GENERAL INFORMATION

Project title (eng)
Two by two factorial randomized controlled multicenter trial and economic evaluation of low-dose ASA vs DOAC and graduated compression stockings vs no graduated compression stockings in patients who undergo primary 'fast-track' total hip arthroplasty for the prevention of venous and arterial thromboembolic disease

Acronym
[15 characters max]
HAVANAS : Hip Arthroplasty Vascular prevention AspiriN Anticoagulant Stocking

First submission to DGOS calls for proposals ? Yes
[Tick {Yes ; No} If "No", mention the year of previous submission[8]]
In the case of a re-submission, complete the entry field EXPERTS COMMENTS AND CORRESPONDING ANSWERS

First name and name of the coordinator
Name : Mottier
First name : Dominique
Town : BREST Cedex
Site hospitalier d'exercice : CHRU HOPITAL CAVALE BLANCHE
Affiliated institution from the ministry of health: C.H.R.U. BREST
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Research Domain : Médecine interne
Speciality : Médecine Interne
2.3. Profession du porteur de projet : Médecin
Previous grants in the frame of DGOS calls
[list with : year, ref number, progress [list]]

Physician, Dental practitioner / Biologist / Nurse, other paramedical
[tick]

Affiliated institution responsible for the budget from the ministry of health

Research Domain
[list of keywords] / Oncology [tick] [if oncology, organ, tumor location]
hip arthroplasty, venous and arterial prevention, aspirin, anticoagulant, compression stocking, fast-track

Name of the methodologist (+ tel + email)

Civility Ms.
Name LAPORTE
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Name of the economist (if any) (+ tel + email)

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Organization responsible for project management

Délégation à la Recherche Clinique et à l'Innovation - CHRU BREST

Organization responsible for quality assurance

Délégation à la Recherche Clinique et à l'Innovation - CHRU BREST

Organization responsible for data management and statistics

Délégation à la Recherche Clinique et à l'Innovation - CHRU BREST
Silvy LAPORTE - SAINT ETIENNE

Anticipated number of recruiting centres (NC)

Noms des co-investigateurs (1/centre) + CV
Combien de malades à inclure / an
Co-investigators (1 à N)
[Table {Name Surname Town Country Hospital EMail Tel Speciality}]

Liste des co-investigateurs recrutés par le Docteur Romain GÉRARD, ayant donné leur accord et adressé leur CV

Civility	Name	First Name	Town	Country	Hospital	E-mail	Phone	Speciality	THAs/y
Mr	GERARD	Romain	Brest	France	Polyclinique Keraudren	dr.romaingerard@gmail.com	0648163789	Orthopaedic Surgery	300
Mr	WESSELY	Loïc	Brest	France	Polyclinique Keraudren	docteur.wessely@gmail.com	0663182424	Orthopaedic Surgery	100
Mr	PHILIPPEAU	Jean-Marie	Nantes	France	Clinique St Augustin	jmphilippeau@hotmail.com	0684543766	Orthopaedic Surgery	200
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Mr	MOUTON	Antoine	Paris	France	CH Croix St Simon	amouton@hopital-dcss.org	0144641640	Orthopaedic Surgery	“
Mr	PASSERON	Dorick	Paris	France	CH Croix St Simon	dpasseron@hopital-dcss.org	0144641640	Orthopaedic Surgery	“
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Mr	WILLIAMS	Thomas	Brest	France	CHRU Brest	thomas.williams@chu-brest.fr	0624643642	Orthopaedic Surgery	100
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Mr	ACQUITTER	Yvan	Rennes	France	CHP St Grégoire	acquitter-y@wanadoo.fr	0223253992	Orthopaedic Surgery	300
Mr	CLAVE	Arnaud	Nice	France	Clinique St Georges	arnaud.clave@orange.fr	0493817150	Orthopaedic Surgery	100
Mr	D'HONDT	Didier	Nice	France	Clinique St Georges	didier.dhondt@wanadoo.fr	0610712925	Orthopaedic Surgery	500
Mr	LACROIX	Jérôme	Morlaix	France	CH Morlaix	jlacroix@ch-morlaix.fr	0640958975	Orthopaedic Surgery	150

Liste des co-investigateurs recrutés par le Professeur Jean-Yves JENNY, ayant donné leur accord et adressé leur CV

Mr	HAZAPARU	Nicolae	Strasbourg	France	Hôpitaux Universitaires de Strasbourg	nicolae.hazaparu@chru-strasbourg.fr	0652777140	Orthopaedic Surgery	150
Mr	JENNY	Jean-Yves	Strasbourg	France	Hôpitaux Universitaires de Strasbourg	jean-yves.jenny@chru-strasbourg.fr	0388552145	Orthopaedic Surgery	200

Liste des co-investigateurs recrutés par le Professeur Pierre ALBALEDEJO, ayant donné leur accord et adressé leur CV

Liste des co-investigateurs recrutés par le Professeur Marc SAMAMA, ayant donné leur accord et adressé leur CV

Liste des co-investigateurs recrutés par le Professeur Patrick MISMETTI, ayant donné leur accord et adressé leur CV

Liste des co-investigateurs recrutés par le Professeur Alain SAUTET, ayant donné leur accord et adressé leur CV

RESEARCH PROJECT

Rational (context and hypothesis)
[max. 320 words]

To date, anticoagulants given for 30 to 40 days, combined with graduated compression stockings are established as the standard of care for the prevention of VTE disease after total hip arthroplasty (THA). Their favorable benefit to risk ratio has been largely demonstrated.
However incidence of VTE has decreased over time in THA patients. In the early 2000's trials, in prophylactic LMWH-treated patients, symptomatic venous thromboembolic (VTE) event's rate at 3 months was between 2 and 4 % and major bleeding rate at 1%. In the current trials the symptomatic VTE event's rate is much lower, down to 0.4%, but major bleeding rate has remained unchanged. This reduction in VTE incidence is mainly related to novel surgical and anaesthetic procedures and "Enhanced Recovery After Surgery" protocols evolving a better management of patients. This leads to questioning the risk-benefit balance of anticoagulant use in such population. Moreover, THA postoperative risk of arterial complications (myocardial infarction, ischemic stroke) reaches 0.5% at 70 days, i.e. similar to venous complications.
Anticoagulants (LMWH and DOACs) are largely used in orthopaedic patients in Europe, and especially in France. However the efficacy of aspirin-acetylsalicylic acid (ASA) has been recently reviewed and is now also recommended for VTE prophylaxis after THA or TKA (grade 1B ESA 2017) especially in patients without high risk of VTE (1C). Moreover, a reduced risk of arterial events should be expected with aspirin.
Graduated compression stockings or socks are still often prescribed in order to reduce the risk of DVT (deep venous thrombosis) after lower limb total joint arthroplasty. The ACCP guidelines do not recommend graduated compression stockings routinely if pharmacological prophylaxis is given as they do not reduce symptomatic DVT or PE, but they do increase skin complications by 4-fold. As they are costly, time-consuming to measure and fit, extremely uncomfortable to wear, with an increased risk of wrong move and THA dislocation, the routine use is not recommended.
According to the decreasing risk of postoperative venous thromboembolic events over time, the risk of arterial events, the lack of efficacy for compression stockings use and the burden of their use, in postoperative THA patients, it is of interest to evaluate a new strategy for VTE prophylaxis corresponding to a switch from DOACS to ASA and discontinuation of graduated compression stockings. Of note, ASA use in comparison with DOAC as venous anti-thrombotic prophylaxis in this setting could result in a reduction in arterial events.
Given the respective unit costs of DOACs (€80 for 35 days) and stockings (€60 for 35 days) versus aspirin (€2 for 35 days), the proposed switch could be as best dominant (cost saving and outcome improving) or as least decrementally cost effective.

Originality and innovative aspects
[max. 160 words]

Seven main aspects will ensure the originality of this project:

- *Reduction in the intensity of postoperative prevention of VTE*
- *Combined management of both venous and arterial thromboembolic risks in patients who underwent a primary elective 'fast-track' THA.*
- *Risk, assessment of only symptomatic venous thromboembolic events (for venous thromboembolism risk)*
- *Evaluation of the role or futility of graduated compression stockings in patients undergoing first-line THA*
- *Measurement of the incidence of overall arterial and venous thromboembolic events in patients undergoing first-line 'fast-track' THA*
- *Economic evaluation*

- *Factorial design to allow to answer to two independent questions in the same trial*

Focus of Research
Health technology [tick & then detail] : drugs ; devices ; procedures and organizational systems used in health care (including Health services[9]).
If relevant : date of CE mark / market authorization

Keywords [5]: vascular thromboprophylaxis, primary total hip arthroplasty, fast-track, graduated compression stockings, aspirin, oral anticoagulant

Main Objective
[detail, max 48 words]
[Tick one: Hypothesis; Description Feasibility; Tolerance Efficacy ; Safety Efficiency ; Budget Impact ; Organisation of Care]
[Tick one : Etiology Causality[10] ; Diagnosis ; Prognosis ; Therapeutics (impact on clinical end-points[11]) ; Therapeutics (impact on intermediate end-points[12]) ; Compliance ; Effective Practice ; Research methodology ; Qualitative Research ; Others]

A two by two factorial randomized controlled multicentric trial and economic evaluation of low-dose ASA vs DOAC and graduated compression stockings vs no graduated compression stockings in patients who undergo 'fast-track' primary THA

Primary efficacy objective

- *To show that compare Aspirin is non-inferior to DOAC, according to the overall thromboembolic events (arterial & venous).*
- *To show that non compression stockings in non-inferior to graduated compression stockings on venous thromboembolic events*

Secondary Objectives
[detail, max 160 words]

- *To evaluate the incidence of arterial thromboembolic complications*
- *To evaluate the incidence of venous thromboembolic complications*
- *Primary safety objective: incidence of major bleeding complications*
- *Secondary safety objective : major bleeding and clinically relevant non-major bleeding*
- *Secondary safety objective : revision for periprosthetic hip infection*
- *Cost-effectiveness analysis*

Primary End Point (linked with the main objective)

Primary efficacy outcome for the comparison of aspirin to DOAC: composite of adjudicated symptomatic deep-vein thrombosis, non fatal and fatal pulmonary embolism, arterial embolism, myocardial infarction, stroke, transient ischemic attack, cardio-vascular mortality from randomization to day 90.

Primary efficacy outcome for the comparison of compression stockings vs. no compression stockings: composite of adjudicated symptomatic deep-vein thrombosis, non-fatal pulmonary embolism and fatal pulmonary embolism, during the same period.

Secondary End Points (linked with the secondary objectives)

- *Primary safety outcome: major bleeding during the treatment period or until 3 days after the last dose of study medication is administered. The definition of major bleeding is acute, clinically overt bleeding accompanied by one or more of the following findings : a decrease in the haemoglobin level of 2 g per deciliter or more over a 24-hour period; transfusion of 2 or more units of packed red blood cells; bleeding at a critical site (including intracranial, intraspinal, intraocular, pericardial, and retroperitoneal bleeding); bleeding into the operated joint, requiring reoperation or intervention; intramuscular bleeding with the compartment syndrome; or fatal bleeding.*
- *Secondary safety outcome is major bleeding and clinically relevant non-major bleeding during the treatment period or until 3 days after the last dose of study medication is administered. The definition of clinically relevant non-major bleeding include acute, clinically overt episodes such as wound haematoma, bruising or ecchymosis, gastrointestinal bleeding, haemoptysis, haematuria, or epistaxis that do not meet the criteria for major bleeding.*
- The other secondary safety outcome: periprosthetic hip infection *from randomization to day 90.*
- *The secondary efficacy outcome for venous thrombotic complications is the composite of adjudicated symptomatic deep-vein thrombosis, non-fatal pulmonary embolism, or death related to venous thromboembolism, from randomization to day 90.*
- *The other secondary efficacy outcome for arterial complications is the composite of adjudicated myocardial infarction, stroke, transient ischemic attack, cardio-vascular mortality, from randomization to day 90. .*
- *Cost effectiveness and cost utility analyses.*

Study Population
Main inclusion and exclusion criteria

Inclusion criteria :

- *Patient aged > = 18 years*
- *Elective primary total hip arthroplasty*
- *Included in fast-track program*

Exclusion criteria :

- *Patients who already receive anticoagulant or antiplatelet therapy for any indication*
- *History of prior venous thromboembolism*
- *Active bleeding or high risk of bleeding*
- *Creatinine clearance < 15 ml/min*
- *Unable or unwilling to consent*
- *Hip revision arthroplasty*
- *Hypersensitivity to acetylsalicylic acid (ASA) or to excipient or other non-steroidal anti-inflammatory drugs (NSAIDs)*
- *History of aspirin-induced or NSAID-induced asthma*
- *Progressive gastro-duodenal (peptic)ulcer*
- *Hereditary or acquired bleeding disorders*
- *Hypersensitivity to Apixaban or Rivaroxaban*
- *Intake of CYP3A4 and P-gp inducers*
- *Intake of CYP3A4 and P-gp inhibitors such as azole-antimyotics and HIV protease inhibitor drugs*

Design
[tick + detail max 320 words]
Meta analysis
Randomized clinical trial
If yes : Open - Single Blind - Double Blind *[tick]*
Systematic reviews
Pragmatic studies
Quasi-experimental studies (non randomized cohorts)
Prospective cohort study
Case-control study
Cross-sectional study
Retrospective cohort
Administrative / hospital inpatient database research
Modelisation
Case Series
Others
Qualitative study

The HAVANAS trial is a 2 x 2 multicenter factorial randomized controlled trial of low-dose aspirin vs DOAC and compression stockings vs no compression stockings

9 http://htaglossary.net
10 Studies designed to determine the causes of a disease, the risk of being exposed to a drug, a pollutant etc
11 Example : reduction of myocardial infarction incidence, of mortality
12 Example : reduction of serum cholesterol, improvement of a pain scale

If Health-Economics Analysis
[tick + detail max 320 words]
Cost-utility analysis
Cost-effectiveness analysis
Cost-benefit analysis
Budget impact analysis
Cost-minimization analysis
Cost-consequence analysis
Cost of illness analysis
Others

The economic evaluation based upon the non-inferiority design assumes a decremental cost effectiveness of aspirin compared to stockings or DOACs. We will use the collective viewpoint and a time horizon of 90 days. Healthcare resources at the patient level will be recorded prospectively and valued using costs for hospital care and prices or tariffs for other treatments, drugs /devices. Outcomes will be measured by 1) the primary efficacy endpoint (major cardio vascular event averted) which has been commonly used in cost effectiveness analyses and for which benchmarks are available, and 2) quality adjusted life years, based upon the EQ5D questionnaire and the French utility values. The 5Q5D will be self administered at inclusion, and monthly after discharge up to 3 months. The difference in QALYs will be computed as the difference in the areas under the utility curves in each over the 3-month period. Incremental (decremental) cost effectiveness and cost utility ratios will be computed as the ratios of the difference in costs to the difference in outcomes and the uncertainty explored by bootstrap.
The budget impact analysis will use the current prevalence of 140 000 interventions per year and model a progressive substitution of DOACs with or without graduated compression stockings by aspirin (with or without graduated compression stockings*)* over a 5-year period. The budget impact analysis will be conducted from the viewpoint of the social health insurance.

Technology Readiness Level[13]
[1 digit + 1 letter]

In the case of a drug trial, phase : III
[tick {I, II, I/II, III, IV}]

If comparison groups:

Experimental group *[detail max 48 words] Please see the Figure 1: two by two study design*

To assess the non-inferiority of aspirin to DOAC, patients in the experimental group will receive 100 mg ASA for 35 days.
To compare graduated compression stockings vs. no graduated compression stockings, the experimental group will have no graduated compression stockings.

Control group *[detail max 48 words]*

To assess the non-inferiority of aspirin to DOAC, control group patients will receive a DOAC (DOAC choice will be left to physician's discretion) for 35 days.
To compare graduated compression stockings vs no compression stockings, the control group will have compression stockings.

Duration of participation of each patient
[3 digits + days / months / years]
90 days

Anticipated Duration of Recruitment (DUR)

[2 digits, in months]
2 years

Total number of scheduled patients /observations to be recruited (NP)
[3 digits + Justification of sample size max 80 words]

For the comparison of aspirin to DOAC, assuming a rate of venous and arterial thromboembolic events of 1% in both group, with a one-sided error of 0.025 and a statistical power of 80%, a non-inferiority margin for the relative risk of 2, 1555 patients per group are needed. For the comparison of compression stockings vs. no compression, the rate of venous thromboembolisms is expected to 0.6% in both group. Based on the same statistical consideration, 2601 patients by group are needed. Then we need to include the largest calculated sample size to answer to the two questions, i.e. 5202 patients overall.

Number of patients / observations to be recruited / month / centre ((NP/DUR)/NC)
[2 digits + justification if more than 2 patients/month/centre]

5202 patients to enroll over 2 years

Number of recruiting centers: 10

Recruitment rate per center: an average of 400 THA / year / center

Recruitment rate: 20 patients per month per center

Expected number of patients eligible in the centers

[Table : {Name ; Surname ; Town ; Country ; Expected recruitment/month ; Total}]

Co-investigateurs regroupés par centre, recrutés par le Docteur Romain GERARD

Hospital	Town	Country	THAs/y
Polyclinique Keraudren	Brest	France	400
Clinique St Augustin	Nantes	France	200
GH Diaconesses Croix St Simon	Paris	France	1200
CHRU Brest	Brest	France	300
CHP St Grégoire	Rennes	France	600
Clinique St Georges	Nice	France	600
CH Morlaix	Morlaix	France	150

Co-investigateurs regroupés par centre, recrutés par le Professeur Jean-Yves JENNY

Co-investigateurs regroupés par centre, recrutés par le Professeur Pierre ALBALADEJO

Co-investigateurs regroupés par centre, recrutés par le Professeur Marc SAMAMA

Co-investigateurs regroupés par centre, recrutés par le Professeur Patrick MISMETTI

Co-investigateurs regroupés par centre, recrutés par le Professeur Alain SAUTET

Participation of a research network
[Detail max 32 words]
INNOVTE : F-CRIN NETWORK (Investigation Network On Venous Thrombo-Embolism)

Participation of industry
[Detail max 64 words]

Other aspects to insure the feasibility of the project
[Detail max 64 words]

Expected patient or public health benefit
[Detail max 320 words]

13 https://www.medicalcountermeasures.gov/federal-initiatives/guidance/about-the-trls.aspx

REFERENCES
Please join a maximum of 5 articles that justify the project in the national / international context.

Afshari, A. A., Walter; Ahmed, Aamer; Duranteau, Jacques; Faraoni, David; Kozek-Langenecker, Sibylle; Llau, Juan; Nizard, Jacky; Solca, Maurizio; Stensballe, Jakob; Thienpont, Emmanuel; Tsiridis, Eleftherios; Venclauskas, Linas; Samama, Charles Marc; for the ESA VTE Guidelines Task Force (2018). "European Guidelines on perioperative venous thromboembolism prophylaxis: Executive summary." Eur J Anaesthesiol 35(2): 77-83.

Eriksson, B. I., et al. (2008). "Rivaroxaban versus enoxaparin for thromboprophylaxis after hip arthroplasty." N Engl J Med 358(26): 2765-2775.

Lassen, M. R., et al. (2010). "Apixaban versus enoxaparin for thromboprophylaxis after hip replacement." N Engl J Med 363(26): 2487-2498.

Jørgensen, C. C., Kehlet, H., Lundbeck Foundation Centre for Fast-track Hip and Knee replacement collaborative group. (2016). Early thromboembolic events ≤1week after *fast-track total hip and knee arthroplasty. Thrombosis Research, 138, 37–42.*

Kehlet, H. (2013). Fast-track hip and knee arthroplasty. The Lancet, 381(9878), 1600–1602.

APPROXIMATE LEVEL OF FUNDING REQUIRED
[en k euros]

KEY WORDS
Coordinator domain
Wished rapporteur domain

EXPERTS COMMENTS *[quote]* **AND CORRESPONDING ANSWERS**[14]
[max 320 words]

[14] To complete if the project has been previously submitted to a DGOS call for proposals