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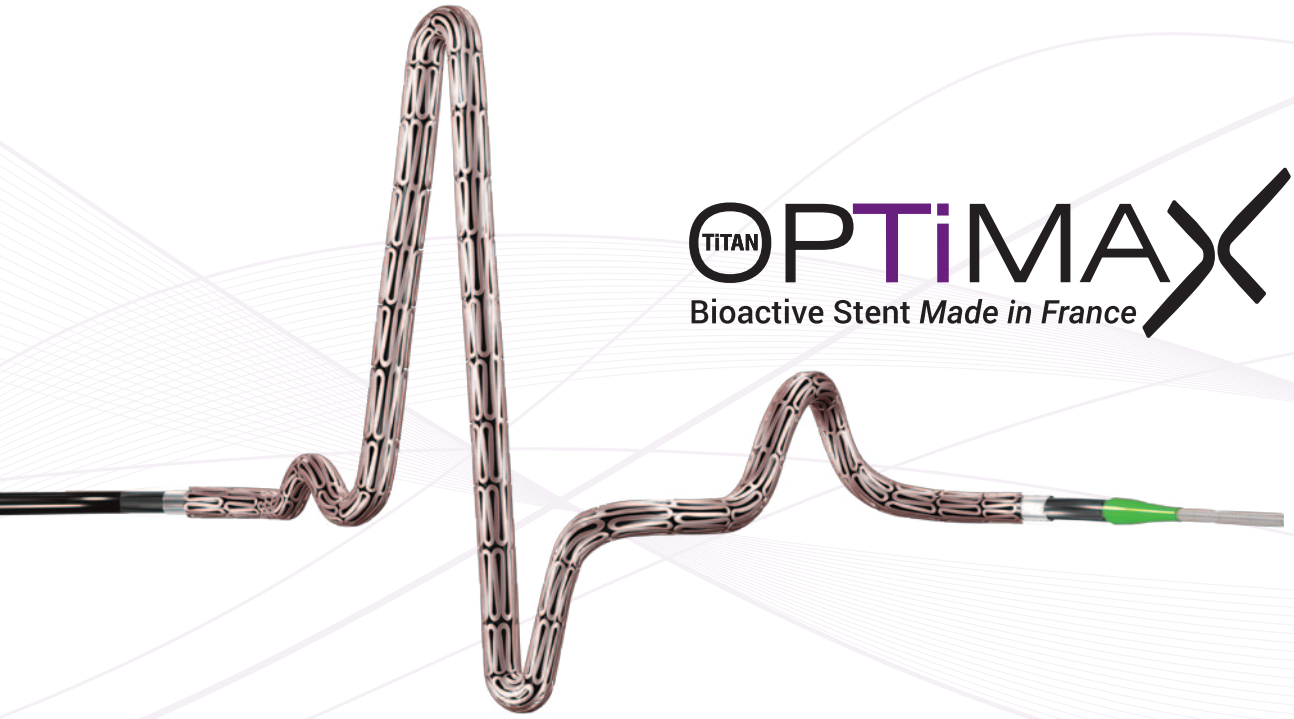
HEXACATH
PIONEER IN BIO ACTIVE COATING

Summary of safety and clinical performance

TiTAN OPTIMAX



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Summary of safety and clinical performance for users/healthcare professionals

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This Summary of Safety and Clinical Performance is intended to provide public access to an updated summary of the main aspects of the safety and clinical performance of the device.

The Summary of Safety and Clinical Performance is not intended to replace the Instructions for use as the main document to ensure the safe use of the device, nor is it intended to provide diagnostic or therapeutic suggestions to intended users or patients.

The following information is intended for users/healthcare professionals.

1 DEVICE IDENTIFICATION AND GENERAL INFORMATION

1.1 Device trade name

Trade names of devices are TITAN OPTIMAX

1.2 Manufacturer's name and address

Name and address of the legal manufacturer are the following:

- Name: HEXACATH (Headquarters)
- Address: 4, passage Saint-Antoine, 92500 Rueil-Malmaison - FRANCE

1.3 Manufacturer's single registration number (SRN)

The single registration number of Hexacath is FR-MF-000010342

1.4 Basic UDI-DI

Basic UDI-DI of TITAN OPTIMAX is: 037003857OPT00015T

1.5 Medical device nomenclature description

- Global Medical Device Nomenclature (GMDN) Code

53616: Coronary stent

- « European Medical Device Nomenclature » (EMDN) Code

P0704020105: Coronary stent Bioactive

1.6 Class of the device

TITAN OPTIMAX coronary endoprosthesis devices are class III medical device following the Regulation 2017/745.

1.7 Year when the first certificate (CE) was issued covering the device

TITAN OPTIMAX was first CE marked in 2011 following the Directive 93/42.
Since October 2021 TITAN OPTIMAX is CE marked following the Regulation (EU) 2017/745 of the european parliament and of the council of 5 April 2017.

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1.8 Notifed body's name and single identification number

The name and the single identification number of the notified body validating this Summary of Safety and Clinical Performance are the following:

- Name: GMED
- Single identification number: 0459

2 DEVICE DESCRIPTION

2.1 Description of the device

a) General description

The TITAN OPTIMAX stents are medical devices manufactured by HEXACATH consisting of a Titanium Nitride Oxide coated balloon-expandable stent, pre-mounted on a rapid exchange delivery catheter.

The stent is made from L605 cobalt-chromium alloy which consists of a cobalt*, chromium, tungsten and nickel alloy. It is a flexible tubulo-modular structure entirely coated with Titanium Nitride Oxyde and deployable by means of a balloon catheter. The surface area in contact with the artery varies from 9 mm^2 to 69 mm^2 depending on the diameter and length of the stent.

The delivery catheter on which the stent is pre-mounted is mainly composed of a flexible distal tip, balloon and tubes made from polymers (Polyamid, Polyether) and a stainless steel hypotube. The outer surface is coated with a non-active hydrophilic coating.

The balloon has two radiopaque markers made from platinium/iridium, proximal and distal, to identify the location of the stent on the balloon.

Two proximal markers located at 90 and 100 cm from the distal end help to assess the position of the catheter in relation to the tip of a guide catheter used for radial, brachial or femoral approaches.

The delivery catheter is equipped with a proximal luer-lock port made from polycarbonate for connection to an inflation device.

The TITAN OPTIMAX stents are sterile, sterilized by Ethylene oxide gas, for single use only, and packed in individual unit. Its shelf life is 5 years

**Note: The presence of Cobalt material representing more than 0.1% of the stent structure weight classifies it as CMR (carcinogenic, mutagenic or toxic to reproduction) type 1B according to regulation (CE) 1272/2008. However, this substance is unlikely to come in contact with the human body, or to be released in the body tissues due to the existence of the Titanium Nitride Oxide coating which covers the entire surface of the stent. Therefore, no particular precaution has to be taken due to the presence of the Cobalt*

b) General description of the key functional elements

TITAN OPTIMAX coronary endoprosthesis devices are composed of:
- A tip
- A balloon
- A crimping stent
- A catheter

- Marker bands
- A hypotube
- A strain relief
- A hub to connect the inflation system

c) Materials or substances in contact with patient's tissues

The following materials are in contact with patient's tissues and blood:

- Concerning the catheter:
  - Polycarbonate
  - Stainless steel
  - PTFE coating
  - Polyamide
  - Polyethylene
  - Acrylic

- Concerning the stent
  - Titanium Nitride Oxide

d) Principe of operation and mode of action

The TITAN OPTIMAX coronary premounted stent system makes it possible to treat local contraction of coronary arteries caused by certain illnesses such as arteriosclerosis, which can impede blood circulation. The general principle of these permanent protheses is the insertion of a metal mesh in the damaged area to keep the duct open at a normal diameter. It is a meshed, cylindrical structure that can be implanted and later adapt itself to the walls of the vessel while retaining permeability for the side branches.

This product treats local shortening of coronary arteries, allowing a myocardial revascularization for patients displaying myocardial ischemia related to a coronaropathy.
A sheath is introduced in the groin (or occasionally in the femoral artery). Through this sheath, a long, flexible, soft plastic tube or guiding catheter is advanced and the soft-tip positioned into the opening of the coronary artery. The tube measures 2 to 3 mm in diameter. The soft-tip of the catheter is directed or controlled when the cardiologist gently advances and rotates the end of the catheter that sits outside the patient.

Once the catheter soft-tip is seated within the opening of the coronary artery, x-ray movie pictures are recorded during the injection of contrast material.
After evaluating the x-ray movie pictures, the cardiologist estimates the size of the coronary artery and selects the type of balloon catheter and guide-wire that will be used during the case.
The guide wire which is an extremely thin wire with a flexible tip is inserted into through the catheter guide and into the coronary artery. The tip of the wire is then guided across the blockage and advanced beyond it. The cardiologist controls the movement and direction of the guide wire by gently manipulating the end that sits outside the patient. This wire now serves as a "guide" or rail over which the balloon catheter stent system can be advanced up to the target lesion and the stent delivered at the lesion.

Then, the balloon is inflated by connecting it to a special indeflation device. A mixture of saline and contrast material is used to inflate the balloon and deploy the stent. The balloon catheter also has metallic markers to be located. This helps the cardiologist know the location. The balloon is kept inflated for a few seconds and then deflated.
The deflated balloon and guide-wire are withdrawn when the cardiologist is satisfied with the results. Final angiograms or movie x-ray pictures are taken upon completion of the case. The guiding catheter is then withdrawn.

The sheath is secured to the groin with a suture and the patient is sent to his or her room. In case of radial road, a simple compression is required.

How the stent is fitted:

Before fitting a stent, the surgeon generally begins with an angioplasty. This involves inflating a balloon at the damaged segment of artery, so as to open it sufficiently for the stent to be introduced.
The result of angioplasty is not perfect: the artery is still obstructed and the blood flow restricted.
The surgeon then has the option of implanting a stent. The stent is mounted on a catheter equipped with a balloon and is thus guided towards the obstructed section of artery.
The balloon is inflated, which deploys the stent to the desired diameter.
Then the balloon is deflated and withdrawn with the catheter. As the stent's form has been altered, it stays in place wedged against the vessel walls.
In this way the stent keeps the artery completely open, allowing a free passage for the blood.

2.1 Reference to previous generation and variants

a) Reference to previous generation

TITAN OPTIMAX is the third generation of coronary premounted stent systems developed by Hexacath since 1999, the first two generations being Helistent (bare Stainless-steel stent) followed by Helistent TITAN 2 (Stainless steel stent coated with TiNO = Titanium Nitride Oxide).

TITAN OPTIMAX (previously called TITAN III) has been developed based on the Helistent TITAN 2 technology. The main differences between both systems are the material and the cell design of the stent platform as well as some minor improvements in the carrier catheter, intended to achieve better deliverability.

While TITAN OPTIMAX stent is made of L605 alloy, Helistent TITAN 2 is made of 316L stainless steel. CoCr has been selected for its biocompatibility, strength, non-ferromagnetism, and high resistance to fatigue and corrosion. The higher strength of CoCr allows thinner stent struts while maintaining good radial strength. The use of this material enables to reduce the metallic surface in contact with vessel wall in order to decrease inflammation reactions while maintaining the mechanical characteristics. Moreover, the stent design was improved to achieve better flexibility and easier navigability in tortuous vasculature while maintaining the radial force.

As TITAN 2, TITAN OPTIMAX is also coated with TiNO.

b) Various configuration and variants

TITAN OPTIMAX devices are available in ten stent lengths: 7, 10, 13, 16, 19, 22, 25, 28, 32, 38 mm, and in nine different stent diameters: 2.0, 2.25, 2.5, 2.75, 3.0, 3.5, 4.0, 4.5 and 5.0 mm in the following combinations:

Diameter (mm) / **Lengths (mm)**	**(Size)**	**7**	**10**	**13**	**16**	**19**	**22**	**25**	**28**	**32**	**38**
2.0	(XS)	✓	✓	✓	✓						
2.25	(XS)	✓	✓	✓	✓						
2.5	(XM)	✓	✓	✓	✓	✓	✓	✓	✓		
2.75	(XM)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
3.0	(XM)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
3.5	(XM)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
4.0	(XM)		✓	✓	✓	✓	✓	✓	✓	✓	✓

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4.5	(XL)			✓	✓	✓					
5.0	(XL)			✓	✓	✓					

2.2 Recommended equipment

- A puncture kit
- Appropriately sized guide catheter: 5F guide catheters, with a minimum inner lumen of 0.058" (1.47 mm), allow for the advancement of pre-mounted TiTAN OPTIMAX stents from 2.0 mm to 4.0 mm in diameter. The 6F guide catheters, with a minimum internal lumen of 0.064" (1.62 mm), allow for the advancement of pre-mounted TiTAN OPTIMAX stents from 4.5 and 5.0 mm in diameter).
- A 0.014" coronary guide of appropriate length
- An appropriate syringe
- An appropriately sized haemostasis valve
- A 3-way stopcock
- An inflation device
- Heparinized saline solution
- Contrast agent diluted with saline solution in a 1:1 ratio
- A flushing needle

3 INTENDED USE OF THE DEVICE

3.1 Intended purpose

The TITAN OPTIMAX is a coronary premounted stent system (stent crimped on the balloon of carrier catheter).
The carrier catheter introduces and deploys the stent into the native coronary arteries or vessel grafts of the targeted patients. The TITAN OPTIMAX stent is intended to be implanted in the native coronary arteries or vessel grafts of targeted patients for improving coronary luminal diameters.

3.2 Indications and target population

a) Indications

The TITAN OPTIMAX is indicated for improving coronary luminal diameters in adult patients with symptomatic ischemic heart disease including patients with acute myocardial infarction (STEMI/NSTEMI, unstable angina) and patients with concomitant diabetes mellitus due to de novo coronary artery lesions. The treated lesion length should be less than the nominal stent length (7mm to 38 mm) with a reference vessel diameter of 2.0 to 5.0 mm.

b) Intended patient population

The TITAN TITAN OPTIMAX stent system is intended to be implanted, in adult patients, with symptomatic ischemic heart disease including patients with acute myocardial infarction (STEMI/NSTEMI, unstable angina) and patients with concomitant diabetes mellitus due to de novo coronary artery lesions".

c) Intended user population

TITAN OPTIMAX stenting should only be performed at hospitals or clinics authorized for the practice of coronary angioplasty by physicians with technical expertise in coronary angioplasty and who can be assisted by physicians capable of treating major clinical complications by cardiac-surgery.

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3.3 Contraindications

- Patients with contraindications to anticoagulant/ antiplatelet therapy
- Allergy to contrast agents.
- Patient with a known hypersensitivity or allergy to Titanium Nitride Oxide (TiNO)
- Major surgery within the previous two weeks, childbirth, puncture of an incompressible vessel or biopsy.
- History of bleeding.
- Pregnancy.
- Lesions proximal to an untreatable segment, significantly limiting blood flow.
- Fibrous or calcified lesions, refractory to dilation (resistant to pre-dilations at high pressure of 20 Bars).
- In stent restenosis in coronary artery lesions.
- Implantation in tortuous vessels with limited access to the site to be treated, diffuse vascular disease with reduced flow, and lesions located after acute angles, can be challenging situations for stenting.

4 RISKS AND WARNINGS

4.1 Residual risks and undesirable effects

In the risk management process carried out by HEXACATH; all residual risks have been analyzed. The benefit / risk ratio of each individual risks is favorable to the benefit. In addition, all the risks in relation with the use of the TITAN OPTIMAX devices have been reduced to an acceptable or tolerable level and the overall residual risk is low enough to put on the market the device with a favorable benefit/risk balance.
All residual risks are mentioned in the instruction for used of TITAN OPTIMAX in the section warnings and precautions.

Observed adverse effects comes from the TIDES-ACS[1] clinical trial, the TIOMAX[2] registry and the OPTIMAX "first in man" study[3]. They are summarized in the table below.

	TIDES-ACS	**TIOMAX**	**OPTIMAX first in man**
1 month follow-up			
Death		1.4% (7/511)	
Cardiac death		1% (5/511)	
Stent thrombosis (definite or probable)		0.4% (2/511)	
12 months follow-up			
All-cause Death	0.9% (9/989)	4.1% (21/511)	2.2% (5/224)
Non cardiac Death	0.4% (4/989)	2.3% (12/511)	0.9% (2/224)
Cardiac Death	0.5% (5/989)	1.8% (9/511)	1.3% (3/224)
Stent thrombosis (definite or probable)	1.1% (11/989)	0.6% (3/511)	0% (0/224)
Myocardial infarction (MI)	1.8% (18/989)	2.5% (13/511)	3.1% (7/224)

[1] *Tonino P. et al., Titanium-Nitride-Oxide-Coated versus Everolimus-Eluting Stents in acute coronary syndrome the randomized TIDES-ACS-Trial, JACC Cardiovascular Intervention*
[2] *López-Mínguez JR. et al, TIOMAX; A Spanish Multicenter Registry of the real-world use of the Titanium Optimax biostent, Catheter Cardiovascular Intervention*
[3] *Karjalainen PP. et al, Clinical outcome of titanium-nitride-oxide-coated cobalt chromium stents in patients with de novo coronary lesions: 12-month results of the OPTIMAX first-in-man study, Catheter Cardiovascular Intervention*

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	TIDES-ACS	TIOMAX	OPTIMAX first in man
Target lesion revascularisation (TLR)	5.4% (53/989)	2.9% (15/511)	3.1% (7/224)
Target vessel revascularisation (TVR)	6.6% (65/989)	2.9% (15/511)	4.0% (9/224)
Major bleeding	1.2% (12/989)		
18 months follow-up			
All-cause Death	1.1% (11/989)		
Non cardiac Death	0.5% (5/989)		
Cardiac Death	0.6% (6/989)		
Stent thrombosis (definite or probable)	1.1% (11/989)		
Myocardial infarction (MI)	2.2% (22/989)		
Target lesion revascularisation (TLR)	5.8% (57/989)		
Target vessel revascularisation (TVR)	7.1% (70/989)		
Major bleeding	1.4% (14/989)		

Potential adverse effects associated with the stenting procedure include but are not limited to:

- Allergic reaction to contrast media, antiplatelet aggregation and/or anticoagulant medications, stent TiNO coating
- Angina
- Arteriovenous fistula
- Arrhythmias, including ventricular fibrillation
- Bleeding
- Coronary artery spasm
- Death
- Embolism
- Fever
- Haemorrhage or haematoma
- Hypotension/hypertension
- Infection, local or systemic (sepsis)
- Myocardial infarction (MI)
- Need for immediate coronary bypass surgery
- Vessel and/or coronary artery injury, perforation, rupture and/or dissection
- Restenosis of the dilated artery
- Stent migration
- Stent thrombosis
- Vessel and/or coronary artery total occlusion c

4.2 Warnings and precautions

a) Warnings

- TITAN OPTIMAX should only be implanted in hospitals or clinics authorised to perform coronary angioplasty and by physicians with technical expertise in coronary angioplasty who may be assisted by physicians capable of treating major clinical complications with cardiac surgery.
- Check the expiry date on the packaging protecting the product's sterility. Do not use the device if the expiry date has passed.

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- Do not re-sterilise, reprocess and/or re-use the device. Do not re-use the stent if it fails to pass. Re-sterilisation, reprocessing and/or re-use may compromise the performance of the device and its integrity. Such actions may result in contamination of the device and/or cause patient infection or cross-infection. HEXACATH cannot be held responsible for any accidental, direct or consequential damage resulting from re-sterilisation or re-use of the product.
- Ensure the integrity of the catheter before use.
- Do not use if the stent or catheter is damaged (leakage, breakage, cracking, loose stent, stent not centred on the balloon etc.).
- Observe aseptic conditions during all phases of use.
- Do not use gauze pads; the fibres can damage the stent.
- Do not loosen and re-tighten the stent on another catheter. Do not reposition the stent on its catheter.
- Do not use any gas, air or other liquids to inflate the balloon other than those recommended in the instruction manual.
- Never inflate the balloon before final stent placement at a pressure exceeding 0.5 bar. This could result in the stent opening prematurely and being unable to progress through the artery.
- Do not inflate the balloon beyond the rated burst pressure (RBP). This increases the risk of balloon rupture, which can lead to vessel occlusion, balloon entrapment and associated complications.
- The catheter must be observed under fluoroscopy throughout the procedure.
- Never move the balloon with a pre-mounted stent forwards without ensuring that the stent is perfectly attached to the balloon. This could result in the loss of the stent before it is deployed in the vessel and could lead to acute myocardial infarction or death.
- Stents can cause nuclear magnetic resonance (or MRI) artefacts due to magnetic field distortion. These artefacts caused by the cobalt-chromium alloy of the stent are comparable to those caused by metallic surgical clips. In order to minimise the risk of stent migration under a strong magnetic field, it is recommended that a nuclear magnetic resonance examination is performed only after complete endothelialisation of the stent, i.e. at least three months after implantation.

b) Precautions

- Use the device before the expiry date.
- Store above 0°C and below 40°C, protected from light and moisture.
- Do not use if package has been damaged or opened.
- Before performing the angioplasty, check that the device is working properly and that it is the right size and shape for the procedure. Do not use the device if there is any damage or if there is any doubt about its integrity.
- Prior to inserting the catheter, administer the appropriate dose of coronary anticoagulant and vasodilator.
- Check that the air exhaust in each system is complete and that there are no leaks in the various connections

4.3 Other relevant aspect of safety

TITAN OPTIMAX has not been subject to any field safety corrective actions.

5 SUMMARY OF CLINICAL EVALUATION AND POST-MARKET CLINICAL FOLLOW-UP

5.1 Summary of clinical evaluation

The clinical evaluation of TITAN OPTIMAX stent systems is supported by clinical studies TITAN OPTIMAX as well as post-market follow-up and post market surveillance information inherent to TITAN OPTIMAX itself.

The main outcomes of the present TITAN OPTIMAX stent systems clinical evaluation are the following:

- The performance surveys conducted on TITAN OPTIMAX stents in normal conditions of use highlighted a very good customer acceptance and better performance results compared its predicate Helistent TITAN2;
- The publicly available safety information on competitive bare-metal coronary stents did not highlight any significant issue nor any new risk associated with bare-metal coronary stents in general;
- The results of post-market studies related to TITAN OPTIMAX demonstrate adequate performance and safety of the device. Clinical studies specific to TITAN OPTIMAX have shown satisfactory vascular healing and adequate 12-month clinical outcome in patients with de novo coronary lesions.

In addition, two trials on TITAN OPTIMAX were presented, providing additional clinical evidence versus second-generation drug-eluting stents on larger population:

- A trial intended to compare TITAN OPTIMAX versus the Everolimus-eluting stent Synergy in 1800 randomized patients with acute coronary syndrome;
- A study, exploring the 1- and 6-month neointimal healing response to the TITAN-OPTIMAX stent versus the Synergy stent evaluated by OCT, also in patients with acute coronary syndrome.

The clinical evidence allowed to state that the TITAN OPTIMAX stent system achieves its intended performance during normal conditions of use;
The clinical evidence and the post-market surveillance support that the use of the TITAN OPTIMAX does not compromise the safety of patients;
The state of the art and the clinical data have permit to demonstrate that the claimed clinical benefit for TITAN OPTIMAX stent systems is congruent and established.

5.2 Summary of clinical investigation

Name of study	# 1 Tides-ACS (Completed study)
Title of publication	Titanium-Nitride-Oxide–Coated Versus Everolimus-Eluting Stents in Acute Coronary Syndrome The detail data of the article is available in JACC, PubMed, Science Direct Reference : NCT : NCT02049229
Place of the study	Finland (6 centers), France (five centers) and Holland (2 centers)
Period and duration	January 2014 – (estimated) October 2015
Identity of the device	OPTIMAX stent (Experimental device) SYNERGY stent (Comparator)
Intended use of the device in the investigation	Percutaneous coronary intervention

Name of study	# 1 Tides-ACS (Completed study)
Objectives of the study	The purpose of the prospective, randomized and a multicenter trial is to compare clinical outcome in patients presenting with ACS, treated with PCI using Optimax-BAS versus Synergy-EES. Second objective is to explore whether the Optimax-BAS use is superior compared with Synergy-EES use with respect of hard end points (cardiac death, MI and major bleeding).
Study design:	The Randomized TIDES-ACS Trial
Primary and secondary endpoint(s)	The primary end point (MACE) is the composite of cardiac death, myocardial infarction (MI) and target lesion revascularization (TLR) during 12 months of follow-up (non-inferiority). Cardiac death, any myocardial infarction and major bleeding [Time Frame: 18 months] Co-Primary end point is the composite of during 18 months of follow-up (superiority).
	Secondary endpoint Composite of cardiac death, MI, stent thrombosis and TLR [Time Frame: 1, 6, 12 and 18 months, and at 2, 3, 4 and 5 years.] Composite of cardiac death, MI, stent thrombosis and TLR - Cardiac death or myocardial infarction [Time Frame: Cardiac death or myocardial infarction] 1, 6, 12 and 18 months, and at 2, 3, 4 and 5 years. - Stent thrombosis [Time Frame: Stent thrombosis] 1, 6, 12 and 18 months, and at 2, 3, 4 and 5 years - All cause death [Time Frame: All cause death] 1, 6, 12 and 18 months, and at 2, 3, 4 and 5 years. - TLR [Time Frame: Target lesion revascularization] 1, 6, 12 and 18 months, and at 2, 3, 4 and 5 years. - TVR [Time Frame: Target vessel revascularization] 1, 6, 12 and 18 months, and at 2, 3, 4 and 5 years. - Major Bleeding (ARC-definition) [Time Frame: Major Bleeding (ARC-definition)] 1, 6, 12 and 18 months.
Inclusion/exclusion criteria for subject selection	**A) Patients presenting with non-ST elevation acute coronary syndrome:** Ischemic symptoms suspected to represent a non-ST-elevation acute coronary syndrome (UAP / NSTE-MI) defined as: New onset of characteristic ischemic chest pain occurring at rest or within minimal exercise (lasting longer than 10 minutes) and planned to be managed with an invasive strategy, AND at least one of the following; • ECG changes compatible with new ischemia (ST depression of at least 1mm or transient ST elevation or ST elevation of ≤ 1mm or T wave inversion greater than 2 mm in at least 2 contiguous leads). • Already elevated troponin I or T above the upper limit of normal. • Patients > 60 years of age with normal ECG at admission are eligible provided there is a high degree of certainty that patient's presenting symptoms are due to myocardial ischemia. These patients must have documented evidence of previous coronary artery disease (CAD) with at least one of the following: previous MI, previous PCI or CABG Positive exercise test, other evidence of CAD. **B) Patients presenting with ST-elevation myocardial infarction (STEMI)** Ischemic symptoms suspected to represent ST-elevation myocardial infarction defined as:

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Name of study	# 1 Tides-ACS (Completed study)
	Patients presenting with sign or symptoms of acute MI and planned to be managed with an invasive strategy with intent to perform a PCI during the index hospitalization. ECG changes compatible with STEMI: persistent ST-elevation (>2mm in two contiguous leads or > 1mm in at least two limb leads), or new left bundle branch block, or Q-wave in two contiguous leads. **Written informed consent for all patients**
	Exclusion criteria • Age < 18 years • Expected survival < 1 year • Allergy to aspirin, clopidogrel, prasugrel or ticagrelol • Allergy to heparins, glycoprotein IIb/IIIa inhibitors or bivalirudin • Allergy to everolimus • Active bleeding or significant increased risk of bleeding • Stent length longer than 28 mm needed • Stent diameter > 4.0 mm needed • Previous coronary artery bypass surgery (CABG) • Aorto-ostial lesion • Previous coronary stenting of the target vessel • Thrombolysis therapy • Cardiogenic shock Planned surgery within 12 months of PCI unless the dual antiplatelet therapy could be maintained throughout the perisurgical period
Number of enrolled subjects,	1491 participants
Study population:	For TITAN OPTIMAX : 989 patients : -Age average :62.7 years -Female 244 (24.7%) For SYNERGY 502 patients -Age average :62.6 years -Female 119 (23.7%)
Summary of study methods	A prospective, randomized, multicenter trial (ClinicalTrials.gov Identifier: NCT02049229), will be conducted in interventional centres in Finland (six centres), France (five centres) and Holland (two centres), including a total of 1800 patients. All patients will be seen at the out-patient examination or contacted via telephone after 1, 6, 12 and 18 months. Thereafter, there will be a yearly contact up to 5 years from randomization, with recording of cardiac death, MI, stent thrombosis, target lesion and vessel revascularization, non-cardiac death, and major bleeding complications. The investigator or a study nurse will review the patient's hospital record and meet the patient at the out-patient clinic or make the phone call
Summary of results:	**Clinical benefit** : Low rate of cardiac death after angioplasty 0.6% at 18 months for TTITAN OPTIMAX Low rate of non fatal myocard infraction after angioplasty (2.2%) at 18 months for TTITAN OPTIMAX **Equate to** 1.8% at **12 months**:

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Name of study	# 1 Tides-ACS (Completed study)
	Equate to 2.2% at **18 months**: **<u>Side -effects after 12 months:</u>** -<u>MACE</u> : **12 months**: 6.3% for OPTIMAX BAS vs 7% for SYNERGY EES **18 months**: 7.2% for OPTIMAX BAS vs 8.8% for SYNERGY EES -<u>Cardiac death</u> **12 months**: 0.5% for OPTIMAX BAS vs 1.6% for SYNERGY EES **18 months**: 0.6% for OPTIMAX BAS vs 2.6% for SYNERGY EES -<u>Non fatal myocard infraction :</u> **12 months**: 1.8% for OPTIMAX BAS vs 4.6% for SYNERGY EES (p=0.004) **18 months**: 2.2% for OPTIMAX BAS vs 5.0% for SYNERGY EES (p=0.004) -<u>Non cardiac death</u> **12 months**: 0.4% for OPTIMAX BAS vs 1.0% for SYNERGY EES **18 months**: 0.5% for OPTIMAX BAS vs 1.2% for SYNERGY EES <u>-Stent thrombosis</u> **12 months**: 1.0 % for OPTIMAX BAS vs 2.0% for SYNERGY EES **18 months**: 1.0 % for OPTIMAX BAS vs 2.2% for SYNERGY EES **<u>Clinical Performance</u>** : -<u>Stent success</u> : 99.7% for OPTIMAX BAS vs 99% for SYNERGY EES -<u>Procedural success</u> 97.6% for OPTIMAX BAS vs 97.4% for SYNERGY EES <u>-Ischemia driven TLR</u> : **12 months**: 5,4% for OPTIMAX BAS vs 3.4% for SYNERGY EES **18 months**: 5,8% for OPTIMAX BAS vs 4.4% for SYNERGY EES **Ischemia driven TVR** **12 months**: 1,2% for OPTIMAX BAS vs 1.0% for SYNERGY EES **18 months**: 1,3% for OPTIMAX BAS vs 1,2% for SYNERGY EES **Residual restenosis** Not available
Limitations of the study	First, a major limitation is the fact that the number of patients initially planned was decreased after interim analysis showed a lowerthan- expected event rate. This could potentially have favored reaching noninferiority for the primary endpoint. Second, the choice of a different primary endpoint at 12 months and co-primary endpoint at 18 months as defined in the initial protocol can be argued, but was justified by the increasing recognition of the clinical relevance of bleeding with respect to outcome Third, not having performed routine angiographic follow-up may explain the absence of an efficacy signal (TLR) in favor of DES. However, routine angiographic follow-up is not performed in daily practice

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Name of study	# 1 Tides-ACS (Completed study)
	Fourth, the trial was underpowered to address the individual safety and efficacy outcome events; any statistical significance of the relative effect size for these events should be interpreted as hypothesis-generating Fifth, we report a higher combined definite and probable ST rate in the TIDES-ACS trial for the EES arm than in some previous studies (i.e., EXAMINATION trial). Last, extended follow-up beyond 18 months is needed to determine whether the observed effect size of the outcome persists at long-term follow-up.
device deficiency / replacements	Stent failure was defined as inability to deliver or deploy the study stent in the culprit lesion. For TITAN OPTIMAX : Stent failure 3 (0.3%) For SYNERGY : Stent failure 5 (1.0%)

Name of study	# 2 **TIOMAX (completed study)**
Title of publication	TIOMAX: A Spanish Multicenter Registry of the real–world use of the TItanium OptiMAX® biostent The detail data of the article is available in PubMed,
Place of the study	Spain (21 Centers)
Period and duration	March 1st 2013 and July 31st 2014
Identity of the device	OPTIMAX (Hexacath, Paris, France) TITAN 2(Hexacath, Paris, France)
Intended use of the device in the investigation	Percutaneous coronary intervention
Objectives of the study	The aim of the study was to compare the safety and efficacy of the new cobalt-chromium bioactive stent Titan Optimax® (Hexacath, France) with its predecessor, Titan-2
Study design:	Multyfendpointcenter registry
Primary and secondary endpoint(s)	The primary study endpoint was the incidence of the composite outcome of death (D), non-fatal acute myocardial infarction (AMI), stent thrombosis (ST), and target lesion revascularization (TLR).
	Secondary endpoints were the incidence of the individual components, the device-oriented composite endpoint of target lesion failure CD/AMI/ TLR and the non-fatal composite event, i.e., the combination AMI/ST/ TLR.
Inclusion/exclusion criteria for subject selection	**Inclusion criteria** The registry initially comprises 814 patients with symptomatic coronary disease and angiographic lesions greater than 50% on de novo lesions
	Exclusion criteria Exclusion criteria were revascularization within the previous 9 months of the same artery, implantation of a stent other than the Titan-2 or the Optimax (depending on the study phase) in the index procedure, existence of a previous drug-eluting stent or bare metal stent in the treated vessel, lesion in saphenous vein bypass, cardiogenic shock or life expectancy of less than 1 year. Other reasons for exclusion were allergy to aspirin, thienopyridines or heparin, and pregnancy.
Number of enrolled subjects,	784 patients (273 patients with Titan-2 stent and 511 patients with an Optimax stent)
Study population:	**For TITAN 2** : 273 patients : - Age average :66.2 years - Men 207 (75.8%) **For TITAN OPTIMAX** 511 patients

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Name of study	# 2 **TIOMAX (completed study)**
	-Age average :65.6 years -Men 405 (79.3%)
Summary of study methods	The TIOMAX registry includes 784 patients who underwent percutaneous coronary intervention with these stents in 21 Spanish hospitals. Follow-up with check-ups in outpatient clinic and/or telephone calls at 1, 6, and 12 months after the intervention was performed by an independent clinical event committee. HEXACATH Spain sponsored the protocol development, contracting an independent contract research organization (CRO) (ANAGRAM-ESIC) to process, monitor and validate the electronic data collection. The CRO was also responsible for collecting data in case of a clinical event.
Summary of results:	**Clinical benefit** : Low rate of cardiac death after angioplasty (1.8%) at 12 months for TTITAN OPTIMAX Low rate of non fatal myocard infraction after angioplasty (2.5. %) at 18 months TTITAN OPTIMAX **Side -effects after 12 months:** -MACE : Not available -Cardiac death : **1 month**: 1% for OPTIMAX BAS vs 0,7% for Helistent TITAN 2 **12 months**: 1,8% for OPTIMAX BAS vs 1,8% for Helistent TITAN 2 BAS -Non fatal myocard infraction : **1 month**: 0% for OPTIMAX BAS vs 0,4% for Helistent TITAN 2 BAS % **12 months**: 2,5% for OPTIMAX BAS vs 3,3% for Helistent TITAN 2 BAS -Non cardiac death : **1 month**: 1,4% for OPTIMAX BAS vs 0,7% for Helistent TITAN 2 **12 months**: 4,1% for OPTIMAX BAS vs 5,5% for Helistent TITAN 2 BAS -Stent thrombosis : **1 month**: 0,4% for OPTIMAX BAS vs 0,4% for Helistent TITAN 2 BAS **12 months**: 0,6% for OPTIMAX BAS vs 0,7% for Helistent TITAN 2 BAS **Clinical Performance** : -Stent success : Not available -Procedural success 100% 97.3% for OPTIMAX BAS vs 94.7% for Helistent TITAN 2 -Ischemia driven TLR : 2,9% for OPTIMAX BAS vs 3.7% for Helistent TITAN 2 -Ischemia driven TVR : TVR coincided with TLR -Residual restenosis : RR>20% (procedural failure) in 2,7% for OPTIMAX BAS vs 5.3% for Helistent TITAN 2
Limitations of the study	In this type of studies there may be a certain risk of bias due to selection of less complex patients. A lack of data on eligible patients not enrolled in the study could cause a certain selection bias; however, the characteristics of the patients included are similar to those usually treated in daily practice.Moreover, the results are in line with those reported on this type of stent and, in comparison with patients in the TITAN2 group, design improvements in the Optimax stent seem to be associated with at least the same effectiveness and safety outcomes as the previous model.
device deficiency / replacements	Not available

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Name of study	# 3 OPTIMAX first man (completed study)
Title of publication	12-Month Results of the OPTIMAX First-in-Man Study The detailed data of the article is available in PubMed
Place of the study	Finland
Period and duration	January 2013 to July 2013
Identity of the device	OPTIMAX™ stent (Hexacath, Paris, France)
Intended use of the device in the investigation	Patients with symptomatic coronary artery disease, and angiographically documented significant stenosis (at least 50% diameter stenosis by visual estimation) of a de novo lesion, in a native coronary artery or a coronary bypass graft
Objectives of the study	Exploration of 12-month clinical outcome of the titanium-nitride-oxide coated OPTIMAX stent based on cobalt-chromium platform in the treatment of patients with *de novo* coronary lesions.
Study design	First in man study, single-center, observational, prospective, non-comparative, study
Primary and secondary endpoint(s)	The primary endpoint was a composite of MACE at 12-month follow-up, defined as the first occurrence of any of the following: cardiac death, non-fatal myocardial infarction (MI), or ischemia-driven TLR.
	Secondary endpoints included the individual components of the primary endpoint, non-cardiac death, ischemia-driven target vessel revascularization (TVR), and definite ST at 12-month follow-up. ST was adjudicated according to the criteria of definite ST described by the Academic Research Consortium.
Inclusion/exclusion criteria for subject selection	**Inclusion criteria** Patients presenting -symptomatic coronary artery disease -angiographically documented significant stenosis (at least 50% diameter stenosis by visual estimation) of a de novo lesion, in a native coronary artery or a coronary bypass graft.
	Exclusion criteria Patients with: -congestive heart failure or left ventricular systolic dysfunction (defined as a left ventricular ejection fraction <30%), -cardiogenic shock, -chronic renal impairment, prior revascularization of the -target vessel, -allergy to aspirin, thienopyridines, heparin, glycoprotein IIb IIIa inhibitors, or bivalirudin -active bleeding, or a significant increase in bleeding risk -life expectancy less than 12 months
Number of enrolled subjects,	224 participants
Study population	The mean age of the cohort was 67 +/-8 years, 168 male gender (75%)
Summary of study methods	An observational prospective, single-center trial is conducted in an interventional centre in Finland including a total of 224 patients. Patients were prospectively followed up for 12 months by means of clinic visits or telephone contact by cardiologists to obtain information concerning their clinical status, hospitalization as well as invasive and non-invasive diagnostic tests. Follow-up coronary angiography was performed for patients developing recurrent symptoms during follow-up. The decision to perform further revascularization for the target lesion at follow-up coronary angiography was based on clinical clinical justification (described above). All patient data available from hospital records, institutional electronic database, or referring physicians, were entered in case report forms. At the end of follow-up, all case report forms were carefully reviewed to ensure quality-control of the registered data. An independent clinical event committee adjudicated all clinical events.
Summary of results:	**Clinical benefit** : -Low rate of cardiac death after angioplasty (1.30%) -Low rate of non fatal myocard infraction after angioplasty (3.10%)

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Name of study	# 3 OPTIMAX first man (completed study)
	Side -effects after 12 months: - MACE : 6.3% - Cardiac death : 1.30% - Non fatal myocard infraction : 3.10% - Non cardiac death : 0.90% - Stent thrombosis : 0% **Clinical Performance** : -Stent success:(successful implantation with residual stenosis <20% and final TIMI 3 flow, absence of dissection or thrombosis): 100% -Procedural success : 100% (no dissection or thrombosis) -Ischemia driven TLR : 3.10% -Ischemia driven TVR ; Not available -Residual restenosis : 0%
Limitations of the study	The current study was based on a relatively small cohort studied in a single center, with a relatively short period of follow-up; therefore, its results should be interpreted with caution. Moreover, in this first-in-man study, stents were deployed in de novo lesions, which do not reflect real-world practice
device deficiency / replacements	No deficiency or replacement of the device has been observed.

5.3 Overall summary of the clinical performance and safety

a) Safety of TITAN OPTIMAX

Claimed clinical safety for the TITAN OPTIMAX stent systems is defined as non inferior to drug-eluting stent regarding the rate of the major adverse cardiac events (MACE) and stent thrombosis.

The safety of the device is based on the combined outcomes of major cardiovascular events MACE (cardiac death, MI, target lesion revascularization (TLR)) at 12-months of follow-up.

Evidence from Randomized controlled trials shows a similar incidence of MACE in BAS (Helistent TITANT 2 and TITAN OPTIMAX) and DES but a lower incidence of stent thrombosis and a lower incidence in MI with BAS at 1 year and 5 years, in all patients but particularly in ACS.

Compared to Helistent TITAN 2, the 12-months MACE values reported for TITAN OPTIMAX (6.3% #1, 5.3% #2, 6.3% #3, and 3.6% #5) appears lower than the values reported for Helistent TITAN 2 (14.5%, [4]7.2% [5], 21.1[6] %), whereas definite ST is comparable for the both devices (Helistent 2: 0% [7], 0.3%[8] and 0.7% [9]).

[4] López-Mínguez et al., « A Randomized Study to Compare Bioactive Titanium Stents and Everolimus-Eluting Stents in Diabetic Patients (TITANIC XV) ».
[5] Angioi et al., « French Ministry of Health Prospective Multicentre Study Using Bio-Active Stents Coated with Titanium Nitride Oxide ».
[6] Pilgrim et al., « Comparison of Titanium-Nitride-Oxide-Coated Stents with Zotarolimus-Eluting Stents for Coronary Revascularization a Randomized Controlled Trial ».
[7] López-Mínguez et al., « A Randomized Study to Compare Bioactive Titanium Stents and Everolimus-Eluting Stents in Diabetic Patients (TITANIC XV) ».
[8] Angioi et al., « French Ministry of Health Prospective Multicentre Study Using Bio-Active Stents Coated with Titanium Nitride Oxide ».
[9] Pilgrim et al., « Comparison of Titanium-Nitride-Oxide-Coated Stents with Zotarolimus-Eluting Stents for Coronary Revascularization a Randomized Controlled Trial ».

In addition, results are congruent with values obtained at 12 months for the PRO-Kinetic Energy similar device: MACE reported at 4.9%[10] and ST reported at 0.6%[11] and 1.3%[12].

Based on these results, TITAN OPTIMAX stent systems are considered as non-inferior to drug-eluting stents regarding the rate of the major adverse cardiac events (MACE) and stent thrombosis, hence providing reasonable evidence that the TITAN OPTIMAX stent systems achieve their safety claims.

b) Performance of TITAN OPTIMAX

TiTAN OPTIMAX coronary stent has the ability to reopen stenotic arteries when deployed and minimise post-operative restenosis (due to its specific TiNO coating).
The performance of the device is based on procedural success rate, defined as residual stenosis of less than 30%, and 12-months target lesion revascularization (TLR) rate.

The data retrieved from the literature review and the studies provided allowed to:

- showed that the procedure success rate[13] reported for TITAN OPTIMAX stents, are always superior to 97%, are consistent regarding the different studies and are comparable to the success rate obtained with drug-eluting stent.

- showed that the rates of target lesion revascularization (TLR) vary to one another study depending on the follow-up period taken in account. Regarding 1 year follow-up data, the TLR rates are equivalents in the first in man study (3,1%), in the TIOMAX study (2,9%), and in the TITANIUM (2,4%), whereas it appears a bit higher in the preliminary results of the TIDE-ACS (5,4%). TLR rates is also not significantly different between TITAN OPTIMAX (2,9%) and its predicate Helistent 2 (3,7%) as shown in the TIOMAX study. Overall TLR rates remained quite low, and equate to the TLR rates reported for drug-eluting stents.

- showed that TITAN-OPTIMAX allowed a satisfactory vascular healing and adequate 12-month efficacy outcome in patients with de novo coronary lesions in terms of procedural success, vascular healing and revascularization rate during follow-up (#3);

- demonstrated good efficacy outcome in patients with acute coronary syndrome (ACS) in terms of procedural success (#2 TIOMAX,) and at least comparable procedural success, TLR and TVR compared to EES (#1).

The information provided by the post-market highlight that user complaints received since the TITAN OPTIMAX was launched in 2013 have not raised any concern regarding the device performances.

- The results of post-market studies and post-market surveillance related to TITAN OPTIMAX demonstrate the adequate performance achievement of TITAN OPTIMAX stent system to its performance claims.

c) Benefit/risk profile of TITAN OPTIMAX

The main clinical benefits expected from performance of TiTAN OPTIMAX coronary stent is to prevent a heart attack (myocardial infarction) or to minimize the consequences of a heart attack. As well, stenting is a minimally invasive procedure which does not require general anaesthesia and major surgery for the patient.

- Concerning the minimally invasive procedure:

[10] Erbel et al., « Prospective, Multi-Center Evaluation of a Silicon Carbide Coated Cobalt Chromium Bare Metal Stent for Percutaneous Coronary Interventions ».
[11] Erbel et al.
[12] Roncalli et al., « Paclitaxel Drug-Coated Balloon After Bare-Metal Stent Implantation, an Alternative Treatment to Drug-Eluting Stent in High Bleeding Risk Patients (The Panelux Trial) ».
[13] The procedure success rate is specifically defined in each study.

The device related mode of action, the procedure of use reported in the clinical data on the device and the description of PCI principle in the state of the art allow to support the clinical benefit "minimally invasive procedure which does not require general anesthesia and major surgery". This benefit is additionally congruent with the data and stenting procedures reported in the clinical studies on benchmark devices, similar device and predicate Helistent 2 device analyzed in the state of the art.

- Concerning the prevention of a heart attack (myocardial infarction) or minimalization of the consequences of heart attack";
-

The analysis of clinical data on TITAN OPTIMAX further allows to states that:
- the rate of non-fatal myocardial infarction (MI) given for TITAN OPTIMAX:
  - equates to 0.2% (#5) immediately post-procedure;
  - ranges from 0.5% to 3.1 % 12-months post procedure
  - equates to 2.2% 18-months post procedure in the TIDE-ACS study
  - is reported as significantly lower than the values obtained for SYNERGY EES (#1: 1.8% vs 4.6% at 12-months; 2.2% vs 5% at 18-months).
    - the rate of cardiac death after angioplasty given for TITAN OPTIMAX
  - equates to 0.5% (#5) immediately post-procedure;
  - ranges from 0.5% to 1.8 % 12-months post procedure
  - equates to 0.6% 18-months post procedure in the TIDE-ACS
  - is reported as significantly lower than the values obtained for SYNERGY EES (#1: 0.5% vs 1.6% at 12-months; 0.6% vs 2.6% at 18-months).

Clinical data on the evaluated device allow to state that 12-months MACE rate reported for TITAN OPTIMAX is consistent between studies (#1, #2, #3) and not significantly different to that of benchmark device EES in the TIDE-ACS randomized trial (#1);

Moreover, the post-market data currently available provide reasonable evidence that the residual risks associated with the use of the TITAN OPTIMAX stent systems are acceptable:

- The results of post-market studies specific to TITAN OPTIMAX demonstrate an adequate safety profile in terms of procedural complications and post-procedural cardio-vascular events such as myocardial infarctions, stent thrombosis and death (#1, #2, #3);

- A meta-analysis carried out on results retrieved from 5 randomized clinical trials (TITAX AMI, TIDE, TITANIC XV, BASE ACS and TIDES ACS) shows that BAS (including TITAN OPTIMAX) appears to offer a better efficacy/risk than DES;

- The performance surveys conducted on TITAN OPTIMAX stents in normal conditions of use highlighted a very good customer acceptance and adequate peri-procedural safety results;
- As of today, around 96 500 TITAN OPTIMAX have been used worldwide with a low user complaint rate and none of the complaints received have raised any concern with the device safety

In conclusion, the risks associated with TITAN OPTIMAX stent system, when used as intended, are acceptable when weighed against the benefits to the patients,

5.4 Post-market clinical follow-up

The method consists to use collect data in order to ensure a post market clinical follow up. It consists to carry out every year:

- Literature screening:

Any scientific publications, abstracts, articles relevant to similar or equivalent devices identified through research on dedicated database (such as PubMed, google scholar), subscription to online newsletter (PCRonline, interventional news, TCT magazine).

- Annual participation to international congress
- Review of vigilance databases for similar or equivalent devices such as MAUDE database, ANSM database
- Collect and analyse complaints and vigilance data
- Clinical studies (if necessary)
- Evaluation performed by physicians

6 POSSIBLE THERAPEUTIC ALTERNATIVES

Treatments for coronary artery disease usually involves lifestyle changes and if necessary, drugs and certain medical procedures:

•**Lifestyle changes:** Quit smoking, eat healthy foods, exercise regularly, lose excess weight, reduce stress.

• **Pharmacological treatment**: it may include cholesterol-modifying medications, anti-thrombotics , anti-ischemic, and prophylactic or symptomatic lipid lowering drugs.

• **Drug-eluting stent for percutaneous Coronary Intervention (PCI):** The drug-eluting stents consist to a metallic stent platform with controlled release of antiproliferative drugs, mostly regulated by surface polymers.
The drug eluting stent are an alternative to TITAN OPTIMAX. It should be noted that despite the new generation DES have improved clinical outcomes versus first generation DES, there is still a concern in DES linked late stent thrombosis associated with a concern with long term DAPT and bleeding risks.
Comparing to TITAN OPTIMAX, 3 randomized studies (TiTAX-AMI, BASE-ACS, TiDES-ACS) in ACS demonstrated the non-inferiority of its TiNO stent technology versus the 1st generation DES (Taxus, Boston Scientific), the second generation DES (Xience V, Abbott) and versus the 3rd generation DES (Synergy, Boston Scientific) in terms of efficacy (MACE or Major Adverse Cardiac Events).
Last, it should be noted that the 3rd generation Biological Active Stent TiTAN Optimax has demonstrated its superiority versus the 3rd generation DES at 18 months follow up in terms of safety (cardiac death, AMI, major bleeding).

• **Coronary Artery Bypass Graft (CABG):** CABG consists to use blood vessels from another part of the body and connects them to blood vessels above and below the narrowed artery, bypassing the narrowed or blocked coronary artery. One or more blood vessels may be used, depending on the severity and number of blockages. The blood vessels are usually arteries from the arm or chest, or veins from the legs.

Hybrid coronary revascularization (HCR): HCR for multivessel coronary artery disease (CAD) also emerged and integrates coronary artery bypass grafting (CABG) and percutaneous intervention in a planned revascularization strategy. HCR is an interesting approach for multivessel CAD but should not be considered a 'one-size-fits-all' procedure

As mentioned in the 2018 ESC/EACTS guidelines from expert consensus on myocardial revascularization, whether medical therapy, PCI, or CABG have to be preferred to treat CADs (Coronary artery disease), should be depend on the risk–benefit ratios of these treatment strategies, weighting the risks of periprocedural death, myocardial infarction and stroke against improvements in health-related quality of life, as well as long-term freedom from death, myocardial infarction or repeat revascularization.

The 2021 ACC/AHA/SCAI Guideline for Coronary Artery Revascularization added that treatment decisions regarding coronary revascularization in patients with coronary artery disease (CAD) should

be based on clinical indications. In patients being considered for coronary revascularization for whom the optimal treatment strategy is unclear, a multidisciplinary Heart Team approach is strongly recommended. Treatment decisions should be patient-centered, incorporate patient preferences and goals, and include shared decision-making.

7 REFERENCE TO HARMONIZED STANDARDS AND COMMON SPECIFICATIONS

HEXACATH applies the following harmonized standards and common specifications published in the Official Journal of the European Union, according to Decision (EU) 2021/1182 of 16 July 2021 and Decision (EU) 2022/6 of 4 January 2022:

- EN ISO 13485 :2016 Medical devices - Quality management systems - Requirements for regulatory purposes

- - EN 15223-1:2021 Medical Devices – Symbols to be used with medical devices labels, labeling and information to be supplied — Part 1: General requirements

- EN ISO 11135:2014 - Sterilization of health-care products — Ethylene oxide — Requirements for the development, validation and routine control of a sterilization process for medical devices.

- EN ISO 11737-1:2018 Sterilization of medical devices - Microbiological methods - Part 1: Determination of a population of microorganisms on products.

- EN ISO 11737-2 2020 Sterilization of health care products — Microbiological methods — Part 2: Tests of sterility performed in the definition, validation and maintenance of a sterilization process.

- EN ISO 14971:2019 Medical devices – Application of risk management to medical devices

Other standards applied by HEXACATH have not yet been harmonized with the Regulation (EU) 2017/745

Summary of safety and clinical performance for patients

Table of contents

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This Summary of Safety and Clinical Performance (SSCP) is intended to provide public access to an updated summary of the main aspects of the safety and clinical performance of the device. The information presented below is intended for patients or lay persons. A more extensive summary of its safety and clinical performance prepared for healthcare professionals is found in the first part of this document.

The SSCP is not intended to give general advice on the treatment of a medical condition. Please contact your healthcare professional in case you have questions about your medical condition or about the use of the device in your situation. This SSCP is not intended to replace an Implant card or the Instructions For Use to provide information on the safe use of the device.

Following this information is a summary for patients.

1 DEVICE IDENTIFICATION AND GENERAL INFORMATION

1.1 Device trade name

The trade names are TITAN OPTIMAX

1.2 Manufacturer's name and address

Name and address of the legal manufacturer are the following:

- Name: HEXACATH (Headquarters)
- Address: 4, passage Saint-Antoine, 92500 Rueil-Malmaison - FRANCE

1.3 Basic UDI-DI

Basic UDI-DI of TITAN OPTIMAX is: 037003857OPT00015T

1.4 Year when the first certificate (CE) was issued covering the device

TITAN OPTIMAX was CE marked in 2011. following the Directive 93/42.
Since October 2021 TITAN OPTIMAX is CE marked following the Regulation (EU) 2017/745 of the european parliament and of the council of 5 April 2017.
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2 DEVICE DESCRIPTION

2.1 Description of the device

a) General description

The TITAN OPTIMAX stents are medical devices manufactured by HEXACATH consisting of a Titanium Nitride Oxide coated balloon-expandable stent, pre-mounted on a rapid exchange delivery catheter.

The stent is made from L605 cobalt-chromium alloy which consists of a cobalt*, chromium, tungsten and nickel alloy. It is a flexible tubulo-modular structure entirely coated with Titanium Nitride Oxyde and deployable by means of a balloon catheter. The surface area in contact with the artery varies from 9 mm^2 to 69 mm^2 depending on the diameter and length of the stent.

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The delivery catheter on which the stent is pre-mounted is mainly composed of a flexible distal tip, balloon and tubes made from polymers (Polyamid, Polyether) and a stainless steel hypotube. The outer surface is coated with a non-active hydrophilic coating.

The balloon has two radiopaque markers made from platinium/iridium, proximal and distal, to identify the location of the stent on the balloon.

Two proximal markers located at 90 and 100 cm from the distal end help to assess the position of the catheter in relation to the tip of a guide catheter used for radial, brachial or femoral approaches.

The delivery catheter is equipped with a proximal luer-lock port made from polycarbonate for connection to an inflation device.

The TITAN OPTIMAX stents are sterile, sterilized by Ethylene oxide gas, for single use only, and packed in individual unit. Its shelf life is 5 years

b) General description of the key functional elements

TITAN OPTIMAXcoronary endoprosthesis devices are composed of:
- A tip
- A balloon
- A crimping stent
- A catheter
- Marker bands
- A strain relief
- A hub to connect the inflation system

c) Materials or substances in contact with patient's tissues

The following materials are in contact with patient's tissues and blood:
- Concerning the catheter:
  - Polycarbonate
  - Stainless steel
  - PTFE coating
  - Polyamide
  - Polyethylene
  - Acrylic

- Concenring the stent
  - Titanium Nitride Oxide

d) Principe of operation and mode of action

The TITAN OPTIMAXcoronary premounted stent system makes it possible to treat local contraction of coronary arteries caused by certain illnesses such as arteriosclerosis, which can impede blood circulation. The general principle of these permanent protheses is the insertion of a metal mesh in the damaged area to keep the duct open at a normal diameter. It is a meshed, cylindrical structure that can be implanted and later adapt itself to the walls of the vessel while retaining permeability for the side branches.

This product treats local shortening of coronary arteries, allowing a myocardial revascularization for patients displaying myocardial ischemia related to a coronaropathy.
A sheath is introduced in the groin (or occasionally in the femoral artery). Through this sheath, a long, flexible, soft plastic tube or guiding catheter is advanced and the soft-tip positioned into the opening of

the coronary artery. The tube measures 2 to 3 mm in diameter. The soft-tip of the catheter is directed or controlled when the cardiologist gently advances and rotates the end of the catheter that sits outside the patient.

Once the catheter soft-tip is seated within the opening of the coronary artery, x-ray movie pictures are recorded during the injection of contrast material.
After evaluating the x-ray movie pictures, the cardiologist estimates the size of the coronary artery and selects the type of balloon catheter and guide-wire that will be used during the case.
The guide wire which is an extremely thin wire with a flexible tip is inserted into through the catheter guide and into the coronary artery. The tip of the wire is then guided across the blockage and advanced beyond it. The cardiologist controls the movement and direction of the guide wire by gently manipulating the end that sits outside the patient. This wire now serves as a "guide" or rail over which the balloon catheter stent system can be advanced up to the target lesion and the stent delivered at the lesion.

Then, the balloon is inflated by connecting it to a special indeflation device. A mixture of saline and contrast material is used to inflate the balloon and deploy the stent. The balloon catheter also has metallic markers to be located. This helps the cardiologist know the location. The balloon is kept inflated for a few seconds and then deflated.
The deflated balloon and guide-wire are withdrawn when the cardiologist is satisfied with the results. Final angiograms or movie x-ray pictures are taken upon completion of the case. The guiding catheter is then withdrawn.

The sheath is secured to the groin with a suture and the patient is sent to his or her room. In case of radial road, a simple compression is required.

How the stent is fitted:

Before fitting a stent, the surgeon generally begins with an angioplasty. This involves inflating a balloon at the damaged segment of artery, so as to open it sufficiently for the stent to be introduced.
The result of angioplasty is not perfect: the artery is still obstructed and the blood flow restricted.
The surgeon then has the option of implanting a stent. The stent is mounted on a catheter equipped with a balloon and is thus guided towards the obstructed section of artery.
The balloon is inflated, which deploys the stent to the desired diameter.
Then the balloon is deflated and withdrawn with the catheter. As the stent’s form has been altered, it stays in place wedged against the vessel walls.
In this way the stent keeps the artery completely open, allowing a free passage for the blood.

2.2 Recommended equipment

- A puncture kit
- Appropriately sized guide catheter: 5F guide catheters, with a minimum inner lumen of 0.058” (1.47 mm), allow for the advancement of pre-mounted TiTAN OPTIMAX stents from 2.0 mm to 4.0 mm in diameter. The 6F guide catheters, with a minimum internal lumen of 0.064” (1.62 mm), allow for the advancement of pre-mounted TiTAN OPTIMAX stents from 4.5 and 5.0 mm in diameter).
- A 0.014” coronary guide of appropriate length
- An appropriate syringe
- An appropriately sized haemostasis valve
- A 3-way stopcock
- An inflation device
- Heparinized saline solution
- Contrast agent diluted with saline solution in a 1:1 ratio
- A flushing needle

3 INTENDED USE OF THE DEVICE

3.1 Intended purpose

The TITAN OPTIMAX is a coronary premounted stent system (stent crimped on the balloon of carrier catheter).
The carrier catheter introduces and deploys the stent into the native coronary arteries or vessel grafts of the targeted patients. The TITAN OPTIMAX stent is intended to be implanted in the native coronary arteries or vessel grafts of targeted patients for improving coronary luminal diameters.

3.2 Indications and target population

a) Indications

The TITAN OPTIMAX is indicated for improving coronary luminal diameters in adult patients with symptomatic ischemic heart disease including patients with acute myocardial infarction (STEMI/NSTEMI, unstable angina) and patients with concomitant diabetes mellitus due to de novo coronary artery lesions. The treated lesion length should be less than the nominal stent length (7mm to 38 mm) with a reference vessel diameter of 2.0 to 5.0 mm.

b) Intended patient population

The TITAN OPTIMAX stent system is intended to be implanted, in adult patients, with symptomatic ischemic heart disease including patients with acute myocardial infarction (STEMI/NSTEMI, unstable angina) and patients with concomitant diabetes mellitus due to de novo coronary artery lesions".

c) Intended user population

TITAN OPTIMAX stenting should only be performed at hospitals or clinics authorized for the practice of coronary angioplasty by physicians with technical expertise in coronary angioplasty and who can be assisted by physicians capable of treating major clinical complications by cardiac-surgery.

3.3 Contraindications

- Patients with contraindications to anticoagulant/ antiplatelet therapy
- Allergy to contrast agents.
- Patient with a known hypersensitivity or allergy to Titanium Nitride Oxide (TiNO)
- Major surgery within the previous two weeks, childbirth, puncture of an incompressible vessel or biopsy.
- History of bleeding.
- Pregnancy.
- Lesions proximal to an untreatable segment, significantly limiting blood flow.
- Fibrous or calcified lesions, refractory to dilation (resistant to pre-dilations at high pressure of 20 Bars).
- In stent restenosis in coronary artery lesions.
- Implantation in tortuous vessels with limited access to the site to be treated, diffuse vascular disease with reduced flow, and lesions located after acute angles, can be challenging situations for stenting.

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4 RISKS AND WARNINGS

4.1 Residual risks and undesirable effects

Contact your healthcare professional if you believe that you are experiencing side effects related to the device or its use or if you are concerned about risks. This document is not intended to replace a consultation with your healthcare professional if needed.

In the risk management process carried out by HEXACATH, all risks are controlled and managed. All residual risks have been analyzed. The benefit / risk ratio of each individual risks is favorable to the benefit. In addition, all the risks in relation with the use of the TITAN OPTIMAX devices have been reduced to an acceptable or tolerable level and the overall residual risk is low enough to put on the market the device with a favorable benefit/risk balance.
All residual risks are mentioned in the instruction for used of TITAN OPTIMAX in the section warnings and precautions.

Observed adverse effects comes from the TIDES-ACS[14] clinical trial, the TIOMAX[15] registry and the OPTIMAX "first in man" study[16]. They are summarized in the table below.

	TIDES-ACS	**TIOMAX**	**OPTIMAX first in man**
1 month follow-up			
Death		1.4% (7/511)	
Cardiac death		1% (5/511)	
Stent thrombosis (definite or probable)		0.4% (2/511)	
12 months follow-up			
All-cause Death	0.9% (9/989)	4.1% (21/511)	2.2% (5/224)
Non cardiac Death	0.4% (4/989)	2.3% (12/511)	0.9% (2/224)
Cardiac Death	0.5% (5/989)	1.8% (9/511)	1.3% (3/224)
Stent thrombosis (definite or probable)	1.1% (11/989)	0.6% (3/511)	0% (0/224)
Myocardial infarction (MI)	1.8% (18/989)	2.5% (13/511)	3.1% (7/224)
Target lesion revascularisation (TLR)	5.4% (53/989)	2.9% (15/511)	3.1% (7/224)
Target vessel revascularisation (TVR)	6.6% (65/989)	2.9% (15/511)	4.0% (9/224)
Major bleeding	1.2% (12/989)		
18 months follow-up			
All-cause Death	1.1% (11/989)		
Non cardiac Death	0.5% (5/989)		
Cardiac Death	0.6% (6/989)		

[14] *Tonino P. et al., Titanium-Nitride-Oxide-Coated versus Everolimus-Eluting Stents in acute coronary syndrome the randomized TIDES-ACS-Trial, JACC Cardiovascular Intervention*
[15] *López-Mínguez JR. et al, TIOMAX; A Spanish Multicenter Registry of the real-world use of the Titanium Optimax biostent, Catheter Cardiovascular Intervention*
[16] *Karjalainen PP. et al, Clinical outcome of titanium-nitride-oxide-coated cobalt chromium stents in patients with de novo coronary lesions: 12-month results of the OPTIMAX first-in-man study, Catheter Cardiovascular Intervention*

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Stent thrombosis (definite or probable)	1.1% (11/989)		
Myocardial infarction (MI)	2.2% (22/989)		
Target lesion revascularisation (TLR)	5.8% (57/989)		
Target vessel revascularisation (TVR)	7.1% (70/989)		
Major bleeding	1.4% (14/989)		

Potential adverse effects associated with the stenting procedure include but are not limited to:

- Allergic reaction to contrast media, antiplatelet aggregation and/or anticoagulant medications, stent TiNO coating
- Angina
- Arteriovenous fistula
- Arrhythmias, including ventricular fibrillation
- Bleeding
- Coronary artery spasm
- Death
- Embolism
- Fever
- Haemorrhage or haematoma
- Hypotension/hypertension
- Infection, local or systemic (sepsis)
- Myocardial infarction (MI)
- Need for immediate coronary bypass surgery
- Vessel and/or coronary artery injury, perforation, rupture and/or dissection
- Restenosis of the dilated artery
- Stent migration
- Stent thrombosis

4.2 Warnings and precautions

a) Warnings

- TITAN OPTIMAXshould only be implanted in hospitals or clinics authorised to perform coronary angioplasty and by physicians with technical expertise in coronary angioplasty who may be assisted by physicians capable of treating major clinical complications with cardiac surgery.
- Check the expiry date on the packaging protecting the product's sterility. Do not use the device if the expiry date has passed.
- Do not re-sterilise, reprocess and/or re-use the device. Do not re-use the stent if it fails to pass. Re-sterilisation, reprocessing and/or re-use may compromise the performance of the device and its integrity. Such actions may result in contamination of the device and/or cause patient infection or cross-infection. HEXACATH cannot be held responsible for any accidental, direct or consequential damage resulting from re-sterilisation or re-use of the product.
- Ensure the integrity of the catheter before use.
- Do not use if the stent or catheter is damaged (leakage, breakage, cracking, loose stent, stent not centred on the balloon etc.).
- Observe aseptic conditions during all phases of use.
- Do not use gauze pads; the fibres can damage the stent.
- Do not loosen and re-tighten the stent on another catheter. Do not reposition the stent on its catheter.

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- Do not use any gas, air or other liquids to inflate the balloon other than those recommended in the instruction manual.
- Never inflate the balloon before final stent placement at a pressure exceeding 0.5 bar. This could result in the stent opening prematurely and being unable to progress through the artery.
- Do not inflate the balloon beyond the rated burst pressure (RBP). This increases the risk of balloon rupture, which can lead to vessel occlusion, balloon entrapment and associated complications.
- The catheter must be observed under fluoroscopy throughout the procedure.
- Never move the balloon with a pre-mounted stent forwards without ensuring that the stent is perfectly attached to the balloon. This could result in the loss of the stent before it is deployed in the vessel and could lead to acute myocardial infarction or death.
- Stents can cause nuclear magnetic resonance (or MRI) artefacts due to magnetic field distortion. These artefacts caused by the cobalt-chromium alloy of the stent are comparable to those caused by metallic surgical clips. In order to minimise the risk of stent migration under a strong magnetic field, it is recommended that a nuclear magnetic resonance examination is performed only after complete endothelialisation of the stent, i.e. at least three months after implantation.

b) Precautions

- Use the device before the expiry date.
- Store above 0°C and below 40°C, protected from light and moisture.
- Do not use if package has been damaged or opened.
- Before performing the angioplasty, check that the device is working properly and that it is the right size and shape for the procedure. Do not use the device if there is any damage or if there is any doubt about its integrity.
- Prior to inserting the catheter, administer the appropriate dose of coronary anticoagulant and vasodilator.
- Check that the air exhaust in each system is complete and that there are no leaks in the various connections.

4.3 Other relevant aspect of safety

TITAN OPTIMAX has not been subject to any field safety corrective actions.

5 SUMMARY OF CLINICAL EVALUATION AND POST MARKET CLINICAL FOLLOW-UP

5.1 Clinical background of the device:

The first materials used for stents were metals like stainless steel, tantalum, nitinol (a nickel-titanium alloy) and cobalt-chromium alloy These materials have the advantage of fast re endothelialization but they also have a disadvantage that they induce neointimal restenosis. Titanium has shown superior, biocompatibility compared to stainless steel, gold or cobalt-chromium such as high corrosion resistance and low tissue reaction characteristics.

TITAN OPTIMAX (ref LCIM) has been CE marked in October 2011 and is the third generation of coronary premounted stent systems developed by Hexacath since 1999. The first three generations being Helistent (bare stainless-steel stent) followed by Helistent TITAN and Helistent TITAN 2 (Stainless steel stents coated with TiNO. The Helistent TITAN 2 has been subjected to several clinical trials : TITAX AMI, BASE ACS, TITANIC XV, registries : TIOMAX, EVIDENCE I and EVIDENCE II, and meta-analysis that largely allowed to support the clinical performance and safety of the device.).

TITAN OPTIMAX stent system has been developed based on the Helistent TITAN 2 technology. TITAN 2 was a stent made with 316L stainless steel. Entirely coated with TiNO. TITAN OPTIMAX is a cobalt-chromium stent entirely coated with TiNO. Titanium nitride oxide presents some attractive properties such as diffusion barrier, inertness, hardness, and adhesion. Interestingly, some studies demonstrated that NO prevents platelet aggregation and reduces proliferation of smooth muscle cell. Furthermore, titanium nitride oxide (TiNO) coatings also demonstrated diminished platelet adhesion and reduced fibrinogen binding, allowing minimal affinity for bacterial and tissue cell adhesion.

Some clinical studies have been carried out on TITAN OPTIMAX to collect information about it safety, performance and confirm it benefit.

5.2 Clinical data:

The clinical evaluation of TITAN OPTIMAX stent systems is supported by clinical studies TITAN OPTIMAX as well as post-market follow-up and post market surveillance information inherent to TITAN OPTIMAX itself. The clinical studies are name OPTIMAX first in man and, TIOMAX and TIDES-ACS.

5.2.1 OPTIMAX first in man:

Name of study	# 1 Tides-ACS (Completed study)
Title of publication	Titanium-Nitride-Oxide–Coated Versus Everolimus-Eluting Stents in Acute Coronary Syndrome The detail data of the article is available in JACC, PubMed, Science Direct Reference : NCT : NCT02049229
Period and duration	January 2014 – (estimated) October 2015
Identity of the device	OPTIMAX stent (Experimental device) SYNERGY stent (Comparator)
Objectives of the study	The purpose of the prospective, randomized and a multicenter trial is to compare clinical outcome in patients presenting with ACS, treated with PCI using Optimax-BAS versus Synergy-EES. Second objective is to explore whether the Optimax-BAS use is superior compared with Synergy-EES use with respect of hard end points (cardiac death, MI and major bleeding).
Summary of results:	**Clinical benefit** : Low rate of cardiac death after angioplasty 0.6% at 18 months for TTITAN OPTIMAX Low rate of non fatal myocard infraction after angioplasty (2.2%) at 18 months for TTITAN OPTIMAX **Equate to** 1.8% at **12 months**: **Equate to** 2.2% at **18 months**: **Side -effects after 12 months:** -MACE : **12 months**: 6.3% for OPTIMAX BAS vs 7% for SYNERGY EES **18 months**: 7.2% for OPTIMAX BAS vs 8.8% for SYNERGY EES -Cardiac death **12 months**: 0.5% for OPTIMAX BAS vs 1.6% for SYNERGY EES **18 months**: 0.6% for OPTIMAX BAS vs 2.6% for SYNERGY EES -Non fatal myocard infraction :

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Name of study	# 1 Tides-ACS (Completed study)
	12 months: 1.8% for OPTIMAX BAS vs 4.6% for SYNERGY EES (p=0.004) **18 months**: 2.2% for OPTIMAX BAS vs 5.0% for SYNERGY EES (p=0.004) -Non cardiac death **12 months**: 0.4% for OPTIMAX BAS vs 1.0% for SYNERGY EES **18 months**: 0.5% for OPTIMAX BAS vs 1.2% for SYNERGY EES -Stent thrombosis **12 months**: 1.0 % for OPTIMAX BAS vs 2.0% for SYNERGY EES **18 months**: 1.0 % for OPTIMAX BAS vs 2.2% for SYNERGY EES **Clinical Performance** : -Stent success : 99.7% for OPTIMAX BAS vs 99% for SYNERGY EES -Procedural success 97.6% for OPTIMAX BAS vs 97.4% for SYNERGY EES -Ischemia driven TLR : **12 months**: 5,4% for OPTIMAX BAS vs 3.4% for SYNERGY EES **18 months**: 5,8% for OPTIMAX BAS vs 4.4% for SYNERGY EES **Ischemia driven TVR** **12 months**: 1,2% for OPTIMAX BAS vs 1.0% for SYNERGY EES **18 months**: 1,3% for OPTIMAX BAS vs 1,2% for SYNERGY EES **Residual restenosis** Not available

Name of study	# 2 **TIOMAX (completed study)**
Title of publication	TIOMAX: A Spanish Multicenter Registry of the real–world use of the TItanium OptiMAX® biostent
Period and duration	March 1st 2013 and July 31st 2014
Identity of the device	OPTIMAX (Hexacath, Paris, France) TITAN 2(Hexacath, Paris, France)
Objectives of the study	The aim of the study was to compare the safety and efficacy of the new cobalt-chromium bioactive stent Titan Optimax® (Hexacath, France) with its predecessor, Titan-2
Number of patients	784 patients (273 patients with Titan-2 stent and 511 patients with an Optimax stent)
Summary of results:	**Clinical benefit** : Low rate of cardiac death after angioplasty (1.8%) at 12 months for TTITAN OPTIMAX Low rate of non fatal myocard infraction after angioplasty (2.5. %) at 18 months TTITAN OPTIMAX **Side -effects after 12 months:** -MACE : Not available -Cardiac death : **1 month**: 1% for OPTIMAX BAS vs 0,7% for Helistent TITAN 2 **12 months**: 1,8% for OPTIMAX BAS vs 1,8% for Helistent TITAN 2 BAS -Non fatal myocard infraction :

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Name of study	# 2 **TIOMAX (completed study)**
	1 month: 0% for OPTIMAX BAS vs 0,4% for Helistent TITAN 2 BAS % **12 months**: 2,5% for OPTIMAX BAS vs 3,3% for Helistent TITAN 2 BAS -Non cardiac death : **1 month**: 1,4% for OPTIMAX BAS vs 0,7% for Helistent TITAN 2 **12 months**: 4,1% for OPTIMAX BAS vs 5,5% for Helistent TITAN 2 BAS -Stent thrombosis : **1 month**: 0,4% for OPTIMAX BAS vs 0,4% for Helistent TITAN 2 BAS **12 months**: 0,6% for OPTIMAX BAS vs 0,7% for Helistent TITAN 2 BAS **Clinical Performance** : -Stent success : Not available -Procedural success 100% 97.3% for OPTIMAX BAS vs 94.7% for Helistent TITAN 2 -Ischemia driven TLR : 2,9% for OPTIMAX BAS vs 3.7% for Helistent TITAN 2 -Ischemia driven TVR : TVR coincided with TLR -Residual restenosis : RR>20% (procedural failure) in 2,7% for OPTIMAX BAS vs 5.3% for Helistent TITAN 2

Name of study	# 3 OPTIMAX first man (completed study)
Title of publication	12-Month Results of the OPTIMAX First-in-Man Study
Period and duration	January 2013 to July 2013
Identity of the device	OPTIMAX™ stent (Hexacath, Paris, France)
Objectives of the study	Exploration of 12-month clinical outcome of the titanium-nitride-oxide coated OPTIMAX stent based on cobalt-chromium platform in the treatment of patients with *de novo* coronary lesions.
Number of patients	224 participants
Summary of results:	**Clinical benefit** : -Low rate of cardiac death after angioplasty (1.30%) -Low rate of non fatal myocard infraction after angioplasty (3.10%) **Side -effects after 12 months:** - MACE : 6.3% - Cardiac death : 1.30% - Non fatal myocard infraction : 3.10% - Non cardiac death : 0.90% - Stent thrombosis : 0% **Clinical Performance** : -Stent success:(successful implantation with residual stenosis <20% and final TIMI 3 flow, absence of dissection or thrombosis): 100% -Procedural success : 100% (no dissection or thrombosis) -Ischemia driven TLR : 3.10% -Ischemia driven TVR ; Not available -Residual restenosis : 0%

5.2.2 Discussion about claimed safety

Claimed clinical safety for the TITAN OPTIMAX stent systems is defined as non inferior to drug-eluting stent regarding the rate of the major adverse cardiac events (MACE) and stent thrombosis.

The safety of the device is based on the combined outcomes of major cardiovascular events MACE (cardiac death, MI, target lesion revascularization (TLR)) at 12-months of follow-up.

Evidence from Randomized controlled trials shows a similar incidence of MACE in BAS (Helistent TITANT 2 and TITAN OPTIMAX) and DES but a lower incidence of stent thrombosis and a lower incidence in MI with BAS at 1 year and 5 years, in all patients but particularly in ACS.
Compared to Helistent TITAN 2, the 12-months MACE values reported for TITAN OPTIMAX (6.3% #1, 5.3% #2, 6.3% #3, and 3.6% #5) appears lower than the values reported for Helistent TITAN 2 (14.5%, [17]7.2% [18], 21.1[19] %), whereas definite ST is comparable for the both devices (Helistent 2: 0% [20], 0.3%[21] and 0.7% [22]).
In addition, results are congruent with values obtained at 12 months for the PRO-Kinetic Energy similar device: MACE reported at 4.9%[23] and ST reported at 0.6%[24] and 1.3%[25].

Based on these results, TITAN OPTIMAX stent systems are considered as non-inferior to drug-eluting stents regarding the rate of the major adverse cardiac events (MACE) and stent thrombosis, hence providing reasonable evidence that the TITAN OPTIMAX stent systems achieve their safety claims.

5.2.3 Discussion about claimed performance

The claimed performance is that: TiTAN OPTIMAX coronary stent has the ability to reopen stenotic arteries when deployed and minimise post-operative restenosis (due to its specific TiNO coating).
The performance of the device is based on procedural success rate, defined as residual stenosis of less than 30%, and 12-months target lesion revascularization (TLR) rate.

The data retrieved from the literature review and the studies provided allowed to:

- showed that the procedure success rate[26] reported for TITAN OPTIMAX stents, are always superior to 97%, are consistent regarding the different studies and are comparable to the success rate obtained with drug-eluting stent.

- showed that the rates of target lesion revascularization (TLR) vary to one another study depending on the follow-up period taken in account. Regarding 1 year follow-up data, the TLR rates are equivalents in the first in man study (3,1%), in the TIOMAX study (2,9%), and in the TITANIUM (2,4%), whereas it appears a bit higher in the preliminary results of the TIDE-ACS (5,4%). TLR rates is also not significantly different between TITAN OPTIMAX (2,9%) and its predicate Helistent 2 (3,7%) as shown in the TIOMAX study. Overall TLR rates remained quite low, and equate to the TLR rates reported for drug-eluting stents.

Clinical evidences demonstrate that the TITAN OPTIMAX stent system achieves its intended performance during normal conditions of use.

"[17] López-Mínguez et al., « A Randomized Study to Compare Bioactive Titanium Stents and Everolimus-Eluting Stents in Diabetic Patients (TITANIC XV) ».
[18] Angioi et al., « French Ministry of Health Prospective Multicentre Study Using Bio-Active Stents Coated with Titanium Nitride Oxide ».
[19] Pilgrim et al., « Comparison of Titanium-Nitride-Oxide-Coated Stents with Zotarolimus-Eluting Stents for Coronary Revascularization a Randomized Controlled Trial ».
[20] López-Mínguez et al., « A Randomized Study to Compare Bioactive Titanium Stents and Everolimus-Eluting Stents in Diabetic Patients (TITANIC XV) ».
[21] Angioi et al., « French Ministry of Health Prospective Multicentre Study Using Bio-Active Stents Coated with Titanium Nitride Oxide ».
[22] Pilgrim et al., « Comparison of Titanium-Nitride-Oxide-Coated Stents with Zotarolimus-Eluting Stents for Coronary Revascularization a Randomized Controlled Trial ».
[23] Erbel et al., « Prospective, Multi-Center Evaluation of a Silicon Carbide Coated Cobalt Chromium Bare Metal Stent for Percutaneous Coronary Interventions ».
[24] Erbel et al.
[25] Roncalli et al., « Paclitaxel Drug-Coated Balloon After Bare-Metal Stent Implantation, an Alternative Treatment to Drug-Eluting Stent in High Bleeding Risk Patients (The Panelux Trial) ».
[26] The procedure success rate is specifically defined in each study.

5.2.4 Discussion about benefit/risk

The main clinical benefits expected from performance of TITAN OPTIMAX is to prevent a heart attack (myocardial infarction) or to minimize the consequences of heart attack. As well, stenting is a minimally invasive procedure which does not require general anesthesia and major surgery for the patient.

- Concerning minimally invasive procedure

The device related mode of action, the procedure of use reported in the clinical data on the device and the description of PCI principle in the state of the art allow to support the clinical benefit "minimally invasive procedure which does not require general anesthesia and major surgery". This benefit is additionally congruent with the data and stenting procedures reported in the clinical studies on benchmark devices, similar device and predicate Helistent 2 device analyzed in the state of the art

- Concenring the prevention of a heart attack (myocardial infarction) or minimalization of the consequences of heart attack:

The analysis of clinical data on TITAN OPTIMAX further allows to states that:
- the rate of non-fatal myocardial infarction (MI) given for TITAN OPTIMAX
    - o equates to 0.2% (#5) immediately post-procedure;
    - o ranges from 0.5% to 3.1 % 12-months post procedure (#1, #2, #3, #5);
    - o equates to 2.2% 18-months post procedure in the TIDE-ACS study (#1)
    - o is reported as significantly lower than the values obtained for SYNERGY EES (#1: 1.8% vs 4.6% at 12-months; 2.2% vs 5% at 18-months).

- the rate of cardiac death after angioplasty given for TITAN OPTIMAX
    - o equates to 0.5% (#5) immediately post-procedure;
    - o ranges from 0.5% to 1.8 % 12-months post procedure (#1, #2, #3, #5);
    - o equates to 0.6% 18-months post procedure in the TIDE-ACS (#1)
    - o is reported as significantly lower than the values obtained for SYNERGY EES (#1: 0.5% vs 1.6% at 12-months; 0.6% vs 2.6% at 18-months).

- The results of post-market studies specific to TITAN OPTIMAX demonstrate an adequate safety profile in terms of procedural complications and post-procedural cardio-vascular events such as myocardial infarctions, stent thrombosis and death;

- A meta-analysis carried out on results retrieved from 5 randomized clinical trials (TITAX AMI, TIDE, TITANIC XV, BASE ACS and TIDES ACS) shows that BAS (including TITAN OPTIMAX) appears to offer a better efficacy/risk than DES;

- The performance surveys conducted on TITAN OPTIMAX stents in normal conditions of use highlighted a very good customer acceptance and adequate peri-procedural safety results;
- As of today, around 96 500 TITAN OPTIMAX have been used worldwide with a low user complaint rate and none of the complaints received have raised any concern with the device safety

In conclusion, the risks associated with TITAN OPTIMAX stent system, when used as intended, are acceptable when weighed against the benefits to the patients,

5.3 Post-market clinical follow-up

The method used to collect data in order to ensure a post market clinical follow up. It consists to carry out every year:

- Literature screening:

Any scientific publications, abstracts, articles relevant to similar or equivalent devices identified through research on dedicated database (such as PubMed, google scholar), subscription to online newsletter (PCRonline, interventional news, TCT magazine).

- Annual participation to international congress
- Review of vigilance databases for similar or equivalent devices such as MAUDE database, ANSM database
- Collect and analyse complaints and vigilance data
- Clinical studies (if necessary)
- Evaluation performed by physicians

6 POSSIBLE THERAPEUTIC ALTERNATIVES

When considering alternative treatments, it is recommended to contact your healthcare professional who can take into account your individual situation.

Treatments for coronary artery disease usually involves lifestyle changes and if necessary, drugs and certain medical procedures:

•**Lifestyle changes:** Quit smoking, eat healthy foods, exercise regularly, lose excess weight, reduce stress.

• **Pharmacological treatment**: it may include cholesterol-modifying medications, anti-thrombotics , anti-ischemic, and prophylactic or symptomatic lipid lowering drugs.

• **Drug-eluting stent for percutaneous Coronary Intervention (PCI):** The drug-eluting stents consist to a metallic stent platform with controlled release of antiproliferative drugs, mostly regulated by surface polymers.
The drug eluting stent are an alternative to TITAN OPTIMAX. It should be noted that despite the new generation DES have improved clinical outcomes versus first generation DES, there is still a concern in DES linked late stent thrombosis associated with a concern with long term DAPT and bleeding risks.
Comparing to TITAN OPTIMAX, 3 randomized studies (TiTAX-AMI, BASE-ACS, TiDES-ACS) in ACS demonstrated the non-inferiority of its TiNO stent technology versus the 1st generation DES (Taxus, Boston Scientific), the second generation DES (Xience V, Abbott) and versus the 3rd generation DES (Synergy, Boston Scientific) in terms of efficacy (MACE or Major Adverse Cardiac Events).
Last, it should be noted that the 3rd generation Biological Active Stent TiTAN Optimax has demonstrated its superiority versus the 3rd generation DES at 18 months follow up in terms of safety (cardiac death, AMI, major bleeding).

• **Coronary Artery Bypass Graft (CABG):** CABG consists to use blood vessels from another part of the body and connects them to blood vessels above and below the narrowed artery, bypassing the narrowed or blocked coronary arteries. One or more blood vessels may be used, depending on the severity and number of blockages. The blood vessels are usually arteries from the arm or chest, or veins from the legs.

Hybrid coronary revascularization (HCR): HCR for multivessel coronary artery disease (CAD) also emerged and integrates coronary artery bypass grafting (CABG) and percutaneous intervention in a planned revascularization strategy. HCR is an interesting approach for multivessel CAD but should not be considered a 'one-size-fits-all' procedure

As mentioned in the 2018 ESC/EACTS guidelines from expert consensus on myocardial revascularization, whether medical therapy, PCI, or CABG have to be preferred to treat CADs (Coronary artery disease), should be depend on the risk–benefit ratios of these treatment strategies, weighting the risks of periprocedural death, myocardial infarction and stroke against improvements in health-related

quality of life, as well as long-term freedom from death, myocardial infarction or repeat revascularization.

The 2021 ACC/AHA/SCAI Guideline for Coronary Artery Revascularization added that treatment decisions regarding coronary revascularization in patients with coronary artery disease (CAD) should be based on clinical indications. In patients being considered for coronary revascularization for whom the optimal treatment strategy is unclear, a multidisciplinary Heart Team approach is strongly recommended. Treatment decisions should be patient-centered, incorporate patient preferences and goals, and include shared decision-making.

7 REFRENCE TO HARMONIZED STANDARDS AND COMMON SPECIFICATIONS

HEXACATH applies the following harmonized standards and common specifications published in the Official Journal of the European Union, according to Decision (EU) 2021/1182 of 16 July 2021 and Decision (EU) 2022/6 of 4 January 2022:

- EN ISO 13485 :2016 Medical devices - Quality management systems - Requirements for regulatory purposes

- - EN 15223-1 :2021 Medical Devices – Symbols to be used with medical devices labels, labeling and information to be supplied — Part 1: General requirements

- EN ISO 11135:2014 - Sterilization of health-care products — Ethylene oxide — Requirements for the development, validation and routine control of a sterilization process for medical devices.

- EN ISO 11737-1:2018 Sterilization of medical devices - Microbiological methods - Part 1: Determination of a population of microorganisms on products.

- EN ISO 11737-2 2020 Sterilization of health care products — Microbiological methods — Part 2: Tests of sterility performed in the definition, validation and maintenance of a sterilization process.

- EN ISO 14971:2019 Medical devices – Application of risk management to medical devices

Other standards applied by HEXACATH have not yet been harmonized with the Regulation (EU) 2017/745

8 ABBREVIATIONS

ACS: Acute coronary syndrome
AMI: Acute myocardial infarction
BAS: “Bioactive stents” (generic name for TiNo coated stents, including HELISTENT TITAN 2 and TITAN OPTIMAX)
BMS: Bare-metal stent(s)
CABG: Coronary artery bypass graft
EES: Everolimus-eluting stent(s)
ESC: European Society of Cardiology
MACE: Major cardiovascular events
MAUDE: Manufacturer And User Facility Device Experience database
MI: Myocardial infarction
NSTEMI: Non ST-elevation myocardial infarction
ST: Stent thrombosis
STEMI: ST-elevation myocardial infarction
TiNO: Titanium Nitride oxide
TLR: Target lesion revascularization
TVR: Target vessel revascularization

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