, rivaroxaban, apixaban and edoxaban, don't report cholesterol crystal embolisms as adverse reactions [1-4].

Concerning other antithrombotic drugs, cholesterol crystal embolism is reported as an adverse drug reaction with unknown frequency of occurrence in the SmPC of alteplase [8].

Literature

Pubmed describes one case of a male 71 years and older, whose medical history included hypertension and hyperlipidemia, who developed acute renal failure six weeks after start of dabigatran for atrial fibrillation. Peripheral eosinophils were elevated (value of 10, with a reference of 0-6%). Renal biopsy showed cholesterol emboli [9].

Cholesterol crystal embolisms have been described for several other antithrombotic drugs including heparin, low molecular weight heparin, warfarin, and thrombolytic therapy [10-13]. The embolization syndrome may occur four to eight weeks after anticoagulation therapy in patients with an underlying atheromatous disease [14].
The role of anticoagulants as an independent risk factor for cholesterol crystal embolisms is not conclusive though [15-17]. An article by Tunick *et al* retrospectively describes the outcome of 519 patients with severe aortic plaque on transesophageal echocardiography, treated with statins, warfarin or antiplatelet medication. In this study the atheroemboli syndrome occurred in five patients, where only two patients were taking warfarin [18]. Furthermore, in a review from 221 cases with histologically proven cholesterol crystal embolization from the literature, published in 1987 the possible predisposing factor of the use of anticoagulants was reported in thirty patients [19].

Databases

In the Eudravigilance database, Lareb can search on Preferred Term (PT) level, but not LLT level. The LLT term “cholesterol crystal embolism”, is displayed under the PT “fat embolism”. Therefore, in table 1 and 2 the numbers of reports concerning the PT “fat embolism” are reported.

Table 1. Reports of the PT “fat embolism” associated with the DOACs, in the Lareb [20], WHO [21] and Eudravigilance database [22]*.

Database	MedDRA PT	Drug	Number of reports**	ROR (95% CI) ***
Lareb	Fat embolism	Dabigatran	1	
		Rivaroxaban	1	
		Edoxaban	1	
WHO	Fat embolism	Dabigatran	3	3.7 (1.2-11.6)
		Rivaroxaban	4	3.03 (1.1-8.1)
		Apixaban	4	9.9 (3.7-26.6)
		Argobatran	1	
Eudravigilance	Fat embolism	Dabigatran	4	1.5 (0.6-4.1)
		Rivaroxaban	5	1.6 (0.6-3.8)
		Apixaban	5	5.8 (2.4-14.0)
		Edoxaban	1	

* Due to differences in procedure like speed of processing, the numbers in the different databases may vary
** a single report can contain one or more suspect drugs
*** a reliable ROR can only be calculated in three or more reports

Table 2. Reports of the PT “fat embolism” associated with all antithrombotic drugs (ATC B01A) excluding the DOACs in the WHO database [21].

Database	MedDRA PT	Drug	Number of reports**

Database	MedDRA PT	Drug	Number of reports**
WHO	Fat embolism	Heparin	18
		Warfarin	23
		Enoxoparin	11
		Clopidogrel	12
		Alteplase	6
		Acetylsalicyic acid	14
		Fluindione	4
		Ozagrel	2
		Tenecteplase	2
		Phenprocoumon	2
		Parnaparin	1
		Reteplase	1
		Eptifibatide	1
		Prasugrel	1
		Acenocoumarol	1
		Ticlopidine	1
		Total	**100**

** a single report can contain one or more suspect drugs

Eudravigilance

The Eudravigilance database contains a total of 214 reports of the PT “fat embolism” in all drugs [22]. When excluding the Lareb cases, the Eudravigilance database contains thirteen cases of the PT “fat embolism” associated with a DOAC. In one case there is great uncertainty regarding the diagnosis, and in four cases the reaction occurred right after a vascular intervention or hip surgery or the patient had hip fracture as concurrent condition. When excluding these five reports, eight reports remain.
In the eight remaining reports, the patients concerned six men and two women. Ages varied between seventy up to and including 81 years (mean and median 78 years), where in one report only the age in his seventies was reported. Suspect drugs were dabigatran in two reports, rivaroxaban in two reports and apixaban in four reports. In one report amlodipine and hydrochlorothiazide were also reported as suspect drugs. In the other seven reports the DOAC was the single suspect drug. Latencies were reported in five cases, varying from one month to eight months after start of the DOAC. In three reports the presence of eosinophilia was reported. One report described that cholesterol crystals were observed in a skin biopsy specimen, and three other reports in a kidney biopsy specimen.

Prescription data

The number of patients using DOACs and in the Netherlands is shown in table 3 [23].

Table 3. Number of patients using DOACs in the Netherlands between 2011 and 2015 [23].

Drug	2011	2012	2013	2014	2015
Dabigatran	2,066	4,678	13,055	18,896	27,305
Rivaroxaban	7,035	9,850	12,720	20,618	34,938
Apixaban	.	3	730	4,765	15,632
Edoxaban	.	.	.	.	54

Mechanism

A postulated mechanism how anticoagulants may induce cholesterol embolims, is by inducing haemorrhage in the atheromatous plaque, or by dissolution of a fibrous cap around the atheromatous core, resulting in the release of cholesterol in the systemic circulation [13].

Discussion and conclusion

The Netherlands Pharmacovigilance Centre Lareb received two cases of a DOAC associated with cholesterol embolism, in which in one case the diagnosis was confirmed through skin biopsy. Of course a coincidental effect of starting a DOAC and spontaneous cholesterol embolzation can't be ruled out, but the time relationship of one week and five weeks after start of the DOAC, may indicate a possible causal relationship. Other possible causes like arterial or other surgical interventions, were not described in the reports.

The cases by Lareb were supported by another eight strong Eudravigilance cases, where in four cases the diagnosis was proven by skin or kidney biopsy. Furthermore, one case of dabigatran associated cholesterol embolization with a latency of six weeks after start (diagnosis proved with renal biopsy) was described in the literature [9].

In the literature, the causal relationship between antithrombotic therapy other than the DOACs, and cholesterol embolization, is still a matter of debate. There are twelve cases in the WHO database concerning DOACs associated with the PT fat embolism. Concerning all other antithrombotic drugs, the total number is a hundred cases. The number of reports do not reflect incidence of a reaction but reporting behavior, and the relatively large number of reports for the DOACs may indicate special attention for this new class of drugs.

Based on the reports received by Lareb and the other cases in Eudravigilance, supported by one case in the literature, with a plausible time relationship and possible mechanism, it is suggested that the DOACs might cause cholesterol crystal embolization in patients with pre-existing atherosclerotic plaques.

References

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Addendum (Confidential information for the regulatory authorities CBG and EMA)

Eudravigilance cases

On 20 June 2017 the Eudravigilance database contained fourteen reports of a direct oral anticoagulant (DOAC) in association with cholesterol crystal embololisms of fat embolisms.

In one case there is great uncertainty of the diagnosis (case VE-BAYER-2015-020564), in three cases the reaction occurred right after a vascular intervention or hip surgery (case JP-EMA-20150220-pdevhumanwt-160242078, case BE-BAYER-2015-262399 and case PH-BRISTOL-MYERS SQUIBB COMPANY-BMS-2015-071686), and in one case the patient had hip fracture as concomitant disease (case CA-Boehringer Ingelheim GmbH, Germany-2009-CN-00811CN).

In a limited number of cases latency was reported or could be calculated from start date of the suspect drug and reaction. These cases were:
JP-BRISTOL-MYERS SQUIBB COMPANY-21180088 (latency about a month)
FR-AFSSAPS-TS20170264 (latency about 8 months)
US-JNJFOC-20130800681 (latency about five and a half weeks after start and one week after withdrawal)
FR-AFSSAPS-ST20130782 (latency about 7 months)
JP-BAYER-2015-013415 (latency about two and a half months)

In one case (FR-AFSSAPS-TS20170264) olmesartan and hydrochoorthiazide and were also reported as suspect drugs.

This addendum consists of the summaries of all the reports:

JP-BRISTOL-MYERS SQUIBB COMPANY-21180088
A physician reported that a male patient 71 years and older experienced cholesterol embolisation while on therapy with apixaban for thromboembolism prophylaxis. The patient had received dabigatran etexilate prior to apixaban. During the dabigatran therapy, function kidney decreased developed, for which the patient was admitted to hospital and followed up. After dabigatran etexilate was discontinued, laboratory test data improved. In middle May-2014, the patient started receiving oral apixaban 2.5 mg twice daily as an inpatient. In Jun-2014, cholesterol embolisation developed with eosinophil count increased and creatinine increased. The patient's creatinine clearance was 16 to 17 and serum creatinine was 1.9. At the time of this report, the event did not resolve. Therapy with apixaban was ongoing. There was no action taken with apixaban therapy in response to the event. The patient's pre-existing disease included non-valvular atrial fibrillation.

JP-BRISTOL-MYERS SQUIBB COMPANY-BMS-2016-075467
This case was derived from the scientific literature
Commend Lareb: This case was not available through Pubmed
Kawabata M, et al. A case of cholesterol embolization with abdominal pain and renal impairment. The 209th Tohoku Regional Meeting of the Japanese Society of Internal Medicine;2016:36.
A physician reported that an Asian male patient in his 70's (8 decades) was hospitalized due to cholesterol embolization while on therapy with apixaban for prophylaxis stroke. The event renal impairment was subsumed under cholesterol embolization. The patient was admitted to a previous hospital with cerebral infarction about 4 months ago. An intermittent abdominal pain of the infra-umbilical site was noted one month before the hospitalization. The patient had an abdominal aortic aneurysm on the bilateral renal arteries was suggested by tests. He also visited the previous hospital one day before the hospitalization and was presented with acute worsening of renal impairment with serum creatinine values from 1.3 mg/dL to 5.1 mg/dL. On an unspecified date, the apixaban was started. At the time of visit, the patient had blue toe and eosinophil's increased. He was then hospitalized for further investigations and treatment. His skin biopsy revealed presentations of arterioles embolism and needle-shaped cholesterol cleft. He was diagnosed with cholesterol embolization. In response to the event, he was treated with oral statin and oral prednisolone. The patient's renal impairment was improving gradually. Outcome of the event cholesterol embolization was unknown.

FR-AFSSAPS-NC20161288
A female patient 71 years and older was hospitalized for hyponatraemia and renal impairment (creatinine more than 600 umol/L) after starting apixaban for atrial fibrillation. There was fluctuating hypereosinophilia and mild proteinuria. Renal biopsy showed cholesterol embolisms.
Medical history indicated ischemic stroke, dyslipidaemia, arrhythmia, arterial hypertension, ex-smoker.
Event onset 04-09-2016
Start date of apixaban not reported.

FR-AFSSAPS-TS20170264
A male patient 71 years and older, had renal failure aggravated and cholesterol embolization. Suspect medication were apixaban for auricular fibrillation, amlodipine with unknown indication and hydrochoorthiazide / olmesartan for arterial hypertension. Concommitant medications were sotalol and rosuvastatine.
Medical history included cholesterol embolization and ischaemic heart disease.
Start date apixaban: 11-05-2016 Stop date apixaban: 15-03-2017
In January 2017 the patient was hospitalized because of toe necrosis.

CA-Boehringer Ingelheim GmbH, Germany-2009-CN-00811CN
Commend from Lareb: Reaction with a broken hip as concomitant disease
Commends of Lareb: Concommitant disease included a broken hip
a male patient of unknown age, was on dabigatran for the treatment of an indication that was not reported. The patient developed fat emboli. The outcome of the event was fatal. An autopsy was performed and the cause of death was fat emboli. Concomitant medications were not reported. Concomitant disease included broken hip.

US-Boehringer Ingelheim GmbH, Germany-2012-BP-06518BP
A male patient, was on dabigatran for the treatment of non-valvular atrial fibrillation. The patient experienced Cholesterol Embolization Syndrome. The status of Pradaxa capsule therapy was not reported. The outcome of the event was not reported. Concomitant medications and diseases were not reported.

NL-LRB-150073
Lareb report

US-JNJFOC-20130800681
71 years and older male patient who's medical history and concurrent conditions included atrial fibrillation, coronary artery disease status post coronary artery bypass graft, colon cancer, gout, hyperlipidemia, hypertension, peripheral vascular disease and type 2 diabetes mellitus. The patient was a non-smoker and abstained from consuming alcohol. The patient had previously experienced drug allergy while taking intravenous contrast. The patient was treated with rivaroxaban, initiated on 08-FEB-2013 for stroke prevention in atrial fibrillation. Concomitant medications were not reported. The patient had a CHADS (congestive heart failure, hypertension, age, diabetes, prior stroke) score of 2. Treatment with rivaroxaban was stopped on 12-MAR-2013. It was reported that on an unspecified date, the patient was presented to the emergency department with complaints of acute left lower extremity pain. It was reported that the patient's left foot was painful, cool to touch and purple. The patient was also evaluated by vascular surgery and deemed to have atheroembolism related to the initiation of anticoagulation on 19-MAR-2013. Action taken with rivaroxaban was not applicable. The patient had recovered from the event atheroembolism on an unspecified date.

FR-AFSSAPS-ST20130782
a 71 years and older female, had cholesterol crystal emboli and acute kidney failure, with as suspect drug dabigatran. There was hypereosinophiala (458 / mm3). Renal biopsy showed cholesterol crystal emboli. Other causes in the differential diagnosis included findings at angiography and a thoracic aneurysm. Concommitant drugs were lercanidipine, ramipril, bisoprolol, pantoprazol, prazepam.
Medical history included hypertension arterial, arrhythmia atrial Aneurysm Sleep apnea syndrome
Reported event onset:18-04-2013. On 10-04 creatinin clearance 22 and hypereosiphilia.
Therapy dates of dabigatran: 09-2012 to 11-04-2013

JP-EMA-20150220-pdevhumanwt-160242078

Commend from Lareb: Reaction occurred after vascular intervention

This case was derived from the literature. This case concerns a literature report from The Japanese journal of vascular surgery, 2014; page 629, Vol:23 (2), entitled: "A case which developed cholesterol embolization after coronary angiography and abdominalaorta replacement", based on information received by Pfizer from MitsubishiTanabe (Manufacturer control number: MTPC2014-0001319), license party for argatroban.

This literature case report refers to a 61-70 years old female patient who had a history of undergoing cholecystectomy at the age of 29 and hysterectomy at the age of 40, and was being followed by an outpatient basis for abdominal aorticaneurysm at the reporter's hospital. However, the patient was hospitalized for operation since aneurysm enlarged to over 50mm. Seg6 75% was noted by the coronary angiography (brachial artery approach) performed four days before the operation, but it was subclinical; therefore operation of the abdominal aortic aneurysm was determined to be preceded. The operation was performed approaching by abdominal median incision. As the patient had a history of laparotomy, division of adhesions was slightly difficult. Systemic heparinization was conducted after the peripheral side was detached by taping the central part of the abdominal aorta. After blocking the peripheral side of both arteria iliaca communis, the abdominal aorta was blocked just below the renal artery. Considerable amount of atheroma was observed to the blocked area and inside the abdominal aortic aneurysm. The lumbar artery and the inferior mesenteric artery were occluded. Formation of the stump of the central side was performed by using internal and external felt strips and aorta replacement was performed by using Gelsoft 16 x 8mm. The operation required 3 hours and 3 minutes. No problem was noted when awakening from the anesthesia after the operation and palpating the peripheral artery was favorable; thus the patient was admitted to the ICU. On POD 1, numbness, pain and cyanosis of the lower limb (the area from the dorsal artery of foot and below) occurred. These symptoms were considered as the embolism due to mural thrombus of the blocked area and anticoagulation therapy by ARGATROBAN and administration of PROSTAGLANDIN were started; however, the condition of the lower limb gradually worsened. Also, serum creatinine value before the operation was 0.85mg/dL, but it aggravated to 2.84 on POD 2. Five signs indicating cholesterol embolization (pain of lower extremities, livedo reticularis, availability of palpating the peripheral artery, progressive renal failure, history of intravascular operation) was noted as of POD 7, and although the definite diagnosis of skin biopsy was not made, it was diagnosed as cholesterol embolization and the anticoagulation therapy was discontinued. Improvement of the symptom of the lower limb was not observed thereafter and toe amputation of right side dorsal artery of foot and below was performed on POD 71. Cholesterin crystal was observed to the amputated specimen by the histopathologic examination. Renal failure improved afterwards. As of POD 96, although the general condition was favorable, the patient was still under hospitalization since the healing of the wound of the amputated site of the lower limb was delaying. As of 07May2014, it was unknown whether ARGATROBAN was manufactured by MTPC or other company.

VE-BAYER-2015-020564

Commend from Lareb: Diagnosis not evident

This spontaneous case report was received from a physician on 09-FEB-2015 which refers to a 41-50 years old female patient who received XARELTO (rivaroxaban). PULMONARY EMBOLISM was reported. The patient's medical history included surgery in the hip. On 13-NOV-2014 the patient started XARELTO (rivaroxaban) oral for three weeks (no specify the indication). Product lot number and expiration date were not provided. XARELTO was discontinued on 27-DEC-2014. On the third week, the patient died due to PULMONARY EMBOLISM. He mentioned that it was not sure that the patient had a PULMONARY EMBOLISM, but a FAT EMBOLISM SYNDROME. The necropsy had been requested, but he did not have the information at the time of report.

BE-BAYER-2015-262399

Commend from Lareb: Reaction occurred after a vascular intervention

This spontaneous case report was received from a physician in BELGIUM on 21-MAY-2015 referring to a female patient of unspecified age who received XARELTO (rivaroxaban) and COVERSYL (perindopril). Patient experienced DECREASED RENAL FUNCTION. The patient's medical history included renal function of 68, drug history included marcoumar (fenprocoumon) and concomitant medications included flecainide acetate. On an unspecified date the patient started XARELTO at 20 mg, at unspecified frequency for stroke prevention in atrial fibrillation with DVT problems. The patient received co-suspect medication. On an unspecified date the patient started COVERSYL at an unspecified dose and frequency. It was reported that in a short of period after starting XARELTO, patient had renal function decreased to 28 (DECREASED RENAL FUNCTION). Treatment and

outcome details were not provided. XARELTO and COVERSYL treatment were stopped on an unspecified date. It was reported that patient consulted nephrologist (and according to nephrologist, decreased renal function is not related to Xarelto, but perhaps to Coversyl). At the time of report renal function was improved "with approx. +20%". The reported reactions included CONTRAST NEPHROPATHY/CHOLESTEROL EMBOLIZATION AFTER VASCULAR INTERVENTION (the event split for coding purpose into RADIOCONTRAST NEPHROPATHY (serious due to medical significance, unlisted) and CHOLESTEROL EMBOLIZATION (serious due to medical significance, unlisted) was reported in the subsequent follow-up.
The medical history included partial thrombectomy semi-elective (at a. tibialis post. and ant.) followed by thrombolysis for remaining clots at a.orsalis pedis and arcus plantaris

JP-BAYER-2015-013415
This spontaneous case report was received from a internalmedicine/internist on 28-JAN-2015 and refers to a 61-70 years old male patient who received XARELTO (rivaroxaban). On 04-JUL-2014, patient started XARELTO 10 mg once daily, orally for stroke prevention in atrial fibrillation. On 20-SEP-2014, renal failure aggravated with Cr of 2.25 was observed. He was admitted to hospital. Nephritis interstitial and RPGN (glomerulonephritis rapidly progressive) were suspected. On 25-SEP-2014 XARELTO was withdrawn. On 29-SEP-2014, Creatinine of 3.84 was observed. Administration of Prednisolone at 50 mg was started. On 30-SEP-2014, biopsy kidney was performed. CHOLESTEROL EMBOLISM was diagnosed. The event had resulted in Disability. Patient had not recovered from the events at the time of report. Concomitant drug included Nexium, Esomeprazole magnesium hydrate, Thyradin S, Cefzon. adalat Cr, Alositol, Calonal and the tretment included antibiotics, Other Analgesics And Antipyretics, prednisolone. Bayaspirin, melavon, prednisolone. Medical history included atrial fibrillation, chronic kidney disease, paroxysmal atrial fibrillation, sedative therapy, smoker, alcohol use.
Medical history included hypertension and peripheral vascular disease.

PH-BRISTOL-MYERS SQUIBB COMPANY-BMS-2015-071686
Commend from Lareb: Reaction occurred six hours after hip replacement
A physician reported that a 71 years and older male patient, who had pulmonary embolism, received apixaban 10 mg twice a day starting 6 hours after hip replacement surgery and then died due to fat embolism. The patient passed away quietly in his hospital bed.
BMS medical evaluation comment:
This patient, who was started on apixaban therapy six hours after hip replacement surgery, was reported to have died due to fat embolism. Fat embolism was likely a post surgical complication of hip replacement surgery; hence, considered not related to apixaban therapy.

This signal has been raised on August 28, 2017. It is possible that in the meantime other information became available. For the latest information, including the official SmPC's, please refer to website of the MEB www.cbg-meb.nl