Assessment of the WATCHMAN TM Device in Patients Unsuitable for Oral Anticoagulation (ASAP-TOO)

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The primary objective of this study is to establish the safety and effectiveness of the WATCHMAN TM Left Atrial Appendage Closure (LAAC) Device including the post-implant medication regimen for subjects with non-valvular atrial fibrillation who are...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Cardiac arrhythmias
Study type	Interventional

Summary

ID

NL-OMON47674

Source
ToetsingOnline

Brief title
ASAP-TOO

Condition

- Cardiac arrhythmias
- Embolism and thrombosis

Synonym
thromboembolic ischemic stroke and systemic embolism.

Research involving
Human

Sponsors and support

Primary sponsor: Boston Scientific
Source(s) of monetary or material Support: Boston Scientific

Intervention

Keyword: Left Atrial Appendage Closure (LAAC) Device., Reduce the risk of thromboembolic ischemic stroke and systemic embolism., Safety and effectiveness.

Outcome measures

Primary outcome

The occurrence of one of the following events between the time of implant and within 7 days following the procedure or by hospital discharge, whichever is later: all-cause death, ischemic stroke, systemic embolism, or device- or procedure- related events requiring open cardiac surgery or major endovascular intervention such as pseudoaneurysm repair, AV fistula repair, or other major endovascular repair. Percutaneous catheter drainage of pericardial effusions, percutaneous retrieval of an embolized device, thrombin injection to treat femoral pseudoaneurysm and nonsurgical treatments of access site complications are excluded from this endpoint

Secondary outcome

1. The time to first occurrence of stroke (including ischemic and/or hemorrhagic), cardiovascular death (cardiovascular and/or unexplained cause) and systemic embolism

2. The time to first occurrence of major bleeding (defined as a BARC type 3 or 5 event)

3. The time to first occurrence of non-procedure related major bleeding (defined as a BARC type 3 or 5 event)

4. Non-disabling vs. disabling and fatal stroke analysis as defined using VARC-2

5. The time to occurrence of cardiovascular death (cardiovascular and/or

unexplained cause)

6. The time to occurrence of all-cause death

7. The time to first occurrence of all-cause stroke (ischemic and/or

hemorrhagic)

8. The time to first occurrence of hemorrhagic stroke

9. Procedural success defined as a completed WATCHMAN implant procedure with no

primary safety endpoint and no device embolization.

10. Rates of effective (defined as jet size of <=5mm) and complete (defined as

no peri-device flow) LAA closure at 3 and 12 months post implant.

Study description

Background summary

Atrial fibrillation (AF) is one of the most common abnormal rhythm disturbances and affects
approximately 5.5 million people worldwide, including 10% of people older than 75 years.
The most debilitating consequence of AF is thrombus formation from stagnant blood flow
leading to thromboembolism and stroke. As such, the rate of ischemic stroke attributed to
non-valvular AF is estimated to average 5% per year, which is 2-7 times that of those without
AF.2
Treatment with warfarin therapy for the prevention of thromboemboli originating in the left
atrial appendage has been well documented. Warfarin therapy targeting an International
Normalized Ratio (INR) between 2.0 - 3.0 has been considered the gold standard treatment
historically for patients with non-valvular AF for prevention of stroke. While warfarin has
remained the optimum treatment for many years, there are numerous challenges with the
drug, such as frequent need for monitoring and dosage adjustments, dietary and

metabolic
interactions, and concerns of patient compliance. Additionally, the potential for frequent and
fatal bleeding are high concerns for patients and caregivers, and often it is found this drug is
not well tolerated.
Currently available alternatives to warfarin are the direct oral anticoagulants (DOACs),
which include dabigatran, rivaroxaban, apixaban, and edoxaban. Unlike warfarin, DOACs
can be administered without the need for monitoring, have fewer food and drug interactions,
and provide an improved effectiveness/safety ratio. Dabigatran at the dose of 150 mg twice
daily is shown to be superior to warfarin in prevention of stroke and systemic thromboembolism, has a favorable safety profile including significantly less intracranial
bleeding and comparable extracranial bleeding, and is associated with less cardiovascular
mortality. Rivaroxaban at a daily dose of 20 mg is shown to be non-inferior to warfarin in
prevention of stroke or systemic embolism. The risk of major bleeding is not significantly
different for rivaroxaban versus warfarin; however, intracranial and fatal bleeding is less
frequent with rivaroxaban. In comparison to warfarin, apixaban at a dose of 5 mg twice
daily is also shown to be superior in prevention of stroke and systemic thromboembolism,
causes less bleeding, and is associated with a lower mortality rate. Edoxaban is shown to be
non-inferior to warfarin with respect to the prevention of stroke or systemic embolism, and is
associated with significantly lower rates of bleeding and death from cardiovascular causes.
While these direct agents, and warfarin, are effective and safe in their intended patient
populations, there are patients who, based on a determination of benefit and risk, cannot
tolerate exposure to systemic anticoagulation with these agents even for a short period of
time.
As the risk of stroke increases with age and the disability and tolerance concerns with
available drug therapy persist, the need for permanent protection against thromboembolism
in AF patients remains unmet. The sponsor has developed the WATCHMAN® Left

Atrial
Appendage Closure (LAAC) Device, a permanent implantable device to seal off the left atrial
appendage, the location where the vast majority of thrombi originate in AF patients. This
device has been shown to provide an alternative to warfarin therapy in non-valvular AF
patients who require thromboembolic protection.

The WATCHMAN LAAC Device has primarily been studied with the post implant drug regimen consisting of: 45-days of warfarin, followed by dual antiplatelet therapy (DAPT)
until 6-months post-implant, followed by indefinite single antiplatelet therapy of aspirin.
Several studies have been conducted that look at alternative post-implant drug regimens
which exclude warfarin, including 6-months DAPT followed by stand-alone aspirin and 6-
weeks of DAPT followed by stand-alone aspirin. The ASAP Feasibility trial and the
EWOLUTION and WASP registries utilized the WATCHMAN device with post procedure DAPT . Other LAA closure devices have
utilized post procedure DAPT consisting of clopidogrel for 1 to 6 months and aspirin 100 mg
for at 5 months. Early data suggest that shortened DAPT may be acceptable for subjects
that can*t take oral anticoagulants.
The current study is designed to collect data for the WATCHMAN LAA Closure Device, in
subjects with non-valvular AF who are unable to take oral anticoagulants, even for a short
period of time.

Study objective

The primary objective of this study is to establish the safety and effectiveness of the WATCHMAN TM Left Atrial Appendage Closure (LAAC) Device including the post-implant medication regimen for subjects with non-valvular atrial fibrillation who are deemed not to be eligible for anti-coagulation therapy to reduce the risk of stroke. The device is intended to reduce the risk of thromboembolic ischemic stroke and systemic embolism.

Study design

This study is a prospective, randomized, multi-center, global investigation to

determine the safety and effectiveness of the WATCHMAN Device for subjects with non-valvular atrial fibrillation who are deemed not suitable for anti-coagulation therapy to reduce the risk of stroke.

Intervention

No concomitant procedures are to be performed at the time of the WATCHMAN implant procedure. This includes, but is not limited to, cardiac ablation procedures, transcutaneous valve procedures, cardioversions, coronary stent, pacemaker or ICD generator change, etc.

Study burden and risks

Additional risks that are associated with implanting the WATCHMAN TM Device include:
• misplacement of the Device
• dislodgement of the Device in your heart if it does not fit properly, which could lead to a procedure or major surgery to remove the Device
• the inability to place the Device in the correct position or inability to remove the Device if necessary
• excessive bleeding
• Device infection
• allergic reaction to the implant materials
• blood clots on the Device
• Device fracture
• scarring or clotted veins
• the Device may not properly close off your LAA
• inability to implant the Device

Contacts

Public
Boston Scientific

Lambroekstraat (Green Square) 5D
Diegem 1831
BE
Scientific
Boston Scientific

Lambroekstraat (Green Square) 5D
Diegem 1831
BE

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1. The subject is of legal age to participate in the study per the laws of their respective geography.
2. The subject has documented paroxysmal, persistent, permanent or long-term/longstanding persistent non-valvular atrial fibrillation (i.e., the subject has not been diagnosed with rheumatic mitral valvular heart disease).
3. The subject has a calculated CHA2DS2-VASc score of 2 or greater.
4. The subject is deemed by two study physicians to be unsuitable for oral anticoagulation.
5. The subject is deemed by a study physician to be suitable for the defined protocol pharmacologic regimen of aspirin and clopidogrel* therapy following WATCHMAN Closure Device implant.
6. The subject or legal representative is able to understand and willing to provide written informed consent to participate in the trial.
7. The subject is able and willing to return for required follow-up visits and examinations.

Exclusion criteria

1. The subject is unable or unwilling to return for required follow-up visits and examinations.
2. The subject had or is planning to have any invasive cardiac procedure within 30 days prior to randomization (e.g., cardioversion, ablation).
3. The subject is planning to have any cardiac or non-cardiac invasive or surgical procedure that would necessitate stopping or modifying the protocol required medication regimen within 90 days after the WATCHMAN Closure Device implant (e.g., cardioversion, ablation, cataract surgery).
4. The subject had a prior stroke (of any cause) or TIA within the 30 days prior to randomization.
5. The subject had a prior BARC type 3 or 4 bleeding event within the 14 days prior to randomization. Lack of resolution of related clinical sequelae, or planned and pending

interventions to resolve bleeding/bleeding source, are a further exclusion regardless of timing of the bleeding event.
6. The subject has a history of atrial septal repair or has an ASD/PFO device.
7. The subject has an implanted mechanical valve prosthesis in any position.
8. The subject suffers from New York Heart Association Class IV Congestive Heart Failure.
9. The subject has LVEF < 30%.
10. The subject is of childbearing potential and is, or plans to become pregnant during the time of the study (method of assessment upon study physician*s discretion).
11. The subject is currently enrolled in another investigational study or registry that would directly interfere with the current study, except when the subject is participating in a mandatory governmental registry, or a purely observational registry with no associated treatments. Each instance should be brought to the attention of the sponsor to determine eligibility.
12. The subject has a life expectancy of less than two years.
13. The subject has a known or suspected hypercoagulable state.

Study design

Design

Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Single blinded (masking used)
Control:	Active
Primary purpose:	Prevention

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	28-08-2018
Enrollment:	50
Type:	Actual

Medical products/devices used

Generic name:	WATCHMAN Left Atrial Appendage Closure (LAAC) Device
Registration:	Yes - CE intended use

Ethics review

Approved WMO Date:	01-12-2017
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	09-02-2018
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	23-02-2018
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	03-07-2018
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	11-09-2018
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	05-10-2018
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	31-07-2019
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
CCMO	NL61037.100.17