**Research project: HEMODYNAMICS Study Protocol**

**I. Project title**

**Cardiovascular complications after adrenalectomy for pheochromocytoma and non-secreting tumors – A prospective observational multicenter European Study (HEMODYNAMICS)**

**II. Aggregated European data**

This project involves the pan-European EUROCRINE® data sets and additional my-EUROCRINE® data, which are open to clinics in Europe participating in EUROCRINE®. This study is a Eurocrine Council study and being proposed to all European centers participating in Eurocrine for a period of two years (September 1, 2025–September 1, 2027).

**III. Background**

Pheochromocytoma is an adrenomedullary chromaffin cell tumour that releases catecholamines. Adverse cardiovascular events are considered the main cause of morbidity and mortality in patients with pheochromocytoma. Consequently, preoperative medical preparations using alpha-blockers or other antihypertensive drugs and the control of hemodynamic instability during adrenalectomy for pheochromocytoma are recommended by guidelines to prevent vasoconstriction, perioperative cardiovascular complications, and the risk of death. However, the definition of a catecholamine-induced hypertensive crisis in patients with pheochromocytoma has only recently been validated by an international consortium as the occurrence of systolic/diastolic blood pressure >180/120 mmHg 1. Limitations of published studies include small sample sizes, and single institution analysis. Some studies have reported substantial variability in the management of pheochromocytomas, with the use of routine preoperative medical preparation varying from 49% to 100%, whereas others have questioned the utility of this preparation for postoperative cardiovascular complications. The aim of this study was to evaluate pan-European practices in terms of specific preoperative medical preparation before surgery and to identify risk factors for postoperative cardiovascular complications 30 days after adrenalectomy for pheochromocytoma and non-secreting tumors (indication for surgery = « excluding malignancy » or « metastasis »).

The EUROCRINE® registry offers a valuable opportunity to assess clinical practices for preoperative medical preparation and the morbidity linked to adrenalectomy for pheochromocytoma and non-secreting tumors. This prospective study aims to refine surgical protocols and inform updates to existing guidelines, thereby advancing the management of adrenalectomy for pheochromocytoma.

**IV. Aim, main hypothesis and importance of research project**

The primary objective of this study is to evaluate intraoperative and postoperative cardiovascular complications 30 days after adrenalectomy for pheochromocytoma and non-secreting tumors, using a validated and published definition of cardiovascular complications 2. The secondary objectives correspond to the evaluation of specific preoperative preparation practices in terms of antihypertensive drugs, and the evaluation of the incidence of intraoperative hypertensive crisis and hypotensive crisis (duration in minutes from induction to discharge from the operating room).

Our hypothesis suggests that specific medical preparation prior to surgery depends on clinical practice rather than patient criteria, that incidence of hypertensive crisis is higher in pheochromocytoma patients, and that the perioperative cardiovascular complications rate is similar in pheochromocytoma versus non-secreting tumors group patients.

If this hypothesis is confirmed, the role of specific medical preparation prior to pheochromocytoma surgery will need to be re-evaluated in a randomized study comparing specific preparation with no specific preparation.



**V. Method:**

We propose a prospective, observational, multicenter, multinational study based on the EUROCRINE® registry. The study will use the my-EUROCRINE® module to add study-specific variables for patients included in the study protocol. Centers that transfer data to the EUROCRINE® registry will be invited to participate in this project. Patients with pheochromocytoma and non-secreting tumor (corresponding to patients with indication for surgery = « excluding malignancy » or « metastasis ») will be included.

All patients included will undergo a preoperative biological assessment (blood, urine, or not performed), an assessment of the dosage and duration of preoperative medical preparation using alpha-blockers (or not performed), an assessment of all intraoperative hypertensive and hypotensive crises (duration of all episodes defined according to validated criteria), and an assessment of cardiovascular complications at D30 using a predefined definition of nine cardiovascular events.

Consecutive patient enrolment is necessary to accurately reflect real clinical conditions. The standard variables are recorded as usual, with the addition of extra-variables (using My Eurocrine) and detailed in the CRF.

For defining intraoperative hypertensive episode(s), we opted to utilize the established Nazari et al. definition published in 2023 1 (> 180 mmHg for systolic blood pressure and/or > 120 mmHg for diastolic blood pressure). For defining intraoperative hypotensive episode(s), we used the Sessler and al. published definition in 2019 (mean arterial pressure < 65 mmHg)(POQI consensus) 3 . For these two intraoperative criteria, the total duration (in minutes from induction to discharge from the operating room) of the episodes is collected at the end of the surgery in collaboration with the anesthesia team.

For defining intraoperative cardiovascular complications and at 30 days after adrenalectomy, we used the definition by Beattie et al. 2, which corresponds to the presence of one or more of the nine clearly defined following events: myocardial infarction (MI), myocardial injury, cardiovascular death, non-fatal cardiac arrest (NFCA), coronary revascularization (CR), major adverse cardiac events (cardiac death or MI or CR or NFCA), pulmonary embolism, deep vein thrombosis, and atrial fibrillation.

Inclusion Criteria:

- Adult patients (≥ 18 years of age) undergoing adrenalectomy for pheochromocytoma and non-secreting tumors. Patients with non-secreting tumors are those with indication for adrenalectomy in Eurocrine corresponding to « excluding malignancy » or « metastasis ».

Exclusion Criteria:

- Children and minors (<18 years). - Pregnant women.

- Patients with other indication for adrenalectomy in Eurocrine (i.e. Adrenocortical cancer, Cushing, Primary aldosteronism).

Sample Size Calculation:

The sample size for this study was determined based on the desired power (1- β), and expected complication rate (*p*). A significance level (α) of 0.05 was chosen for hypothesis testing. For this study, a desired power of 0.9 was selected. In this study, the expected complication rate of cardiovascular complications in the pheochromocytoma group was estimated at 6% and in the non-secreting tumor group at 1% (5% difference). The calculated total sample size was approximately 522 participants (261 in each group)

To compare patient outcomes in pheochromocytoma versus non-secreting tumor, a sample size of 522 patients is necessary based on the given assumptions. Data collection will continue for two years or until 522 patients are included.

**VI. Planned Study**

As of August 2025, the European registry for endocrine surgery, EUROCRINE®, has documented 215,000 endocrine surgical procedures conducted across 141 centers in Europe. Among these, an estimated 150 cases per year underwent adrenalectomy for pheochromocytoma. This study by the Eurocrine Council is intended for all European centers participating in Eurocrine (n=141). Data collection will continue for two years or until 522 patients are included.

Statistical analyses will be performed using SAS software. The descriptive analyses will comprise measures of central tendency, dispersion, and location for quantitative variables, as well as frequency distributions for qualitative variables. Logistic regression will be used to compare the complication rate (primary endpoint) between groups (pheochromocytoma versus non-secreting tumor). Adjustments will be made for covariates such as age, gender, comorbidities, BMI, clinical volume, specific preoperative preparation (use, dosage, and duration), and the duration of intraoperative hypertensive and hypotensive episodes. The level of statistical significance will be set at p < 0.05.

**VII. Study timeframe**

The study is expected to run for two years beginning in September 2025, with the duration depending on the number of participating clinics.

**VIII. Variables extracted from Eurocrine (routine data)**

* All variables in the Eurocrine database must be used and filled in as is routinely done (core variables).

**IX. Additional variables (my Eurocrine® module):  additional variables are listed in the CRF for data acquisition “on the go”.**

**- Preoperative variables:** preoperative plasma catecholamines levels (x times normal upper limit), preoperative urinary catecholamines levels (x times normal upper limit), alpha-blockade for specific preoperative medical preparation (dosage in mg per day, duration in days)

**- Intraoperative variables:** duration of all intraoperative blood pressure episode(s) > 180 mmHg systolic and/or > 120 mmHg diastolic between induction and discharge from the operating room (duration in minutes), duration of all intraoperative mean arterial pressure episode(s) below 65 mmHg between induction and discharge from the operating room (duration in minutes).

**- Postoperative variables:** cardiovascular complications at postoperative day 30 among the following cardiovascular events: myocardial infarction (MI), myocardial injury, cardiovascular death, non-fatal cardiac arrest (NFCA), coronary revascularization (CR), major adverse cardiac events (cardiac death or MI or CR or NFCA), pulmonary embolism, deep vein thrombosis, and atrial fibrillation.

**X. Importance of research project**

Previously, only retrospective studies could analyse data on cardiovascular complications after adrenalectomy for pheochromocytoma. However, with the EUROCRINE® registry, which has a large number of cases and high-quality data collection, we can now address this question in a prospective study. This is expected to provide a higher level of evidence. If confirmed, the data from this study could be used to justify conducting a large-scale randomized study evaluating the role of alpha-blockers in specific preoperative medical preparation prior to adrenalectomy for pheochromocytoma.

**XI. Principal Investigator (PI) and all coworkers**

**Principal Investigator**

Claire Nomine-Criqui, MD, University of Lorraine, CHRU Nancy, Department of Metabolic and Endocrine Surgery (CVMC), INSERM – NGERE, 54000 Nancy, France

**Coworkers** (other EUROCRINE® coworkers could be added voluntarily):

Eurocrine Council group members

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**Authors from each participating clinic that enrolled patients Senior author:**

XX (EUROCRINE®- board; manuscript revision)

**XII. Ethical and legal aspects**

In accordance with applicable ethical and legal guidelines, including the CNIL (Commission Nationale Informatique et Liberté) and the Declaration of Helsinki.

**XIII. Application to Ethical Committee**

Name of Ethical Committee: CHRU Nancy Ethics approval 15.05.2025 (number 8372 - Endocrine Tumour Database)( [dporecherche@chru-nancy.fr](mailto:dporecherche@chru-nancy.fr)). Approved by the Eurocrine Council 24.01.2025.

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**XV. References**

1 Nazari MA, Hasan R, Haigney M, et al. Catecholamine-induced hypertensive crises: current insights and management. *Lancet Diabetes Endocrinol* 2023; **11**: 942-54

2 Beattie WS, Lalu M, Bocock M, et al. Systematic review and consensus definitions for the Standardized Endpoints in Perioperative Medicine (StEP) initiative: cardiovascular outcomes. *Br J Anaesth* 2021; **126**: 56-66

3 Sessler DI BJ, Aronson S, Berry C, Gan TJ, Kellum JA, Plumb J, Mythen MG, Grocott MPW, Edwards MR, Miller TE; Perioperative Quality Initiative-3 workgroup; POQI chairs; Miller TE, Mythen MG, Grocott MP, Edwards MR; Physiology group; Preoperative blood pressure group; Intraoperative blood pressure group; Postoperative blood pressure group. Perioperative Quality Initiative consensus statement on intraoperative blood pressure, risk and outcomes for elective surgery. *Br J Anaesth* 2019; **122**: 563-74