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CLINICAL RESEARCH

Major ischaemic and bleeding risks following current drug-eluting stent implantation: Are there differences across current drug-eluting stent types in real life?

Risques ischémiques et hémorragiques après pose de stents coronaires : y a t-il des différences en vie réelle entre les types de stents actifs ?

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Abbreviations: c-DES, Current drug-eluting stent; CI, Confidence interval; DAPT, Dual antiplatelet therapy; DES, Drug-eluting stent; HR, Hazard ratio; ICD-10, International Statistical Classification of Diseases and Related Health Problems, Tenth Revision; PCI, Percutaneous coronary intervention; RCT, Randomized clinical trial; SNDS, *Système National des Données de Santé* (French National Health Insurance Claims database).

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KEYWORDS
Drug-eluting stents;
Ischaemic risks;
Major bleeding risks;
Real life;
French National Health Insurance Claims database

Summary
Background. — Current drug-eluting stents (c-DESs) reduce the occurrence of ischaemic events, but expose recipients to stent thrombosis and bleeding secondary to preventive antiplatelet therapy. To date, comparative data on the relative effectiveness and safety of the various c-DESs in real life are limited.
Aim. — To compare ischaemic and bleeding risks across the major c-DESs used in France.
Methods. — French national health insurance reimbursement and hospitalization databases were used. Patients implanted with a c-DES in 2014 were followed for 1 year. The risks of ischaemic events (revascularization, myocardial infarction and/or stroke), major bleeding events and death were compared across six c-DESs (XIENCE®, PROMUS®, RESOLUTE®, BIOMATRIX®, NOBORI® and ORSIRO®), using multilevel Cox models adjusted for baseline individual and hospital characteristics.
Results. — A total of 52,891 subjects were included: 34.4% with XIENCE®; 27.6% with PROMUS®; 24.0% with RESOLUTE®; 8.0% with BIOMATRIX®; 5.0% with NOBORI®; and 1.0% with ORSIRO®. Among them, 9378 had at least one event (ischaemic, 6064; major bleeding, 1968; death, 2411), resulting in an overall incidence rate of 19 per 100 person-years. In the multivariable analysis, the risk of ischaemic events, major bleeding events or death did not differ between the c-DESs overall (adjusted hazard ratios between 0.85 [95% confidence interval 0.68—1.07] and 1.04 [95% confidence interval 0.98—1.10] compared with XIENCE® used as the reference) and when each outcome was considered separately.
Conclusions. — In real life, major ischaemic and bleeding risks do not differ across the various c-DESs over the first year following implantation. Future studies are needed to assess comparative c-DES effectiveness and safety longer term.

MOTS CLÉS
Stents actifs ;
Risques ischémiques ;
Risques hémorragiques majeurs ;
Pratique clinique ;
Système national des données de santé (SNDS)

Résumé
Contexte. — Les stents actifs (DES) diminuent la survenue d'évènements ischémiques, mais peuvent entraîner des thromboses et des hémorragies secondaires au traitement antiagrégant plaquettaire. Les données d'efficacité et de sécurité comparant les DES en vie réelle sont limitées.
Objectif. — Cette étude avait pour objectif de comparer les risques ischémiques et hémorragiques entre les DES couramment utilisés dans la pratique française.
Méthodes. — Les données utilisées sont issues du Système national des données de santé. Les patients implantés de DES en 2014 ont été suivis pendant un an. Les risques d'évènements ischémiques (regroupant nouvelle revascularisation, infarctus du myocarde et/ou accident vasculaire cérébral), d'évènements hémorragiques majeurs et de décès ont été comparés entre XIENCE®, PROMUS®, RESOLUTE®, BIOMATRIX®, NOBORI® et ORSIRO®, à l'aide d'un modèle de Cox multiniveaux ajusté sur les caractéristiques des patients et des centres implanteurs à l'inclusion.
Résultats. — Au total, 52 891 patients étaient inclus : 34,4 % recevaient XIENCE® ; 27,6 % PROMUS® ; 24,0 % RESOLUTE® ; 8,0 % BIOMATRIX® ; 5,0 % NOBORI® ; et 1,0 % ORSIRO®. Parmi eux, 9378 présentaient au moins un évènement (ischémique, 6064 ; hémorragique, 1968 ; décès, 2411), avec une incidence de 19 pour 100 personnes-années. En analyse multivariée, le risque global ne différait entre les DES (HRs ajusté entre 0,85 [IC 95 % 0,68—1,07] et 1,04 [IC 95 % 0,98—1,10] comparé à XIENCE®) et également pour chaque évènement considéré séparément.
Conclusions. — En vie réelle, les risques ischémiques et hémorragiques ne diffèrent pas entre les DES jusqu'à un an après l'implantation. D'autres études en pratique clinique sont nécessaires pour comparer l'efficacité et la sécurité à long terme entre les DES.

Background

Percutaneous coronary intervention (PCI) with stenting is the standard approach for the treatment of most cases of coronary artery stenosis.

Implantation of drug-eluting stents (DESs) gives overall excellent results and reduces the occurrence of ischaemic events, but the first generation exposed recipients to early stent failure as a result of stent thrombosis related to delayed strut endothelialization, leading to myocardial infarction with a high death rate. Moreover, dual antiplatelet therapy (DAPT), administered to prevent stent thrombosis, causes bleeding complications in high-risk patients or in case of prolonged use.

Current drug-eluting stents (c-DESs) are preferred over first-generation DESs because of the reduction in acute stent thrombosis, enabling a reduction in DAPT duration; this allows c-DESs to be used in patients with a high bleeding risk, with a shorter DAPT duration pattern, similar to what is proposed for bare-metal stents [1—4].

A large variety of c-DESs are available, with various designs, which can differ in terms of the metal mesh thickness (stainless steel or thinner struts with chromium-cobalt or similar alloys), the antiproliferative drug analogue of sirolimus (everolimus, zotarolimus, biolimus) and the polymer coating (durable or bioresorbable). Although these structural differences may result in different clinical risks, especially ischaemic, across the various types of commercially available c-DESs, data available to date have not allowed such differences to be assessed properly. Indeed, data from randomized clinical trials (RCTs) are limited, and patients included in these RCTs are often not representative of the population treated in clinical practice [5—12]. Moreover, meta-analyses are based mostly on indirect network comparisons, which include the few RCTs comparing c-DESs with each other and several RCTs assessing first-generation DESs [6,8,9,13—17]. Finally, the few observational studies providing comparative data across various types of c-DESs are limited to selected settings and/or groups of patients [18—23].

In order to compare real-life ischaemic and bleeding risks across the various types of c-DESs used in France in 2014, we conducted an observational unselected cohort study based on national French health insurance and hospitalization databases.

Methods

Data sources

We used the French National Health Insurance Claims database (SNDS, *Système national des données de santé*). Only claims reimbursed from the general health insurance plan (which covers private and public employees and the unemployed, accounting for 77% of the population) were considered, because of their availability and quality.

The reimbursement data have been recorded prospectively since 2008 for every reimbursed healthcare expenditure, and include individual information on sociodemographic characteristics (sex, age, supplementary insurance coverage providing free access to healthcare for French people whose annual income is < 50% of the poverty threshold); reimbursed drugs with date of delivery; laboratory prescriptions; and medical information. Medical information was based on a list of disabling long-term diseases giving entitlement to full insurance coverage, with the diagnosis coded according to the International Statistical Classification of Diseases and Related Health Problems, Tenth Revision (ICD-10). Date of disease onset and, if appropriate, date of death were available, but no information was available about the cause of death.

Reimbursement data were linked to the national hospital discharge database by an anonymous and unique identification number. The hospital database provides information on all hospital stays in short-stay wards or emergency or intensive care units in public hospitals or private clinics since 2006, including information on discharge diagnoses (coded according to ICD-10), inpatient treatments, medical or surgical procedures and expensive medical devices, such as coronary stents, implanted during hospital stay. A unique identification number enables identification of the successive admission of each individual patient in various hospitals.

The SNDS database has been described extensively and used for epidemiological research previously [24—26]. The quality of data has been demonstrated, particularly in the field of cardiovascular diseases [27—30]. No informed consent is required for studies based on French medicoadministrative databases because of the anonymous nature of the data, by agreement of the French Data Protection Supervisory Authority (*Commission nationale de l'informatique et des libertés*).

Inclusion and exclusion criteria

All patients aged ≥18 years with at least one hospitalization for PCI with c-DES implantation between 01 January and 31 December 2014 were eligible for inclusion. Stents considered as c-DESs were all DESs implanted, with the exception of DESs no longer marketed in 2016, bare-metal stents and polytetrafluoroethylene-covered stents used for coronary rupture.

Patients with more than one type of c-DES implanted during the same procedure or with a hybrid procedure combining PCI and coronary artery bypass graft within 15 days before or after stenting were excluded.

Exposure and follow-up

Six c-DESs were considered: durable-polymer everolimus-eluting Cr-Co stent XIENCE® (Abbott, Abbott Park, IL, USA); durable-polymer everolimus-eluting Pt-Cr stent PROMUS® (Boston Scientific, Marlborough, MA, USA); durable-polymer zotarolimus-eluting Cr-Co stent RESOLUTE® (Medtronic Inc., Minneapolis, MN, USA); biodegradable-polymer biolimus-eluting Fe-Co stents BIOMATRIX® (Biosensors Inc., Latham, NY, USA) and NOBORI® (Terumo Medical Corporation, Somerest, NJ, USA); and biodegradable-polymer sirolimus-eluting Cr-Co stent ORSIRO® (Biotronik Inc., Lake Oswego, OR, USA).

Patients were included on the day of their first hospital admission for PCI with c-DES implantation in 201, and were followed up for 1 year after c-DES implantation (or until

death or transfer to a non-general health insurance plan if this occurred during the year following c-DES implantation).

Outcomes

The outcomes of interest included ischaemic events, major bleeding events and all-cause deaths occurring after stent implantation. Each outcome was measured separately and included in a composite outcome combining ischaemic events, major bleeding events and/or death.

Ischaemic events were defined by the occurrence of: a new hospitalization of > 24 hours' duration with a discharge diagnosis of myocardial infarction, cardiogenic shock, cardiac arrest or stroke; or a new hospitalization for non-scheduled revascularization.

Non-scheduled PCI revascularizations were not recorded specifically in the coding system, and were considered as probable if they occurred > 45 days after stent implantation or were associated with at least one of the following criteria: hospital admission through emergency or intensive care unit; in-hospital death, cardiogenic shock or cardiac arrest; and first hospital discharge diagnosis of myocardial infarction or heart failure (codes listed in Table A.1).

Major bleeding events were defined by the occurrence of a new hospitalization with a discharge diagnosis of bleeding or a blood transfusion procedure.

Covariates

Covariates considered in the study included characteristics of the individual, of the PCI procedure and of the centre where the PCI was done, and duration of the hospital stay at inclusion.

Individual characteristics included sociodemographics (sex, age, affiliation to the supplementary insurance health coverage) and clinical presentation at baseline, defined on the basis of ICD-10 codes of the c-DES implantation hospital stay, and categorized as: stable angina (I201, I208, I209, I25)/unstable angina (I200, I24)/myocardial infarction (I21, I22, I23, I200 + 0)/cardiogenic shock and or cardiac arrest (R570, I46)/other.

Cardiovascular risk factors, co-morbidities and clinical score predicting the risk of bleeding (modified HAS-BLED score [31], categorized as low [score between 0 and 2] or high [score between 3 and 9]) at baseline, defined using ICD-10 codes of hospital discharge or long-term disabling disease diagnoses, and also specific procedures or medications within the 8 years before stent implantation were recorded.

Consumption of antiplatelet drugs, oral anticoagulants, systemic corticosteroids, non-steroidal anti-inflammatory drugs, antidepressants and proton pump inhibitors were defined at baseline by the existence of at least one reimbursement per 6-month period. These treatments were analysed according to patient participation during follow-up: for example, patients were considered exposed to DAPT after stent implantation if reimbursed for a combination of aspirin and a $P2Y_{12}$ inhibitor for at least two-thirds of the first 6 months following implantation (Table A.1).

Characteristics of the PCI procedure included the number of vessels treated and the number and diameter of implanted stents. The stent length, type of vessel (left main, left anterior descending, circumflex or right coronary artery), details of the procedure and lesion characteristics were not available.

The characteristics of the centre of implantation included hospital type (private or public) and volume of activity, defined as the number of PCIs performed during the study period.

Statistical analysis

Age and sex-standardized incidence rates were estimated to assess the risk of each outcome of interest, considered combined or separately, by type of c-DES.

Cox proportional-hazard frailty models were used to estimate crude and adjusted hazard ratios (HRs), comparing these risks across the various types of c-DES, considering the most commonly implanted stent (XIENCE®) as the reference.

Two levels of clustering (patients and centres) were considered in order to account for the non-independence between patients in the same implanting centre [32].

Multivariable models were adjusted for baseline characteristics of the individual (demographics, clinical presentation, cardiovascular risk factors, co-morbidities, prescribed medical regimen), of the PCI procedure and of the centre where the procedure was done, and duration of the hospital stay at inclusion.

In addition, the following subgroup analyses (restricted to the combined outcome of interest) were conducted:

- analysis restricted to patients at high risk of bleeding as assessed by a modified HAS-BLED score ≥ 3, treatment with an oral anticoagulant or active cancer at baseline;
- analysis restricted to patients with a non-acute clinical presentation at baseline (i.e. no myocardial infarction, cardiogenic shock or cardiac arrest);
- analysis stratified by the number of vessels treated (one or more than one), the diameter of the implanted c-DES (<3 or $\geq$3 mm), the presence of diabetes or use of DAPT (i.e. during the first 6 months after implantation).

Various sensitivity analyses, including additional adjustment for treatments reimbursed during follow-up, and alternative modelling methods based on Cox regression, with inverse probability of treatment weighting propensity score [33] or multilevel logistic regression were conducted to test the robustness of the findings.

Statistical analyses were performed with SAS software, version 9.3 (SAS Institute, Cary, NC, USA) and STATA software, version 14.1 (Stata Corp., College Station, YX, USA).

Results

Description of the study population

Between 01 January and 31 December 2014, among a total of 82,225 adult patients who underwent a PCI with stent implantation, 52,891 were implanted with a single c-DES type without associated coronary artery bypass graft, and were thus included: 18,190 (34.4%) were implanted with XIENCE®; 14,573 (27.6%) with PROMUS®; 12,727 (24.0%) with RESOLUTE®; 4216 (8.0%) with BIOMATRIX®; 2634 (5.0%) with NOBORI®; and 551 (1.0%) with ORSIRO® (Fig. 1). Patients

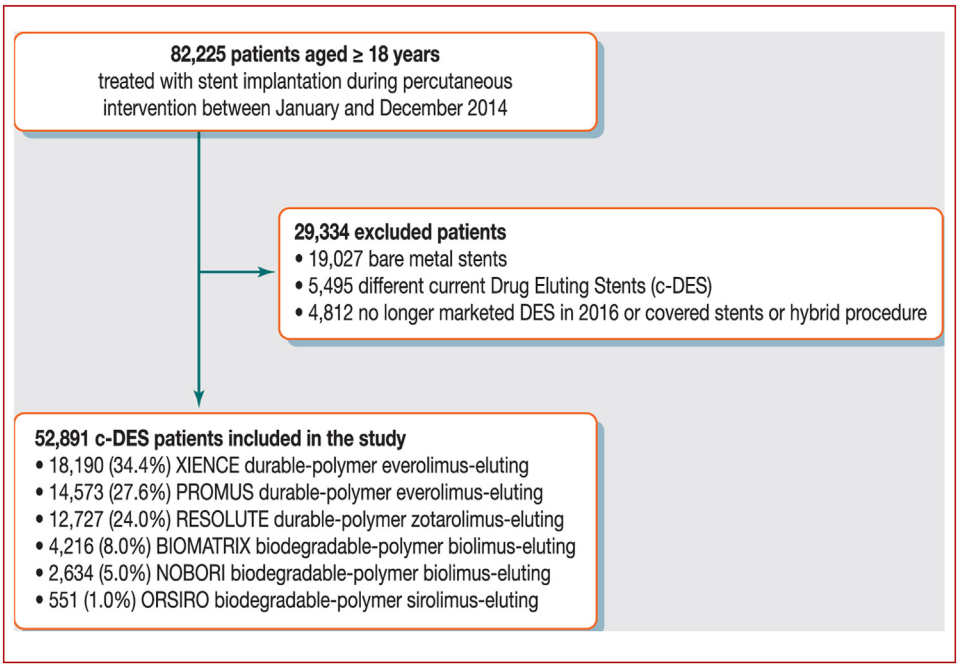

Figure 1. Flow chart of study population treated with coronary stents during 2014, taken from the French Insurance Database. c-DES: current drug-eluting stent; DES: drug-eluting stent; y: years.

were followed for a mean time of 353 days after c-DES implantation (365 days for 90% of the entire cohort).

Characteristics of the study population are shown in Tables 1—3. Mean age was 66.2 years (interquartile range 58—75 years), and 15% were aged > 80 years. Patients were mainly men (75%), with a majority treated for acute events, such as myocardial infarction or unstable angina (53.3%). At baseline, about 42% had a high bleeding risk, and 7% were already being treated with an oral anticoagulant.

Hypertension, dyslipidaemia disorders, diabetes, morbid obesity and smoking-related conditions concerned about 77%, 71%, 35.5%, 23% and 34% of patients, respectively. Half of the population had a history of coronary disease, heart failure was described in 18% and 10% had active cancer. After stent implantation, about 79% received antihypertensive drugs, 72% received beta-blockers and 87% received lipid-lowering drugs. DAPT was given as recommended in most patients (92% exposed during the first 6 months following c-DES implantation), regardless of c-DES type (Table A.3).

In most cases (81.5%), only one vessel was treated, and 55% received at least one stent of diameter < 3 mm. The centres of implantation were mainly public hospitals (59.3%) with a high volume of PCI activity (82.4% performed 600 procedures or more in 2014). The mean duration of the PCI procedure hospital stay was 4 days (interquartile range 2—5 days).

Individual characteristics, such as age, clinical presentation, history of heart failure, bleeding risk and oral anticoagulant therapy at baseline, hardly differed according to type of c-DES implanted. Notably, NOBORI® and ORSIRO® were more likely to be implanted in private centres than the other c-DESs (overall $P < 0.0001$), and PROMUS®, BIOMATRIX®, NOBORI® and ORSIRO® were more likely to be implanted in centres with a high volume of PCI activity (overall $P < 0.0001$).

Risks of ischaemic events, major bleeding events and all-cause deaths across the various types of c-DES

Overall, 9378 patients had at least one outcome of interest during follow-up (6064 had ischaemic events; 1968 had major bleeding events; 2411 died). The age and sex-standardized incidence rate of ischaemic, bleeding events and/or death was 19 per 100 patient-years overall, ranging from 15.4 for ORSIRO® to 21.4 for RESOLUTE® (Table 4).

The incidence rate of ischaemic events considered separately was 12 per 100 patient-years overall, ranging from 10.9 for ORSIRO® to 13.1 for RESOLUTE®. The incidence rate of bleeding events was 4 per 100 patient-years, ranging from 2.4 for ORSIRO® to 4.4 for RESOLUTE®. The incidence rate of death was 4 per 100 patient-years, ranging from 2.3 for ORSIRO® to 5.5 for RESOLUTE®.

In the multivariable analysis, the combined risk of ischaemic, bleeding events and/or death did not differ significantly across the various types of c-DES (compared with XIENCE®: PROMUS® adjusted HR 0.99, 95% confidence interval [CI] 0.93—1.05; RESOLUTE® adjusted HR 1.04, 95% CI 0.98—1.10; BIOMATRIX® adjusted HR 0.97, 95% CI 0.89—1.05; NOBORI® adjusted HR 0.92, 95% CI 0.83—1.03; ORSIRO® adjusted HR 0.85, 95% CI 0.68—1.07) (Table 4). Likewise, the combined risk of ischaemic events and/or death, the combined risk of ischaemic events and/or bleeding events and the risk of ischaemic events considered separately did not significantly differ across the various types of c-DES. Of note, compared with XIENCE®, the risk of bleeding and the risk of death were increased for RESOLUTE® (major bleeding events: adjusted HR 1.12, 95% CI 1.00—1.26; death: adjusted HR 1.13, 95% CI 1.01—1.26) and the risk of death was decreased for NOBORI® (adjusted HR 0.78, 95% CI 0.62—0.98).

Table 1 Individual characteristics of the study population (sociodemography, clinical presentation and cardiovascular risk factors), overall and by current drug-eluting stent.

	Overall	c-DES						*P*
		XIENCE®	PROMUS®	RESOLUTE®	BIOMATRIX®	NOBORI®	ORSIRO®	
	(*n* = 52,891)	(*n* = 18,190)	(*n* = 14,573)	(*n* = 12,727)	(*n* = 4216)	(*n* = 2634)	(*n* = 551)	
Age (years)	66 (58—75)	66 (58—75)	66 (58—75)	66 (58—76)	66 (60—75)	66 (58—75)	67 (60—75)	<0.0001
Age groups								<0.0001
18—59 years	15,484 (29.3)	5546 (30.5)	4348 (29.8)	3543 (27.8)	1171 (27.8)	742 (28.2)	134 (24.3)	
60—69 years	15,996 (30.2)	5445 (29.9)	4420 (30.3)	3818 (30.0)	1298 (30.8)	827 (31.4)	188 (34.1)	
70—79 years	13,533 (25.6)	4585 (25.2)	3699 (25.4)	3287 (25.8)	1112 (26.4)	694 (26.3)	156 (28.3)	
≥80 years	7878 (14.9)	2614 (14.4)	2106 (14.5)	2079 (16.3)	635 (15.1)	371 (14.1)	73 (13.2)	
Sex								0.35
Male	39,740 (75.1)	13,671 (75.2)	11,010 (75.6)	9500 (74.6)	3196 (75.8)	1956 (74.3)	407 (73.9)	
Female	13,151 (24.9)	4519 (24.8)	3563 (24.4)	3227 (25.4)	1020 (24.2)	678 (25.7)	144 (26.1)	
Affiliation to supplementary health coverage[a]	3703 (7.0)	1232 (6.8)	1088 (7.5)	907 (7.1)	269 (6.4)	174 (6.6)	33 (6.0)	0.06
Clinical presentation[b]								<0.0001
Stable angina	22,710 (42.9)	7627 (41.9)	6304 (43.3)	5303 (41.7)	1868 (44.3)	1323 (50.2)	285 (51.7)	
Unstable angina	7575 (14.3)	2406 (13.2)	2117 (14.5)	1844 (14.5)	742 (17.6)	383 (14.5)	83 (15.1)	
Myocardial infarction	20,640 (39.0)	7433 (40.9)	5616 (38.5)	5057 (39.7)	1485 (35.2)	872 (33.1)	177 (32.1)	
Cardiogenic shock, cardiac arrest, other	1966 (2.9)	724 (4.0)	536 (3.7)	523 (4.1)	121 (2.9)	56 (2.1)	6 (1.1)	
Cardiovascular risk factors[b]								
Hypertension	40,620 (76.8)	13,919 (76.5)	11,148 (76.5)	9798 (77.0)	3259 (77.3)	2060 (78.2)	436 (79.1)	0.22
Dyslipidaemia disorders	37,584 (71.1)	12,920 (71.0)	10,244 (70.3)	9052 (71.1)	3029 (71.8)	1926 (73.1)	413 (75.0)	0.01
Diabetes	18,750 (35.5)	6460 (35.5)	5130 (35.2)	4499 (35.4)	1501 (35.6)	959 (36.4)	201 (36.5)	0.87
Morbid obesity	12,068 (22.8)	4279 (23.5)	3330 (22.9)	2766 (21.7)	941 (22.3)	614 (23.3)	138 (25.0)	0.006
Smoking-related conditions/chronic pulmonary disease	18,160 (34.3)	6507 (35.8)	4758 (32.6)	4433 (34.8)	1449 (34.4)	829 (31.5)	184 (33.4)	<0.0001

Data are expressed as mean (interquartile range) or number (%). c-DES: current drug-eluting stent.

[a] Free access to healthcare for French people whose annual income is < 50% of the poverty threshold.

[b] Definition based on International Statistical Classification of Diseases and Related Health Problems, Tenth Revision codes.

Table 2 Individual characteristics of the study population (co-morbidities, score predicting the risk of bleeding and treatments), overall and by current drug-eluting stent.

	Overall	c-DES						*P*
		XIENCE®	PROMUS®	RESOLUTE®	BIOMATRIX®	NOBORI®	ORSIRO®	
	(*n* = 52,891)	(*n* = 18,190)	(*n* = 14,573)	(*n* = 12,727)	(*n* = 4216)	(*n* = 2634)	(*n* = 551)	
Co-morbidities[a]								
History of coronary disease	25,824 (48.8)	8770 (48.2)	7154 (49.1)	6182 (48.6)	2086 (49.5)	1345 (51.1)	287 (52.1)	0.04
Previous PCI	11,846 (22.4)	4140 (22.8)	3341 (22.9)	2762 (21.7)	908 (21.5)	598 (22.7)	97 (17.6)	0.006
Previous CABG	440 (0.8)	162 (0.9)	135 (0.9)	93 (0.7)	24 (0.6)	22 (0.8)	4 (0.7)	0.006
Heart failure	9433 (17.8)	3194 (17.6)	2616 (18.0)	2477 (19.5)	680 (16.1)	397 (15.1)	69 (12.5)	<0.0001
Peripheral vascular disease	7098 (13.4)	2388 (13.1)	1939 (13.3)	1772 (13.9)	562 (13.3)	348 (13.2)	89 (16.2)	0.16
History of stroke	2215 (4.2)	704 (3.9)	612 (4.2)	597 (4.7)	172 (4.1)	111 (4.2)	19 (3.4)	0.02
History of hospitalization for bleeding	5921 (11.2)	2044 (11.2)	1596 (11.0)	1485 (11.7)	431 (10.2)	313 (11.9)	52 (9.4)	0.06
History of liver disease	2319 (4.4)	764 (4.2)	655 (4.5)	597 (4.7)	170 (4.0)	110 (4.2)	23 (4.2)	0.28
Active cancer	5134 (9.7)	1740 (9.6)	1371 (9.4)	1291 (10.1)	408 (9.7)	256 (9.7)	68 (12.3)	0.11
Renal insufficiency	4458 (8.4)	1486 (8.2)	1200 (8.2)	1212 (9.5)	328 (7.8)	192 (7.3)	40 (7.3)	<0.0001
Alcohol abuse	2867 (5.4)	1020 (5.6)	773 (5.3)	694 (5.5)	229 (5.4)	121 (4.6)	30 (5.4)	0.39
Score predicting bleeding risk (modified HAS-BLED score[b])								<0.0001
0	6122 (11.6)	2200 (12.1)	1713 (11.8)	1460 (11.5)	422 (10.0)	279 (10.6)	48 (8.7)	
1—2	24,440 (46.2)	8519 (46.8)	6748 (46.3)	5693 (44.8)	2020 (48.0)	1203 (45.7)	257 (46.7)	
3—5	22,211 (42.0)	7434 (40.9)	6086 (41.8)	5533 (43.5)	1766 (41.9)	1146 (43.5)	246 (44.6)	
6—9	118 (0.2)	37 (0.2)	26 (0.2)	41 (0.3)	8 (0.2)	6 (0.2)	0 (0.0)	
Treatments[c]								
Antiplatelets	28,944 (54.7)	9837 (54.1)	8083 (55.5)	6899 (54.2)	2313 (54.9)	1491 (56.6)	321 (58.3)	0.01
Oral anticoagulants	3507 (6.6)	1183 (6.5)	883 (6.1)	1002 (7.9)	257 (6.1)	141 (5.4)	41 (7.4)	<0.0001
Systemic corticosteroids	2925 (5.5)	956 (5.3)	831 (5.7)	730 (5.7)	240 (5.7)	147 (5.6)	21 (3.8)	0.35
NSAIDs	4843 (9.2)	1652 (9.1)	1391 (9.5)	1117 (8.8)	381 (9.0)	248 (9.4)	54 (9.8)	0.17
Antidepressants	5063 (9.6)	1785 (9.8)	1337 (9.2)	1219 (9.6)	387 (9.2)	274 (10.4)	61 (11.1)	0.15
Proton pump inhibitors	19,800 (37.4)	6787 (37.3)	5402 (37.1)	4764 (37.4)	1622 (38.5)	1009 (38.3)	216 (39.2)	0.48

Data are expressed as number (%). CABG: coronary artery bypass graft; c-DES: current drug-eluting stent; NSAID: non-steroidal anti-inflammatory drug; PCI: percutaneous coronary intervention.

[a] Definition based on International Statistical Classification of Diseases and Related Health Problems, Tenth Revision codes.

[b] As defined in Table A.1.

[c] Defined as one reimbursement within the 6 months before stent implantation.

Table 3 Procedure and centre of implantation characteristics and duration of hospital stay of the study population, overall and by current drug-eluting stent.

	Overall	c-DES						*P*
		XIENCE®	PROMUS®	RESOLUTE®	BIOMATRIX®	NOBORI®	ORSIRO®	
	(*n* = 52,891)	(*n* = 18,190)	(*n* = 14,573)	(*n* = 12,727)	(*n* = 4216)	(*n* = 2634)	(*n* = 551)	
Procedure								
One vessel treated	43,130 (81.5)	14,735 (81.0)	11,852 (81.3)	10,385 (81.6)	3490 (82.8)	2209 (83.9)	459 (83.3)	0.002
One stent implanted	37,408 (70.7)	12,720 (69.9)	10,314 (70.8)	8902 (69.9)	3041 (72.1)	2039 (77.4)	392 (71.1)	<0.0001
One or more stent of diameter < 3 mm implanted	29,253 (55.3)	9956 (54.7)	8212 (56.4)	7067 (55.5)	2284 (54.2)	1416 (53.8)	318 (57.7)	0.001
Hospital centre type								<0.0001
Private	21,513 (40.7)	6925 (38.1)	6162 (42.3)	4896 (38.5)	1449 (34.4)	1659 (63.0)	422 (76.6)	
Public	31,378 (59.3)	11,265 (61.9)	8411 (57.7)	7831 (61.5)	2767 (65.6)	975 (37.0)	129 (23.4)	
Centre volume (number of PCIs during study period)								<0.0001
<600	9308 (17.6)	4261 (23.4)	1972 (13.5)	2131 (16.7)	559 (13.3)	320 (12.1)	65 (11.8)	
≥600	43,583 (82.4)	13,929 (76.6)	12,601 (86.5)	10,596 (83.3)	3657 (86.7)	2314 (87.9)	486 (88.2)	
Duration of hospital stay (days)	4.2 (2—5)	4.3 (2—5)	4.1 (2—5)	4.3 (2—5)	3.9 (2—4)	3.8 (2—4)	3.5 (2—4)	<0.0001

Data are expressed as number (%) or mean (interquartile range). c-DES: current drug-eluting stent; PCI: percutaneous coronary intervention.

Table 4 Risk of ischaemic events and/or bleeding events and/or death (52,891 patients).

	No. of patients	No. with at least one event during follow-up	Standardized incidence rate[a] (per 100 person-years)	Crude HR (95% CI)	*P*	Adjusted[b] HR (95% CI)	*P*
Ischaemic events and/or bleeding events and/or death from any cause[c]							
XIENCE®	18,190	3241	20.10	1.00 (Reference)		1.00 (Reference)	
PROMUS®	14,573	2525	19.42	0.97 (0.91—1.02)	0.26	0.99 (0.93—1.05)	0.71
RESOLUTE®	12,727	2426	21.39	1.06 (1.00—1.12)	0.05	1.04 (0.98—1.10)	0.18
BIOMATRIX®	4216	699	18.36	0.91 (0.84—1.00)	0.04	0.97 (0.89—1.05)	0.43
NOBORI®	2634	409	17.09	0.88 (0.79—0.98)	0.02	0.92 (0.83—1.03)	0.13
ORSIRO®	551	78	15.35	0.81 (0.64—1.01)	0.06	0.85 (0.68—1.07)	0.18
Ischaemic events and/or death from any cause[d]							
XIENCE®	18,190	2787	16.99	1.00 (Reference)		1.00 (Reference)	
PROMUS®	14,573	2184	16.57	0.97 (0.91—1.03)	0.34	1.00 (0.94—1.06)	0.88
RESOLUTE®	12,727	2072	17.92	1.05 (0.98—1.11)	0.15	1.03 (0.97—1.10)	0.32
BIOMATRIX®	4216	582	15.03	0.88 (0.80—0.97)	0.011	0.94 (0.86—1.04)	0.22
NOBORI®	2634	343	14.04	0.85 (0.76—0.96)	0.009	0.90 (0.80—1.02)	0.09
ORSIRO®	551	67	13.10	0.81 (0.63—1.04)	0.098	0.87 (0.68—1.12)	0.29
Ischaemic events and/or bleeding events[e]							
XIENCE®	18,190	2632	16.32	1.00 (Reference)		1.00 (Reference)	
PROMUS®	14,573	2076	15.97	0.98 (0.92—1.04)	0.46	0.98 (0.92—1.05)	0.61
RESOLUTE®	12,727	1925	17.08	1.03 (0.97—1.10)	0.35	1.02 (0.96—1.08)	0.58
BIOMATRIX®	4216	594	15.62	0.95 (0.86—1.04)	0.26	0.97 (0.88—1.07)	0.55
NOBORI®	2634	356	14.88	0.93 (0.83—1.05)	0.25	0.97 (0.87—1.09)	0.64
ORSIRO®	551	67	13.10	0.82 (0.64—1.05)	0.12	0.84 (0.66—1.08)	0.17
Ischaemic events[f]							
XIENCE®	18,190	2097	12.78	1.00 (Reference)		1.00 (Reference)	
PROMUS®	14,573	1675	12.71	0.98 (0.91—1.05)	0.57	0.99 (0.92—1.06)	0.77
RESOLUTE®	12,727	1502	13.12	1.00 (0.93—1.08)	0.95	1.00 (0.93—1.08)	0.97
BIOMATRIX®	4216	456	11.81	0.91 (0.81—1.01)	0.07	0.94 (0.84—1.04)	0.23
NOBORI®	2634	278	11.38	0.91 (0.80—1.04)	0.17	0.96 (0.84—1.09)	0.51
ORSIRO®	551	56	10.87	0.86 (0.66—1.13)	0.28	0.89 (0.68—1.17)	0.40

Table 4 (*Continued*)

	No. of patients	No. with at least one event during follow-up	Standardized incidence rate[a] (per 100 person-years)	Crude HR (95% CI)	*P*	Adjusted[b] HR (95% CI)	*P*
Bleeding events[g]							
XIENCE®	18,190	650	3.76	1.00 (Reference)		1.00 (Reference)	
PROMUS®	14,573	502	3.61	0.97 (0.86—1.10)	0.68	0.97 (0.86—1.09)	0.64
RESOLUTE®	12,727	538	4.38	1.19 (1.06—1.34)	0.01	1.12 (1.00—1.26)	0.05
BIOMATRIX®	4216	167	4.08	1.10 (0.92—1.31)	0.30	1.11 (0.94—1.32)	0.22
NOBORI®	2634	98	3.88	1.04 (0.84—1.29)	0.74	1.09 (0.88—1.36)	0.42
ORSIRO®	551	13	2.39	0.66 (0.38—1.15)	0.14	0.66 (0.38—1.14)	0.14
Death from any cause[h]							
XIENCE®	18,190	835	4.75	1.00 (Reference)		1.00 (Reference)	
PROMUS®	14,573	629	4.45	0.95 (0.85—1.06)	0.37	1.04 (0.93—1.17)	0.45
RESOLUTE®	12,727	698	5.48	1.19 (1.07—1.33)	0.02	1.13 (1.01—1.26)	0.03
BIOMATRIX®	4216	150	3.57	0.80 (0.67—0.96)	0.02	0.95 (0.79—1.14)	0.60
NOBORI®	2634	87	3.33	0.73 (0.58—0.91)	0.01	0.78 (0.62—0.98)	0.03
ORSIRO®	551	12	2.29	0.54 (0.30—0.95)	0.03	0.63 (0.36—1.12)	0.12

CI: confidence interval; HR: hazard ratio; No.: number.

[a] Age and sex standardized; XIENCE® considered as reference.

[b] Multivariable Cox frailty model with two levels of frailty (patient and centre) adjusted for baseline covariates, including age, sex, affiliation to supplementary health coverage, clinical presentation, cardiovascular risk factors, co-morbidities, treatments at baseline, characteristics of procedure, characteristics of the centre of implantation and duration of hospital stay.

[c] 9378 patients with at least one event during follow-up.

[d] 8035 patients with at least one event during follow-up.

[e] 7650 patients with at least one event during follow-up.

[f] 6064 patients with at least one event during follow-up.

[g] 1968 patients with at least one event during follow-up.

[h] 2411 patients with at least one event during follow-up.

Table 5 Subgroup analyses in patients with a high risk of bleeding, on oral anticoagulants, with active cancer or with no acute clinical presentation at baseline. Risk of ischaemic events and/or bleeding events and/or death from any cause.

	No. of patients	No. with at least one event during follow-up	Standardized incidence rate[a] (per 100 person-years)	Crude HR (95% CI)	*P*	Adjusted[b] HR (95% CI)	*P*
High bleeding score (modified HAS-BLED score[c] $\geq$ 3)[d]							
XIENCE®	7471	1660	25.74	1.00 (Reference)		1.00 (Reference)	
PROMUS®	6112	1310	24.70	0.97 (0.90—1.05)	0.44	1.01 (0.93—1.09)	0.84
RESOLUTE®	5574	1321	27.72	1.09 (1.01—1.17)	0.04	1.08 (1.00—1.16)	0.06
BIOMATRIX®	1774	358	23.14	0.89 (0.79—1.00)	0.05	0.96 (0.86—1.08)	0.53
NOBORI®	1152	240	24.02	0.95 (0.83—1.10)	0.49	1.01 (0.88—1.16)	0.90
ORSIRO®	246	40	18.17	0.75 (0.54—1.03)	0.07	0.79 (0.57—1.08)	0.14
Patients who received oral anticoagulants[e]							
XIENCE®	1183	320	32.41	1.00 (Reference)		1.00 (Reference)	
PROMUS®	883	216	28.64	0.88 (0.73—1.05)	0.16	0.92 (0.77—1.11)	0.39
RESOLUTE®	1002	300	37.03	1.16 (0.99—1.37)	0.07	1.16 (0.98—1.36)	0.09
BIOMATRIX®	257	73	33.33	1.02 (0.78—1.32)	0.90	1.06 (0.81—1.38)	0.68
NOBORI®	141	28	23.37	0.68 (0.46—1.01)	0.06	0.72 (0.48—1.07)	0.10
ORSIRO®	41	8	24.29	0.71 (0.35—1.44)	0.34	0.82 (0.40—1.67)	0.58
Patients with active cancer[f]							
XIENCE®	1740	389	25.89	1.00 (Reference)		1.00 (Reference)	
PROMUS®	1371	308	26.52	1.02 (0.88—1.20)	0.77	1.11 (0.95—1.30)	0.19

Table 5 (*Continued*)

	No. of patients	No. with at least one event during follow-up	Standardized incidence rate[a] (per 100 person-years)	Crude HR (95% CI)	*P*	Adjusted[b] HR (95% CI)	*P*
RESOLUTE®	1291	309	28.08	1.13 (0.96—1.32)	0.13	1.11 (0.95—1.30)	0.20
BIOMATRIX®	408	81	22.71	0.88 (0.69—1.12)	0.30	0.96 (0.75—1.23)	0.73
NOBORI®	256	64	29.93	1.13 (0.86—1.48)	0.39	1.22 (0.92—1.60)	0.16
ORSIRO®	68	13	19.24	0.89 (0.51—1.56)	0.69	0.97 (0.55—1.71)	0.92
Patients with no acute clinical presentation at baseline[g,h]							
XIENCE®	10,246	1608	17.26	1.00 (Reference)		1.00 (Reference)	
PROMUS®	8599	1380	17.65	1.02 (0.94—1.10)	0.63	1.01 (0.94—1.09)	0.75
RESOLUTE®	7322	1279	19.25	1.12 (1.03—1.21)	0.01	1.09 (1.00—1.17)	0.04
BIOMATRIX®	2663	419	17.32	0.98 (0.87—1.09)	0.70	1.01 (0.90—1.12)	0.93
NOBORI®	1730	259	16.29	0.96 (0.84—1.10)	0.58	1.00 (0.88—1.15)	0.97
ORSIRO®	372	59	17.61	1.04 (0.80—1.35)	0.79	1.05 (0.81—1.37)	0.72

CI: confidence interval; HR: hazard ratio; No.: number.

[a] Age and sex standardized; XIENCE® considered as reference.

[b] Multivariable Cox frailty model with two levels of frailty (patient and centre) adjusted for baseline covariates, including age, sex, affiliation to supplementary health coverage, cardiovascular risk factors, co-morbidities, treatments at baseline, characteristics of procedure, characteristics of the centre of implantation, duration of hospital stay and clinical presentation.

[c] As defined in Table A.1.

[d] 22,329 patients including 4929 patients with at least one event.

[e] 3507 patients including 945 patients with at least one event.

[f] 5134 patients including 1164 patients with at least one event.

[g] 30,392 patients including 5004 patients with at least one event.

[h] Without myocardial infarction, cardiogenic shock or cardiac arrest.

Results were consistent when analysis was restricted to patients at high bleeding risk or with a non-acute clinical presentation at baseline (Table 5). Likewise, results were consistent regardless of the number of vessels treated, the diameter of stents implanted, the presence of diabetes or the use of DAPT after stent implantation. Nevertheless, for ORSIRO®, the combined risk of ischaemic events, bleeding events and/or death decreased in patients with diabetes, and for RESOLUTE®, it increased in patients with no DAPT during the first 6 months after stent implantation compared with XIENCE® (adjusted HR 0.64, 95% CI 0.43—0.94 and adjusted HR 1.27. 95% CI 1.06—1.51, respectively).

As expected, the incidence rate of events in patients with diabetes was higher than in patients without diabetes (22.5 vs. 16.6 per 100 patient-years) (Table A.4).

All the results remained unchanged in the various sensitivity analyses (Table A.5).

Discussion

To date, this study is the first conducted in an unselected population comparing the risks of various outcomes across the different c-DES types used in real-life clinical practice (with a biodegradable or durable polymer, and delivering everolimus, sirolimus or zotarolimus).

In our study, which included more than 50,000 patients, no significant differences in ischaemic and bleeding complications were observed between the six c-DES types used in France in 2014 within the first year following implantation. Our results corroborate the overall findings of RCTs assessing PROMUS® [5,34,35], RESOLUTE® [10,12], NOBORI® [6,7,11], BIOMATRIX® [9] and ORSIRO® [8,36]. RCTs, mostly based on a non-inferiority assumption, failed to demonstrate any significant difference between c-DESs regarding the risk of ischaemic events without stroke and/or death at 1 year [7,8,10—12,34—36]. However, the numbers of patients included were limited, ranging from 200 to 6472 patients by study, those with a high bleeding risk were excluded and few of the RCTs considered stroke and major bleeding as endpoints [5,7,14]. Our study did not show differences in the risk of ischaemic events, including stroke, nor in the risk of bleeding events, in the whole stented population or in specific subgroups of patients with high bleeding risk at baseline, as assessed by a modified HAS-BLED score ≥ 3, an oral anticoagulant treatment or active cancer.

The incidence rates found in our study of 12 per 100 patient-years for ischaemic events and 4 per 100 patient-years for bleeding events and death were consistent with those reported in observational studies assessing outcomes following c-DES implantation. USA studies after market approval (XIENCE V [37] and PROMUS PE-plus [38]), as well as REAL (an Italian regional PCI registry [23]) and SCAAR (the national Swedish PCI registry [39]), reported ischaemic events and/or death rates ranging between 11.6% and 13.8% (without including stroke) and death rates between 2.3% and 4.5%. The XIENCE V study [37] reported a 2.5% rate of major bleeding complications at 1 year according to Thrombolysis in myocardial infarction (TIMI) grade. However, to date, no study has attempted to compare ischaemic and/or bleeding risks following c-DES implantation across the various c-DES types in real life. The observational REWARDS study compared two c-DESs in a selected population of 1552 patients implanted in high volume centres in the USA [40]. After adjustment, the risk of ischaemic composite endpoint measured did not differ for PROMUS® compared with XIENCE® (adjusted HR 0.69, 95% CI 0.45—1.05; $P = 0.07$).

The key strength of our study was the use of exhaustive national medicoadministrative databases, giving access to a population of 50,000 patients. Information on reimbursed health products are automatically and immediately collected by electronic transmission from pharmacists to the French Health Insurance network. For each patient identified by a personal card, a specific code for each product reimbursed is entered, avoiding recall or recording bias (SNDS database). Information on hospital admissions are accurate and precise, as they are used to finance public and private hospitals' activities; that is why the discharge diagnosis codes and expensive medical devices implanted are checked against patients' medical records. Independent data collection between the two databases were retrospectively linked, which theoretically excludes the possibility of a differential information bias. As a result of its nationally-representative nature, our study also provides insight into routine clinical practice in coronary disease care (the general health scheme insures 77% of French people who are all covered by a solidarity-based health care system).

Study limitations

Our study has some limitations. First, there was no formal clinical validation of the diagnoses. Nevertheless, ischaemic, death and bleeding risks were consistent with those from other studies [23,37—40]. In addition, an external validity of coronary artery disease diagnosis based on the hospital database showed a positive predictive value of 90% in 2011 for the most frequent ICD-10 code for myocardial infarction (code I21) [41]. Moreover, compared with three sites of the MONICA registry included in the WHO project, a sensitivity of 76.2% was found for myocardial infarction [42]. Another study of cases of stroke compared the hospital database with a French stroke registry, and reported a positive predictive value and a sensitivity of about 82% in 2008, the last year of the study, with an improvement observed over time [43]. Although no studies have assessed bleeding diagnosis validity, like Maura et al. [29] we selected only primary hospitalized discharge diagnoses corresponding to the standardized definition of major Bleeding Academic Research Consortium grade [44]. Thus, although we cannot exclude an outcome misclassification, it would probably be non-differential, if it occurred.

Second, we were unable to specify the extent and severity of the disease, as no information on biological and imaging results are available in the databases (such as the length and complexity of coronary lesions or of the procedure). Nevertheless, subgroup and sensitivity analyses suggested that this is unlikely to have biased our results. Indeed, results were consistent regardless of the number of vessels treated or diameter of stents implanted, as well as in patients managed outside an acute setting. Moreover, adjusted HRs were not affected in the sensitivity analysis with additional adjustment or with the propensity score-adjusted Cox model.

Third, although most comparisons were non-significant, multiple testing for several outcomes or residual confounding of unmeasured factors (such as lifestyle, obesity, alcohol and tobacco use, etc.) and/or unknown factors probably explains the very weak differences in death risks and/or bleeding observed for RESOLUTE® and NOBORI® compared with XIENCE®. In patients with diabetes, the number of major ischaemic and bleeding events was small for ORSIRO®. The difference in risk observed with this c-DES needs additional investigation, as it was used in a very limited number of patients, being the last one to become commercially available in 2014.

Fourth, our study was not adapted to reliably assess intrastent thrombosis, a rare adverse event. However, intrastent thrombosis underlies 50—70% of myocardial infarctions early after DES implantation, and we included myocardial infarctions and rehospitalizations for PCI stenting in the ischaemic outcome. Moreover, results were consistent according to the use or not of DAPT during the first 6 months after implantation, with the exception of RESOLUTE®, where unmeasured/unknown factors probably explain the very weak difference in ischaemic events, major bleeding events and/or death observed compared with XIENCE®. In the REWARDS study, the intrastent thrombosis risk was higher with PROMUS® (1.1% vs. 0.3%; $P = 0.04$), whereas ischaemic risk tended to be lower (5.8% vs. 8.0%) [40].

Finally, we could not consider biodegradable-polymer everolimus-eluting c-DESs, such as SYNERGY®, or c-DESs with no polymer, because they were not reimbursed at the time of the study. We considered in our study the c-DESs approved in 2014 in France, which still accounted for 60% of DES implantations in 2017, as observed in other European countries, such as Sweden [39].

Conclusions

These findings suggest that in real life, ischaemic and bleeding risks do not differ across the various types of c-DES over the first year following c-DES implantation. These findings provide useful information for patients, clinical practice and public health decision makers. Future studies are needed to assess effectiveness and safety risks over longer-term follow-up, as well as with the next generations of c-DESs.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version at: https://doi.org/10.1016/j.acvd.2019.04.007.

Disclosure of interest

The authors declare that they have no competing interest.

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