THE DETECT STUDY

The "Drug EluTing dEvices FrenCh safeTy survey "

Statistical Analyses Plan (SAP) – 2 February 2022, Version 1.8

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I. SAP in context

We propose here a short Statistical Analyses Plan (SAP) of the DETECT study. This SAP was written before any actual access to the study data.

The aim of the DETECT study is to assess the safety of paclitaxel-eluting devices such as paclitaxel-coated balloon and paclitaxel-eluting stents, used for intraluminal dilatation of lower limb artery. For this purpose, we will use "real-life" data collected from the French SNDS (*Système National des Données de Santé,* or National Healthdata Information System).

The complete protocol of the DETECT study, in French, describes the general methodology of the study.

II. Study Population

1) Eligibility criteria

Inclusion criteria

- Female or male age ≥ 18 years old on day of hospital admission for the hereafter related surgical procedure ("the Procedure")
- Affiliated to the French Social Security System
- Admitted in a French hospital, public or private, between October 2011 and December 2019
- Benefitting from an endovascular surgical procedure coded with ≥ 1 of the 9 codes of the Common Classification of Medical Procedures (French "CCAM", see Table 1)

Non-inclusion criteria

- History of chemotherapy involving paclitaxel (TAXOL ®) in the last two years before procedure

The rational for inclusion period is the following:

- **Starting October 2011:** corresponds to the first reimbursement for the study devices by the national Health Insurance scheme (6th September 2011, Zilver PTX, Cook medical)
- **Until December 2019:** giving two years of inclusion time for the last device of interest to be reimbursed by the national Health Insurance scheme (14th September 2011, ELUVIA 75 and 130 cm, Boston Scientific)

2) Definition of subgroups

The different groups of patients are defined according to the devices used during the procedure of interest, hereafter "the Procedure".

(i) Unexposed group

Patients without paclitaxel-eluting devices (neither balloons nor stent) used during the Procedure.

(ii) Exposed group

Patients with ≥ 1 paclitaxel-eluting devices (balloon and/or stent) used during the Procedure.

(iii) Bare metal stent group

Patients with at least one stent but no paclitaxel-eluting stent used during the Procedure.

(iv) Paclitaxel-eluting stent group

Patients with ≥ 1 paclitaxel-eluting stent used during the Procedure.

(v) No paclitaxel-coated balloon group

Patients with at least one balloon but no paclitaxel-coated balloon used during the Procedure.

(vi) Paclitaxel-coated balloon group

Patients with ≥ 1 paclitaxel-coated balloon used during the Procedure.

(vii) Groups with specific devices

Patients with at least one device among one but only one of the following:

- Zilver PTX®: "Zilver Group"
- Eluvia®: "Eluvia Group"
- Ranger®: "Ranger Group"
- In.pact admiral®: "Inpact Group"
- Lutonix®: "Lutonix Group"
- Sequent Please OTW®: "Sequent Group"
- Stellarex®: "Stellarex Group"

(viii) Group with specific ICD-10 coding

Patients with/without ICD-10 code L97 as diagnosis (main, related and/or associated) linked with the hospitalisation for the procedure of interest.

- L97: ulcer of skin of lower limb not otherwise specified

Table 1. French Common Classification of Medical Procedures (CCAM) codes of the nine surgical procedures of interest

CCAM code	Procedure	Balloon	Stent	Localization
EEAF003	Intraluminal dilation of a lower limb artery **without stent**, using percutaneous transluminal angioplasty	Yes	No	Lower limb
EEAF004	Intraluminal dilation of a lower limb artery **with stent**, using percutaneous transluminal angioplasty	Yes	Yes	Lower limb
EEAF005	Intraluminal dilation of a lower limb artery with dilation of the common iliac artery and/or of the ipsilateral external iliac artery, **without stent,** using percutaneous transluminal angioplasty	Yes	No	Lower limb and iliac
EEAF002	Intraluminal dilation of a lower limb artery with dilation of the common iliac artery and/or of the ipsilateral external iliac artery, **with stent,** using percutaneous transluminal angioplasty	Yes	Yes	Lower limb and iliac
EEAF001	Intraluminal dilation of several lower limb artery **without stent**, using percutaneous transluminal angioplasty	Yes	No	Lower limb
EEAF006	Intraluminal dilation of several lower limb artery **with stent**, using percutaneous transluminal angioplasty	Yes	Yes	Lower limb
EEPF002	Recanalization of one lower limb artery **without stent**, percutaneous transluminal angioplasty	Yes	No	Lower limb
EEPF001	Recanalization of one lower limb artery **with stent**, percutaneous transluminal angioplasty	Yes	Yes	Lower limb
EELF002	Covered stent placement in a lower limb artery, using percutaneous transluminal angioplasty	No	Yes	Lower limb

III. Definition of patients' history

The "history period" is defined as the two years preceding the hospital admission related with the surgical procedure of interest. For patients admitted before January 2013, this hindsight will be left-censored, as we will not be able to trace it back before January 2011.

1) Three socio-economic data on admission date for the procedure

Age, sex, and the deprivation index, a socio-economic proxy built using patients' last known address on admission date for the procedure.

2) Medical treatment before the procedure, assessed for 5 types of drugs

Treatments will be considered using a binary approach: yes/no, defined as "≥2 deliveries (≥1 in case of big packaging, that is 3-month therapy) during the last year before the hospital admission related with the surgical procedure of interest".

- Statin therapy: simvastatin, pravastatin, fluvastatin, atorvastatin and rosuvastatin (including their association with fenofibrate or ezetimibe)

- Oral antiplatelet agent: aspirin, clopidogrel, prasugrel, ticagrelor

- Anticoagulant therapy, including
    - vitamin-K antagonists: acenocoumarol, fluindione, warfarin
    - heparin: calciparin, enoxaparin, fragmin, tinzaparin
    - X-a inhibitors: apixaban, dabigatran, edoxaban, fondaparinux, rivaroxaban

- Any Angiotensin-Converting Enzyme inhibitors (ACEi)

3) Coronary artery disease (CAD)

CAD history will be defined as any of the following during the "history period".

- Known long-term disease: "coronary disease" during the last (French LTD n°13)

and/or

- Any hospitalization with at least one of the following ICD-10 codes as the diagnosis (main, related and/or associated) linked with the hospitalization:
    - I20: Angina pectoris
    - I21: Acute myocardial infarction
    - I22: Subsequent Myocardial Infarction
    - I23: Certain current complications following acute myocardial infarction
    - I24: Other acute ischaemic heart diseases
    - I25: Chronic ischaemic heart disease

4) Stroke and/or Transient Ischaemic attack (TIA)

Stroke/TIA history will be defined as any of the following during the "history period".

- Known long-term disease: "Disabling stroke" (French LTD n°1)

and/or

- Any hospitalization with at least one of the following ICD-10 codes as the diagnosis (main, related and/or associated) linked with the hospitalization:
    - G45: Transient cerebral ischemic attacks and related syndromes
    - I60: Subarachnoid haemorrhage
    - I61: Intracerebral haemorrhage
    - I62: Other nontraumatic intracranial haemorrhage
    - I63: Cerebral infarction
    - I64: Stroke, not specified as haemorrhage or infarction
    - I69: Sequelae of cerebrovascular disease

5) Heart failure (HF)

HF history will be defined as any of the following during the "history period".

- Any hospitalization or LTD with at least one of the following ICD-10 codes as the diagnosis (main, related and/or associated) linked with the hospitalization:
    - I50: Heart failure
    - I11.0: Hypertensive heart disease with (congestive) heart failure
    - I13.0: Hypertensive heart and renal disease with (congestive) heart failure
    - I13.2: Hypertensive heart and renal disease with both (congestive) heart failure and renal failure
    - I13.9: Hypertensive heart and renal disease, unspecified
    - R57.0: Cardiogenic shock

6) Previously known Lower Extremity Artery Disease (LEAD)

Previously known lower LEAD will be defined as any hospitalization without lower-limb procedure (cf. Table 1) and at least one of the following ICD-10 codes as the diagnosis (main, related and/or associated) linked with the hospitalization:

- I70.2: Atherosclerosis of arteries of extremities
- I70.8: Atherosclerosis of other arteries
- I70.9: Generalized and unspecified atherosclerosis
- I73.8: Other specified peripheral vascular diseases
- I73.9: Peripheral vascular disease, unspecified
- I74.0: Embolism and thrombosis of abdominal aorta
- I74.3: Embolism and thrombosis of arteries of lower extremities
- I74.4: Embolism and thrombosis of arteries of extremities, unspecified

- I74.5: Embolism and thrombosis of iliac artery
- I77.1: Stricture of artery
- I79.2: Peripheral angiopathy in diseases classified elsewhere

7) Lower limb amputation (LLA), minor and major

LLA history will be defined as any hospitalization with at least one of the following CCAM codes during the "history period", with a distinction between minor and major LLA:

Minor

- NZFA004: Amputation or disarticulation of several toes
- NZFA005: Amputation or disarticulation of the midfoot or of the forefoot, without stabilisation of the hindfoot
- NZFA009: Amputation or disarticulation of the ankle or of the hindfoot
- NZFA010: Amputation or disarticulation of one toe
- NZFA013: Amputation or disarticulation of the midfoot or of the forefoot, with stabilisation of the hindfoot

Major

- NZFA002: Transtibial amputation
- NZFA006: Amputation or disarticulation of the lower limb through thigh bone, sacroiliac joint or sacrum
- NZFA007: Transfemoral amputation

8) Malignant tumour

Malignant tumour history will be defined as at least one of the following during the "history period":

- Known long-term disease: "Cancer" (French LTD n°30)

and/or

- Any hospitalization with at least one of the following ICD-10 codes as the diagnosis (main, related and/or associated) linked with the hospitalization:
  - Any code starting with "C": malignant neoplasms
  - Any code starting with any character from "D37" to "D48": Neoplasms of uncertain and unknown behaviour

Therefore, this definition does not include:

- D10-D36: benign neoplasms
- D00-D09: in situ neoplasms

9) Diabetes mellitus

Known diabetes mellitus will be defined using the "Diabetes TOP" encoded in the French SNDS, and built according to previously published work: see Fuentes S. et al, CONSTANCES -Diab Group, Int J Public Health 2019, "*Identifying diabetes cases in health administrative databases: a validation study based on a large French cohort*", PMID 30515552.

10) Known dialysis/end-stage renal failure (ESRD)

Known dialysis/ESRD will be defined as any of the following during the "history period:

- Any hospitalization with at least one of the following ICD-10 codes as the diagnosis (main, related and/or associated) linked with the hospitalization:
    - Z94.0: Kidney transplant status
    - T86.1: Failure and rejection of transplanted kidney

and/or

- Any hospitalization with at least one of the following French CCAM code:
    - JAEA003: Kidney graft
    - HNEA003: Double Kidney-pancreas graft

and/or

- Any hospitalization with at least one of the following French GHM code ("*Groupe Homogène de Malade*", sometimes translated as "Diagnosis Related Group"):
    - 27C06: Kidney graft
    - 11M17: Monitoring of kidney graft
    - 11K02 or 28Z01Z to 28Z06Z: Training for peritoneal dialysis or hemodialysis or hemodialysis session

11) Known chronic kidney disease without dialysis/ESRD

Known chronic kidney disease without dialysis/ESRD will be defined as "no Known dialysis/ESRD" (see previous item) and any hospitalization with at least one of the following ICD-10 codes as the diagnosis (main, related and/or associated) linked with the hospitalization:

- E10.2/E11.2/E12.2/E13.2/E14.2: Diabetes with renal complication
- I12.0: Hypertensive chronic kidney disease
- I13.1: Hypertensive heart and renal disease with renal failure
- I13.2: Hypertensive heart and renal disease with both (congestive) heart failure and renal failure
- N08.3: Diabetic nephropathy
- N18: Chronic Kidney Disease

12) History of paclitaxel-eluting device on coronary artery

This parameter will be defined using hospitalization codes, but the associated codes list still needs to be laid done.

IV. Definition of the outcomes

1) The main outcome for this study is all-cause death

These data are readily available in the French SNDS by using two different sources:

i. The vital status associated with the end of any hospitalisation
ii. The vital status from the French CepiDc (Epidemiology Centre on Medical Causes of Death)

Due to data accessibility, a subgroup of patients will have less information regarding vital status, with the risk of missing outpatients' death. This will concern the patients not included in the general scheme (French "Régime general"), or approximately 15 to 20% of the patients (see section V for the consequences on the statistical approach).

For the record, causes of death will not be studied for two reasons:

- The data are expected to be scarce and incomplete. For example, the causes of death of the year 2018 were not available in 2020
- The quality of the data source is not guaranteed for this study, as many patients are usually classified as dead secondarily to a cardiorespiratory arrest. The risk being that a lack of sensitivity makes this information useless.

2) Secondary outcome n°1: "all-cause hospitalization"

Any hospitalisation:

- ≥ 1 day
- and/or associated with patient's death
- and/or associated with CCAM code for surgical procedure

This definition is proposed in order to exclude programmed day hospitalisation.

3) Secondary outcome n°2: "Coronary Artery Disease (CAD)"

Any of the following events, whichever comes first:

- For a patient without history of CAD: declaration of "coronary disease" as long-term disease (French LTD n°13)

- For all patients: any hospitalization ≥1 day with at least one of the following ICD-10 codes as main diagnosis or diagnosis related with hospitalization:
    - I20: Angina pectoris
    - I21: Acute myocardial infarction
    - I22: Subsequent Myocardial Infarction
    - I23: Certain current complications following acute myocardial infarction
    - I24: Other acute ischaemic heart diseases
    - I25: Chronic ischaemic heart disease

4) Secondary outcome n°3: "Stroke or Transient Ischaemic attack (TIA)"

Stroke will be defined as any of the following events, whichever comes first:

- For a patient without history of stroke/TIA: declaration of "Disabling stroke disease" as long-term disease (French LTD n°1)

- For all patients: any hospitalization ≥1 day with at least one of the following ICD-10 code as main diagnosis or diagnosis related with hospitalization:
    - I60: Subarachnoid haemorrhage
    - I61: Intracerebral haemorrhage
    - I62: Other nontraumatic intracranial haemorrhage
    - I63: Cerebral infarction
    - I64: Stroke, not specified as haemorrhage or infarction
    - I69: Sequelae of cerebrovascular disease

TIA will be defined as any hospitalization (of any duration) with at least one of the following ICD-10 codes as the diagnosis (main and/or related) linked with the hospitalization:

- G45: Transient cerebral ischemic attacks and related syndromes

5) Secondary outcome n°4: "Heart failure (HF)"

Any of the following events, whichever comes first:

- For a patient without history of HF: declaration of "Heart Failure" as long-term disease (French LTD associated with any of the ICD-10 codes listed below)

- For all patients: any hospitalization ≥1 day with at least one of the following ICD-10 codes as main diagnosis or diagnosis related with hospitalization:
    - I50: Heart failure
    - I11.0: Hypertensive heart disease with (congestive) heart failure
    - I13.0: Hypertensive heart and renal disease with (congestive) heart failure
    - I13.2: Hypertensive heart and renal disease with both (congestive) heart failure and renal failure
    - I13.9: Hypertensive heart and renal disease, unspecified
    - R57.0: Cardiogenic shock

6) Secondary outcome n°5: "New lower-limb artery procedure"

Any hospitalization with at least one CCAM code for lower limb artery procedure (cf. Table 1 and Table 2).

Table 2. French Common Classification of Medical Procedures (CCAM) codes for iliac artery procedures	
CCAM code	**Procedure**
EDAF002	Intraluminal dilation of the common iliac artery and/or of the external iliac artery, **without stent,** using percutaneous transluminal angioplasty
EDAF003	Intraluminal dilation of the common iliac artery and/or of the external iliac artery, **with stent,** using percutaneous transluminal angioplasty
EDAF004	Intraluminal dilation of the internal iliac artery, **without stent**
EDAF006	Intraluminal dilation of the internal iliac artery, **with stent**
EDPF001	Recanalisation of the internal iliac artery, **with stent**
EDPF006	Recanalisation of the internal iliac artery or of the external iliac artery, **with drug-eluting stent**
EDPF007	Recanalisation of the internal iliac artery, **without stent**
EDPF008	Recanalisation of the internal iliac artery or of the external iliac artery, **without stent**
EDPF009	Recanalisation of the internal iliac artery or of the external iliac artery, **with stent**
EDLF004	**Stenting (drug-eluted stent)** of the internal iliac artery and/or of the external iliac artery, with embolization of the internal iliac artery
EDLF005	**Stenting (drug-eluted stent)** of the internal iliac artery and/or of the external iliac artery
DGPF002	Recanalisation of the aortic bifurcation, **with stent,** using percutaneous transluminal angioplasty

7) Secondary outcome n°6: "Aggravation of lower-limb arteries, without surgery"

Any hospitalization ≥1 day without lower-limb procedure (cf. Tables 1 & 2) and at least one of the following ICD-10 code as main diagnosis or diagnosis related with hospitalization:

- I70.2: Atherosclerosis of arteries of extremities
- I70.8: Atherosclerosis of other arteries
- I70.9: Generalized and unspecified atherosclerosis
- I73.8: Other specified peripheral vascular diseases
- I73.9: Peripheral vascular disease, unspecified
- I74.0: Embolism and thrombosis of abdominal aorta
- I74.3: Embolism and thrombosis of arteries of lower extremities
- I74.4: Embolism and thrombosis of arteries of extremities, unspecified
- I74.5: Embolism and thrombosis of iliac artery
- I77.1: Stricture of artery
- I79.2: Peripheral angiopathy in diseases classified elsewhere

8) Secondary outcome n°7: "Lower limb amputation (LLA)", minor and major

Any hospitalization with at least one of the following CCAM codes, with a distinction between minor and major LLA:

Minor

- NZFA004: Amputation or disarticulation of several toes (2 or more)
- NZFA005: Amputation or disarticulation of the midfoot or of the forefoot, without stabilisation of the hindfoot
- NZFA009: Amputation or disarticulation of the ankle or of the hindfoot
- NZFA010: Amputation or disarticulation of one toe
- NZFA013: Amputation or disarticulation of the midfoot or of the forefoot, with stabilisation of the hindfoot

Major

- NZFA002: Transtibial amputation
- NZFA006: Amputation or disarticulation of the lower limb through thigh bone, sacroiliac joint or sacrum
- NZFA007: Transfemoral amputation

9) Secondary outcome n°8: Major Adverse Cardiovascular Event (MACE)

The first occurrence of any of the following 5 outcomes:

- CAD
- Stroke/TIA
- New lower limb artery procedure
- Major LLA
- Death

10) Secondary outcome n°9: duration of hospital stay

For this outcome, we will calculate the total number of days spent in hospital (public and/or private) per year, following the Procedure.

V. Statistical analyses

1) Description of the study populations: main and subgroups

First, all data regarding patients' history, that is age, sex, deprivation index, medical treatment and main comorbidities (see. **Section III** for details) will be described in the whole study population, and in the different subgroups defined in **Section II**.

Categorical data will be described using no. (%). Quantitative data will be described using mean (SD) or median (25^{th} percentile – 75^{th} percentile), according to the distribution of the parameter.

2) Between-group comparison: study population, analysis of the main outcome, all-cause death

Proportional hazard model

The main analysis is a longitudinal analysis, using time-to-event models. We will compare two groups: "unexposed" vs "exposed" group. The Cox model based on proportional hazard hypothesis will be first considered but, according to data distribution, other statistical models may also be discussed. Patients' follow-up will begin on admission date for the procedure of interest, and will end on the first among the following events, whichever comes first (right-censoring):

- Death
- Last information regarding any healthcare reimbursement available in the SNDS
- New procedure associated with paclitaxel-eluting devices
- Cancer chemotherapy implying paclitaxel (as TAXOL®)

The results of the following models will be presented, using Cox with different adjustment:

- Model 1 (M_1): no adjustment
- Model 2 (M_2): M_1 + adjusted on age (quantitative), sex (female, male), deprivation index (categorical with 4 modalities or quantitative, between 0 and 1), unscheduled Procedure (boolean)
- Model 3 (M_3): M_2 + adjusted on routine treatment with antiplatelet agent (boolean), anticoagulant (boolean), statin (boolean), ACE (boolean)
- Model 4 (M_4): M_3 + adjusted on history of: CAD (boolean), stroke/TIA (boolean), HF (boolean), lower limb artery disease without procedure (boolean), lower-limb amputation (nominal: no amputation/minor/major), malignant tumour (boolean), chronic kidney disease (boolean), dialysis/end-stage renal disease (boolean), diabetes (boolean), ulcer of skin of lower limb (boolean), other paclitaxel-eluting stent
- Model 5 (M_5): M_4 + considering interaction term between the exposure and "ulcer of skin of lower limb"

In model 5, a p-value < 0.05 associated with HR between exposed/unexposed group will be considered as statistically significant. The 95% CI of this HR represents the main endpoint of our study.

Propensity score approach

Propensity-score base model (PSM) will also be considered. We will discuss results obtained using 4 approaches:

- PS matching, both calliper (1) and optimal matching (2) and
- Inverse probability of treatment weighting (IPTW) with both stabilized weights (3) and trimmed weights (4), allowing calculation of average treatment effect (ATE) and average treatment effect for the treated (ATT), as proposed by Austin[1]

In the presence of large biomedical datasets from medico administrative origin, this should enable us to assess the robustness of the results by comparing multiple mathematical modelling strategies.

Covariates used for PSM will be the same as above listed for model M_4. Their balance before and after weighting will be assessed using the standardized mean difference approach.

We reserve the option to adapt it according to confounding factors distribution, particularly with discussion regarding pair- and full-matching. For each modelling approach, when relevant, Kaplan-Meier curves will also be produced (crude comparison, matched sample with calliper matching, and with optimal matching, ATE and ATT weighted samples).

3) Between-group comparison: study population, analysis of the secondary outcomes

The same approach will be used for the secondary outcomes, considering death as competing event. The scientific question being etiological, cumulative incident function (CIF) will be used to represent risk function over time, and both subdistribution hazard models and Cox models will be considered to calculate hazard ratios (for details see Austin and coll., "*Introduction to the Analysis of Survival Data in the Presence of Competing Risks"*, Circulation 2016 Feb;133(6), PMID 26858290).

In model 4, a p-value < 0.005 (≈5%/10, considering multiple testing for 10 different outcomes) associated with HR between exposed/unexposed group will be considered as statistically significant.

4) Time of analysis

The same approaches (steps 2 to 3) will be applied with data available on the following times:

- 2021: "proof of concept" analysis (≥1 year of follow-up for all patients)
- 2022: main analysis (≥2 years of follow-up for all patients)
- 2025: long term analysis (≥5 years of follow-up for all patients)

5) Between-group comparison: subgroup analyses

[1] Austin, P. C. The use of propensity score methods with survival or time-to-event outcomes: reporting measures of effect similar to those used in randomized experiments. Stat Med 33, 1242–1258 (2014).

The same approaches (steps 2 to 4) will be reproduced in the following subgroups:

- Bare metal stent vs. paclitaxel-eluting stent group
- No paclitaxel-coated balloon vs. paclitaxel-coated balloon

These analyses being considered as exploratory, without correction for multiple testing.

6) Analysis of the first 30 days after the procedure

The different subgroups will be compared for the following outcomes in the next 30 days after the procedure, using Poisson regression model:

- All-cause death
- All-cause hospitalisation
- Hospitalisation associated with a new lower limb artery procedure

These analyses being considered as exploratory, without correction for multiple testing.

7) Other sensitivity analyses

The following sensitivity analyses will be performed (parts 1 to 4):

- Exclusion of patients included before 2013 (that is with an expected "history period" of less than two years)

- In order to account for the difference regarding death event collection between patients under general scheme (about 80% of the population):

    - As declared in V.2, all patients will be right censored after their last healthcare reimbursement in the database, therefore considered as a "life sign"
    - Death rate will be compared between the two group, separating inpatients and outpatient's death
    - As a sensitivity analyses, affiliation to the general scheme (yes/no) will be considered as a potential interaction factor, and the results will be given separately for the two groups defined by this covariate

- As a proxy for dose-exposure, according to data availability, we will propose a secondary analysis using the number of paclitaxel-eluting medical devices associated with the Procedure as the exposure.