MLCTO
SHARING KNOWLEDGE

CLINICAL INVESTIGATION PLAN

JetCTO:

A retrospective, multi-center registry evaluating the clinical and angiographic outcome of covered stents for the treatment of coronary perforation during CTO procedures.

Protocol Code:
MLCTO_001 Version 1.0 05/10/2021

Written by:
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Protocol title:

JetCTO: a retrospective, multi-center registry evaluating the clinical and angiographic outcome of covered stents for the treatment of coronary perforation during CTO procedures.

Compliance Statement

This study will be performed in compliance with Declaration of Helsinki, EN ISO 14155:2011 guidelines and MEDDEV 2.7/1_4 guidance

INVESTIGATOR AGREEMENT

I have read and understood the protocol and agree that it contains all the ethical, legal an scientific information necessary to conduct this study. I will personally conduct the study as described in this protocol. I will provide copies of the protocol to all physicians, nurses and other professional personnel who will be involved in the study. I will discuss the protocol with them and make sure they are sufficiently informed regarding the conduct of the study in general.

I am aware that this protocol must be approved by the Ethics Committee responsible for such matters in the Clinical Study Facility where the study will be performed prior to commencement of this study.

I agree to strictly adhere to the attached protocol and agree that clinical data entered on case report forms by me and my staff will be utilized by the Sponsor for non-for-profit purposes including presentations and publications in the medical literature.

I further agree to report to the Sponsor/Ethics Committee any adverse experiences in accordance with the terms of this protocol.

Principal Investigator _____ *Date* _____

1 STUDY ORGANIZATION

Executive Committee

Alexandre Avran, Kambis Mashayekhi, Stéphane Carlier

Project Management

Chadi Ghafari

Statistics Coordinator

Alessandro Scalia

Data Safety Monitoring Board

Roberto Garbo, Thomas Hovasse

SPONSOR

UMONS, University of Mons, a public university incorporated under the laws of Belgium, with registered office at Place du Parc, 20, 7000 Mons, Belgium, registered with the VAT under the number BE 0850 123 935.

With an unrestricted educational grant from

MLCTO Academy

15, boulevard Grawitz, 13016 Marseille 16

FRANCE

2 PROTOCOL SYNOPSIS

Title	**JetCTO:** a retrospective, multi-center registry evaluating the clinical and angiographic outcome of covered stents for the treatment of coronary perforation during CTO procedures.
Sponsor	**UMONS** With an unrestricted educational grant from **MLCTO Academy.**
Principal Investigator	*Alexandre AVRAN*, MD
Participating centers	BELGIUM : Centre Hospitalier Universitaine Ambroise Paré, Mons; Universitair Ziekenhuis Gent; Ziekenhuis Oost-Limburg Genk; Centre Hospitalier Jolimont, La Louvière; FRANCE : Clinique Pasteur, Nancy ; Groupe Cardiologie Interventionnelle Nice Côte d'Azur (GCINCA), Clinique St George, Nice; *Full list and registration available on https://academy.mlcto.com/*
Starting Date	November 1, 2021
Version	1.1
Principle of Good Clinical Pactice	The study will be conducted in accordance with the ethical principles of the Helsinki declaration and are consistent with ICH good clinical practice and regulatory requirements.
Confidentiality	This protocol is owned by the principal investigators and cannot - in whole or in part - be transmitted, reproduced, published or otherwise used without permission.
Device	Any CE mark approved covered stent.
Trial Design	Retrospective, observational registry.
Study Population	Retrospective clinical data of eligible patients, who meet the inclusion criteria, will be collected in an on-line database.
Duration of the Study	Study Initiation: November 2021 Study End: March 2023

2 PROTOCOL SYNOPSIS

Rationale	Coronary perforation occurring during a CTO procedure is a rare complication with potential major adverse cardiac events. The long-term clinical and angiographic outcome of such perforation that needs sealing with a covered stent need to be refined in a large international registry.
Study Endpoints	**Primary Endpoint:** To assess the long-term (>6 months) angiographic patency of any covered stent used to seal the perforation during a CTO procedure. **Secondary Endpoint:** **1 -** Clinical follow up of such patients suffering from a coronary perforation treated with a covered stent; **2 -** Rate of complications (composite of cardiac death, myocardial infarction, major bleeding and cardiac tamponade) of the index procedure.
Follow up	Clinical and angiographic status at 6-month.
Sample Calculation	The objective of the registry is to collect retrospective multicentric observational data of a rare major adverse event that can occur during a percutaneous coronary intervention (PCI) for the treatment of a chronically occluded coronary artery (CTO). As such a power calculation is not indicated and we will collect the events from all centers willing to parciape in this collective registry.
Inclusion Criteria	**1 -** Chronic total occlusion lesion **2 -** Objective perforation during CTO procedure **3 -** Covered stent implantation **4 -** Angiographic follow-up procedure
Exclusion Criteria	**1 -** Patient <18 years old **2 -** Pregnant female **3 -** Contraindication to dual antiplatelet therapy **4 -** Thrombocytopenia <100 000 **5 -** Patients not willing to participate retrospectively to clinical research
Procedure Protocole	Patients will be treated following local standards. For this registry, the clinical events will be anonymously collected in a secured on-line database indicated for clinical research *(https://projectredcap.org/).*

3 PURPOSE

The purpose of this study is to describe in a large international collaborative network the occurrence and outcome of coronary perforations complicating a CTO procedure.

4 SCOPE

The scope of this protocol is the clinical and angiographic outcome after a coronary perforation in patients treated by a percutaneous coronary intervention (PCI) for the treatment of a chronically occluded coronary artery (CTO).

5 BACKGROUND

Coronary artery perforation (CAP) is a rare but dreadful complication of percutaneous coronary intervention (PCI) which in several cases may lead to cardiac tamponade, myocardial infarction, cardiogenic shock or even death [1]. Global incidence of CAP recently reported in a meta-analysis was 0.43% [2]. This incidence varies according to the technique used and is more frequently associated with debulking techniques such as rotational atherectomy [3].

Predictive risk factors have been identified in multiple studies and can be classified in two groups. Patient's related risk factors include female gender, previous coronary artery bypass graft, age and additional cardiovascular risk factors. Procedure's related risk factors are chronic total occlusion treatment, the use of rotational atherectomy, number of stent used and complex coronary artery lesions (ACC/AHA classification) [4, 5].

Ellis defined a classification for coronary perforation. Type I perforation is an extraluminal crater without extravasation while type II is a pericardial or myocardial blush and type III is an extravasation through a frank perforation of >1mm. This third type can shunt in an anatomic cavity (chamber or coronary sinus). Pooled mortality rate were higher in the Ellis class III patients (21,2% vs 0,4%) [2]. Indeed, the prognosis depends on the severity of CAP and the most adverse outcomes are reported in the Ellis type III. Chetana Krishnegowda & al reported a 6% periprocedural myocardial infarction, 10% in-hospital mortality rate and 16% mortality at 6 months [6]. In the report by Lemmert & al CAP is associated with a considerable morbidity and mortality rate around 10,7% at 30 days and 17,8% at 1 year [7].

Treatment of coronary perforation requires urgent detection, classification, hemodynamic stabilization and specific treatment. Adequate blood pressure support, reversal of anticoagulation treatment, platelet transfusion and pericardiocentesis are the primary life-saving measures. Specific treatment depends on Ellis classification and rely on prolonged balloon inflation in type II CAP and covered stents and coil induced embolization for type III CAP.

Clinical outcomes evaluation of CAP treatment have highlighted that polytetrafluoroethylene stent is associated to a higher risk of stent thrombosis, pericardiocentesis and emergency surgery when compared to papyrus or pericardial stents [8, 9]. Emergency surgery to repair and ligate the vessel and bypass the others is associated with poor outcomes and prognosis [10].

6 INTRODUCTION TO STUDY PLAN

6.1 - RATIONALE

Percutaneous transluminal coronary angioplasty (PTCA) consists in coronary stenosis dilatation through the inflation of a balloon in the lumen of the vessel improving coronary lumen diameter and consequently perfusion. PTCA is associated with a controlled injury of the vessel involving a plaque fracture and subsequent stretching of the vessel wall.

6.2 - CLINICAL NEED

Balloon angioplasty (POBA) has been for years the only method employed in percutaneous treatment of patients with coronary artery disease (CAD). The later development of stent-based technologies improved the safety and effectiveness of percutaneous coronary intervention (PCI) as compared to balloon angioplasty alone. In some circumstances, overstrechting of the vessel, or a perforation by the wire used to cross the coronary narrowing / occlusion will lead to a perforation.

6.3 - COVERED STENTS

One or more stents are placed after POBA in most PCI procedure at the end to keep the artery widely patent and avoid liminal recoil. It is made of a metallic mesh. Some of them have been specifically designed with a polytetrafluoroethylene membrane, or other biocompatibel material in order to seal coronary perforation.

Under fluoroscopy, while maintaining guidewire position, the device is advanced out of the guide catheter into the selected coronary artery and positioned within the lesion by centering the two radiopaque markers. Then it should be inflated to nominal pressure and sealing of the perforation checked with contrast injection

7 STUDY PLAN

7.1 - STATISTICAL PLAN

No power calculation is indicated in a retrospective collaborative registry aiming to give a cross-section incidence of this rare PCI complication in all participating centers.

7.1.1 - Inclusion criteria

- ☐ Chronic total occlusion lesion
- ☐ Objective perforation during CTO procedure
- ☐ Covered stent implantation
- ☐ Angiographic follow-up procedure

7.1.2 - Exclusion criteria

- ☐ Patient <18 years old
- ☐ Pregnant female
- ☐ Contraindication to dual antiplatelet therapy
- ☐ Thrombocytopenia <100 000

7.1.3 - Risks and benefits

Indication to PCI, PCI itself and medical management of patients will follow scientific evidences and guidelines. No adjunctive riks than those included in a standard PCI can be foreseen from a retrospective examination of their files.

7.1.4 - Safety

Safety evaluation will rely on all adverse events (AE) and serious adverse events (SAE) found in the patients' hospital records collecting clinically relevant abnormalities on physical examinations, vital signs and laboratory tests.

Procedure-related expected complications

PUNCTURE RELATED:

- Local hematoma
- Local hemorrhage
- Local or distal thromboembolic episodes
- Thrombosis
- AV fistula
- Pseudo aneurysm
- Local infection

PTCA DILATATION RELATED:

- Dissection in the dilated vessel wall
- Perforation of the vessel wall
- Prolonged spasms
- Acute re-occlusion necessitation surgical intervention
- Restenosis of the vessel
- Total occlusion of the vessel

ANGIOGRAPHY RELATED:

- Hypotension
- Pain
- Arrhythmias
- Sepsis/infection
- Systemic embolization
- Endocarditis
- Short-term hemodynamic deterioration
- Death
- Drug reactions
- Allergic reaction to contrast medium
- Pyrogenic reaction

7 STUDY PLAN

7.1 - STATISTICAL PLAN

7.1.5 - Rationale and justification of chosen study design

The study was designed to retrospectively record procedural success and long-term clinical and angiographic outcome in patients who suffered from a coronary perforation during a PCI performed on their CTO.

7.1.6 - Study site and investigators

The primary investigator site is the Clinique Pasteur in Nancy, FRANCE which is considered to be an appropriate clinical facility. The PI will be Dr Alexandre Avran. The hospital has a high load of PCI cases with a high number of complex cases.

The following other centers in Belgium are involved in this study
- Centre Hospitalier Universitaire Ambroise Paré, Mons, Dr. Carlier S. and colleagues
- UZ Gent, Gent, Dr. Kayert P. and colleagues
- ZOL Genk, Genk, Dr. Dens J. and colleagues
- Hôpital Jolimont, La Louvière, Dr. Ungearu C. and colleagues

Many other centers will be included and recruited via https://academy.mlcto.com/

Approval by each local ethic committee will be asked.

The study will be conducted by trained physicians who have acquired the necessary expertise and experience in executing PCI procedures and Good Clinical Practice.

7.1.7 - Organization, data collection and interim reporting

The Sponsor of this clinical trial will be UMONS, that takes the responsibility to initiate and manage this registry with an unrestricted educational grant from the MLCTO Academy. The University of Mons (UMONS) will host the anonymized clinical database on a Redcap server suited for clinical research. Safety of the registry will be assessed by an independent safety committee. Where applicable follow-up actions will be defined and executed.

The data will be collected in a on-line Case Report Form given in appendix 2.
No interim analyses will be performed.
At the end of the study a report/publication will be written under the responsibility of the steering committee.

7.1.8 - Procedures/ criteria for early study termination

Not applicable

7.1.9 - Ethical considerations

Evaluation by a local ethical review will be seeked before starting data collection in each participating center.

7 STUDY PLAN

7.2 - INFORMED CONSENT

No informed consent is deemed necessary in this retrospective review of clinical charts, for unpractical reasons related to the foreseen difficulties to reach out to these patients.

7.3 - INSURANCE

In accordance with the European Law relating to experiments on human persons, Sponsor shall assume, even without fault, the responsibility of any breach in anonymized data incurred by a Study Patient and linked directly or indirectly to the participation to this registry, and shall provide compensation therefore through its insurance. Sponsor shall enter into an insurance agreement in order to cover the liability for any damages incurred by a Study Patient.

7.4 - CONFIDENTIALITY

Patient confidentiality will be maintained throughout the study. It will be ensured that the information can always be tracked back to the source data, if required. Data relating to the study might be made available to regulatory authorities preconditioned the data are treated confidentially and that the patient's privacy is guaranteed.

8 REFERENCES

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[4] Hussain HI, Protty MB, Gallagher S, et al. The impact of coronary perforation in percutaneous interventions involving the left main stem coronary artery in the United Kingdom 2007-2014: Insights from the British Cardiovascular Intervention Society database. Catheter Cardiovasc Interv Off J Soc Card Angiogr Interv 2021; 97: E179–E185.

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[6] Krishnegowda C, Puttegowda B, Krishnappa S, et al. "Incidence, clinical and angiographic characteristics, management and outcomes of coronary artery perforation at a high volume cardiac care center during percutaneous coronary intervention". Indian Heart J 2020; 72: 232–238.

[7] Lemmert ME, van Bommel RJ, Diletti R, et al. Clinical Characteristics and Management of Coronary Artery Perforations: A Single-Center 11-Year Experience and Practical Overview. J Am Heart Assoc; 6. Epub ahead of print 22 September 2017. DOI: 10.1161/JAHA.117.007049.

[8] Nagaraja V, Schwarz K, Moss S, et al. Outcomes of patients who undergo percutaneous coronary intervention with covered stents for coronary perforation: A systematic review and pooled analysis of data. Catheter Cardiovasc Interv Off J Soc Card Angiogr Interv 2020; 96: 1360–1366.

[9] Elison D, Dean LS. Cover up: Clinic outcomes of covered stent usage for coronary perforation during PCI. Catheter Cardiovasc Interv 2020; 96: 1367–1368.

[10] Nair P, Roguin A. Coronary perforations. EuroIntervention J Eur Collab Work Group Interv Cardiol Eur Soc Cardiol 2006; 2: 363–370.

APPENDIX - DATA PROCESSING ANNEX
DATA PROCESSING ANNEX ("DPA") TO THE PROTOCOL

Definitions:

"Protocol" means the document entitled **JetCTO** a retrospective, multi-center registry evaluating the clinical and angiographic outcome of covered stents for the treatment of coronary perforation during CTO procedures containing the details of the academic study as developed by the Sponsor as approved by the relevant ethics committee.

"Sponsor" means UMONS

Participating site acts as a data processor as defined under article 4, 8) of the Regulation (EU) 2016/679 **("Data Processor")** for the Sponsor who acts as data controller as defined under article 4, 7) of the Regulation (EU) 2016/679 **("Data Controller").**

"Applicable Law" means any applicable data protection or privacy laws, including:

(i) the European Data Protection Directive (95/46/EC) and upon its entry into force the Regulation (EU) 2016/679 also referred as the General Data Protection Regulation ("GDPR");

(ii) other applicable laws that are similar or equivalent to or that are intended to or implement the laws that are identified in (a) of this definition;

"Personal Data" means any information relating to an identified or identifiable natural person **('Data Subject'),** including without limitation pseudonimized information, as defined in Applicable Law and described in the Protocol.

Rights and obligations:

1) The Data Processor is instructed to process the Personal Data for the term of the Protocol and only for the purposes of providing the data processing tasks set out in the Protocol.

2) The Data Processor must ensure that persons authorized to process the Personal Data have committed themselves to confidentiality or are under an appropriate statutory obligation of confidentiality.

3) The Data Processor shall implement appropriate technical and organizational measures to prevent that the Personal Data processed is:

   (i) accidentally or unlawfully destroyed, lost or altered,
   (ii) disclosed or made available without authorization, or
   (iii) otherwise processed in violation of Applicable Law.

4) The appropriate technical and organizational security measures must be determined with due regard for:

   (i) the current state of the art,
   (ii) the cost of their implementation, and
   (iii) the nature, scope, context and purposes of processing as well as the risk of varying likelihood and severity for the rights and freedoms of natural persons.

APPENDIX - DATA PROCESSING ANNEX
DATA PROCESSING ANNEX ("DPA") TO THE PROTOCOL

5) The Data Processor shall upon request provide the Data Controller with sufficient information to enable the Data Controller to ensure that the Data Processor's obligations under this DPA are complied with, including ensuring that the appropriate technical and organizational security measures have been implemented.

6) The Data Controller is entitled to appoint at its own cost an independent expert, reasonably acceptable to Data Processor, who shall have access to the Data Processor's data processing facilities and receive the necessary information for the sole purpose of auditing whether the Data Processor has implemented and maintained said technical and organizational security measures. The expert shall upon the Data Processor's request sign a non-disclosure agreement provided by the Data Processor, and treat all information obtained or received from the Data Processor confidentially, and may only pass on, after conferral with Data Processor, the findings as described under 8) (ii) below to the Data Controller.

7) The Data Processor must give authorities who by Union or Member State law have a right to enter the Data Controller's or the Data Controller's processors' facilities, or representatives of the authorities, access to the Data Processor's physical facilities against proper proof of identity and mandate, during normal business hours and upon reasonable prior written notice.

8) The Data Processor must without undue delay in writing notify the Data Controller about:

   (i) any request for disclosure of Personal Data processed under the Protocol by authorities, unless expressly prohibited under Union or Member State law,

   (ii) any finding of (a) breach of security that results in accidental or unlawful destruction, loss, alteration, unauthorized disclosure of, or access to, Personal Data transmitted, stored or otherwise processed by the Data Processor under the Protocol, or (b) other failure to comply with the Data Processor's obligations, or

   (iii) any request for access to the Personal Data (with the exception of medical records for which the Data Processor is considered data controller) received directly from the data subjects or from third parties.

9) Such a notification from the Data Processor to the Data Controller with regard to a breach of security as meant in 8) (ii)(a) above will contain at least the following information:

   (i) The nature of the Personal Data breach, stating the categories and (by approximation) the number of Data Subjects concerned, and stating the categories and (by approximation) the number of the personal data registers affected (datasets);

   (ii) The likely consequences of the Personal Data breach;

   (iii) A proposal for measures to be taken to address the Personal Data breach, including (where appropriate) measures to mitigate any possible adverse effects of such breach.

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10) The Data Processor shall document (and shall keep such documentation available for the Data Controller) any Personal Data breaches, including the facts related to the Personal Data breach, its effects and the corrective measures taken. After consulting with the Data Controller, the Data Processor shall take any measures needed to limit the (possible) adverse effects of Personal Data breaches (unless such consultation cannot be awaited due to the nature of the Personal Data breach).

11) The Data Processor must promptly reasonably assist the Data Controller (with the handling of (a) responses to any breach of security as described in 8) (ii) above and (b) any requests from Data Subjects under Chapter III of the GDPR (upon its entry into force), including requests for access, rectification, blocking or deletion. The Data Processor must also reasonably assist the Data Controller by implementing appropriate technical and organizational measures for the fulfilment of the Data Controller's obligation to respond to such requests. The Data Processor must reasonably assist the Data Controller with meeting the other obligations that may be incumbent on the Data Controller according to Union or Member State law where the assistance of the Data Processor is implied, and where the assistance of the Data Processor is necessary for the Data Controller to comply with its obligations. This includes, but is not limited to, at the request to provide the Data Controller with all necessary information about an incident under 8) (ii), and all necessary information for an impact assessment in accordance with Article 35 and Article 36 of the GDPR.

Subprocessor:

12) The Data Processor may only engage a subprocessor, with prior specific or general written consent from the Data Controller. The Data Processor undertakes to inform the Data Controller of any intended changes concerning the addition or replacement of a subprocessor by providing a reasonable prior written notice to the Data Controller. The Data Controller may reasonably and in a duly substantiated manner object to the use of a subprocessor. The Data Processor must inform the Data Controller in writing of the discontinued use of a subprocessor.

13) Prior to the engagement of a subprocessor, the Data Processor shall conclude a written agreement with the subprocessor, in which at least the same data protection obligations as set out in this DPA shall be imposed on the subprocessor, including obligations to implement appropriate technical and organizational measures and to ensure that the transfer of Personal Data is done in such a manner that the processing will meet the requirements of the Applicable Law.

14) The Data Controller has the right to receive a copy of the relevant provisions of Data Processor's agreement with the subprocessor related to data protection obligations. The Data Processor shall remain fully liable to the Data Controller for the performance of the subprocessor obligations under this DPA. The fact that the Data Controller has given consent to the Data Processor's use of a subprocessor is without prejudice for the Data Processor's duty to comply with this DPA.