

Ilek. Jakub Maksym

**“Analiza zastosowania zabiegów zamykania uszka lewego przedsionka jako metody prewencji
udarów mózgu u pacjentów z niezastawkowym migotaniem przedsionków.”**

**Rozprawa na stopień doktora nauk medycznych i nauk o zdrowiu
w dyscyplinie nauki medyczne.**

Promotor: dr hab. n. med. Tomasz Mazurek

I Katedra I Klinika Kardiologii

Warszawski Uniwersytet Medyczny



Obrona rozprawy doktorskiej przed Radą Dyscypliny Nauk Medycznych
Warszawskiego Uniwersytetu Medycznego

Warszawa 2025

Słowa kluczowe: migotanie przedsionków, leczenie przeciwkrzepliwe, przezcewnikowe zamknięcie uszka lewego przedsionka, uszkodzenie lewego przedsionka, udar mózgu

Key words: atrial fibrillation, anticoagulation therapy, transcatheter left atrial appendage closure, left atrial appendage, ischaemic stroke

Serdeczne podziękowania Promotorowi, Panu doktorowi habilitowanemu Tomaszowi Mazurkowi za okazane wsparcie, inspirację do pracy naukowej i pomoc w realizacji projektu.

Serdeczne podziękowania dla Pana Profesora Grzegorza Opolskiego i Pana Profesora Marcina Grabowskiego za dobre warunki do pracy naukowej i wsparcie merytoryczne.

Najbardziej chciałbym podziękować swojej rodzinie, szczególnie mojej żonie Dominice i rodzicom za wieloletnie wsparcie, motywację i wyrozumiałość.

Wykaz publikacji stanowiących pracę doktorską

1. Maksym J. Kapłon-Cieślicka A, Scisło P, Huczek Z, Marchel M, Piątkowski R, Kochman J, Opolski G, Grabowski M, Mazurek T. Safety and efficacy of percutaneous atrial appendage closure followed by antiplatelet therapy in a high-risk population: single-center experience with a WATCHMAN device. *Postepy Kardiol Interwencyjnej*. 2023 Sep;19(3):262-269. doi: 10.5114/aic.2023.131480. [IF 1.5, MEiN 70]
2. Maksym J. Scisło P, Kapłon-Cieślicka A, Huczek Z, Marchel M, Kochman J, Zbroński K, Opolski G, Grabowski M, Mazurek T. Incidence and predictors of device-related thrombus after left atrial appendage closure with Watchman device. *Postepy Kardiol Interwencyjnej*. 2024 Jun;20(2):164-171. doi: 10.5114/aic.2024.140315. [IF 1.5, MEiN 40]
3. Maksym J. Grabowski M, Mazurek T. Percutaneous left atrial appendage closure with the Watchman device: a systematic review. *Postepy Kardiol Interwencyjnej*. 2024 Mar;20(1):18-29. doi: 10.5114/aic.2024.136406. [IF 1.5, MEiN 40]

Spis treści

1.	Wykaz stosowanych skrótów.....	6
2.	Streszczenie w języku polskim.....	7
3.	Streszczenie w języku angielskim.....	11
4.	Wstęp	
4.1.	Migotanie przedsionków i zapobieganie incydentom zakrzepowo-zatorowym.....	15
4.2.	Zamykanie uszka lewego przedsionka.....	17
4.3.	Farmakoterapia po zabiegu zamknięcia uszka lewego przedsionka.....	18
4.4.	Skrzeplina związana z urządzeniem po skutecznym zabiegu zamknięcia uszka lewego przedsionka.....	20
4.5.	Uzasadnienie połączenia prac w cykl publikacji.....	21
5.	Cel pracy.....	22
6.	Prace stanowiące cykl publikacji	
6.1.	Safety and efficacy of percutaneous atrial appendage closure followed by antiplatelet therapy in a high-risk population: single-center experience with a WATCHMAN device.....	24
6.2.	Incidence and predictors of device-related thrombus after left atrial appendage closure with Watchman device.....	33
6.3.	Percutaneous left atrial appendage closure with the Watchman device: a systematic review.....	42
7.	Podsumowanie i wnioski.....	55
8.	Piśmiennictwo.....	58
9.	Opinia Komisji Bioetycznej lub Etycznej.....	65
10.	Oświadczenia współautorów.....	66

1. Wykaz stosowanych skrótów

AF - *atrial fibrillation*, migotanie przedsionków

CT - *computed tomography*, tomografia komputerowa

DAPT – *dual antiplatelet therapy*, podwójna terapia przeciwplateletowa

DRT - *device-related thrombus*, skrzeplina związana z urządzeniem

LA - *left atrium*, lewy przedsionek

LAA - *left atrial appendage*, uszko lewego przedsionka

LAAC - *left atrial appendage closure*, zamknięcie uszka lewego przedsionka

LMWH - *low-molecular-weight heparin*, heparyna drobnocząsteczkowa

NOAC - *new oral anticoagulants*, nowe doustne antykoagulanty

OAC - *oral anticoagulants*, doustne antykoagulanty

PDL - *peri-device leak*, przeciek wokół urządzenia

TEE - *transesophageal echocardiography*, echokardiografia przezprzełykową

TIA - *transient ischaemic attack*, przejściowy epizod niedokrwienności

VKA - *vitamin K antagonists*, antagoniści witaminy K

2. Streszczenie w języku polskim.

Migotanie przedsionków (z ang. *Atrial Fibrillation* - AF) jest najczęstszą tachyarytmią przedsionkową, a częstość jej występowania wzrasta wraz z wiekiem populacji. Charakteryzuje się nieskoordynowaną czynnością elektryczną przedsionków, która powoduje utratę ich czynności skurczowej. Migotanie przedsionków jest głównym czynnikiem ryzyka zdarzeń zakrzepowo-zatorowych, niezależnie czy jest napadowe, przetrwałe lub utrwalone. Nielezione wiąże się z 5-krotnie większym ryzykiem wystąpienia udaru niedokrwinnego mózgu.

Doustne leczenie przeciwkrzepliwe jest podstawową metodą zapobiegania incydentom zakrzepowo-zatorowym u pacjentów z rozpoznanym AF. Wytyczne Europejskiego Towarzystwa Kardiologicznego dotyczące migotania przedsionków z 2024 roku zastąpiły dotychczas wykorzystywaną skalę CHA₂DS₂-VASc, nową skalą CHA₂DS₂-VA i zalecają jej wykorzystanie u wszystkich pacjentów w celu stratyfikacji ryzyka wystąpienia zdarzenia zakrzepowo-zatorowego. Pozwala ona podjąć decyzję odnośnie rozpoczęcia leczenia doustnymi antykoagulantami (z ang. *Oral Anticoagulants* - OAC). U pacjentów, którzy uzyskali 2 punkty lub więcej należy rozpocząć przewlekłą terapię przeciwwzakrzepową (klasa zaleceń: I, poziom dowodu A), a u pacjentów z 1 punktem należy rozważyć włączenie takiej terapii (klasa zaleceń: IIa, poziom dowodu C). Preferowanym leczeniem jest wykorzystanie nowych doustnych antykoagulantów (z ang. *New Oral Anticoagulants* - NOAC) zamiast antagonistów witaminy K (z ang. *Vitamin K Antagonists* - VKA) (klasa zaleceń: I, poziom dowodu A).

Pośród chorych wymagających OAC jest duża grupa pacjentów, u których takie leczenie jest przeciwwskazane lub nieskuteczne. Do przeciwwskazań takiego leczenia należy m. in. bardzo wysokie ryzyko krwawienia lub przebyte poważne krwawienie, a o nieskuteczności terapii mówimy, gdy w trakcie odpowiedniego leczenia u pacjenta wystąpił incydent zakrzepowo-zatorowy. Na podstawie danych z badań pokazujących, że ponad 90% materiału zatorowego u chorych z niezastawkowym AF pochodzi z uszka lewego przedsionka (z ang. *Left Atrial Appendage* - LAA), zaproponowano procedurę polegającą na zamknięciu LAA. Skuteczny

zabieg ma za zadanie zapobiec wytworzeniu się skrzepliny w LAA, a następnie jej migracji do krwioobiegu. Takie postępowanie wydaje się zapobiegać incydom zatorowym, jednocześnie zmniejszając ryzyko krwawienia związane z przewlekłym stosowaniem OAC. Obecnie zamykanie uszka lewego przedsionka (a ang. *Left Atrial Appendage Closure* - LAAC) stanowi niefarmakologiczną metodę prewencji zdarzeń zakrzepowo-zatorowych u pacjentów z niezastawkowym AF. Wytyczne Europejskiego Towarzystwa Kardiologicznego dotyczące migotania przedsionków z 2024 wskazują, że LAAC można rozważyć u pacjentów z przeciwwskazaniami do długotrwałej terapii przeciwkrzepliwej (klasa zaleceń: IIb, poziom dowodu C).

Zabieg LAAC jest procedurą inwazyjną i wiąże się z występowaniem powikłań takich jak udar niedokrwienny, poważne krwawienie, tamponada oraz uszkodzenie naczynia. Ponadto skuteczna implantacja okcludera do LAA wiąże się z możliwością wytworzenia się skrzepliny związanej z urządzeniem (z ang. *Device-Related Thrombus* - DRT), dlatego też zaleca się leczenie przeciwzakrzepowe w okresie pozabiegowym. Postępowanie to ma na celu zmniejszyć ryzyko wytworzenia się DRT. Pierwotnie po zabiegu stosowano VKA, jednakże z uwagi na wysokie ryzyko krwawienia w populacji poddanej procedurze rozpoczęto poszukiwania innych metod leczenia. Zastosowanie NOAC lub leków przeciwplatekowych było przedmiotem wielu badań klinicznych, w których wykazano, że takie postępowanie może być skuteczne przy zachowanym profilu bezpieczeństwa. W chwili obecnej nie ma jednoznacznych zaleceń dotyczących farmakoterapii pozabiegowej. Trwają badania randomizowane, które w przyszłości pomogą nam ustandaryzować farmakoterapię po skutecznym zabiegu LAAC, jednak do tego czasu eksperci zalecają indywidualizację leczenia.

W ramach pierwszego badania retrospektywnie przeanalizowano 91 pacjentów poddanych zabiegowi LAAC z wykorzystaniem urządzenia WATCHMAN w jednym ośrodku akademickim. Celem pracy była ocena zabiegu, okresu okołozabiegowego oraz skuteczności i bezpieczeństwa pozabiegowej terapii przeciwplatekowej. Urządzenie udało się skutecznie implantować u 90

pacjentów. Poważne krwawienie w skali BARC (z ang. Bleeding Academic Research Consortium) > 3 wystąpiło u 3 pacjentów, tamponada u 3 pacjentów, a z przyczyn sercowo-naczyniowych zmarła 1 osoba. Ponadto 1 osoba zmarła nie z przyczyn sercowo-naczyniowych. Po zabiegu, do czasu kontrolnego badania echokardiograficznego przezprzełykowego (z ang. *Transesophageal Echocardiography* - TEE), 85 pacjentów otrzymało podwójną terapię przeciwplatekową, składającą się z kwasu acetylosalicylowego i kłopidogrelu. Pozostałe 3 osoby zostały wypisane z zaleceniem pojedynczej terapii przeciwplatekowej jednym z powyższych leków. Po medianie 67 dni od zabiegu u wszystkich pacjentów wykonano ocenę kliniczną, a kontrolne badanie TEE wykonano u 78 badanych. Pierwszorzędowy punkt końcowy oceniający bezpieczeństwo terapii, zdefiniowany jako duże krwawienie, wystąpił u 2 pacjentów, z których żaden nie wymagał hospitalizacji, ani przetoczenia krwi. Natomiast, pierwszorzędowe punkty oceniające skuteczność terapii wystąpiły u 4 pacjentów (1 udar niedokrwienny, 1 zgon z przyczyny sercowo-naczyniowej i 2 zgony nie z przyczyny sercowo-naczyniowej). W kontrolnym badaniu TEE nie stwierdzono istotnego przecieku wokół urządzenia (z ang. *Peri-Device Leak* - PDL), a skrzeplinę na urządzeniu stwierdzono u 5 pacjentów. Wyniki badania pokazują, że terapia przeciwplatekowa po LAAC wydaje się być skuteczną i bezpieczną opcją leczenia.

Celem drugiej pracy była ocena częstości wytworzenia się skrzepliny na urządzeniu WATCHMAN i określenie predyktorów jej wystąpienia. Grupę badaną stanowili wszyscy pacjenci, którzy mieli wykonane kontrolne badanie TEE po skutecznej implantacji okludera. Skrzeplinę związaną z urządzeniem stwierdzono u 5 pacjentów. W porównaniu do grupy pacjentów bez DRT, chorzy z DRT byli młodszy, mieli niższą frakcję wyrzucania lewej komory, niższą prędkość opróżniania LAA, oraz mieli głębiej implantowane urządzenie w LAA. Wszyscy badani ze stwierdzonym DRT otrzymali leczenie przeciwkrzepliwie heparyną drobnocząsteczkową uzyskując rezolucję skrzepliny przy braku wystąpienia powikłań krwotocznych.

W ostatniej pracy przedstawiono podsumowanie aktualnej wiedzy na temat LAAC z wykorzystaniem urządzenia WATCHMAN. W sposób szczegółowy omówiono istotę zabiegu,

wskazania oraz różne wersje okludera. Przedstawiono również możliwe formy leczenia przeciwzakrzepowego po skutecznym zabiegu LAAC. Analizie poddano powikłania zabiegu, takie jak wystąpienie DRT oraz PDL i omówiono metody ich leczenia.

Podsumowując, w cyklu publikacji stanowiących poniższą rozprawę poddano analizie rozwijającą się metodę LAAC, która stanowi alternatywę dla OAC u chorych z niezastawkowym AF i z przeciwwskazaniami do leczenia przeciwkrzepliowego. Na podstawie publikacji wydaje się, że terapia przeciwpłytkowa po LAAC jest skuteczna i bezpieczna u pacjentów wysokiego ryzyka. Ponadto biorąc pod uwagę czynniki ryzyka wystąpienia DRT jesteśmy w stanie bardziej świadomie zindywidualizować leczenie pozabiegowe minimalizując ryzyko wystąpienia DRT. Praca pogładowa porusza najistotniejsze aspekty zabiegowej metody prewencji udaru mózgu i przedstawione w tej pracy dane stanowią przydatne narzędzie w codziennej praktyce klinicznej.

3. Streszczenie w języku angielskim.

“Analysis of left atrial appendage closure procedures as a method of stroke prevention in patients with nonvalvular atrial fibrillation.”

Atrial fibrillation (AF) is the most common atrial tachyarrhythmia, and its prevalence increases with age. It is characterized by uncoordinated electrical activity of the atria, which causes loss of their contractile function. Atrial fibrillation is a major risk factor for thromboembolic events, regardless of whether it is paroxysmal, persistent or permanent. If left untreated, it is associated with a 5-fold increased risk of ischemic stroke.

Oral anticoagulation therapy is the default method for preventing thromboembolic events in patients with diagnosed AF. The 2024 European Society of Cardiology guidelines on atrial fibrillation replaced the previously used CHA2DS2-VASc score with the new CHA2DS2-VA score and recommends its use in all patients to stratify the risk of a thromboembolic event. It allows doctors to decide whether to initiate treatment with oral anticoagulants (OAC). In patients with 2 points or more, chronic anticoagulation therapy should be initiated (class of recommendation: I, level of evidence A), while in patients with 1 point, such therapy should be considered (class of recommendation: IIa, level of evidence C). The preferred treatment is the use of new oral anticoagulants (NOAC) instead of vitamin K antagonists (VKA) (class of recommendation: I, level of evidence A).

Among patients requiring OAC, there is a large group of patients in whom such treatment is contraindicated or ineffective. Contraindications to such treatment include a very high risk of bleeding or a history of serious bleeding, while therapy ineffectiveness is defined as appearance of thromboembolic event during appropriate anticoagulation treatment. Based on data from studies showing that over 90% of embolic material in patients with nonvalvular AF comes from the left atrial appendage (LAA), a procedure involving closure of the LAA was proposed. An effective procedure prevents the clot formation in the LAA and its subsequent migration into the bloodstream. This approach appears to prevent embolic events while reducing the risk of bleeding

associated with chronic OAC use. Currently, left atrial appendage closure (LAAC) is a non-pharmacological method for preventing thromboembolic events in patients with nonvalvular AF. The 2024 European Society of Cardiology Guidelines on Atrial Fibrillation indicate that LAAC may be considered in patients with contraindications to long-term OAC (class of recommendation: IIb, level of evidence C).

Left atrial appendage closure is an invasive procedure and is associated with complications such as ischemic stroke, major bleeding, tamponade, and vessel injury. In addition, successful occluder implantation is associated with the possibility of device-related thrombus (DRT) development, therefore post-procedural antithrombotic treatment is recommended. This approach is intended to reduce the risk of DRT. Initially, VKA was used after the procedure, however, due to the high risk of bleeding in the population undergoing the procedure, a search for alternative treatment methods began. The use of NOAC or antiplatelet drugs has been the subject of many clinical trials, which have shown that such treatment can be effective with a preserved safety profile. There are currently no clear recommendations for post-procedure pharmacotherapy. Randomized trials are underway and will help us standardize pharmacotherapy after a successful LAAC procedure, but until then, experts recommend individualizing the treatment.

The first study retrospectively analyzed 91 patients who underwent LAAC using the WATCHMAN device at a single academic center. The aim of the study was to evaluate the procedure, the periprocedural period, and the efficacy and safety of postprocedural antiplatelet therapy. The device was successfully implanted in 90 patients. Major bleeding with BARC (Bleeding Academic Research Consortium) scale > 3 occurred in 3 patients, tamponade in 3 patients, and 1 person died of cardiovascular causes. Additionally, 1 non-cardiovascular death occurred. After the procedure, until the follow-up transesophageal echocardiography (TEE) examination, 85 patients received dual antiplatelet therapy consisting of acetylsalicylic acid and clopidogrel. The remaining 3 patients were discharged with a recommendation for single antiplatelet therapy with one of the above drugs. After a median of 67 days after the procedure, all

patients underwent clinical evaluation, and follow-up TEE examination was performed in 78 subjects. The primary endpoint assessing the safety of the therapy, defined as major bleeding, occurred in 2 patients, none of whom required hospitalization or blood transfusion. However, the primary endpoints assessing the efficacy of the therapy occurred in 4 patients (1 ischemic stroke, 1 cardiovascular death, and 2 non-cardiovascular deaths). The control TEE examination did not reveal any significant peri-device leak (PDL), and a DRT was found on the device in 5 patients. The results of the study show that antiplatelet therapy after LAAC seems to be an effective and safe treatment option.

The aim of the second study was to assess the frequency of thrombus formation on the WATCHMAN device and to determine the predictors of its occurrence. The study group consisted of all patients who had a control TEE examination after successful implantation of the occluder. Device-related thrombus was found in 5 patients. Compared to the group of patients without DRT, patients with DRT were younger, had a lower left ventricular ejection fraction, a lower LAA emptying velocity, and had the device implanted deeper in the LAA. All patients with confirmed DRT received anticoagulation with low-molecular-weight heparin, achieving thrombus resolution without bleeding complications.

The last study presents a summary of the current knowledge on LAAC using the WATCHMAN device. The essence of the procedure, indications, and different versions of the occluder are discussed in detail. Possible forms of anticoagulation after successful LAAC are also presented. Complications of the procedure, such as DRT and PDL, were analyzed and methods of their treatment were discussed.

In summary, in the series of publications constituting the following dissertation, the developing LAAC method was analyzed, which is an alternative to OAC in patients with nonvalvular atrial fibrillation and contraindications to anticoagulation therapy. Based on the publications, it seems that antiplatelet therapy after LAAC is effective and safe in high-risk patients. Moreover, taking into account the risk factors for DRT, we are able to better individualize

post-procedural treatment, minimizing the risk of DRT. The review paper discusses the most important aspects of the interventional method of stroke prevention and the data presented in this paper are a useful tool in everyday clinical practice.

4. Wstęp

4.1. Migotanie przedsionków i zapobieganie incydom zakrzepowo-zatorowym.

Migotanie przedsionków (z ang. *Atrial Fibrillation* - AF) jest najczęściej występującą arytmia w populacji ogólnej, a częstość jej występowania rośnie wraz z wiekiem [1]. Chorobowość sięga 10-12% u pacjentów po 80 roku życia [1]. Oprócz starzenia się organizmu, kilka innych schorzeń zwiększa ryzyko rozwoju i wystąpienia AF, a należą do nich m.in.: nadciśnienie tętnicze, cukrzyca, niewydolność serca, choroba niedokrwienna serca, zastawkowe wady serca, nadczynność tarczycy, otyłość, nadużywanie alkoholu, przewlekła choroba nerek i choroby płuc [2,3]. Na podstawie momentu wystąpienia arytmii oraz czasu jej trwania wyróżniamy 4 główne rodzaje: pierwszorazowe AF, napadowe, przetrwałe, oraz utrwalone AF [4]. Niezależnie od rodzaju, AF jest czynnikiem ryzyka wystąpienia udaru niedokrwiennego mózgu i zdarzeń zakrzepowo-zatorowych, co znacząco zwiększa śmiertelność oraz może powodować poważne niepełnosprawności [5]. Wystąpienie arytmii wiąże się z pięciokrotnie większym ryzykiem wystąpienia udaru niedokrwiennego mózgu [6]. Migotanie przedsionków diagnozuje się u około 7% pacjentów z ostrym udarem niedokrwiennym w ciągu pierwszych 3-5 dni po incydencie niedokrwiennym [7], a odsetek stwierdzonej arytmii wzrasta do 25% przy przedłużonym monitorowaniu serca [8]. Jednym z proponowanych mechanizmów wystąpienia udaru niedokrwiennego u pacjentów z AF jest nieskoordynowana czynność elektryczna przedsionków, która powoduje utratę ich czynności skurczowej, czego konsekwencją jest zastój krwi i zwiększone ryzyko wystąpienia incydu zakrzepowo-zatorowego [9].

Zapobieganie udarom niedokrwiennym oraz zdarzeniom zakrzepowo-zatorowym stanowi podstawę leczenia pacjentów z AF. Obligatoryjne jest rozpoczęcie terapii doustnymi antykoagulantami (z ang. *Oral Anticoagulants* - OAC) u chorych ze stwierdzonym AF i będących w grupie ryzyka wystąpienia zdarzeń zakrzepowo-zatorowych, a skuteczność terapii OAC została udowodniona w wielu badaniach klinicznych [10]. Dotychczas zalecaną skalą do oceny ryzyka zakrzepowo-zatorowego była skala CHA₂DS₂-VASc, która w wytycznych Europejskiego

Towarzystwa Kardiologicznego dotyczących migotania przedsionków z 2024 roku została zastąpiona nową skalą CHA2DS2-VA. W chwili obecnej zalecane jest rozpoczęcie terapii OAC u wszystkich chorych, którzy w skali CHA2DS2-VA otrzymali 2 punkty lub więcej (klasa zaleceń: I, poziom dowodu A), a u pacjentów z 1 punktem należy rozważyć włączenie takiej terapii (klasa zaleceń: IIa, poziom dowodu C) [4]. W chwili obecnej dostępnych jest kilka doustnych leków przeciwkrzepliwych, z dwóch głównych grup: antagoniści witaminy K (z ang. *Vitamin K Antagonists* - VKA) oraz nowe doustne antykoagulanty (z ang. *New Oral Anticoagulants* - NOAC). Terapia przeciwkrzepliwa jest wysoce skuteczna w zapobieganiu występowania zdarzeń zakrzepowo-zatorowych. Badania porównujące VKA z placebo wykazały, że zastosowanie OAC zmniejsza ryzyko udaru niedokrwinnego o 64% i zgonu z jakiegokolwiek przyczyny o 26% [10]. Od czasu wprowadzenia NOAC w 2009 roku, leki z tej grupy prawie całkowicie wyparły VKA z leczenia chorych z niezastawkowym AF. Leki z tej grupy są porównywalne do VKA pod względem zapobiegania zdarzeniom zakrzepowo-zatorowym i lepsze pod względem ryzyka krwawienia [11]. W metaanalizie badań porównujących VKA z NOAC, obejmującej ponad 70 000 pacjentów z migotaniem przedsionków, zastosowanie NOAC wiązało się z istotną redukcją liczby wszystkich udarów o 19%, co wynikało głównie ze znacznego zmniejszenia liczby udarów krwotocznych (HR 0,49, 95% CI 0,38–0,64) [12]. Zgodnie z wytycznymi Europejskiego Towarzystwa Kardiologicznego preferowanym leczeniem jest wykorzystanie NOAC zamiast VKA (klasa zaleceń: I, poziom dowodu A) [4].

Pacjentom z wysokim ryzykiem krwawienia i/lub z wywiadem poważnego krwawienia, lub chorym u których wystąpił epizod zakrzepowo-zatorowy pomimo odpowiednio zastosowanej terapii przeciwkrzepliwej, można proponować interwencyjne metody prewencji powikłań zakrzepowo-zatorowych w miejsce leczenia OAC. Zastosowanie niefarmakologicznej profilaktyki przeciwzakrzepowej dodatkowo znacząco zmniejsza obciążenie wynikające z długotrwałego przyjmowania OAC. Spośród dostępnych technik, przezcewnikowe zamykanie uszka lewego

przedsionka (z ang. *Left Atrial Appendage Closure* - LAAC) jest dobrą alternatywą dla dotychczas stosowanych OAC u pacjentów z niezastawkowym AF.

4.2. Zamykanie uszka lewego przedsionka.

Zamykanie uszka lewego przedsionka jest stale rozwijającą się metodą nefarmakologicznej prewencji udaru mózgu u pacjentów z niezastawkowym AF. Zapoczątkowanie metody było pokłosiem analizy wyników badań echokardiografii przezprzełykowej (z ang. *Transesophageal Echocardiography* - TEE), autopsji oraz raportów operacyjnych, która określiła i podkreśliła rolę lokalizacji powstawania materiału zatorowego [13]. Powyższe analizy wykazały, że u pacjentów z niezastawkowym AF źródłem skrzeplin powodujących incydenty zakrzepowo-zatorowe jest w ponad 90% uszko lewego przedsionka (z ang. *Left Atrial Appendage* - LAA), w przeciwieństwie do chorych z zastawkowym AF, u których skrzeplina była stwierdzana głównie w jamie lewego przedsionka (z ang. *Left Atrium* - LA) [13, 14]. Ponadto w 2019 opublikowano analizę ponad 1400 badań TEE u pacjentów z niezastawkowym AF, w której wykazano, że w przypadku stwierdzenia materiału zatorowego w jamach serca, to we wszystkich przypadkach była to skrzeplina w LAA i ewentualnie dodatkowo w LA lub prawym przedsionku [15].

Biorąc pod uwagę istotny udział LAA w powikłaniach zatorowych u pacjentów z AF, duża uwaga naukowców skupia się na rozwoju metod wykluczania LAA z obiegu krwi w celu prewencji powstania skrzeplin w jego świetle. W 2009 roku ukazały się wyniki pierwszego, dużego, randomizowanego badania PROTECT AF, które wykazały, że LAAC z wykorzystaniem urządzenia WATCHMAN nie jest gorsze od terapii warfaryną w zakresie pierwszorzędnego punktu końcowego składającego się z udaru, zatoru systemowego i zgonu z przyczyny sercowo-naczyniowej [16]. Kolejne badanie PREVAIL z 2014 roku, które zostało zaprojektowane w celu potwierdzenia bezpieczeństwa metody, wykazało, że LAAC z użyciem urządzenia WATCHMAN nie jest gorsze od warfaryny w zakresie udaru oraz incydentu zatorowego [17]. Po 5 latach obserwacji, LAAC zapewnia profilaktykę udaru porównywalną do VKA z istotną redukcją

istotnych krwawień, udarów krwotocznych, zgonów z przyczyn sercowo-naczyniowych, oraz zgonów z jakiegokolwiek przyczyny [18]. Badanie PRAGUE-17 wykazało również, że LAAC nie jest gorsze od NOAC w zakresie prewencji udaru lub przejściowego epizodu niedokrwiennego (z ang. *Transient Ischamic Attack* - TIA), zgonu z przyczyny sercowo-naczyniowej, istotnego klinicznie krwawienia i jest skuteczniejsze w zakresie prewencji wystąpienia krwawienia nie związanego z zabiegiem w 4-letniej obserwacji [19]. Prowadzone w kolejnych latach metaanalizy oraz rejestry dalej potwierdzały skuteczność i bezpieczeństwo zabiegowej metody prewencji udaru mózgu u chorych z niezastawkowym AF [20, 21]. Niedawno opublikowana metaanaliza porównującą LAAC z NOAC wykazała, że ryzyko udaru mózgu/TIA jest podobne w przypadku obu metod, podczas gdy LAAC wykazał przewagę w zmniejszaniu śmiertelności z przyczyn sercowo-naczyniowych oraz ryzyka poważnych i niewielkich krwawień [22]. Do dzisiaj nie mamy badań randomizowanych porównujących pacjentów poddanych LAAC, z pacjentami, którzy z uwagi na przeciwwskazania lub nietolerancję OAC nie otrzymują żadnej formy leczenia przeciwkrzepliowego. W chwili obecnej okluder WATCHMAN jest najlepiej przebadanym urządzeniem przeznaczonym do LAAC.

Przecewniki LAAC jest coraz częściej stosowaną metodą profilaktyki zdarzeń zakrzepowo-zatorowych u pacjentów z niezastawkowym AF, zwłaszcza w Stanach Zjednoczonych Ameryki [23]. Podczas gdy, w Europie rejestry pokazują, że metoda LAAC jest wykorzystywana u < 1% pacjentów z niezastawkowym AF [24]. Wytyczne Europejskiego Towarzystwa Kardiologicznego z 2024 roku dotyczące migotania przedsionków podtrzymało poprzednią rekomendację, że LAAC można rozważyć u pacjentów z przeciwwskazaniami do długotrwałej terapii przeciwkrzepliowej (klasa zaleceń: IIb, poziom dowodu C) [4].

4.3. Farmakoterapia po zabiegu zamknięcia uszka lewego przedsionka.

Leczenie przeciwzakrzepowe jest wymagane po skutecznym zamknięciu uszka lewego przedsionka w celu uniknięcia powstania skrzepliny związanej z urządzeniem (z ang.

Device-Related Thrombus - DRT) i powinno być kontynuowane przez okres pokrywania się urządzenia śródbłonkiem [25]. Biorąc pod uwagę fakt, że pacjenci z przeciwwskazaniami do OAC mają odnieść największą korzyść z LAAC i mają wyjściowo wysokie ryzyko krwawienia, farmakoterapia po zabiegu stanowi wyzwanie w praktyce klinicznej. Dostępne dane o farmakoterapii pozabiegowej zostały uzyskane z badań rekrutujących chorych bez przeciwwskazań do OAC, jak również z badań i rejestrów oceniających chorych z przeciwwskazaniami do OAC lub nietolerancją takiego leczenia [26].

Do pierwszych badań randomizowanych oceniających urządzenie WATCHMAN włączono pacjentów bez przeciwwskazań do OAC i zgodnie z protokołem badania stosowano VKA przez 45 dni, a następnie podwójną terapię przeciwplateletową (z ang. *Dual Antiplatelet Therapy* - DAPT) przez 6 miesięcy [16,17]. Jednakże, praktyka kliniczna jest inna i często zróżnicowana. Bezpośrednie inhibitory krzepnięcia w pełnych lub zredukowanych dawkach zostały zaproponowane jako alternatywa leczenia do VKA [27]. Wiele badań obserwacyjnych sugerowało również, że zastosowanie terapii przeciwplateletowej jest skuteczną i bezpieczną opcją, bez zwiększonego ryzyka DRT [20, 28]. W zbiorczej analizie danych z badań oceniających stosowanie OAC vs. leczenie przeciwplatetowe po skutecznym LAAC z wykorzystaniem urządzenia WATCHMAN, pacjenci zostali porównani pod kątem wystąpienia poważnego krwawienia i udaru/zatorowości obwodowej w sześciomiesięcznej obserwacji. Badanie wykazało, że częstość wystąpienia incydentu zakrzepowo-zatorowego i poważnego krwawienia niezwiązanego z procedurą były podobne w obu grupach [29].

W praktyce, po skutecznym LAAC zalecana jest indywidualizacja leczenia przeciwzakrzepowego. Powinna ona zapewnić równowagę pomiędzy ryzykiem wystąpienia DRT, a ryzykiem poważnego krwawienia. Decyzja ta powinna zostać podjęta na podstawie danych klinicznych pacjenta, chorób współistniejących, ryzyka zakrzepowo-zatorowego, ryzyka krwawienia, jak i również na podstawie doświadczenia lekarza prowadzącego.

4.4. Skrzeplina związana z urządzeniem po skutecznym zabiegu zamknięcia uszka lewego przedsionka.

Zabieg LAAC jest procedurą inwazyjną i wiąże się z wystąpieniem powikłań okołozabiegowych takich jak krwawienie, udar, tamponada i uszkodzenie naczynia. Ponadto istnieje ryzyko wystąpienia powikłań związanych z samym urządzeniem i należą do nich DRT, przeciek wokół urządzenia (z ang. *Peri-Device Leak* - PDL) oraz też bardzo rzadko spotykana embolizacja urządzenia [11]. Wraz z rozwojem technologii, rejestry oceniające urządzenia nowej generacji pokazują, że ryzyko wystąpienia powikłań związanych z okluderem jest niższe niż obserwowane w pierwszych badaniach randomizowanych [30, 31].

Skrzeplina związana z urządzeniem jest jednym z groźnych powikłań po implantacji okludera do LAA, a częstość występowania waha się od 2% do 4% [32-36]. Wystąpienie DRT jest związane z wyższym ryzykiem wystąpienia udaru niedokrwiennego lub TIA [37]. Najczęściej DRT zostaje wykryte w badaniu TEE lub tomografii komputerowej (ang. *Computed Tomography* - CT), wykonywanych w ramach rutynowej kontroli po zabiegu. Poza związanymi z pacjentem czynnikami ryzyka wystąpienia DRT, istnieją czynniki ryzyka, które są związane z techniką zabiegu i urządzeniem. Badania wykazały, że głęboka implantacja urządzenia w LAA stanowi niezależny czynnik ryzyka wystąpienia DRT [37, 38]. Do innych czynników ryzyka należy niewydolność nerek, stan nadkrzepliwości, jatrogeny wysięk osierdziowy i przetrwałe/utrwalone AF [37].

Stosowana farmakoterapia przeciwzakrzepowa po zabiegu ma celu zapobiegać incydentom DRT, jednak nie zawsze jest skuteczna. Postępowanie w przypadku wystąpienia DRT wymaga eskalacji terapii przeciwzakrzepowej i włączenia heparyny drobnocząsteczkowej (z ang. *Low-Molecular-Weight Heparin* - LMWH) lub OAC [11]. Dobranie odpowiedniej terapii stanowi wyzwanie przy współistniejącym najczęściej wysokim ryzyku powikłań krwotocznych, dlatego też zintensyfikowane leczenie przeciwkrzepliwe powinno trwać jak najkrócej, a jego skuteczność powinna zostać potwierdzona w kontrolnym badaniu obrazowym.

4.5. Uzasadnienie połączenia prac w cykl publikacji.

Prace wchodzące w skład cyklu publikacji tworzą spójną całość, analizując ważne aspekty zabiegu LAAC, farmakoterapii pozabiegowej oraz ewentualnych powikłań związanych z zabiegową metodą prewencji powikłań zakrzepowo-zatorowych u pacjentów z niezastawkowym AF. Pierwsza praca pokazuje skuteczność i bezpieczeństwo metody LAAC w grupie chorych spotykanych w codziennej praktyce klinicznej, która często stanowi większe wyzwanie niż populacje włączane do dużych badań klinicznych. W drugiej pracy przedstawiono czynniki ryzyka wystąpienia DRT, pogłębiając wiedzę na temat groźnego dla pacjenta powikłania oraz przedstawiono dalsze postępowanie w przypadku wystąpienia DRT. Ostatnia publikacja jest pracą poglądową, która szczegółowo opisuje metodę LAAC z wykorzystaniem urządzenia WATCHMAN, wskazania do zabiegu i dostępne dotychczas rodzaje okludera. Ponadto dogłębnie porusza temat leczenia przeciwwakrzepowego po skutecznym zabiegu oraz przedstawia najczęstsze powikłania wraz z dalszym postępowaniem.

5. Cel pracy.

Celem niniejszej rozprawy doktorskiej było przedstawienie prężnie rozwijającej się metody LAAC z wykorzystaniem urządzenia WATCHMAN, a w szczególności:

- ocena skuteczności i bezpieczeństwa metody LAAC
- ocena leczenia przeciwplatekowego po skutecznym zabiegu LAAC u pacjentów wysokiego ryzyka zdarzeń zakrzepowo-zatorowych i wysokiego ryzyka krwawienia.
- określenie predyktorów wystąpienia DRT
- szczegółowe omówienie metody LAAC, wskazań do zabiegu i farmakoterapii pozabiegowej

6. Prace tworzące cykl publikacji.

6.1. Safety and efficacy of percutaneous atrial appendage closure followed by antiplatelet therapy in a high-risk population: single-center experience with a WATCHMAN device.

Safety and efficacy of percutaneous atrial appendage closure followed by antiplatelet therapy in a high-risk population: single-center experience with a WATCHMAN device

Jakub Maksym, Agnieszka Kapłon-Cieślicka, Piotr Scisło, Zenon Huczek, Michał Marchel, Radosław Piątkowski, Janusz Kochman, Grzegorz Opolski, Marcin Grabowski, Tomasz Mazurek

First Chair and Department of Cardiology, Medical University of Warsaw, Warsaw, Poland

Adv Interv Cardiol 2023; 19, 3 (73): 262–269
DOI: <https://doi.org/10.5114/aic.2023.131480>

Abstract

Introduction: In our everyday practice we encounter many patients with non-valvular atrial fibrillation with either a contraindication to oral anticoagulation or with its inefficiency.

Aim: To investigate whether left atrial appendage closure (LAAC) followed by post-procedure antiplatelet therapy is safe and efficient in a high-risk population.

Material and methods: Ninety-one (48 males) consecutive patients with non-valvular atrial fibrillation (NVAf) underwent an LAAC procedure using a first-generation WATCHMAN 2.5 device followed by antiplatelet therapy. Clinical and transesophageal echocardiography data were collected at baseline and at the follow-up visit.

Results: The median (IQR) CHA₂DS₂-VASc score was 5 (4.0–6.0) and the HAS-BLED score was 3 (3.0–4.0); the mean (SD) age was 74.4 (8.4). A bleeding history was observed in 89% of patients and 24.2% of patients had a history of stroke or transient ischemic attack (TIA). The procedure was successful in 98.9%. Post-procedure therapy was dual antiplatelet therapy in 85 patients; 3 patients received single antiplatelet therapy and the therapy was maintained until the follow-up visit. Peri-procedural complications were tamponade (3.3%), pericardial effusion (2.2%) and two deaths (2.2%) with no bleeding or vascular complications. The median follow-up was 67 (52.75–84.75) days. Primary safety endpoint (bleeding BARC type 3 or more, tamponade, pericardial effusion, and device embolization) and primary efficacy endpoint (stroke or TIA, hemorrhagic stroke, peripheral embolism, cardiovascular (CV) and non-CV death) were observed in 2 and 4 patients, respectively.

Conclusions: The LAAC procedure followed by antiplatelet therapy seems to be safe and efficient in the high-risk population. Further studies in this field are required.

Key words: antiplatelet therapy, atrial fibrillation, stroke prevention, left atrial appendage closure.

Summary

Nowadays left atrial appendage closure is a vigorously developing method of stroke prevention in patient with non-valvular atrial fibrillation. The most challenging group consists of high-risk patients. In this population, on the one hand we must cope with the high bleeding risk but on the other hand we have high risk of thromboembolic complication. Moreover, we do not have exact recommendations regarding the optimal post-procedure treatment. Our study suggests that the left atrial appendage closure procedure followed by antiplatelet therapy is safe and efficient in a high-risk population.

Introduction

Atrial fibrillation (AF) is the most commonly diagnosed arrhythmia, and its prevalence increases with the population's age [1]. It is proved that AF is responsible

for up to 20% of ischemic strokes, which are associated with worse prognosis compared to those due to other etiologies [2]. Oral anticoagulation (OAC) therapy, with vitamin-K antagonist (VKA) or with new oral anticoagu-

Corresponding author:

Dr. Jakub Maksym, First Chair and Department of Cardiology, Medical University of Warsaw, Warsaw, Poland,
e-mail: jakub.maksym@gmail.com

Received: 25.04.2023, accepted: 12.06.2023.

lants (NOACs), remains the standard strategy to reduce the risk of ischemic events [3]. However, the application of OAC therapy carries increased risk of bleeding complications. Data show that about 40% of patients who require OAC do not receive the treatment despite the introduction of potentially safe drug therapies [4].

Left atrial appendage closure (LAAC) is the non-pharmacological option for stroke prevention in patients with non-valvular AF who are not good candidates for long-term OAC therapy. The development of the procedure was based on finding that approximately 90% of cardioembolic strokes in AF originate from a thrombus that developed in the left atrial appendage (LAA) [5]. Two randomized trials, PROTECT-AF and PREVAIL, have shown the non-inferiority of LAAC with a WATCHMAN device (Boston Scientific, Marlborough, MA, USA) to warfarin therapy in AF patients [6, 7]. The 5-year outcomes of the trials demonstrated that LAAC with the WATCHMAN provides stroke prevention comparable to warfarin, with additional reduction in major bleeding [8]. These trials included patients without an absolute contraindication to OAC, so warfarin was used after successful device deployment. Current European guidelines recommended LAAC in patients with AF and contraindications to long-term anticoagulant treatment (class IIb indication, level of evidence B) [9]. The same guidelines also recommend antiplatelet therapy after the procedure in patients with high bleeding risk, and this antithrombotic management has never been assessed in a randomized trial [9].

The choice of the antithrombotic regimen after the LAAC procedure seems to be a crucial issue. On the one hand, we must consider the bleeding risk of the patient, but on the other hand, we cannot forget about the possible thromboembolic complications. Nowadays, we have limited data on optimal treatment after the LAAC procedure in a high-risk population.

Aim

The aim of this study was to evaluate the safety and efficacy of the LAAC procedure with the first-generation WATCHMAN 2.5 device followed by an antiplatelet regimen in a high-risk population.

Material and methods

Study population

In our retrospective analysis we included 91 consecutive patients who were scheduled for the LAAC procedure with a WATCHMAN device from March 2015 to September 2019 in a single center (First Department of Cardiology, University Clinical Center, Warsaw, Poland). All patients were diagnosed with non-valvular AF and were at high thromboembolic risk assessed by the CHA₂DS₂-VASc score. Furthermore, all patients who underwent the procedure had one of the following: a contraindication for oral anticoagulation, history of bleeding complication

while using oral anticoagulation, inability to maintain INR level within the therapeutic range, history of stroke while using oral anticoagulation. Exclusion criteria included presence of thrombus in the left atrial appendage, inappropriate size of the left atrial appendage in preprocedural transesophageal echocardiography (TEE), and lack of patients' consent.

At admission, all patients underwent medical evaluation with laboratory testing, and calculation of the CHA₂DS₂-VASc score and bleeding scores such as HAS-BLED, ORBITA and ATRIA. At baseline, in all patients the TEE was performed to exclude the presence of thrombus in the LAA, to assess the feasibility of the procedure and to determine the size of the device.

LAAC procedure

All procedures were performed under general anesthesia with TEE and fluoroscopic guidance. The transcatheter access was the right femoral vein in all patients and then under TEE guidance the transseptal puncture was made to access the left atrium. Each patient received intravenously unfractionated heparin (UFH) at a dose of 1000 U/10 kg to continue the procedure with prolonged activated clotting time (ACT) to at least 250 s. Half of the dosage was given before transseptal puncture and the rest after crossing the intraatrial septum. Following introduction of the sheath into the LAA, the angiographic projection with contrast injection was obtained to evaluate the shape of the LAA. The assessment of LAA anatomy and landing zone was based on acquired angiographic planes and TEE visualization, so the most suitable size of the device could be chosen. When the proper position of the WATCHMAN introduction system was obtained, the first-generation WATCHMAN 2.5 device (Boston Scientific, St. Paul, Minnesota) was deployed under TEE and angiographic guidance. After device implantation, a stability test was performed before its final release. Contrast angiography and color Doppler in TEE were used to eliminate peri-device leaks. Peri-device jet size of 5 mm or more was classified as a significant leak. If needed, recapturing and reimplantation were done. Within 24 h all patients underwent transthoracic echocardiography (TTE) to exclude peri-procedural complications, such as pericardial effusion, as well as to confirm WATCHMAN device position.

Antithrombotic regimen and follow-up

All patients were treated with dual antiplatelet therapy (DAPT) (aspirin 75 mg and clopidogrel 75 mg once a day) or with single antiplatelet therapy (SAPT) (aspirin 75 mg or clopidogrel 75 mg once a day). The treatment regimen was at the discretion of the implanting physician and was maintained until follow-up examination. The treatment regimen choice was guided by patients' medical history, risk scores, and operators' experience.

All patients were clinically evaluated approximately 3 months after the procedure, preferably by in-hospital visit. We excluded from follow-up visits patients who had unsuccessful device implantation. The follow-up TEE was planned during the same visit. If the patient refused to come, the clinical evaluation was done by telephone contact.

Clinical events

Procedural success was defined as a successful deployment of the device that fulfilled all release criteria and an absence of significant peri-device leak, i.e. less than 5 mm as assessed by intra-procedural imaging.

Bleeding events were assessed according to the Bleeding Academic Research Consortium (BARC) defini-

tions [10]. Major bleeding, i.e. that classified as BARC type 3 or more, was overt bleeding requiring blood transfusion or bleeding with hemoglobin drop of ≥ 3 g/dl, cardiac tamponade, bleeding requiring surgical intervention or use of vasoactive agents, intracranial or intraocular bleeding and fatal bleeding.

Peri-procedural adverse events were defined as events that occurred within 7 days after the procedure or before patients' discharge.

Primary safety and efficacy endpoints at follow-up were defined following the Valve Academic Research Consortium consensus [11]. For a more accurate assessment of events related to the postoperative treatment regimen, the peri-procedural events were excluded.

The primary safety endpoint at follow-up was a composite of bleeding BARC type 3 or more, tamponade, pericardial effusion, and device embolization.

The primary efficacy endpoint at follow-up was a composite of stroke or TIA, hemorrhagic stroke, peripheral embolism, cardiovascular (CV) and non-CV death.

The TEE-guided secondary endpoint was the device-related thrombus (DRT).

Statistical analysis

Categorical variables are presented as counts and percentages. Continuous variables are presented as mean with standard deviation (SD) if normally distributed or otherwise by median and interquartile range. All statistical analyses were conducted with SPSS Statistics, version 22 (IBM SPSS Statistics, New York, US).

Results

Patient characteristics

A total of 91 patients were included in the analysis. Baseline demographics and risk factors are summarized in Table I. Fifty-three percent of the patients were male, and the mean (SD) age was 74.4 (8.4). Most patients (87.9%) had a history of hypertension, and more than a half (52.7%) were diagnosed with heart failure. Chronic kidney disease with glomerular filtration rate (GFR) < 60 ml/min/1.73 m² was observed in almost 65% of our patients. Type II diabetes mellitus and vascular disease were present in 39.6% and 40.7% of subjects, respectively. Based on the CHA₂DS₂-VASC risk score, patients enrolled in the study were at high risk of thromboembolic complication with a median (IQR) CHA₂DS₂-VASC score of 5 (4.0–6.0). Almost one fourth (24.2%) of the subjects had a history of stroke or TIA. Moreover, most of the patients (89%) had a history of bleeding and 86.8% of patients had a HAS-BLED score of 3 or more. At baseline, half of the subjects (50.5%) were on OAC therapy with either VKA, NOAC or low molecular weight heparin (LMWH), 9.9% were on single antiplatelet therapy (SAPT), 7.7% were on dual antiplatelet therapy, and 31.9% were not on any form of antithrombotic regimen.

Table I. Baseline characteristics

Parameter	Value
Age [years]	74.4 $\pm$ 8.4
Male	53% (48/91)
BMI [kg/m ²]	27.4 $\pm$ 4.4
Atrial fibrillation:	
Paroxysmal/persistent	60% (55/91)
Permanent	40% (36/91)
Hypertension	87.9% (80/91)
Congestive heart failure	52.7% (48/91)
Diabetes mellitus	39.6% (36/91)
COPD	13.2% (12/91)
Chronic kidney disease:	64.8% (59/91)
Stage 3a	31.9% (29/91)
Stage 3b	23.1% (21/91)
Stage 4	9.9% (9/91)
Stage 5	0% (0/91)
History of ischemic stroke/TIA	24.2% (22/91)
History of hemorrhagic stroke	9.9% (9/91)
Vascular disease	40.7% (37/91)
History of bleeding	89% (81/91)
CHA ₂ DS ₂ -VASC score	4.7 $\pm$ 1.6
HAS-BLED score	3.2 $\pm$ 0.9
ORBITA score	4.4 $\pm$ 2
ATRIA score	4.4 $\pm$ 2.6
OAC before procedure:	
VKA	9.9% (9/91)
NOAC	15.4% (14/91)
LMWH	25.3% (23/91)
SAPT	9.9% (9/91)
DAPT	7.7% (7/91)
None	31.9% (29/91)

Unless indicated otherwise, data are given as the mean (standard deviation), median (interquartile range) or as n (%). BMI – body mass index, COPD – chronic obstructive pulmonary disease, DAPT – dual antiplatelet therapy, LMWH – low molecular weight heparin, NOAC – new oral anticoagulation, OAC – oral anticoagulation, SAPT – single antiplatelet therapy, TIA – transient ischemic attack, VKA – vitamin K antagonist.

Table II. Transesophageal echocardiography parameters

Parameter	Value
Rhythm:	
Sinus	49.5% (45/91)
Atrial fibrillation	50.5% (46/91)
Thrombus in LAA	0% (0/91)
SEC	16.5% (15/91)
LAA flow velocity [cm/s]	53.2 ± 32.3
Ostium diameter [mm]:	
0°	20.1 ± 3.2
45°	19.6 ± 2.6
90°	19.3 ± 3.2
135°	20.2 ± 3.1
Depth of LAA [mm]	29.5 ± 5.6

Unless indicated otherwise, data are given as the mean (standard deviation), median (interquartile range) or as n (%). LAA – left atrial appendage, SEC – spontaneous echo contrast.

A history of bleeding during OAC therapy occurred in 81 patients, and it was the most common indication for the LAAC procedure. Three patients had a history of stroke during OAC therapy, 2 patients were diagnosed with vascular pathologies (one cavernous hemangioma in the occipital lobe and one cerebral arteriovenous malformation), which were contraindications to initiate OAC therapy. The other indications were labile INR ($n = 3$), recurrent thrombus in the left atrial appendage (LAA) despite different OAC regimen ($n = 1$) and intolerance of OAC therapy ($n = 1$).

All patients had TEE before the procedure. No thrombus in the LAA was found and the spontaneous echo contrast (SEC) was observed in 15 patients. Detailed data of LAA are presented in Table II.

Procedural and peri-procedural details

The procedural data are shown in Table III. All procedures were performed under general anesthesia and in 98.9% of the cases the device was implanted successfully, comparing favorably with rates reported in the previously published first-generation WATCHMAN trial (Figure 1). In 1 patient the device could not be implanted due to unfavorable LAA anatomy. In 26 cases the device had to be partially recaptured because of its unstable position, and in only 3 patients the full recapture was necessary. In all 3 cases the device size was changed to a bigger size. Complete sealing of the LAA was achieved in 81% of cases. Peri-device leaks were observed in 17 cases, and in all cases the residual flow was < 5 mm assessed with peri-procedural TEE. The median size of the device and its compression after deployment were 27 mm (24.0–20.0) and 16.67% (14.81–20.21), respectively.

All peri-procedural serious adverse events (SAEs) are summarized in Table IV. Major bleeding assessed as BARC

Table III. Procedural data

Variable	Value
Successful deployment	98.9% (90/91)
Rhythm during procedure:	
Sinus	46.2% (42/91)
Atrial fibrillation	53.8% (49/91)
General anesthesia	100% (91/91)
Procedure time [min]	77.6 ± 19.3
Fluoroscopy time [min]	17.5 ± 7.9
Fluoroscopy dose [mGy]	669.3 ± 458.2
Contrast agent [ml]	124 ± 49.3
Size of device [mm]	29.5 ± 5.6
Partial recapture:	28.6% (26/91)
One	69% (18/26)
Two	27% (7/26)
Three	4% (1/26)
Full recapture	3.3% (3/91)
Change in size of the device	3.3% (3/91)
Compression (%)	17.6 ± 4.8
LAA seal:	
Complete seal	81% (73/90)
Jet size 1–2 mm	14.5% (13/90)
Jet size 3–4 mm	4.5% (4/90)
Jet size 5 and more	0% (0/90)

Unless indicated otherwise, data are given as the mean (standard deviation), median (interquartile range) or as n (%). Abbreviations: see Table II.

≥ 3 was observed in 3 cases excluding tamponade. In the peri-procedural period 3 tamponade occurred, out of which one was during the procedure and was treated successfully by pericardiocentesis after the device deployment. Another 2 were observed several hours after the procedure. One was treated with pericardiocentesis, and the other one required surgical drainage of the pericardial sac. Moreover, 2 cases of mild pericardial effusion were observed and were treated conservatively. A day after the procedure one device embolization was observed during follow-up TTE, which required cardiac surgery and resulted in death. One more death occurred 1 week after

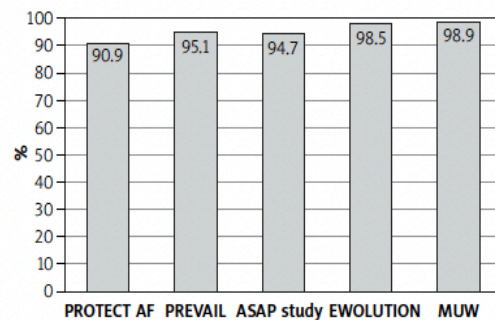
**Figure 1.** Device deployment success in Medical University of Warsaw (MUW) compared to previous WATCHMAN device studies

Table IV. Peri-procedural serious adverse events

Variable	Value
Serious bleeding BARC ≥ 3	3.3% (3/91)
Tamponade	3.3% (3/91)
Pericardial effusion	2.2% (2/91)
Ischemic stroke	0% (0/91)
TIA	0% (0/91)
Hemorrhagic stroke	0% (0/91)
Systemic embolization	0% (0/91)
Air embolization	0% (0/91)
CV death	1.1% (1/91)
Non-CV death	1.1% (1/91)

Unless indicated otherwise, data are given as the mean (standard deviation), median (interquartile range) or as n (%). BARC – Bleeding Academy Research Consortium, CV – cardiovascular, non-CV – non-cardiovascular. *excluding tamponade.

Table V. Primary safety and efficacy outcomes at follow-up

Variable	Value
Primary safety endpoints:	2.2% (2/88)
Serious bleeding BARC ≥ 3	2.2% (2/88)
Tamponade	0% (0/88)
Pericardial effusion	0% (0/88)
Device embolization	0% (0/88)
Primary efficacy endpoints:	4.5% (4/88)
Ischemic stroke	1.1% (1/88)
Hemorrhagic stroke	0% (0/88)
Systemic embolization	0% (0/88)
CV death	1.1% (1/88)
Non-CV death	2.2% (2/88)

Unless indicated otherwise, data are given as the mean (standard deviation), median (interquartile range) or as n (%). BARC – Bleeding Academy Research Consortium, CV – cardiovascular, non-CV – non-cardiovascular.

the procedure at the cardiac intensive care unit due to a septic shock.

The median (IQR) in-hospital period lasted 3 (2.0–5.0) days. Eighty-five patients were discharged on DAPT with aspirin and clopidogrel, and 3 patients on SAPT – two on clopidogrel and one on aspirin alone. All patients with a history of unsuccessful OAC treatment received DAPT.

Clinical follow-up

The median follow-up was 67 (52.75–84.75) days. At this time, an in-clinic visit with TEE was performed in 78 (88.6%) cases. Seven (8%) patients refused to undergo the TEE examination; thus, the clinical assessment was done over the phone. Three (3.4%) deaths occurred. The TEE was performed to confirm or exclude thrombus on the device and confirm complete sealing of the LAA.

The primary safety and efficacy endpoints are presented in Table V.

The primary safety endpoints were observed in 2 patients, and all were serious bleeding. None of these

patients required hospitalization or blood transfusion. Neither tamponade, pericardial effusion nor device embolization was observed within this period.

The primary efficacy endpoints were observed in 4 patients. Three (3.4%) deaths occurred, of which one was due to worsening of heart failure and the other two were non-cardiovascular deaths. One ischemic stroke occurred 1 month after the procedure. At discharge, the patient was prescribed with DAPT, but after 3 weeks the patient abandoned clopidogrel and continued aspirin alone. One week later the patient was admitted with ischemic stroke, resulting in complete recovery after a few days, and no thrombus was detected in follow-up TEE.

All patients who refused to have follow-up TEE were recommended to continue DAPT after the follow-up period. If the follow-up TEE revealed complete sealing of the LAA and no thrombus was detected, lifelong SAPT was recommended. In 7 cases DAPT was continued because of previous percutaneous coronary intervention with stent deployment and 1 patient, who experienced an ischemic event, was discharged on NOAC therapy.

Device-related thrombus (DRT) was observed in 5 patients and all were treated successfully with OAC therapy.

Discussion

Two randomized trials, PROTECT AF and PREVAIL, were conducted to assess the LAAC with a WATCHMAN device. In those studies, OAC therapy with warfarin was continued for 45 days after device implantation, followed by DAPT up to 6 months and aspirin lifelong [7, 12]. Post-LAAC warfarin treatment is feasible in patients without contraindications to anticoagulation therapy. There are also several trials assessing the post-procedure NOAC regimen with favorable outcomes, but until we get the results of ongoing randomized trial, there is no indication for such treatment [13]. There is a growing amount of evidence for the effectiveness of post-procedure antiplatelet therapy, and our population consists of patients with either a contraindication to OAC or its failure, which is why VKA was not administered after the LAAC procedure. In 2018 Bergmann *et al.* evaluated patients treated with DAPT in the EWOLUTION trial and at 1 year they concluded that this treatment regimen after successful LAAC with the WATCHMAN device is safe and is associated with risk reduction regarding ischemic stroke and major bleeding compared to the expected base on risk scores [14]. Investigators of the PRAGUE-17 trial found that the LAAC procedure followed by DAPT for 3 months was noninferior to NOAC in preventing major AF-related cardiovascular, neurological, and bleeding events [15]. According to Glikson *et al.*, DAPT is the currently recommended therapy in high bleeding risk patients during the post-procedure period, although this regimen needs further evaluation [16].

This study aimed to evaluate the safety and efficacy of the antiplatelet regimen after LAAC with the WATCHMAN device in our single-center experience. For this purpose, we evaluated consecutive, high-risk patients who were treated with LAAC. The median CHA₂DS₂-VASC score shows higher thrombo-embolic risk than either the PROTECT AF, PREVAIL or even the EWOLUTION trial. Furthermore, almost 87% of our patients had a HAS-BLED score of ≥ 3 , compared with 40% of EWOLUTION participants, 20% of PROTECT AF participants and 30% of PREVAIL participants. We achieved successful device deployment in 90 out of 91 patients (98.9%), which is higher success in comparison to the 91% in PROTECT AF or 98.5% in the EWOLUTION trial.

The peri-procedural safety that consists of tamponade, pericardial effusion, stroke, major bleeding, and death was observed to be at a similar or higher level than in previously mentioned studies. To our analysis we included the very first cases performed in our department. LAAC has been shown to be a relatively safe procedure with complications related to the operator's experience, so with time fewer complications were noted. The comparison of bleeding complications in the available literature remains an issue because of different types of bleeding classifications used in different studies. We used the BARC classification, and serious bleeding was defined as at least type BARC 3. In the peri-procedural period, we observed all serious bleeding complications in 6.6% of patients, while in another 'real-life' cohort serious bleeding was observed in 5.5%, but major bleeding was defined as in-hospital need for blood transfusion, so it seems that the classification was narrower than ours [17]. On the other hand, in the EWOLUTION trial the major bleeding complications were assessed in a period of 30 days after the procedure, and they occurred in 11% of patients [18]. High bleeding risk among our patients may be a reason for such a rate of major bleeding. We did not observe procedure-related stroke in our population, while in the PROTECT AF, PREVAIL and EWOLUTION registries this complication appeared in 0.9%, 0.3%, and 0.1% of cases, respectively. One device embolization was observed 1 day after the procedure that required surgical intervention and resulted in the patient's death 7 days after surgery.

Similarly to other cardiovascular implants, the LAAC device has potential to develop DRT on the free surface, raising the risk of thromboembolic events [19]. Some studies show that the endothelialization of the implanted device may require up to 90 days [20]. As we mentioned, antiplatelets are recommended in a specific patient population and seem to be an effective strategy to prevent thrombus formation on the surface of the WATCHMAN device until its complete endothelialization. In the EWOLUTION registry 3-month results were obtained in 979 patients and the data revealed that the

WATCHMAN device provides high safety and efficacy. Moreover, there was no significant influence on all SAEs, regardless of whether patients were on VKA, SAPT, DAPT, NOAC, or nothing at all [21]. Among this group, 605 patients were treated with DAPT after LAAC. Major bleeding complications were observed in a similar percentage of patients with DAPT compared to warfarin therapy, 2.4% and 2.0%, respectively. In our study, serious bleeding assessed as at least BARC 3 bleeding was noted in 2.3%.

EWOLUTION registry data showed that in the 92-day follow-up 0.5% of the patients who received DAPT experienced ischemic stroke [21]. In our study, 1 patient experienced a stroke complication 1 month after the procedure. Discontinuation of one antiplatelet drug, despite a different recommendation, could have had an impact on such complication. However, Ledwoch *et al.* in their analysis of patients in the EWOLUTION trial found that post-procedure SAPT or no therapy in high bleeding risk patients is possible. In those two groups, they observed very similar rates of thromboembolic complications in comparison to the DAPT group [22]. In the EWOLUTION registry, only patients on SAPT had a higher rate of ischemic stroke (1.4%) at 3 months compared to those on DAPT. Reddy *et al.* in their 5-year outcomes from PREVAIL and PROTECT AF trials found that there were fewer disabling/fatal strokes related to LAAC compared with those observed in the warfarin-regimen group [8]. In our case, the patient recovered completely after a few days. Moreover, our patient's indication for the procedure was recurrent thrombi in LAA despite OAC therapy, so we suspect that in this case we had to deal with higher prothrombotic propensity of the patient. Yaghi *et al.* reported that patients with AF and a history of ischemic stroke on anticoagulation may have higher ischemic risk compared with anticoagulation-naïve patients, probably because of different underlying pathomechanisms [22]. A recent trial published by Pracon *et al.* evaluated patients with OAC failure compared to those with classic indications of OAC contraindications [23]. They found that the CHA₂DS₂-VASC predicted to observed annual stroke/TIA rate was smaller in the study vs control group and concluded that long-term OAC or prolonged DAPT should be considered. Thus, this population needed further evaluation to identify the optimal post-procedural drug regimen, minimizing risk for stroke or bleeding.

Device-related thrombus was found in 6.4% of our patients who had at 3-month follow-up TEE. All patients were successfully treated within 6 weeks of LMWH administration and none of them experienced a thromboembolic event. Previously mentioned publications of Ledwoch *et al.* and Boersma *et al.* did not report any association with DRT and type of antithrombotic regimen. We assume that there are other clinical, procedural and echocardiographic factors that have an impact on DRT formation, and this field requires further evaluation [24, 25].

This is a retrospective, single-center, observational study. The follow-up was limited to the time of device endothelialization, i.e. to 3 months after device implantation. Results of the study included the first generation WATCHMAN device for the LAAC procedure, so our outcomes do not necessarily relate to other devices, such as the latest generation WATCHMAN Flex device or the Amulet device. Larger population, prospective and randomized trials are needed to provide more powerful data to confirm LAAC safety and efficacy.

Conclusions

The data from our study showed that LAA closure with the WATCHMAN device can be successfully performed with a low rate of adverse events with their reduction with operators' experience. Even using the first generation WATCHMAN device the results are convincing. Safety and efficacy when using the latest generation of the LAAC devices is significantly higher. It seems that the high-risk population requires at least antiplatelet treatment after the LAAC procedure to prevent thrombotic complications. Within the first 3 months after WATCHMAN device implantation, antiplatelet therapy seems to be a safe and effective regimen in this population. In addition, withdrawal of anticoagulation therapy after the LAAC procedure does not increase the rate of stroke, whereas the bleeding rate decreases, as compared to large clinical trials. However, further efforts are needed to define its duration and the population that benefits the most.

Conflict of interest

The authors declare no conflict of interest.

References

1. Zoni-Berisso M, Lercari F, Carazza T, et al. Epidemiology of atrial fibrillation: European perspective. *Clin Epidemiol* 2014; 6: 213-20.
2. Lip GYH, Collet JP, de Caterina R, et al. Antithrombotic Therapy in Atrial Fibrillation Associated with Valvular Heart Disease: Executive Summary of a Joint Consensus Document from the European Heart Rhythm Association (EHRA) and European Society of Cardiology Working Group on Thrombosis, Endorsed by the ESC Working Group on Valvular Heart Disease, Cardiac Arrhythmia Society of Southern Africa (CASSA), Heart Rhythm Society (HRS), Asia Pacific Heart Rhythm Society (APHRS), South African Heart (SA Heart) Association and Sociedad Latinoamericana de Estimulación Cardíaca y Electrofisiología (SOLEACE). *Thromb Haemost* 2017; 117: 2215-36.
3. Wu J, Zhang Y, Liao X, et al. Anticoagulation therapy for non-valvular atrial fibrillation: a mini-review. *Front Med* 2020; 7: 350.
4. Kirley K, Qato D, Kornfield R, et al. National trends in oral anticoagulant use in the United States, 2007 to 2011. *Circ Cardiovasc Qual Outcomes* 2012; 5: 615-21.
5. Blackshear JL, Odell JA. Appendage obliteration to reduce stroke in cardiac surgical patients with atrial fibrillation. *Ann Thorac Surg* 1996; 61: 755-9.
6. Holmes DR, Reddy VY, Turi ZG, et al. Percutaneous closure of the left atrial appendage versus warfarin therapy for prevention of stroke in patients with atrial fibrillation: a randomised non-inferiority trial. *Lancet* 2009; 374: 534-42.
7. Holmes DR Jr, Kar S, Price MJ, et al. Prospective randomized evaluation of the Watchman Left Atrial Appendage Closure device in patients with atrial fibrillation versus long-term warfarin therapy: the PREVAIL trial. *J Am Coll Cardiol* 2014; 64: 1-12.
8. Reddy VY, Doshi SK, Kar S, et al.; PREVAIL and PROTECT AF Investigators. 5-year outcomes after left atrial appendage closure: from the PREVAIL and PROTECT AF Trials. *J Am Coll Cardiol* 2017; 70: 2964-75.
9. Hindricks G, Potpara T, Dagres N, et al. 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS): The Task Force for the diagnosis and management of atrial fibrillation of the European Society of Cardiology (ESC) Developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC. *Eur Heart J* 2021; 42: 373-498.
10. Mehran R, Rao SV, Bhatt DL, et al. Standardized bleeding definitions for cardiovascular clinical trials: a consensus report from the Bleeding Academic Research Consortium. *Circulation* 2011; 123: 2736-47.
11. Kappetein AP, Head SJ, Généreux P, et al. Valve Academic Research Consortium (VARC)-2. Updated standardized endpoint definitions for transcatheter aortic valve implantation: the Valve Academic Research Consortium-2 consensus document (VARC-2). *Eur J Cardiothorac Surg* 2012; 42: S45-60.
12. Reddy VY, Sievert H, Halperin J, et al. Percutaneous left atrial appendage closure vs warfarin for atrial fibrillation: a randomized clinical trial. *JAMA* 2014; 312: 1988-98.
13. Cruz-González I, Trejo-Velasco B. Percutaneous left atrial appendage occlusion in the current practice. *Kardiol Pol* 2021; 79: 255-68.
14. Bergmann MW, Ince H, Kische S, et al. Real-world safety and efficacy of WATCHMAN LAA closure at one year in patients on dual antiplatelet therapy: results of the DAPT subgroup from the EWOLUTION all-comers study. *EuroIntervention* 2018; 13: 2003-11.
15. Osmancik P, Herman D, Neuzil P, et al. Left atrial appendage closure versus direct oral anticoagulants in high-risk patients with atrial fibrillation. *J Am Coll Cardiol* 2020; 75: 3122-35.
16. Glikson M, Wolff R, Hindricks G, et al. EHRA/EAPCI expert consensus statement on catheter-based left atrial appendage occlusion – an update. *Europace* 2020; 22: 184.
17. Myrda K, Streb W, Wojakowski W, et al. Long-term outcomes in patients after left atrial appendage occlusion: the results from the LAAO SILESIA registry. *Kardiol Pol* 2022; 80: 332-8.
18. Boersma LV, Schmidt B, Betts TR, et al. Implant success and safety of left atrial appendage closure with the WATCHMAN device: peri-procedural outcomes from the EWOLUTION registry. *Eur Heart J* 2016; 37: 2465-74.
19. Massarenti L, Yilmaz A. Incomplete endothelialization of left atrial appendage occlusion device 10 months after implantation. *J Cardiovasc Electrophysiol* 2012; 23: 1384-5.
20. Schwartz RS, Holmes DR, Van Tassel RA, et al. Left atrial appendage obliteration: mechanisms of healing and intracardiac integration. *JACC Cardiovasc Interv* 2010; 3: 870-7.
21. Bergmann MW, Betts TR, Sievert H, et al. Safety and efficacy of early anticoagulation drug regimens after WATCHMAN left atrial appendage closure: three-month data from the EWOLUTION

- prospective, multicentre, monitored international WATCHMAN LAA closure registry. *EuroIntervention* 2017; 13: 877-84.
22. Yaghi S, Henninger N, Giles JA, et al. Ischaemic stroke on anticoagulation therapy and early recurrence in acute cardioembolic stroke: the IAC study. *J Neurol Neurosurg Psychiatry* 2021; 92: 1062-7.
23. Pracon R, Zielinski K, Bangalore S, et. al. Residual stroke risk after left atrial appendage closure in patients with prior oral anti-coagulation failure. *Int J Cardiol* 2022; 354: 117-21.
24. Ledwoch J, Sievert K, Boersma LVA, et al. Initial and long-term antithrombotic therapy after left atrial appendage closure with the WATCHMAN. *Europace* 2020; 22: 1036-43.
25. Boersma LV, Ince H, Kische S, et al. Evaluating real-world clinical outcomes in atrial fibrillation patients receiving the WATCHMAN left atrial appendage closure technology: final 2-year outcome data of the EWOLUTION trial focusing on history of stroke and hemorrhage. *Circ Arrhythm Electrophysiol* 2019; 12: e006841.

6.2. Incidence and predictors of device-related thrombus after left atrial appendage closure with Watchman device.

Incidence and predictors of device-related thrombus after left atrial appendage closure with Watchman device

Jakub Maksym, Piotr Scisło, Agnieszka Kapłon-Cieślicka, Zenon Huczek, Michał Marchel, Janusz Kochman, Karol Zbroński, Grzegorz Opolski, Marcin Grabowski, Tomasz Mazurek

First Chair and Department of Cardiology, Medical University of Warsaw, Warsaw, Poland

Adv Interv Cardiol 2024; 20, 2 (76): 164–171
DOI: <https://doi.org/10.5114/aic.2024.140315>

Abstract

Introduction: Left atrial appendage closure (LAAC) with Watchman device prevents thromboembolism in patients with atrial fibrillation (AF). However, thrombus may develop on the atrial surface of the device.

Aim: To investigate the incidence and predictors of device-related thrombus (DRT) in patients with AF who were treated with LAAC.

Material and methods: Ninety-one consecutive patients with AF underwent LAAC procedure using first-generation Watchman 2.5 device followed by antiplatelet therapy. In our analysis we have included all patients ($n = 78$) who had clinical follow-up visits with transesophageal echocardiography (TEE) after the procedure.

Results: The median (IQR) CHA₂DS₂-VASC score was 4 (4.0–6.0) and HAS-BLED score was 3 (3.0–4.0). DRTs were observed in 5 (6.4%) patients. When compared with patients without DRT, those with DRT presented more often with lower median ejection fraction (40% (23.5–45.5) versus 55% (48.0–60.0); $p = 0.005$), lower emptying velocity of LAA (25 cm/s (17.5–27.0) versus 53 cm/s (26.5–78.0); $p = 0.009$), and with greater depth of implantation (18 mm (14.0–20.5) versus 8 mm (5.0–11.0); $p < 0.001$). Furthermore, patients with DRT had greater depth of LAA (35 mm (29.5–41.0) versus 29 mm (25.5–31.0); $p = 0.003$), greater mean (SD) dimension in 90° (22.4 mm (3.2) versus 19 mm (2.7); $p = 0.02$). Patients with DRT were also younger than those without DRT (67.4 years (7) versus 75 years (8.3), $p = 0.045$).

Conclusions: The DRT after Watchman device implantation remains a rare complication. Its formation was related to several patient and procedural characteristics, which need to be confirmed in larger studies.

Key words: antiplatelet therapy, atrial fibrillation, device-related thrombus, left atrial appendage closure, stroke prevention.

Summary

Percutaneous left atrial appendage closure (LAAC) is an alternative option to permanent oral anticoagulation (OAC) therapy for stroke prevention in patients with non-valvular atrial fibrillation and who are not a good candidate to lifelong OAC. However, LAAC devices are made of artificial material and initially after implantation they have potential to initiate thrombus formation on the atrial surface of the device. Despite the suggested post-procedural regimen we still observe device-related thrombus (DRT) during a follow-up visit, which becomes an even bigger issue in patients with initially high bleeding risk. In our study we showed that this is not a common complication after LAAC procedure with no further thromboembolic events in our population. Moreover, we were able to demonstrate several risk factors for DRT formation which can be helpful in identification of patients with a higher risk of DRT.

Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia and its most severe complication is ischemic stroke. Oral anticoagulation (OAC) therapy reduces the risk of stroke in patients with AF but simultaneously it

increases the risk of bleeding complications [1]. Percutaneous left atrial appendage closure (LAAC) is an alternative option to permanent OAC for stroke prevention in patients with non-valvular AF and who are not a good candidate to lifelong OAC [2]. The main aim of the procedure is to completely seal the left atrial appendage (LAA)

Corresponding author:

Jakub Maksym MD, First Chair and Department of Cardiology, Medical University of Warsaw, Warsaw, Poland,
e-mail: jakub.maksym@gmail.com

Received: 25.03.2024, accepted: 28.05.2024, online publication: 5.06.2024.

which is the main spot where the blood clots originate [3]. Thereby we eliminate the main source of emboli, thus we also eliminate the indication to OAC therapy [1]. The main evidence supporting LAAC procedure comes from the PROTECT AF (Watchman Left Atrial Appendage System for Embolic Protection in Patients with Atrial Fibrillation) and PREVAIL (Watchman LAA Closure Device in Patients with Atrial Fibrillation Versus Long Term Warfarin Therapy) randomized trials [4, 5]. Large observational studies also support the safety and efficacy of percutaneous LAAC procedure [6–8]. However, LAAC devices are made of artificial material and until its fully endothelialization they have potential to initiate thrombus formation on the atrial surface of the device, by what they promote subsequent systemic embolization [9]. The device-related thrombus (DRT) has been observed in 0% to 17.6% of the patients and it occurs mainly early after the procedure [10]. We still do not know the clinical importance of DRT and whether it is associated with more frequent episodes of ischemic stroke [11]. Moreover, an optimal post-procedural antithrombotic regimen remains unknown. In patients with a high bleeding risk who are not suitable to OAC therapy current guidelines recommend initiating dual antiplatelet therapy (DAPT) after successful LAAC procedure with Watchman device to prevent thrombus formation [2]. However, despite this regimen we still observe DRT during follow-up visits, which becomes an even bigger issue in patients with initially high bleeding risk.

In our department we showed that DAPT seems to be safe and efficient after successful LAAC, while there is still a risk for DRT formation [12].

Aim

Thus, we decided to conduct this study to characterize the incidence and predictor of DRT after LAAC procedure with first-generation Watchman 2.5 device.

Material and methods

Study population

The flow chart of this study is presented in Figure 1. Retrospectively we have reviewed 91 consecutive patients who were qualified to LAAC procedure with first-generation Watchman 2.5 device from March 2015 to September 2019 in the single cardiological department (First Department of Cardiology, University Clinical Center, Warsaw, Poland). All patients were diagnosed with non-valvular AF and were at high thromboembolic risk assessed in CHA₂DS₂-VASC score. Moreover, they also fulfilled at least one of the following inclusion criteria: contraindication for oral anticoagulation, history of the bleeding complication while using oral anticoagulation, inability to maintain the INR level within therapeutic range, history of a stroke while using oral anticoagulation. All patients did not meet any of the following ex-

clusion criteria: presence of the thrombus in left atrial appendage, too small or too big left atrial appendage in qualifying transesophageal echocardiography (TEE), lack of patient's consent. All operators who performed the procedures attended an appropriate training and certification program to minimize the risk of the procedure. In our analysis we have included all patients ($n = 78$) who had clinical follow-up visits with TEE.

LAAC procedure and postimplantation therapy regimen

The procedure was performed under general anesthesia with TEE and fluoroscopic guidance. Left atrial access was obtained through a transseptal puncture at the inferior and posterior part of the fossa. Unfractionated heparin was administered to achieve activated clotting time > 250 s. Several views from 0° to 135° were used initially to assess the LAA to choose the most suitable size of the device. The final deployment of the device was done under TEE and fluoroscopic guidance. After device implantation, a stability test was performed before its final release. Contrast angiography and color-Doppler in TEE were used to eliminate the peri-device leaks. If needed, recapturing and reimplantation were performed. All patients were treated with DAPT (aspirin 75 mg and clopidogrel 75 mg once a day) or with single antiplatelet therapy (SAPT) (aspirin 75 mg or clopidogrel 75 mg once a day). A decision on the therapy regimen was made according to the implanting physician's judgement and was continued until control examination. The

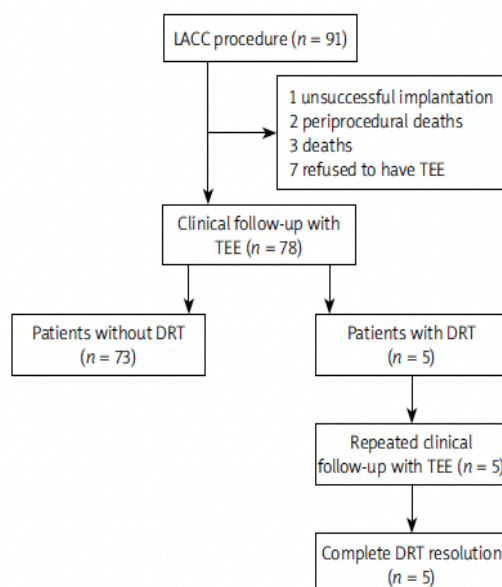


Figure 1. Study flowchart

DRT – device-related thrombus, LAAC – left atrial appendage closure, TEE – transesophageal echocardiography.

decision was based on patients' medical history, especially history of bleeding or ischemic event, bleeding and thromboembolic risk scores, patients' comorbidities, and procedure outcomes.

Follow-up

The follow-up visit was planned to be performed approximately 3 months after successful LAAC procedure. During the follow-up visit clinical data were obtained and all patients had TEE examination to evaluate the device position and the presence of DRT. TEE imaging was performed in 4 planes (0°, 45°, 90°, and 135°) as recommended and was evaluated by an experienced specialist.

DRT was defined as an echo density on the left atrial aspect of the device: (1) not explained by the imaging artifact; (2) inconsistency with normal healing/device incorporation; (3) visible in multiple TEE planes; (4) in contact with the Watchman device; and (5) exhibiting independent motion [13]. In all patients during TEE, color-flow Doppler was used to detect a peri-device leak and measurements were taken in different planes to identify the maximal jet dimension. Non-significant peri-device leak was defined as a jet into the LAA < 5 mm. We also evaluate the depth of the implanted Watchman device. We measured the distance between the left atrial appendage occluder and the ridge of the upper left pulmonary vein, so the distance of the uncovered rim was measured.

Study endpoint

The main endpoint of the study was DRT.

Statistical analysis

Categorical variables, presented as frequencies/counts and percentages, were compared using χ^2 test of Fisher's exact test, as appropriate. Continuous variables,

presented as mean with standard deviation (SD) if normally distributed or by median and interquartile range (IQR) if not, were compared using a Student's *t* test or a Mann-Whitney *U* test, as appropriate. Univariate analysis was performed to evaluate the predictors of DRT in the overall cohort. Results are presented as odds ratio (OR) with 95% confidence intervals (CI). P-value of < 0.05 was considered statistically significant. All statistical analyses were conducted with SPSS Statistics, version 22 (IBM SPSS Statistics, New York, USA).

Results

Incidence of DRT

Ninety-one patients underwent the procedure of LAAC in our clinic in the defined period. A clinical follow-up with imaging was available in 78 (85.7%) patients in our study. Thirteen patients were excluded from further analysis because of one unsuccessful implantation, 2 periprocedural deaths, 3 patients died during follow-up (2 non-cardiovascular death and 1 caused by exacerbation of heart failure), and 7 patients refused to have TEE. The median (IQR) follow-up time for the entire group was 68 (51.75–82.25) days. Among these patients, the diagnosis of DRT was made in 6.4% (5/78) after the median time of 76 (68–302) days. All patients with DRT received DAPT after the procedure.

Patients with and without DRT

Comparison of clinical baseline characteristics of patients with and without DRT is presented in Table I. No significant differences were noted regarding gender (male: 60% versus 52.1%, $p = 1$), but it was observed that patients with DRT were significantly younger than patients without DRT with a mean (SD) age of 67.4 years (7) versus 75 years (8.3) ($p = 0.045$). The medi-

Table I. Baseline characteristics

Variable	All ($n = 78$)	DRT ($n = 5$)	No DRT ($n = 73$)	P-value
Male	41 (52.6%)	3 (60%)	38 (52.1%)	1
Age [years]	74.5 (8.4)	67.4 (7)	75 (8.3)	0.045
Hypertension	68 (87.2%)	4 (80%)	64 (87.7%)	0.51
Diabetes	28 (35.9%)	1 (20%)	27 (37%)	0.65
Permanent AF	29 (37.2%)	4 (80%)	25 (34.2%)	0.06
Heart failure	39 (50%)	3 (60%)	36 (49.3%)	1
Prior thromboembolism	20 (25.6%)	2 (40%)	18 (24.7%)	0.6
History of CAD	44 (56.4%)	4 (80%)	40 (54.8%)	0.38
CHA ₂ DS ₂ -VASc	5 (4.0–6.0)	4 (4.0–5.0)	5 (4.0–6.0)	0.62
HAS-BLED	3 (3.0–4.0)	3 (3.0–4.0)	3 (3.0–4.0)	0.49
ATRIA	4 (2.0–7.0)	2 (1.5–3.5)	4 (2.0–7.0)	0.07
PLT [$\times 10^9/l$]	200 (161.25–244.5)	162 (150.0–196.5)	200 (164.0–248.5)	0.14
GFR [ml/min/1.73 m ²] (SD)	52.6 (39.0–75.5)	64 (39.5–77.0)	52.5 (38.5–76.0)	0.57

Unless indicated otherwise, data are given as the mean (standard deviation), median (interquartile range) or as n (%). AF – atrial fibrillation, CAD – coronary artery disease, PLT – platelets, GFR – glomerular filtration rate.

an thromboembolic risk assessed with CHA₂DS₂-VASC score were similar in both groups (4 (4.0–5.0) versus 5 (4.0–6.0), $p = 0.62$). Furthermore, the median bleeding risk assessed with HAS BLEED was also similar in both groups (3 (3.0–4.0) versus 3 (3.0–4.0), $p = 0.49$), but we have observed a trend of lower bleeding risk assessed with ATRIA in patients with DRT than in patients without, but it did not meet criteria for statistical significance (2 (1.5–3.5) versus 4 (2.0–7.0), $p = 0.07$). Permanent AF had a tendency to be more often diagnosed in patients with DRT than the other group, but it was also not a statistically significant difference (80% versus 34.2%, $p = 0.06$). The prevalence of hypertension (80% versus 87.8%, $p = 0.51$), diabetes (20% versus 37%, $p = 0.65$), and history of prior thromboembolism (40% versus 24.7%, $p = 0.6$) did not differ significantly between both groups. The glomerular filtration rate (GFR) was similar in both groups (64 ml/min/1.73 m² (39.5–77.0) versus 52.5 ml/min/1.73 m² (38.5–76.0), $p = 0.57$), and platelet count was not significantly different in studied populations (162 × 10⁹/l (150.0–196.5) versus 200 × 10⁹/l (164.0–248.5), $p = 0.14$).

All procedural and echocardiographic characteristics are shown in Table II. In transthoracic echocardiography (TTE) evaluation, patients with DRT had significantly lower ejection fraction (EF) (40% (23.5–45.5) versus 55% (48.0–60.0), $p = 0.005$). Regarding preprocedural TEE parameters, patients with DRT showed a significantly larger LAA diameter assessed in 90° plane (22.4 mm (3.2) versus 19 mm (2.7), $p = 0.02$), and in 135° plane (23 mm (3.2) versus 19.9 mm (2.5), $p = 0.03$). We also observed a significantly larger depth of LAA (35 mm (29.5–41.0) versus 29 mm (25.5–31.0), $p = 0.03$), and significantly lower emptying velocity of the LAA (25 cm/s (17.5–27.0) versus 53 cm/s (26.5–78.0), $p = 0.009$). Both groups did not differ significantly with respect to the LAA diameter

in any other plane and to the dimension of the left atrium (51 mm (46.0–52.0) versus 44 mm (40.0–52.0), $p = 0.24$). The rate of spontaneous echo contrast (SEC) in TEE and presence of non-significant peri-device leak was almost equal in both groups (Table II). In follow-up TEE the device compression was comparable in both groups (16.67% (14.07–18.33) versus 16.67% (14.81–20.83), $p = 0.42$), but the depth of the device implantation, measured as a distance between the surface of the device and the edge of the pulmonary ridge, was significantly greater in patients with DRT (18 mm (14.0–20.5) versus 8 mm (5.0–11.0), $p < 0.001$) (Figure 2).

Univariate regression analysis was performed to evaluate predictors of DRT (Table III). This analysis showed that the deeper device implantation (OR = 1.25, 95% CI: 1.04–1.51, $p = 0.02$) and the bigger dimension of LAA in 90° plane (OR = 1.47, 95% CI: 1.0–2.1, $p = 0.02$), the higher the risk of DRT development. Moreover, it has been shown that the lower the emptying velocity of the LAA (OR = 0.94, 95% CI: 0.8–0.99, $p = 0.046$), and EF (OR = 0.89, 95% CI: 0.81–0.96, $p = 0.005$), the higher the risk of DRT.

During the follow-up period only one stroke was diagnosed, and no DRT was found in this patient.

Follow-up and management after DRT diagnosis

All patients diagnosed with DRT were prescribed to have OAC therapy. Four of them had low molecular weighted heparin (LMWH) at a therapeutic dose adjusted to the kidney function and 1 patient was treated with warfarin. The vitamin K antagonist (VKA) was prescribed because the patient refused to have subcutaneous injections with LMWH and refused to have new oral anticoagulants (NOAC) because of their high price. All patients

Table II. Procedural and echocardiographic characteristics

Variable	All (n = 78)	DRT (n = 5)	No DRT (n = 73)	P-value
EF, %	55 (45.0–60.0)	40 (23.5–45.5)	55 (48.0–60.0)	0.005
LA dimension in TTE [mm]	44 (41.0–52.0)	51 (46.0–52.0)	44 (40.0–52.0)	0.24
Emptying velocity of LAA [cm/s]	52.5 (25.75–73.75)	25 (17.5–27.0)	53 (26.5–78.0)	0.009
LAA depth [mm]	29 (26.0–31.25)	35 (29.5–41.0)	29 (25.5–31.0)	0.03
Dimension in 0° [mm]	19.8 (3.1)	22 (2.5)	19.7 (3.1)	0.08
Dimension in 45° [mm]	19.4 (2.4)	21.2 (1.8)	19.3 (2.4)	0.06
Dimension in 90° [mm]	19.2 (2.9)	22.4 (3.2)	19 (2.7)	0.02
Dimension in 135° [mm]	20.1 (2.6)	23 (3.2)	19.9 (2.5)	0.03
SEC	15 (19.2%)	1 (20%)	14 (19.2%)	1
Device size [mm]	27 (24.0–27.75)	30 (25.5–30.0)	27 (24.0–27.0)	0.11
Compression, %	16.67 (14.81–20.21)	16.67 (14.07–18.33)	16.67 (14.81–20.83)	0.42
Depth of implantation [mm]*	9 (5.0–12.0)	18 (14.0–20.5)	8 (5.0–11.0)	< 0.001
Non-significant peri-device leak**	16 (20.5%)	1 (20%)	15 (20.5%)	1

Unless indicated otherwise, data are given as the mean (standard deviation), median (interquartile range) or as n (%). EF – ejection fraction, LA – left atrium, LAA – left atrium appendage, SEC – spontaneous echo contrast, TTE – transthoracic echocardiography. *Depth of the implantation was measured as a distance between the surface of the device and the edge of the pulmonary ridge. **Non-significant leak is defined as the jet < 5 mm observed in color-Doppler TEE.

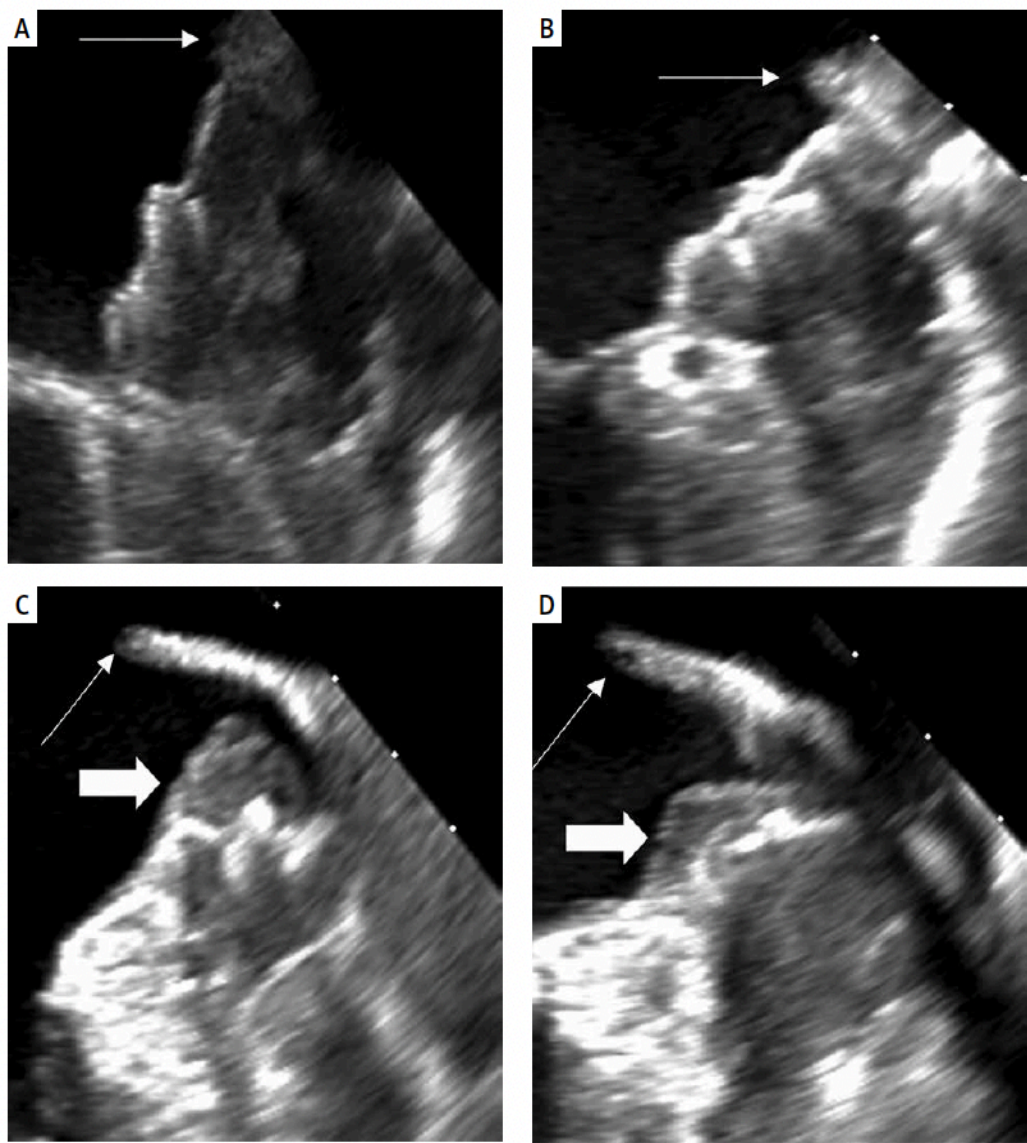


Figure 2. Transesophageal echocardiography follow-up imaging after left atrial appendage closure with the Watchman device. **A, B** – optimal Watchman 30 mm device placement without deep implantation and device-related thrombus (DRT). **C, D** – deep implantation of Watchman 27 mm device with DRT indicated with a thick arrow. Thin arrows indicate the pulmonary ridge

Table III. Univariate analysis evaluating most important predictors of DRT.

Variable	Odds ratio (95% CI)	P-value
Depth of implantation [mm]	1.25 (1.04, 1.51)	0.02
Dimension in 90° [mm]	1.47 (1.07, 2.1)	0.02
Emptying velocity of LAA [cm/s]	0.94 (0.8, 0.99)	0.046
EF, %	0.89 (0.81, 0.96)	0.005

EF – ejection fraction, LAA – left atrium appendage.

have repeated clinical follow-up with TEE after a median time of 63 (54.5–99.0) days. Resolution of DRT was confirmed by follow-up TEE in all patients.

In all patients with a confirmed thrombus at first follow-up imaging, there were no reports of ischemic complications such as a stroke, TIA, or peripheral embolism during the period following DRT detection. Moreover, no one experienced any bleeding complication after the change of the anticoagulation regimen.

Discussion

Device-related thrombus remains one of the most concerning complications after the successful LAAC procedure with Watchman device which can be confirmed by control imaging methods [14]. Initially, the presence of DRT varied from 0% to even up to 17.6% of the cases [10, 15], while currently available data show that the incidence of DRT has dropped, and varies from 2 to 4% [16]. Thus, we may suspect that clinical and echocardiographic, as well as procedure- and device-related factors contribute to the formation of DRT.

In our single center study, thrombus formation following LAAC with Watchman device was observed in 6.4% of the patients after the median time of 76 (68–302) days. In the sub-analysis of the EWOLUTION registry, Sedaghat *et al.* showed that more than 91% of the DRTs were detected relatively early after the procedure after the median of 54 days [17]. Moreover, one of the largest trials regarding DRT has shown that almost 64% of DRT diagnoses were made within the first 180 days after the procedure [18]. Our rate of thrombus incidents with this nitinol cage device is slightly higher than of these observed in PROTECT AF with an incidence of 5.7% [13]. In the ASAP study, 6 out of 142 patients with a successfully implanted Watchman device have developed DRT, with a rate of 4.2% [19]. Dukkupati *et al.* evaluated the incidence of DRT among the patients who underwent Watchman device implantation as a part of PROTECT AF or PREVAIL randomized trials, as well as CAP or CAP2 registries and revealed that the rate of DRT was 3.74% [9]. However, 252 patients included into the PREVAIL trial were not assessed for DRT, thus the incidence of DRT in this population remains unknown [5]. Our study reflects data obtained in everyday clinical practice where we encounter patients who probably have more comorbidities, are older and have higher CHA₂DS₂-VASc score than these included in randomized clinical trials or big registries.

Optimal post-procedural treatment after LAAC for the occurrence of DRT is still controversial. Previously mentioned randomized trials PROTECT AF and PREVAIL used warfarin for the first 45 days after implantation but these studies included patients who did not have absolute contraindications to OAC. The largest multicenter, prospective registry of Watchman device implantation, EWOLUTION registry, assessed patients with a variable post implantation treatment regimen. Single or dual antiplatelet therapy was used in 67% of patients, direct oral anticoagulants in 11%, VKA in 16%, and 6% did not receive any form of antithrombotic treatment [20]. Comparing all these different post-procedure treatment regimens, no significant differences were noted in the rate of DRT frequency and in the overall event rate. Bergmann *et al.* in a subsequent analysis of a group of patients from the EWOLUTION trial, who were treated with DAPT, revealed that the rate of DRT was 4.0% without any ad-

verse consequences using this antithrombotic regimen at 12 months [21]. However, in 2019, Søndergaard *et al.* performed cumulative analysis including several studies of Watchman device and reported that there is an increased risk of DRT in patients without post-procedure OAC [22]. In our study, all patients in whom DRT was detected were on DAPT. It is worth underlying that thrombus formation in patients treated with DAPT may be due to their clopidogrel resistance [23]. However, there are some studies that have proven safety and efficacy of the single antiplatelet therapy without any negative influence on ischemic events [24, 25].

In addition, post-procedural clinical, procedural and echocardiography-related factors have a big impact of the occurrence of DRT. Patients in whom DRTs were diagnosed had lower EF, deeper LAA, and a bigger dimension of LAA especially when assessed in 90° and 135° planes. That may indicate a greater LA dimension in a group with DRT, which would be in line with results from other larger studies, but our results did not show statistical significance in terms of the dimension of LA. Additionally, we have proved that lower emptying velocity of LAA, which reflects impaired left atrial function, is strongly connected with further DRT formation. Surprisingly, it is not associated with SEC detection, which is a known risk factor for thrombus formation inside of LAA [26]. SEC was observed with a similar rate in our population (20% versus 19.2%). Referring to the impairment of LA function, it is proved that remodeling leading to atrial fibrosis is a known risk factor for a thromboembolic complication [27]. The study of Daccarett *et al.* revealed bigger remodeling of the LA detected in cardiac magnetic resonance, especially in patients with permanent AF [28]. In our patients with DRT, we saw a greater prevalence of permanent AF rather than paroxysmal, but the difference did not reach statistical significance. Finally, we were able to demonstrate that the deep Watchman device implantation is associated with a higher risk of DRT. In comparison to DRT-free patients, the distance between the pulmonary ridge and the device was significantly greater in the DRT population. This observation of deep implantation has been described previously claiming that residual LAA has adequate blood stasis promoting thrombus formation [29]. Simard *et al.* confirmed this finding in their larger, multicenter study and they claimed that due to varying anatomies, anatomical landmarks, and different device types, the depth measurement can be challenging [18]. However, it can be helpful in standardizing the evaluation of the occluder as it relates to prediction of DRT.

In comparison to other studies, the presence of DRT in our group was not linked with an increasing risk of thromboembolic complications, which goes along with results of the large EWOLUTION registry [17]. We have not observed any stroke or TIA in patients with diagnosed DRT. Dukkupati *et al.* in the previously mentioned analysis of 4 prospective FDA approved trials, have reported an

increased rate of ischemic stroke and systemic embolism incidence [9]. Other studies also concluded that DRT is strongly associated with a higher risk of stroke and TIA during follow-up [11, 18]. In our population we have not observed many DRTs and all of them were diagnosed after the median time of 76 days after the procedure, so the appropriate treatment was initiated relatively quickly. One patient received VKA with warfarin and the rest of the patients received LMWH after DRT diagnosis. This antithrombotic therapy was continued until next follow-up imaging. Sedaghat *et al.* showed that different treatment regimens, including NOAC, VKA, or heparin have similar resolution rates [27]. Thus, considering high bleeding risk in our population our first choice was LMWH. Finally, we achieved complete resolution of DRT, with no subsequent bleeding complications associated with treatment change.

Until the present day the TEE has remained gold standard in DRT detection. Nevertheless, cardiac computed tomography (CT) has also good clinical value for detection of DRT, and it is a good diagnostic method in patients who cannot tolerate or who have contraindications to TEE. Korsholm *et al.* demonstrated that cardiac CT seems to be equally good as TEE for DRT diagnosis [30]. It has also the ability to detect the presence of low-grade hypoattenuated thickening (HAT) on the device, but no thromboembolic events were present in a group diagnosed with low-grade HAT. However, performing a cardiac CT involves exposure to radiation and the contrast agent. Furthermore, patients with a rapid, irregular heart rate are not a good candidate for CT due to lower scan resolution.

On the basis of our study as well as previous ones we may conclude that DRT remains an issue after first-generation Watchman device implantation and this problem needs further evaluation. Furthermore, a study evaluating the optimal post-procedural drug regimen with regard to DRT risk factors is needed.

Limitations

These results are based on the retrospective registry with all limitations associated with this study design. Further randomized trials are needed to confirm study findings. The population was relatively small. The follow-up imaging was not available in all cases with Watchman implantation and the follow-up time was limited. Therefore the actual rate of DRT may be overestimated or underestimated. Finally, DRT was diagnosed by the physician not blind to primary implantation results, without a central evaluation of images in a core-lab. Results of the study included first-generation Watchman device for LAAC procedure, so our outcomes not necessarily concern other devices, such as last generation of Watchman Flex device or Amulet device.

Conclusions

The DRT after Watchman device implantation remains a rare complication and, in our population, it was not associated with an increased risk for ischemic stroke or any other thromboembolic event. We were able to demonstrate several risk factors for DRT formation which can be helpful in identification of patients with a higher risk of DRT. In general, we do not have any influence on most of the risk factors like age, and LAA dimension, but to minimize the risk of DRT, the deep implantation should be avoided if possible.

Funding

No external funding.

Ethical approval

Not applicable.

Conflict of interest

The authors declare no conflict of interest.

References

- Li SY, Wang J, Hui X, et al. Meta-analysis of postoperative anti-thrombotic therapy after left atrial appendage occlusion. *J Int Med Res* 2020; 48: 300060520966478.
- Hindricks G, Potpara T, Dagres N, et al. 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS): The Task Force for the diagnosis and management of atrial fibrillation of the European Society of Cardiology (ESC) Developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC. *Eur Heart J* 2021; 42: 373-498.
- Holmes DR Jr, Alkhouli M, Reddy V. Left atrial appendage occlusion for the unmet clinical needs of stroke prevention in nonvalvular atrial fibrillation. *Mayo Clin Proc* 2019; 94: 864-74.
- Reddy VY, Sievert H, Halperin J, et al. Percutaneous left atrial appendage closure vs warfarin for atrial fibrillation: a randomized clinical trial. *JAMA* 2014; 312: 1988-98.
- Holmes DR Jr, Kar S, Price MJ, et al. Prospective randomized evaluation of the Watchman Left Atrial Appendage Closure device in patients with atrial fibrillation versus long-term warfarin therapy: the PREVAIL trial. *J Am Coll Cardiol* 2014; 64: 1-12.
- Boersma LV, Schmidt B, Betts TR, et al. Implant success and safety of left atrial appendage closure with the WATCHMAN device: peri-procedural outcomes from the EWOLUTION registry. *Eur Heart J* 2016; 37: 2465-74.
- Tzikas A, Shakir S, Gafoor S, et al. Left atrial appendage occlusion for stroke prevention in atrial fibrillation: multicentre experience with the AMPLATZER Cardiac Plug. *EuroIntervention* 2016; 11: 1170-9.
- López Mínguez JR, Asensio JM, Costa M, et al. Two-year clinical outcome from the Iberian registry patients after left atrial appendage closure. *Heart* 2015; 101: 877-83.
- Dukkipati SR, Kar S, Holmes DR, et al. Device-related thrombus after left atrial appendage closure: incidence, predictors, and outcomes. *Circulation* 2018; 138: 874-85.

10. Lempereur M, Aminian A, Freixa X, et al. Device-associated thrombus formation after left atrial appendage occlusion: a systematic review of events reported with the Watchman, the Amplatzer Cardiac Plug and the Amulet. *Catheter Cardiovasc Interv* 2017; 90: E111-21.
11. Fauchier L, Cinaud A, Brigadeau F, et al. Device-related thrombosis after percutaneous left atrial appendage occlusion for atrial fibrillation. *J Am Coll Cardiol* 2018; 71: 1528-36.
12. Maksym J, Kaplon-Cieślicka A, Scisto P, et al. Safety and efficacy of percutaneous atrial appendage closure followed by antiplatelet therapy in a high-risk population: single-center experience with a WATCHMAN device. *Adv Interv Cardiol* 2023; 19: 262-9.
13. Main ML, Fan D, Reddy VY, et al. Assessment of device-related thrombus and associated clinical outcomes with the WATCHMAN left atrial appendage closure device for embolic protection in patients with atrial fibrillation (from the PROTECT-AF Trial). *Am J Cardiol* 2016; 117: 1127-34.
14. Maksym J, Grabowski M, Mazurek T. Percutaneous left atrial appendage closure with the Watchman device: a systematic review. *Adv Interv Cardiol* 2024; 20: 18-29.
15. Plicht B, Konorza TF, Kahlert P, et al. Risk factors for thrombus formation on the Amplatzer Cardiac Plug after left atrial appendage occlusion. *JACC Cardiovasc Interv* 2013; 6: 606-13.
16. Potpara T, Grygier M, Häusler KG, et al. Practical guide on left atrial appendage closure for the non-implanting physician: an international consensus paper. *Europace* 2024; 26: euae035.
17. Sedaghat A, Nickenig G, Schrickel JW, et al. Incidence, predictors and outcomes of device-related thrombus after left atrial appendage closure with the WATCHMAN device-Insights from the EWOLUTION real world registry. *Catheter Cardiovasc Interv* 2021; 97: E1019-24.
18. Simard T, Jung RG, Lehenbauer K, et al. Predictors of device-related thrombus following percutaneous left atrial appendage occlusion. *J Am Coll Cardiol* 2021; 78: 297-313.
19. Reddy VY, Möbius-Winkler S, Miller MA, et al. Left atrial appendage closure with the Watchman device in patients with a contraindication for oral anticoagulation: the ASAP study (ASA Plavix Feasibility Study With Watchman Left Atrial Appendage Closure Technology). *J Am Coll Cardiol* 2013; 61: 2551-6.
20. Boersma LV, Ince H, Kische S, et al. Efficacy and safety of left atrial appendage closure with WATCHMAN in patients with or without contraindication to oral anticoagulation: 1-year follow-up outcome data of the EWOLUTION trial. *Heart Rhythm* 2017; 14: 1302-8.
21. Bergmann MW, Ince H, Kische S, et al. Real-world safety and efficacy of WATCHMAN LAA closure at one year in patients on dual antiplatelet therapy: results of the DAPT subgroup from the EWOLUTION all-comers study. *EuroIntervention* 2018; 13: 2003-11.
22. Søndergaard L, Wong YH, Reddy VY, et al. Propensity-matched comparison of oral anticoagulation versus antiplatelet therapy after left atrial appendage closure with WATCHMAN. *JACC Cardiovasc Interv* 2019; 12: 1055-63.
23. Ketterer U, D'Ancona G, Siegel I, et al. Percutaneous left atrial appendage occlusion: device thrombosis in clopidogrel non-responders. *Int J Cardiol* 2016; 204: 196-7.
24. Patti G, Sticchi A, Verolino G, et al. Safety and efficacy of single versus dual antiplatelet therapy after left atrial appendage occlusion. *Am J Cardiol* 2020; 134: 83-90.
25. Korsholm K, Nielsen KM, Jensen JM, et al. Transcatheter left atrial appendage occlusion in patients with atrial fibrillation and a high bleeding risk using aspirin alone for post-implant anti-thrombotic therapy. *EuroIntervention* 2017; 12: 2075-82.
26. Lowe BS, Kusunose K, Motoki H, et al. Prognostic significance of left atrial appendage "sludge" in patients with atrial fibrillation: a new transesophageal echocardiographic thromboembolic risk factor. *J Am Soc Echocardiogr* 2014; 27: 1176-83.
27. Sedaghat A, Vij V, Al-Kassou B, et al. Device-related thrombus after left atrial appendage closure: data on thrombus characteristics, treatment strategies, and clinical outcomes from the EUROCC-DRT-Registry. *Circ Cardiovasc Interv* 2021; 14: e010195.
28. Daccarett M, Badger TJ, Akoum N, et al. Association of left atrial fibrosis detected by delayed-enhancement magnetic resonance imaging and the risk of stroke in patients with atrial fibrillation. *J Am Coll Cardiol* 2011; 57: 831-8.
29. Pracon R, Bangalore S, Dzielniska Z, et al. Device thrombosis after percutaneous left atrial appendage occlusion is related to patient and procedural characteristics but not to duration of postimplantation dual antiplatelet therapy. *Circ Cardiovasc Interv* 2018; 11: e005997.
30. Korsholm K, Jensen JM, Nørgaard BL, et al. Detection of device-related thrombosis following left atrial appendage occlusion: a comparison between cardiac computed tomography and transesophageal echocardiography. *Circ Cardiovasc Interv* 2019; 12: e008112.

6.3. Percutaneous left atrial appendage closure with the Watchman device: a systematic review.

Percutaneous left atrial appendage closure with the Watchman device: a systematic review

Jakub Maksym, Marcin Grabowski, Tomasz Mazurek

First Chair and Department of Cardiology, Medical University of Warsaw, Warsaw, Poland

Adv Interv Cardiol 2024; 20, 1 (75): 18–29
DOI: <https://doi.org/10.5114/aic.2024.136406>

Abstract

Atrial fibrillation (AF) is the most commonly observed arrhythmia in the world and its prevalence increases with age. The main and most severe complication of AF is ischemic stroke. Oral anticoagulation (OAC) therapy is the standard of care for stroke prevention in the high risk population. Initiation of this treatment is associated with a substantial risk of bleeding complications. Moreover, there is a group of patients who cannot tolerate OAC. In patients with AF the left atrial appendage (LAA) is the main source of thrombus formation. Percutaneous left atrial appendage closure (LAAC) has become an important non-pharmacological intervention for stroke prevention in patients with non-valvular AF. The procedure aims to reduce the risk of thromboembolism without increasing the risk of bleeding. Over the last few years, the safety and long-term efficacy of the procedure in specific populations have increased and more patients are being treated. The Watchman device is the most studied device in this field. Randomized controlled trials demonstrated non-inferiority of percutaneous left atrial appendage closure using the WATCHMAN 2.5 device to OAC (Boston Scientific, Marlborough, MA, USA). The new generation device, WATCHMAN FLX, was introduced and its use was associated with fewer safety events and a higher success rate of effective appendage closure. Nevertheless, several unsolved problems remain, including device-related thrombosis, the post-LAAC antithrombotic regimen, and peri-device leakage. This review will focus on LAAC with the Watchman device for stroke prevention in AF patients. Current status, available literature, clinical safety and efficacy will be summarized.

Key words: atrial fibrillation, left atrial appendage closure, device-related thrombus, peri-device leak.

Introduction

Atrial fibrillation (AF) is the most commonly observed arrhythmia in the clinical practice, affecting 33.5 million patients worldwide [1]. There is a 5-fold higher risk of cerebrovascular thromboembolic events causing disabling symptoms, with higher mortality compared to other stroke etiologies [2].

Oral anticoagulation (OAC) is the first line treatment in stroke prevention in patient with AF, and regarding the current guidelines direct oral anticoagulants (DOACs) are recommended over vitamin K antagonists (VKA) [3]. Despite the promising safety profile of DOACs, the rate of major bleeding observed in randomized clinical trials remains high [4]. Bleeding is the main cause of under-treatment with OAC therapy. Data show that up to 50% of patients with an indication for OAC therapy are left unprotected because of previous bleeding complication or high bleeding risk [5].

The left atrial appendage (LAA) is considered to have the highest thrombotic potential and probably most of the strokes in patients with AF are caused by thrombus that originated from the LAA [6]. In a review of 23 studies, it was found that more than 90% of atrial thrombi are located in LAA in patients with non-valvular AF [7]. Based on this evidence, left atrial appendage closure (LAAC) was offered as an alternative approach to reduce cardioembolic risk in patients with AF [8]. This transcatheter method was developed to exclude LAA from the blood circulation, preventing the release of the thrombus from its cavity. Such a strategy seems to prevent AF-driven ischemic stroke while overcoming the challenges associated with OAC therapy and reducing long-term bleeding risk [9]. Currently, European guidelines recommend LAAC in patients with non-valvular AF with contraindications to long-term OAC therapy (class IIb indication, level of evidence B) [3].

Corresponding author:

Dr. Jakub Maksym, First Chair and Department of Cardiology, Medical University of Warsaw, Warsaw, Poland, e-mail: jakub.maksym@gmail.com

Received: 23.11.2023, accepted: 3.01.2024, online publication: 15.03.2024.

The Watchman 2.5 (Boston Scientific, Natick, MA, USA) is the most frequently used device for LAAC in the world [10]. Long-term safety and efficacy have been proven in three randomized clinical trials and several registries. In 2019, the second-generation Watchman FLX was presented with the intention to ameliorate LAA sealing, decrease the risk of device-related thrombus and to simplify the implantation of the device. The aim of this review is to summarize the current evidence on transcatheter LAAC with the Watchman 2.5 and Watchman FLX devices.

LAA anatomy and thrombus formation

The LAA is a trabecular structure which is a residue of the original embryonic left atrium (Figure 1) [11]. It is composed of an orifice, neck and body. The body of the LAA is trabeculated with pectinate muscles. The cavi-

ties protruding out of the body of the LAA are defined as lobes. The size and shape are different in each patient. Its morphology is classified into four types assessed with transesophageal echocardiography (TEE) or computed tomography (CT), which is superior to TEE [12]. The dominant shape is “chicken wing” (48%), then “cactus” (30%), “windsock” (19%), and “cauliflower” (3%) [13]. The latter shape was found to be most often associated with embolic events, while the most common one, “chicken wing”, has the lowest risk for thrombus formation [13]. During AF there is an increased maximal appendage size, and decreased filling and emptying velocities causing blood stasis in its cavity. This state predispose to thrombus formation. Moreover, the morphology of LAA has a significant influence on the risk of stroke. Yamamoto *et al.* found that larger volume and depth of LAA, number of lobes, and extensive LAA trabeculation were associ-

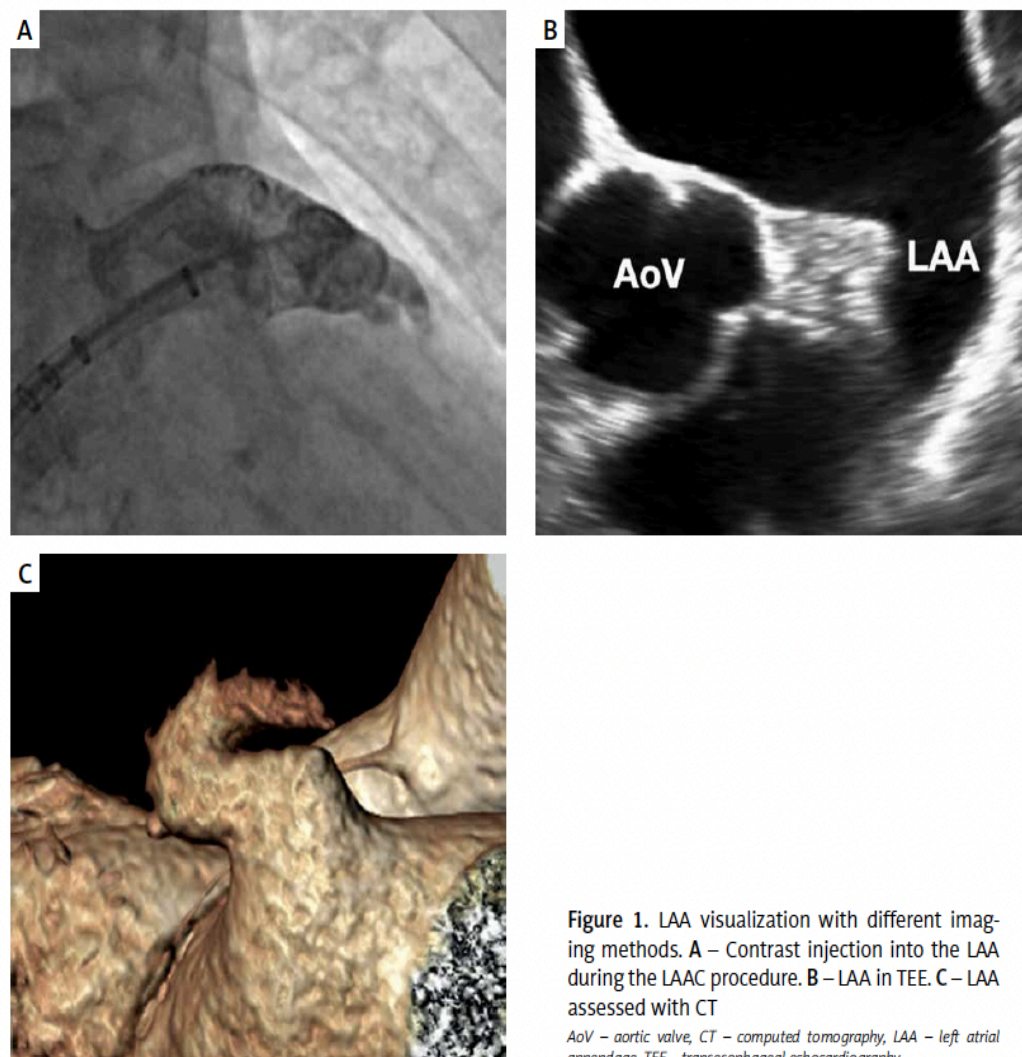


Figure 1. LAA visualization with different imaging methods. **A** – Contrast injection into the LAA during the LAAC procedure. **B** – LAA in TEE. **C** – LAA assessed with CT

AoV – aortic valve, *CT* – computed tomography, *LAA* – left atrial appendage, *TEE* – transesophageal echocardiography.

Table I. Indications and contraindications for percutaneous LAAC

Primary indications for percutaneous LAAC
- Increased thromboembolic risk assessed with CHA₂DS₂-VASC score - Contraindication for long-term OAC (i.e., history of bleeding) - History of thromboembolic event during OAC therapy
Potential indications for percutaneous LAAC
- High bleeding risk during OAC due to: - Severe renal and hepatic dysfunction - Increased risk of intracranial bleeding (i.e., brain tumor, arteriovenous malformation) - Inherited/acquired coagulopathy - OAC intolerance - Lack of consent to OAC therapy
Contraindications for percutaneous LAAC
- Lack of indications for anticoagulation therapy based on CHA₂DS₂-VASC score - Presence of other indications for lifelong OAC (i.e., mechanical heart valves, deep vein thrombosis or pulmonary embolism) - Significant mitral stenosis - Active infection - Unsuitable anatomy of the LAA - Intracardiac thrombus - Lack of patient consent

LAAC – left atrial appendage closure, OAC – oral anticoagulation.

ated with higher risk of stroke and transient ischemic attack (TIA) [14].

Indication for the procedure

LAAC with Watchman device implantation is an alternative method to anticoagulation therapy in order to prevent thromboembolic complications in patients with AF. Both American and European guidelines provide a class IIb recommendation for considering LAAC in patients at high risk of stroke and contraindications to long-term OAC therapy [3, 15]. The indications and contraindications for LAAC are presented in Table I.

Watchman 2.5 device

The Watchman 2.5 occluder is the most extensively studied LAAC device in the world and the only one whose safety and efficacy have been assessed in randomized trials (Table II). It is self-expanding, consisted of a 10-strut nitinol frame which is covered on its atrial surface with a polyethylene terephthalate (PET) membrane that ameliorates device endothelialization (Figure 2) [16]. The open distal part contains 10 anchors responsible for the device's fixation to the LAA. There are 5 available Watchman device sizes to suite the different types of LAA and they range from 21 mm to 33 mm (Figure 2). The device was designed to occlude an LAA with a diameter from around 17 mm to 31 mm; a Watchman 2.5 occluder that is 8% to 20% larger than the LAA ostium is selected to obtain adequate compression. The depth of the LAA should equal the diameter of the device when

fully expanded. Moreover, the device can be partially or fully recaptured to change the deployment position. In March 2015, based on the data from two randomized trials, the US Food and Drug Administration (FDA) approved the Watchman for LAAC to reduce the risk of stroke in patients with non-valvular AF.

The PROTECT-AF trial was the first, multicenter, randomized clinical trial (RCT) designed to assess the safety and efficacy of the Watchman device [17]. This non-inferiority RCT enrolled 707 patients with non-valvular AF and a CHADS₂ score ≥ 1 and randomized them in a two-to-one allocation to receive either device closure of the LAA with Watchman or VKA therapy with warfarin. After successful Watchman implantation all patients received warfarin for 45 days followed by dual antiplatelet therapy (DAPT) with aspirin and clopidogrel for 6 months after the procedure and then lifelong aspirin monotherapy. The primary efficacy endpoint was a composite of stroke, systemic embolism and cardiovascular death. The trial showed that LAAC with the Watchman device is non-inferior to warfarin therapy [17]. This result was mainly driven by a significant reduction in hemorrhagic stroke (Watchman: 0.6% per 100 patient-years vs warfarin: 4% per 100 patient-years) and cardiovascular death (Watchman: 1% per 100 patient-years vs warfarin: 2.6% per 100 patient-years). Ischemic stroke did not reach non-inferiority, but it has been demonstrated that LAAC significantly decreased the rate of fatal and disabling strokes (Watchman: 0.5% per 100 patient-years vs. warfarin: 1.2% per 100 patient-years). The primary safety endpoints (composite of serious bleeding, cardiac tamponade, device embolization, procedure-related stroke) was observed at a higher rate in the intervention group (7.4%) than in the control group (4.4%) (RR = 1.69, 95% CI: 1.01–3.19) with a rate of 4.8% of pericardial effusion that required percutaneous or surgical intervention. None of these patient died; however, patients with pericardial effusion required longer in-hospital stay. The impact of the operator's experience on the safety of the LAAC procedure was evaluated in the analysis of the intervention arm from the PROTECT-AF trial ($n = 542$) and from a subsequent registry of patients undergoing Watchman implantation – Continued Access to PROTECT-AF (CAP) ($n = 460$). There was a significant decrease in the rate of safety events between the first and second half of the PROTECT-AF and CAP patients [18]. Procedure-related safety events within 7 days in the PROTECT-AF trial and CAP registry was 7.7% and 3.7% ($p = 0.007$), respectively. The same event rate in the first and the second half of PROTECT-AF patients was observed in 10% and 5.5% ($p = 0.006$), respectively.

The FDA raised a couple of concerns regarding patients' selection criteria and safety profile of LAAC with the Watchman device. In response to these concerns, the PREVAIL trial was designed specifically to further evaluate the safety of the device and to confirm its efficacy observed in the PROTECT-AF trial [19]. It was a non-in-

Table II. Main studies evaluating outcomes of the Watchman device

Characteristics	PROTECT AF, 2009 ¹⁷	PROTECT AF, 2014	PREVAIL, 2014 ¹⁹	CAP and CAP2, 2019 ²¹	ASAP, 2013 ²³	EVOLUTION, 2017 ²⁵	EVOLUTION, 2019	PINACLE FLX, 2020 ³⁰	FLXILITY study, 2023 ³²
Study design	RCT 2 : 1	47 (20)	RCT 2 : 1	MCR	MCR	MCR		MCR	MCR
Device group: control group, <i>n</i>	463 : 244		269 : 138						
Device group, <i>n</i>				1144	150	1025		400	300
CHADS ₂ mean (SD)	2.2 (1.2)		2.6 (1.1)	2.6 (1.2)	2.8 (1.2)	NA		NA	NA
CHA ₂ DS ₂ -VASc mean (SD)	NA		3.8 (1.2)	4.2 (1.5)	4.4 (1.7)	4.5 (1.6)		4.2 (1.5)	4.3 (1.6)
Follow-up, mean (SD)	18 (10)		12 (6)	50	14 (9)	12	24	12	12
Post-procedural antithrombotic regimen		VKA+ ASA, 45 days ASA + daptidogrel, 6 months ASA, lifelong			DAPT, 6 months ASA, lifelong	DAPT, 60% SAPT, 7% VKA, 16% DOAC, 11%, none 6%		DOAC + ASA, 45 days DAPT, 6 months ASA, lifelong	DAPT, 87% SAPT, 7% DOAC, 5% VKA, < 1% none, < 1%
Implant success, %	88		95.1	94	94.7	98.5		98.8	99
Periprocedural* major adverse event, %	8.7		4.2	4.2	8.7	2.8		0.5	2
Procedure-related stroke, %	1.1		0.4	0.2	0	0		0.5	0
Procedure-related death, %	0		0	0.2	0	0.4		0	0
Pericardial effusion, %	4.8		1.9	2.2	1.3	0.3		0	1
Nonprocedural major bleeding, %	3.5	4.1	NA	6.9	NA	2.3/year	2.7/100 pa- tient-years	7.9	6.8
Hemorrhagic stroke, %	0.1/100 pa- tient-years	0.6	0.4	0.13/100 pa- tient-years	0.6/100 pa- tient-years	0	0.2	0	0
Ischemic stroke/TIA/SE, %	2.5/100 pa- tient-years	1.6/100 pa- tient-years	2.3	1.8/100 pa- tient-years	2.3/100 pa- tient-years	1.5/100 pa- tient-years	2/100 pa- tient-years	2.9	2.7
Mortality, %	3/100 pa- tient-years	3.2/100 pa- tient-years	2.6	5.4/100 pa- tient-years	5/year	9.8	15.7	6.6	10.8
Device embolization, %	0.6		0.7	0.2	1.3	0.2		0	0.3
Device-related thrombus, %	4.2		NA	3.3	4	3.7	4.1	1.8	2.4

*Within 7 days after procedure or by hospital discharge. RCT – randomized controlled trial, MCR – multicenter registry, LAAC – left atrial appendage closure, OAC – oral anticoagulation, TIA – transient ischemic attack.

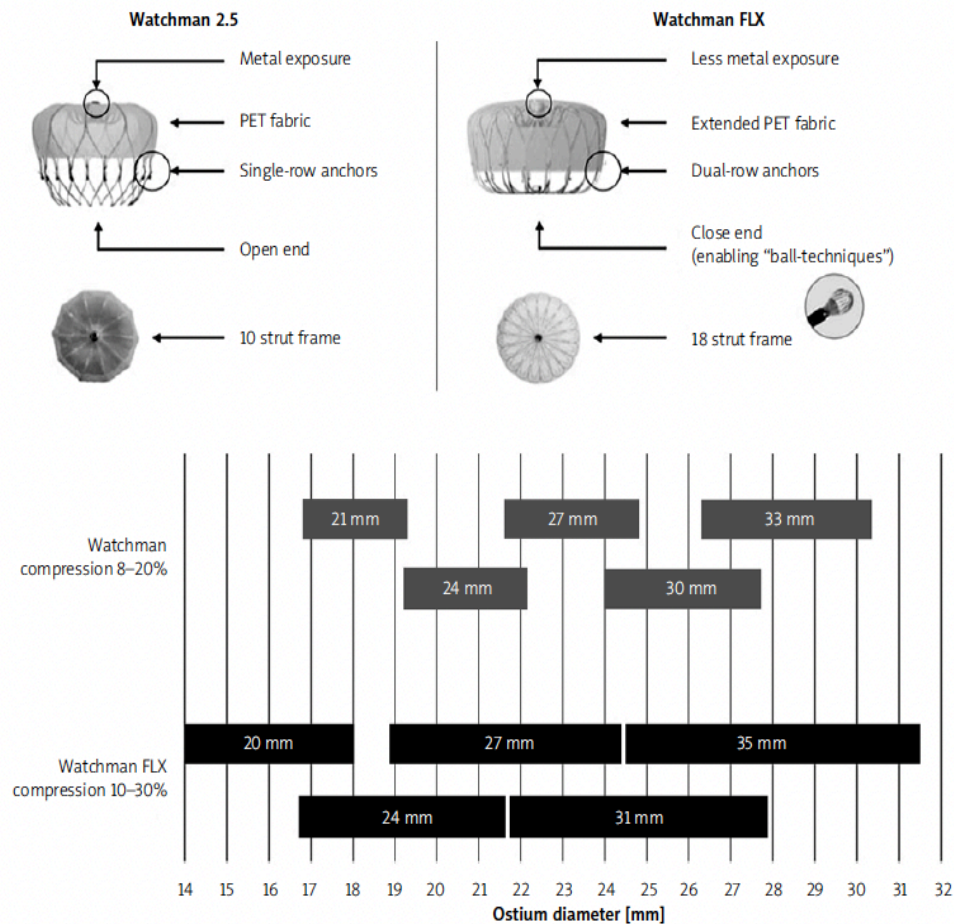


Figure 2. Comparison of Watchman 2.5 and Watchman FLX and the sizing charts. Graphic based on images received by courtesy of Boston Scientific Corporation

PET – polyethylene terephthalate.

feriority trial of 407 subjects who were randomized in two-to-one fashion either to the Watchman device or warfarin therapy. Similarly to PROTECT-AF, the first primary efficacy endpoint was a composite of stroke, systemic embolism, and cardiovascular death. A second, co-primary endpoint was stroke and systemic embolism occurring > 7 days after the procedure. The safety endpoint was a composite of a pre-defined performance criterion set by the FDA including death, ischemic stroke, systemic embolism, and procedure-device related complications requiring major intervention within 7 days after the procedure. The CHADS₂ score was higher than in the first trial with a score of 2.6 ± 1.0 in both groups, and as pre-specified, 38.8% of the patients were randomized at new sites and 39.1% of the procedures were done by new operators. At 18 months, the trial failed to show non-inferiority regarding the primary efficacy endpoint. The rate of the second co-primary efficacy endpoint met non-inferiority criteria. Importantly, the PREVAIL trial showed an improved safety

profile in comparison to the PROTECT-AF trial, with only a 2.2% rate of procedural complications [19]. Furthermore, the procedure success rate increased from 90.9% in PROTECT-AF to 95.1% in PREVAIL.

In 2017 a patient-level meta-analysis of the 5-year follow-up of PROTECT AF and PREVAIL was published. It summarized a total of 4343 patient-years of follow-up. In general the stroke prevention was comparable in both groups with an additional reduction in hemorrhagic stroke and mortality [20]. The rate of ischemic stroke was numerically higher with LAAC, but it did not reach statistical significance.

The Continued Access to PROTECT AF (CAP) and Continued Access to PREVAIL (CAP2) were two registries to evaluate the safety and efficacy of the Watchman device after a longer follow-up period [21]. Holmes *et al.* performed a meta-analysis of two randomized trials and their respective registries. This patient-level meta-analysis included 2406 patients with a mean follow-up of

2.69 years. It showed that patients receiving the Watchman device had significantly lower rates of hemorrhagic stroke (hazard ratio [HR] = 0.22; $p = 0.004$), cardiovascular/unexplained death (HR = 0.48; $p = 0.006$), and non-procedural bleeding (HR = 0.51; $p = 0.006$) in comparison to warfarin therapy [22]. The all-cause stroke or systemic embolism (SE) rate did not differ significantly between the two groups.

Although the PROTECT AF and PREVAIL trials showed good safety and efficacy of LAAC, both enrolled patients eligible for OAC therapy. The ASAP (ASA Plavix Feasibility Study with Watchman Left Atrial Appendage Closure Technology) registry was the first study to evaluate the safety and efficacy of LAAC with the Watchman device in patients unsuitable for OAC therapy [23]. This was a prospective, observational study that included 150 patients who underwent the LAAC procedure followed by 6 months of DAPT and aspirin alone thereafter. At 1 year, the rate of all-cause stroke and SE, ischemic stroke and hemorrhagic stroke was 2.3%, 1.7%, and 0.6%, respectively. The mean CHA₂DS₂-VASC score was 2.8 with the expected risk of stroke of 7.4%. Thus, there were 77% fewer ischemic strokes than expected. The incidence of device-related thrombus (DRT) was 4% (mean: 164 ±135 days after implant), which was similar to the 3.7% reported in previous studies on Watchman device implantation followed by short-term warfarin therapy.

The EWOLUTION (Registry on Watchman Outcomes in Real-Life Utilization) was a prospective, multicenter, single-arm registry that included 1020 patients undergoing Watchman implantation. The mean CHA₂DS₂-VASC score was 4.5 and the HAS-BLED score was 2.3. In comparison to the previously mentioned randomized trials, the population in the EWOLUTION registry had higher thromboembolic and bleeding risk. Watchman implantation succeeded in 98.5% of cases and procedure-/device-related serious adverse events within 7 days after the procedure were observed in 2.8% of patients [24]. Post-procedure therapy included warfarin in 16% of cases, DOACs in 11%, DAPT in 60%, single antiplatelet therapy (SAPT) in 7%, and no anti-thrombotic therapy at all in 6%. So, 73% of patients had contraindications to OAC therapy and were discharged on antiplatelet therapy or without any anti-thrombotic regimen. At 1-year follow-up, ischemic stroke was observed in 1.1% of patients, resulting in an 84% relative risk reduction compared with the estimated 7.2% event rate based on the CHA₂DS₂-VASC score [25]. DRT and non-procedural bleeding were observed in 3.7% and 2.3%, respectively. The rate of these events did not correlate with the post-procedure anti-thrombotic regimen.

Nowadays DOACs are superior to VKA for stroke prevention in non-valvular AF. In 2020 Osmancik *et al.* published the results of the first randomized trial that has sought to compare DOACs with LAAC in high-risk patients with AF [26]. PRAGUE-17 was a multicenter, randomized,

noninferiority trial that included 402 patients who were randomly assigned to LAAC or DOAC in a 1 : 1 ratio. It was a high-risk patient cohort with a CHA₂DS₂-VASC score of 4.7 ±1.5, and the bleeding risk was assessed with the HAS-BLED score as 3.0 ±0.9 and 3.1 ±0.9 in the DOAC and LAAC group, respectively. LAAC was successful in 90.0% of patients. Watchman 2.5 and Watchman FLX devices were used in 35.9% and 2.8% of cases, respectively. In the DOAC group, apixaban was most frequently used (95.5%). At a median 19.9 months of follow-up, the annual rates of the primary outcome were 10.99% with LAAC and 13.42% with DOAC ($p = 0.004$ for noninferiority). In the LAAC cohort major procedure-related complications occurred in 4.5% of patients. The study concluded that LAAC was noninferior to DOACs for the composite of cardioembolic events, cardiovascular death, clinically significant bleeding, or procedure-/device-related complications.

In 2020 the National Cardiovascular Data Registry LAAO presented patient, hospital, and physician characteristics and in-hospital adverse event rates for Watchman procedures in the United States. Between January 2016 and December 2018, 38 158 Watchman procedures were performed by 1318 physicians in United States with a successful deployment rate of 93% [27]. Major in-hospital adverse events occurred in 2.16% of patients including pericardial effusion requiring intervention in 1.39% and major bleeding in 1.25%, whereas stroke (0.17%) and death (0.19%) were rare.

Watchman FLX

The Watchman FLX is the current-generation device designed to improve safety, efficacy, and implantation success. Its new design aimed to simplify the deployment in a wider range of LAA morphologies, coming in five device sizes ranging from 20 mm to 35 mm that accommodate LAA ostia diameters of 15 mm to 32 mm, and a wider range of compression (10–30%) is accepted (Figure 2). It is up to 20% shorter in length compared to the first generation device, which makes it suitable for shallow LAA. Other redesign aspects include the increased number of struts to 18 for better tissue fixation and radial strength, and two rows of 'J'-shaped anchors enhancing its stability (Figure 2). The distal end of the new device is atraumatic, allowing partial and full recapture, and an ability to use the "ball technique" to achieve safe deployment with reduced risk of procedural complications. The device also has an extended fabric for optimal sealing and endothelialization. The Watchman FLX received Conformité Européenne (CE) marked approval in March 2019 and FDA approval in July 2020 after PINNACLE FLX trial results.

The PINNACLE FLX was a prospective, nonrandomized trial designed to evaluate the safety and efficacy of the new-generation LAAC device. The study enrolled 400 AF patients to receive the Watchman FLX. After successful

occluder deployment, the antithrombotic regimen consisted of a DOAC plus aspirin for 45 days, followed by DAPT for 6 months if no peri-device leak > 5 mm was observed on TEE at 45 days. Afterwards, monotherapy with aspirin was prescribed. The trial showed a high implant success rate of 98.8%. The primary safety endpoint, defined as all-cause death, ischemic stroke, systemic embolism, and procedure-related adverse events occurring within 7 days after the procedure or by hospital discharge, was observed in only 0.5% of cases. The primary efficacy endpoint, defined as peri-device leak ≤ 5 mm in control TEE, was achieved in 100% of cases at 1-year follow-up. Moreover, at 1-year follow-up 2.6% of patients experienced ischemic stroke and 7.9% had serious bleeding complications. DRT was noted in 7 patients, with embolic events in 2 patients. Of importance, no device embolization was observed [28].

Those favorable data were supported by another prospective, multicenter registry that enrolled 165 patients in Europe. Successful deployment was achieved in all patients. The procedural related complication rate was low at 1.8% and consisted of 2 access-related complications and 1 pericardial effusion. No peri-procedural strokes, deaths, or device embolizations occurred. During a median follow-up of 55 days there were 6 bleeding complications (4.8%), 1 (0.8%) patient had an ischemic stroke, and 1 (0.8%) died. Imaging follow-up revealed 1 peri-device leak ≥ 5 mm and 7 cases of DRT (4.7%). No late device embolization was observed [29].

Lastly, the recently published FLXibility Post-Approval Study evaluated the Watchman FLX device in a commercial clinical setting. It was a prospective, observational, multicenter, single-arm study that enrolled 301 patients. One patient did not meet eligible criteria, so the implant population consisted of 300 patients. The device was successfully implanted in 99.0% of patients. Neither death nor stroke occurred within 7 days after the procedure. Three patients had pericardial effusions requiring intervention on the day of the procedure, all resolved successfully and there were no additional pericardial effusions through 1 year of follow-up. One device embolization occurred and resulted in death at 13 days after the procedure. Most patients were discharged on DAPT (87.3%), then on SAPT (7.0%) or DOAC (4.7%). The first follow-up was done between 45 and 120 days, and at that time a complete seal was observed in 88.2%, 9.5% had a leak < 3 mm, 2.4% had a leak ≥ 3 mm to ≤ 5 mm, and no > 5 mm leak was observed. The final, 1-year follow-up was performed in 93.3% of cases. Most patients were on SAPT (60.5%), followed by DAPT (21.4%), and no antiplatelet or OAC (12.1%). The all-cause mortality rate was 10.8%. Stroke occurred in 2% of cases, all of which were non-fatal strokes, and half of them were non-disabling. DRT was observed in 2.4% of patients through 1 year and all were detected at routine follow-up imaging [30].

The Watchman FLX is currently being evaluated in the ongoing CHAMPION-AF trial [31]. This is the first large, prospective, randomized, controlled trial whose primary objective is to determine whether LAAC with the WATCHMAN FLX device is a reasonable alternative to non-vitamin K oral anticoagulants in patients with non-valvular AF. The patients are randomized to the Watchman FLX or DOAC in a 1 : 1 allocation. Clinical follow-up visits are scheduled at 3 and 12 months, and then annually for 5 years. The primary outcome measures at 3 years of follow-up are Watchman FLX non-inferiority for the occurrence of stroke, cardiovascular death, and systemic embolism, and Watchman FLX superiority for non-procedural bleeding (International Society on Thrombosis and Haemostasis major bleeding and clinically relevant non-major bleeding). The estimated primary completion date is December 2027.

LAAC procedure

The pre-procedural use of TEE or CT is very important for optimal patient and device selection. This multimodality imaging allows to exclude LAA thrombus, determine dimensions and morphology of the LAA, and establish whether the procedure is feasible.

Precise assessment of LAA morphology is performed by 2-dimensional and 3-dimensional TEE. Transesophageal echocardiography can detect an LAA thrombus with high sensitivity (92%) and specificity (98%). Its negative predictive value reaches 100% and its positive predictive value is 86% [32]. The LAA is assessed at 0, 45, 90, and 135° to obtain its measurements and to establish the landing zone, maximum diameter, and depth.

A multidetector CT provides an accurate anatomical evaluation of the LAA and the perimeter, maximum and minimum diameter of the landing zone can be measured. Moreover, LAA thrombus can be excluded using CT imaging. It has a high sensitivity of 96% and a high negative predictive value of 100% for the assessment of thrombotic complications within the LAA [33]. Saw *et al.* demonstrated that CT provides the largest measurements, followed by TEE and fluoroscopy, concluding that CT more accurately assesses the true LAA dimensions [34].

The procedure is performed under general anesthesia or conscious sedation and guided by fluoroscopy and TEE or intracardiac echocardiography. The delivery sheath is introduced via the right femoral vein. The trans-septal puncture (TSP) should be performed in the postero-inferior segment of the fossa ovalis. The procedure is performed under adequate anticoagulation with unfractionated heparin (UFH) with activated clotting time > 250 s. Once trans-septal access is done, the trans-septal puncture sheath is swapped to the 14-Fr. device access sheath. The pigtail catheter is introduced into the LAA, through which the contrast is injected and angiographic projections of LAA are recorded. The Watchman device is advanced into

the tip of the access sheath and the device is deployed under fluoroscopy and TEE guidance. The Watchman FLX is deployed by forming “a ball” (Figure 2) and either unsheathing while maintaining the position of the ball, or advancing the device distally out of the sheath until it is fully deployed. A combination of both of these techniques is possible. Too proximal position of the Watchman FLX can be corrected with the partial recapture thanks to the ball technique implantation. Before the device is released, the “PASS criteria” need to be fulfilled. P: optimal position of the device, A: checking anchor to the LAA by tug test, S: sealing assessed with color Doppler, and S: sizing for proper compression of the device.

Anti-thrombotic therapy after Watchman device implantation

The optimal anti-thrombotic regimen and its duration after a successful LAAC procedure remains controversial and should be adjusted individually. To date, various antithrombotic strategies following LAAC with the Watchman device have been proposed, including VKA, DOAC, DAPT, aspirin monotherapy, or no therapy. The main aim of this strategy is to prevent thromboembolic complications, especially during the endothelialization period directly after device deployment.

After the LAAC procedure there is a vulnerable period during endothelialization, in which there is a higher risk of developing DRT. Animal studies revealed that the endothelialization process is complete within around 90 days after the procedure [35]. Based on that result and the experience on other implantable cardiac devices, the initial strategy was developed. The first randomized trials included patients eligible for OAC therapy, so the initial protocol treatment after LAAC consisted of warfarin with aspirin for 45 days, followed by DAPT for 6 months and lifelong aspirin. However, current guidelines recommend LAAC in patients who have a contraindications for OAC, so the post-procedural regimen has shifted to less aggressive alternatives.

Numerous observational studies have been performed to assess DAPT therapy as an initial regimen following the LAAC procedure, with further lifelong aspirin. In the ASAP study, patients with a contraindication to OAC received 6-month DAPT therapy; the rate of DRT was 4%, the annual incidence of ischemic stroke was 1.7%, and a 77% reduction in events compared to that expected based on the risk score was observed [23]. The EWOLUTION registry showed that DAPT is the most frequently chosen therapeutic regimen during the first 3 months after LAAC, with 60% of the individuals in the trial on that regimen, and no significant differences in DRT and stroke rate were observed within the different treatment options [24]. The propensity-match analysis by Søndergaard *et al.* compared antiplatelet therapy with anticoagulation therapy following LAAC with the

Watchman device in the PROTECT-AF, PREVAIL, ASAP, and EWOLUTION trials, and concluded that there were no significant differences in the incidence of major bleeding or thromboembolism between these two strategies [36]. However, DRT was more often observed in the antiplatelet therapy group, although no thromboembolic events were reported. The other trial was a meta-analysis of 12,326 patients comparing short-term OAC with antiplatelet therapy [37]. No difference in the occurrence of stroke, major bleeding, DRT, or all-cause mortality was found. Finally, our analysis of 90 patients who underwent successful Watchman 2.5 implantation in our department showed that DAPT seems to be a safe and effective regimen within 3 months after device implantation [38].

Single antiplatelet therapy and no-therapy are also used, but these regimens have a smaller amount of supporting data. Korsholm *et al.* published their single-center data of 110 patients who were at high risk of bleeding and were predominantly treated with SAPT [39]. A low annual major bleeding rate of 3.8% was observed, so the annual risk of major bleeding was reduced by 57%. Moreover, there was no increase in the incidence of DRT or stroke at 1 year, with a rate of 1.9% and 2.3%, respectively. Favorable results were also presented in a multicenter registry that included 600 patients allocated to SAPT ($n = 280$) or DAPT ($n = 330$) at the operator's discretion [40]. In the SAPT group a significant reduction of major bleeding was observed (2.9% vs. 6.7%, $p = 0.04$), without differences in major cardiovascular events or DRT at 1 year. The other multicenter registry of 469 patients, of whom 36.2% were treated with SAPT, showed a high rate of DRT (7.2%) [41]. The multivariate analysis showed that OAC or DAPT acts as protective factor against DRT.

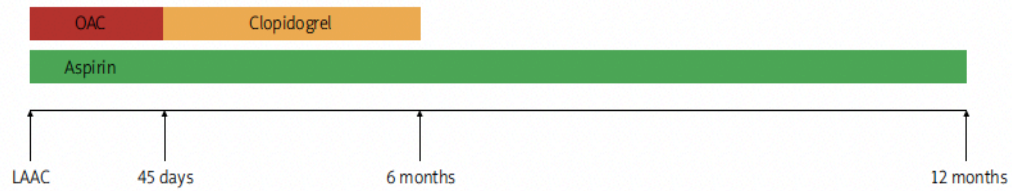
Finally, no therapy after Watchman device implantation has been poorly studied. This regimen can be considered in patients who are at extremely high risk of bleeding and cannot tolerate even short-term SAPT [42]. Alternatively, in this population epicardial LAA closure should be considered.

To conclude, the current data provide some reassurance on the use of DAPT after the LAAC procedure in patients who are not suitable for OAC therapy. The current recommendations from the 2020 European Society of Cardiology Guidelines on AF regarding the antithrombotic regimen after LAAC are presented in Figure 3. However, the choice of the post-procedural therapy should be individualized.

Device-related thrombus (DRT)

DRT is one of the most concerning complications after successful Watchman device implantation that can be detected by TEE (Figure 4) or CT. In the PROTECT-AF trial the rate of DRT was 4.2% [17]. However, in 2018 Dukkkipati *et al.* published cumulative data regarding DRT incidence in PROTECT AF, PREVAIL, and their continuous access

Watchman – low bleeding risk



Watchman – high bleeding risk

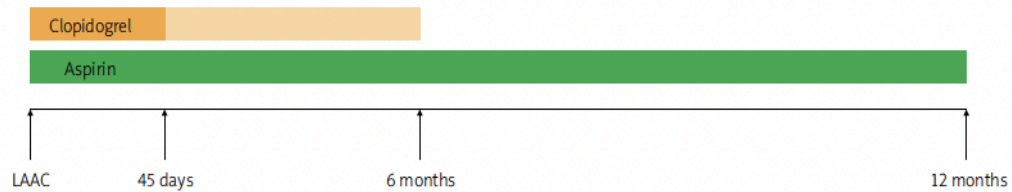


Figure 3. Antithrombotic regimen after LAAC with Watchman device

LAAC – left atrial appendage closure, OAC – oral anticoagulation therapy.

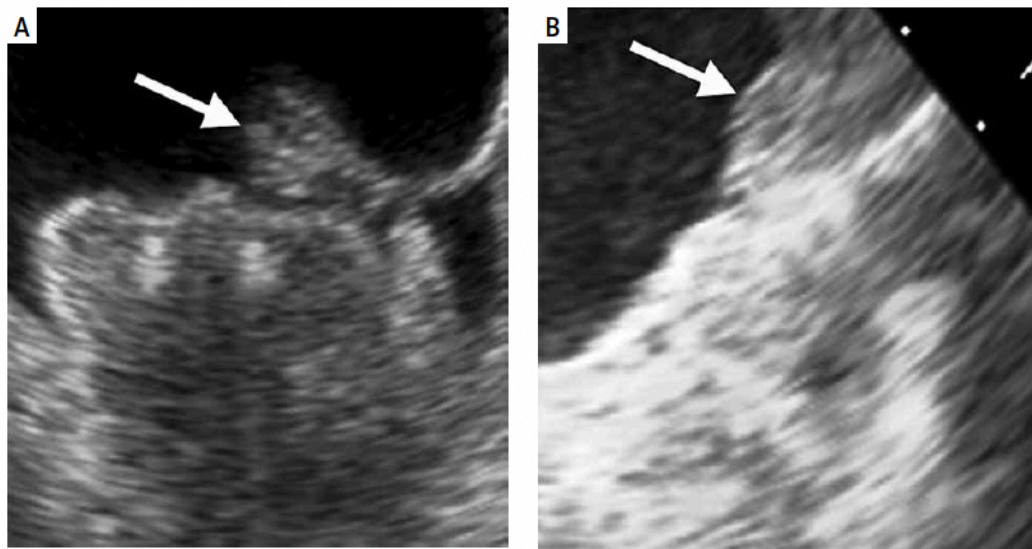


Figure 4. Device-related thrombus on Watchman 2.5 device. The arrow indicates a thrombus on the surface of the implanted device

registries [43]. After a mean follow-up time of 4.1 years, the rate of DRT was 3.74%. The analysis of patients with DRT revealed that they were at higher thromboembolic risk assessed with the CHA₂DS₂-VASC score, were more likely in permanent atrial fibrillation, had a history of TIA or stroke, larger LAA, and had lower ejection fraction (EF). The risk of stroke or systemic embolism was 3.55-fold higher in patients with DRT. In the EWOLUTION registry, at 2-year follow-up DRT was observed in 34 (4.1%) cases among 835 patients with imaging of the LAA after a median time of 54 days (IQR: 41–111 days)

[44]. Thirty-one incidents of DRT were observed at the first follow-up imaging usually within 90 days after the procedure. DRT occurred irrespective of the type of the post-LAAC antithrombotic regimen. Patients with DRT more often had non-paroxysmal AF, evidence of spontaneous echo contrast, and a larger ostium diameter of the LAA [45]. Overall, no significant differences in rate of thromboembolic events were observed in patients with or without DRT (1.7 vs. 2.2%/year, $p = 0.8$). In a prospective registry with the second-generation Watchman FLX device, at 1 year DRT was detected in 7 (1.7%) patients

with 4 cases discovered during scheduled follow-up visits [28]. In the real-world registry of Watchman FLX, DRT was observed in 2.4% of cases through 1 year of follow-up and all were detected during routine imaging [30].

There are several procedural- and patient-related factors that predispose to DRT. The predictors of DRT include reduced EF, a history of a thromboembolic event, or a larger orifice of the LAA [37, 42, 43]. Furthermore, a deep Watchman device implantation, leaving a large volume of uncovered appendage ("neo-appendage"), and a lack of left upper pulmonary vein ridge coverage are linked with increased risk of DRT. In 2018 Pracon *et al.* reported that DRT was more often observed in patients with deep device implantation [46].

To date, management of DRT remains a clinical issue. Most data suggest the use of antithrombotic therapy with heparin or OAC [41]. However, this approach still raises concerns, mainly about the risk of bleeding. Most patients referred for LAAC have contraindications to OAC therapy, so the initiation of OAC significantly increases the risk of bleeding, but on the other hand there is a high risk of embolism because of DRT presence. Secondly, up to 30% of DRTs may persist despite proper anticoagulation therapy; thus, these patients experience higher morbidity and mortality [47]. Moreover, the recurrence rate of DRT while the patient is still on anticoagulation is 35%, while the recurrence rate increases to 50% when the OAC therapy is abandoned [48]. Another treatment option for DRT is thrombus aspiration. Its feasibility has been reported, but the safety and efficacy of this approach have not been established and there are no data at this time to support routine use of aspiration thrombectomy over medical therapy [49].

Further studies are required to investigate the post-procedural optimal antithrombotic regimen to minimize the risk of DRT. This approach should take into account the patient's thromboembolic and bleeding risk, and also predictors of thrombus formation.

Peri-device leak

The Watchman device has a standard circular shape, while the ostium of the LAA is typically elliptical and shows considerable interpatient variability. This mismatch between the shape of the device and the LAA can cause incomplete LAA occlusion with increased risk of residual peri-device leak (PDL). Peri-device leak has been defined as residual flow of any size around the implanted device which is detected with TEE. The PDL around the Watchman device is defined as minor when it is < 3 mm, moderate at 3–5 mm, and significant when > 5 mm.

In the PROTECT AF study, any PDL was observed in 40.9% of cases at 45 days, while at 1 year it had decreased to 32.1% [50]. Peri-device leaks > 3 mm were present in 13.3% at 45 days and in 11.8% at 1 year. The new generation Watchman FLX was evaluated in the

PINNACLE registry, in which the data were assessed with the echocardiography core lab and lower incidence of PDL with the Watchman FLX device was revealed [28]. Any PDL was observed in 17.4% of patients at 45 days, and in 10.5% at 1 year. The recent report from the SURPASS study, which investigated the Watchman FLX in a real-world setting, showed an even lower rate of PDL [51]. In 2022 the SURPASS analysis included data from more than 16,000 patients and showed that after Watchman FLX implantation, 95.3% of the patients had no peri-device leak, and 99.1% had no leak or had a leak of < 3 mm. At 45 days of follow-up, these rates decreased to 83% and 95% respectively.

It has been debated whether the presence of PDL following Watchman device implantation is associated with increased thromboembolic risk. To date we know that leakage after surgical LAA ligation is connected with increased thromboembolic complications [52]. The rate of stroke or systemic embolism is relatively low after percutaneous LAAC, so assessing the independent impact of PDL on thromboembolic outcomes is difficult and would require a very large sample size. Moreover, patients with significant leakage of > 5 mm are recommended to receive anticoagulation therapy [53], and hence the evaluation of the influence of the residual peri-device leak on thromboembolic outcomes may be disturbed by treatment bias. In the PROTECT AF study the PDL size was not associated with an increased risk of thromboembolic complications [50]. However, this study was underpowered in this regard. A recent analysis combined PROTECT AF, PREVAIL, and CAP2 studies to evaluate the impact of PDL in a population of 1054 patients who underwent LAAC with the Watchman 2.5 device [54]. The study showed that 39.8% and 28.4% of patients had a peri-device leak at the 45-day and 1-year TEE, respectively. The presence of PDL ≤ 5 at 1 year, but not at 45 days, was associated with an increased 5-year risk of ischemic stroke or systemic embolism (HR = 1.94; 95% CI: 1.15–3.29; $p = 0.014$), largely driven by an increase in nondisabling stroke (HR = 1.97; 95% CI: 1.03–3.78; $p = 0.04$), while disabling or fatal stroke rates were similar (HR = 0.69; 95% CI: 0.19–2.46; $p = 0.56$).

To date, no ideal management of PDL has been offered. The introduction of pre-procedural CT to obtain optimal sizing and better alignment with the LAA has been advocated to achieve better sealing [55]. In the case of a small PDL < 5 mm, a watchful waiting strategy has been proposed due to a documented regression of small leaks in 20% to 40% of patients [28, 50]. A significant PDL should be managed with anticoagulation therapy. Another option is closure of the PDL with plugs or a coil, and this approach has been reported in several case series [56, 57]. These studies revealed that complete or near-complete PDL occlusion is feasible in most patients with a low rate of complications, but long-term outcomes are still unknown [58].

Conclusions

Percutaneous LAAC with the Watchman device is an attractive treatment alternative for stroke prevention in the growing population of patients who are not good candidates for OAC therapy. As the new device is introduced into clinical practice and operator experience grows, the LAAC procedure becomes an increasingly safe and effective treatment option. However, there are still some concerns regarding long-term adverse events (i.e. DRT and PDL) and optimal post-procedural patient management. Further studies are necessary to optimize patient selection and the post-LAAC antithrombotic regimen, and determine the long-term benefit of LAAC.

Conflict of interest

The authors declare no conflict of interest.

References

1. Chugh SS, Havmoeller R, Narayanan K, et al. Worldwide epidemiology of atrial fibrillation: a Global Burden of Disease 2010 Study. *Circulation* 2014; 129: 837-47.
2. Alkhouli M, Alqahtani F, Aljohani S, et al. Burden of atrial fibrillation-associated ischemic stroke in the United States. *JACC Clin Electrophysiol* 2018; 4: 618-25.
3. Hindricks G, Potpara T, Dagres N, et al. 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS): The Task Force for the diagnosis and management of atrial fibrillation of the European Society of Cardiology (ESC) Developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC. *Eur Heart J* 2021; 42: 373-498.
4. Ruff CT, Giugliano RP, Braunwald E, et al. Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials. *Lancet* 2014; 383: 955-62.
5. Hsu JC, Maddox TM, Kennedy KF, et al. Oral anticoagulant therapy prescription in patients with atrial fibrillation across the spectrum of stroke risk: insights from the NCDR PINNACLE Registry. *JAMA Cardiol* 2016; 1: 55-62.
6. Healey JS, Crystal E, Lamy A, et al. Left Atrial Appendage Occlusion Study (LAAOS): results of a randomized controlled pilot study of left atrial appendage occlusion during coronary bypass surgery in patients at risk for stroke. *Am Heart J* 2005; 150: 288-93.
7. Blackshear JL, Odell JA. Appendage obliteration to reduce stroke in cardiac surgical patients with atrial fibrillation. *Ann Thorac Surg* 1996; 61: 755-9.
8. Casu G, Gulizia MM, Molon G, et al. ANMCO/AIAC/SICI-GISE/SIC/SICCH Consensus document: Percutaneous left atrial appendage occlusion in patients with nonvalvular atrial fibrillation: indications, patient selection, competences, organization, and operator training. *G Ital Cardiol (Rome)* 2016; 17: 594-613.
9. Alfadhel M, Nestelberger T, Samuel R, et al. Left atrial appendage closure – current status and future directions. *Prog Cardiovasc Dis* 2021; 69: 101-9.
10. Galea R, Mahmoudi K, Gräni C, et al. Watchman FLX vs. Watchman 2.5 in a dual-center left atrial appendage closure cohort: the WATCH-DUAL study. *Europace* 2022; 24: 1441-50.
11. Sadler TW. Cardiovascular System. In: Lagmans Med Embryolgy. Langman J (ed.). Williams and Wilkins, Baltimore 2012; 162-200.
12. Beigel R, Wunderlich NC, Ho SY, et al. The left atrial appendage: anatomy, function, and noninvasive evaluation. *JACC Cardiovasc Imaging* 2014; 7: 1251-65.
13. Di Biase L, Santangeli P, Anselmino M, et al. Does the left atrial appendage morphology correlate with the risk of stroke in patients with atrial fibrillation? Results from a multicenter study. *J Am Coll Cardiol* 2012; 60: 531-8.
14. Yamamoto M, Seo Y, Kawamatsu N, et al. Complex left atrial appendage morphology and left atrial appendage thrombus formation in patients with atrial fibrillation. *Circ Cardiovasc Imaging* 2014; 7: 337-43.
15. January CT, Wann LS, Calkins H, et al. 2019 AHA/ACC/HRS Focused Update of the 2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society in Collaboration With the Society of Thoracic Surgeons. *Circulation* 2019; 140: e125-51.
16. Möbius-Winkler S, Sandri M, Mangner N, et al. The WATCHMAN left atrial appendage closure device for atrial fibrillation. *J Vis Exp* 2012; 60: 3671.
17. Holmes DR, Reddy VY, Turi ZG, et al. Percutaneous closure of the left atrial appendage versus warfarin therapy for prevention of stroke in patients with atrial fibrillation: a randomised non-inferiority trial. *Lancet* 2009; 374: 534-42.
18. Reddy VY, Holmes D, Doshi SK, et al. Safety of percutaneous left atrial appendage closure: results from the Watchman Left Atrial Appendage System for Embolic Protection in Patients with AF (PROTECT AF) clinical trial and the Continued Access Registry. *Circulation* 2011; 123: 417-24.
19. Holmes DR Jr, Kar S, Price MJ, et al. Prospective randomized evaluation of the Watchman Left Atrial Appendage Closure device in patients with atrial fibrillation versus long-term warfarin therapy: the PREVAIL trial. *J Am Coll Cardiol* 2014; 64: 1-12.
20. Reddy VY, Doshi SK, Kar S, et al. 5-year outcomes after left atrial appendage closure: from the PREVAIL and PROTECT AF trials. *J Am Coll Cardiol* 2017; 70: 2964-75.
21. Holmes DR Jr, Reddy VY, Gordon NT, et al. Safety and efficacy in continued access left atrial appendage closure registries. *J Am Coll Cardiol* 2019; 74: 2878-89.
22. Holmes DR Jr, Doshi SK, Kar S, et al. Left atrial appendage closure as an alternative to warfarin for stroke prevention in atrial fibrillation: a patient-level meta-analysis. *J Am Coll Cardiol* 2015; 65: 2614-23.
23. Reddy VY, Möbius-Winkler S, Miller MA, et al. Left atrial appendage closure with the Watchman device in patients with a contraindication for oral anticoagulation: the ASAP study (ASA Plavix Feasibility Study With Watchman Left Atrial Appendage Closure Technology). *J Am Coll Cardiol* 2013; 61: 2551-6.
24. Boersma LV, Schmidt B, Betts TR, et al. Implant success and safety of left atrial appendage closure with the WATCHMAN device: peri-procedural outcomes from the EWOLUTION registry. *Eur Heart J* 2016; 37: 2465-74.
25. Boersma LV, Ince H, Kische S, et al. Efficacy and safety of left atrial appendage closure with WATCHMAN in patients with or without contraindication to oral anticoagulation: 1-year fol-

- low-up outcome data of the EWOLUTION trial. *Heart Rhythm* 2017; 14: 1302-8.
26. Osmancik P, Herman D, Neuzil P, et al. Left atrial appendage closure versus direct oral anticoagulants in high-risk patients with atrial fibrillation. *J Am Coll Cardiol* 2020; 75: 3122-35.
27. Freeman JV, Varosy P, Price MJ, et al. The NCDR left atrial appendage occlusion registry. *J Am Coll Cardiol* 2020; 75: 1503-18.
28. Kar S, Doshi SK, Sadhu A, et al. Primary outcome evaluation of a next-generation left atrial appendage closure device: results from the PINNACLE FLX trial. *Circulation* 2021; 143: 1754-62.
29. Cruz-González I, Korsholm K, Trejo-Velasco B, et al. Procedural and short-term results with the new Watchman FLX left atrial appendage occlusion device. *JACC Cardiovasc Interv* 2020; 13: 2732-41.
30. Betts TR, Grygier M, Nielsen Kudsk JE, et al. Real-world clinical outcomes with a next-generation left atrial appendage closure device: the FLXibility Post-Approval Study. *Europace* 2023; 25: 914-21.
31. Kar S, Doshi SK, Alkhouli M, et al. Rationale and design of a randomized study comparing the Watchman FLX device to DOACs in patients with atrial fibrillation. *Am Heart J* 2023; 264: 123-32.
32. Manning WJ, Weintraub RM, Waksmonski CA, et al. Accuracy of transesophageal echocardiography for identifying left atrial thrombi. A prospective, intraoperative study. *Ann Intern Med* 1995; 123: 817-22.
33. Hong SJ, Kim JY, Kim JB, et al. Multidetector computed tomography may be an adequate screening test to reduce periprocedural stroke in atrial fibrillation ablation: a multicenter propensity-matched analysis. *Heart Rhythm* 2014; 11: 763-70.
34. Saw J, Fahmy P, Spencer R, et al. Comparing measurements of CT angiography, TEE, and fluoroscopy of the left atrial appendage for percutaneous closure. *J Cardiovasc Electrophysiol* 2016; 27: 414-22.
35. Schwartz RS, Holmes DR, Van Tassel RA, et al. Left atrial appendage obliteration: mechanisms of healing and intracardiac integration. *JACC Cardiovasc Interv* 2010; 3: 870-7.
36. Søndergaard L, Wong YH, Reddy VY, et al. Propensity-matched comparison of oral anticoagulation versus antiplatelet therapy after left atrial appendage closure with WATCHMAN. *JACC Cardiovasc Interv* 2019; 12: 1055-63.
37. Alkhouli M, Busu T, Shah K, et al. Incidence and clinical impact of device-related thrombus following percutaneous left atrial appendage occlusion: a meta-analysis. *JACC Clin Electrophysiol* 2018; 4: 1629-37.
38. Maksym J, Kaplon-Cieslicka A, Scisio P, et al. Safety and efficacy of percutaneous atrial appendage closure followed by antiplatelet therapy in a high-risk population: single-center experience with a WATCHMAN device. *Adv Interv Cardiol* 2023; 19: 262-9.
39. Korsholm K, Nielsen KM, Jensen JM, et al. Transcatheter left atrial appendage occlusion in patients with atrial fibrillation and a high bleeding risk using aspirin alone for post-implant antithrombotic therapy. *Eurointervention* 2017; 12: 2075-82.
40. Patti G, Sticchi A, Verolino G, et al. Safety and efficacy of single versus dual antiplatelet therapy after left atrial appendage occlusion. *Am J Cardiol* 2020; 134: 83-90.
41. Fauchier L, Cinaud A, Brigadeau F, et al. Device-related thrombosis after percutaneous left atrial appendage occlusion for atrial fibrillation. *J Am Coll Cardiol* 2018; 71: 1528-36.
42. Glikson M, Wolff R, Hindricks G, et al. EHRA/EAPCI expert consensus statement on catheter-based left atrial appendage occlusion – an update. *Europace* 2020; 22: 184.
43. Dukkipati SR, Kar S, Holmes DR, et al. Device-related thrombus after left atrial appendage closure: incidence, predictors, and outcomes. *Circulation* 2018; 138: 874-85.
44. Boersma LV, Ince H, Kische S, et al. Evaluating real-world clinical outcomes in atrial fibrillation patients receiving the WATCHMAN left atrial appendage closure technology: final 2-year outcome data of the EWOLUTION trial focusing on history of stroke and hemorrhage. *Circ Arrhythm Electrophysiol* 2019; 12: e006841.
45. Sedaghat A, Nickenig G, Schrickel JW, et al. Incidence, predictors and outcomes of device-related thrombus after left atrial appendage closure with the WATCHMAN device-Insights from the EWOLUTION real world registry. *Catheter Cardiovasc Interv* 2021; 97: E1019-24.
46. Pracon R, Bangalore S, Dzielinska Z, et al. Device thrombosis after percutaneous left atrial appendage occlusion is related to patient and procedural characteristics but not to duration of postimplantation dual antiplatelet therapy. *Circ Cardiovasc Interv* 2018; 11: e005997.
47. Sedaghat A, Vij V, Al-Kassou B, et al. Device-related thrombus after left atrial appendage closure: data on thrombus characteristics, treatment strategies, and clinical outcomes from the EUROCC-DRT-registry. *Circ Cardiovasc Interv* 2021; 14: e010195.
48. Asmarats L, Cruz-González I, Nombela-Franco L, et al. Recurrence of device-related thrombus after percutaneous left atrial appendage closure. *Circulation* 2019; 140: 1441-3.
49. Frisoli TM, Chiang M, Eng MH, et al. Percutaneous aspiration thrombectomy of thrombus attached to left atrial surface of a Watchman FLX Device. *JACC Clin Electrophysiol* 2022; 8: 277-9.
50. Viles-Gonzalez JF, Kar S, Douglas P, et al. The clinical impact of incomplete left atrial appendage closure with the WATCHMAN device in patients with atrial fibrillation: a PROTECT AF (Percutaneous Closure of the Left Atrial Appendage Versus Warfarin Therapy for Prevention of Stroke in Patients With Atrial Fibrillation) substudy. *J Am Coll Cardiol* 2012; 59: 923-9.
51. Kapadia S. Late breaking clinical trial at cardiovascular Research Technologies (CRT) [Press release]. Meeting: 2022 Results Reinforce Positive Real-World Outcomes with the WATCHMAN FLX-TM LAAC Device (Cardiovascular Research Technologies, 2022). Boston Scientific (2022).
52. Kanderian AS, Gillinov AM, Pettersson GB, et al. Success of surgical left atrial appendage closure: assessment by transesophageal echocardiography. *J Am Coll Cardiol* 2008; 52: 924-9.
53. Jang SJ, Wong SC, Mosadegh B. Leaks after left atrial appendage closure: ignored or neglected? *Cardiology* 2021; 146: 384-91.
54. Dukkipati SR, Holmes DR Jr, Doshi SK, et al. Impact of peridevice leak on 5-year outcomes after left atrial appendage closure. *J Am Coll Cardiol* 2022; 80: 469-83.
55. Wang DD, Eng M, Kupsky D, et al. Application of 3-dimensional computed tomographic image guidance to WATCHMAN implantation and impact on early operator learning curve: single-center experience. *JACC Cardiovasc Interv* 2016; 9: 2329-40.
56. Piayda K, Sievert K, Della Rocca DG, et al. Safety and feasibility of peri-device leakage closure after LAAC: an international, multicentre collaborative study. *Eurointervention* 2021; 17: e1033-40.
57. Della Rocca DG, Horton RP, Di Biase L, et al. First experience of transcatheter leak occlusion with detachable coils following left atrial appendage closure. *JACC Cardiovasc Interv* 2020; 13: 306-19.
58. Alkhouli M. Management of peridevice leak after LAAC: coils, plugs, occluders, or better understanding of the problem? *JACC Cardiovasc Interv* 2020; 13: 320-2.

7. Podsumowanie i wnioski.

Wydłużanie się życia populacji wiąże się z rosnącą liczbą pacjentów z rozpoznawanym AF. Rosnący wiek i wielochorobowość z tym związana będzie zwiększać w tej grupie chorych ryzyko zakrzepowo-zatorowe, przy jednoczesnym zwiększaniu się ryzyka krwawienia w trakcie leczenia OAC. Z uwagi na powyższe uzasadniona jest konieczność poszerzenia wiedzy na temat LAAC i farmakoterapii po skutecznym zabiegu. Niniejszą rozprawę doktorską tworzy cykl publikacji, gdzie retrospektywnie przeanalizowano zabiegi LAAC i omówiono okres okołozabiegowy oraz dokonano analizy zastosowanego po zabiegu leczenia przeciwplatekowego.

W pierwszej pracy oceniono skuteczność oraz bezpieczeństwo zabiegu LAAC z wykorzystaniem urządzenia WATCHMAN. Następnie analizie poddano zastosowane po zabiegu leczenie przeciwplatekowe. Analizowana grupa pacjentów była wysokiego ryzyka zakrzepowo-zatorowego ocenianego w skali CHA₂DS₂-VASc 4.7 ± 1.6 oraz wysokiego ryzyka krwawienia ocenianego w skali HAS-BLED 3.2 ± 0.9 . Obserwowano wysoką skuteczność implantacji okludera do LAA, przy umiarkowanym ryzyku zdarzeń okołozabiegowych. Warto podkreślić, że wraz z rosnącym doświadczeniem zespołu istotnie spadała częstość zdarzeń niepożądanych w badanej populacji. W kolejnym etapie, po ok. 3 miesiącach oceniono pacjentów pod kątem skuteczności i bezpieczeństwa leczenia przeciwplatekowego po zabiegu. Wykazano, że w populacji wysokiego ryzyka zakrzepowo-zatorowego i wysokiego ryzyka krwawienia, DAPT wydaje się być bezpieczną i skuteczną formą leczenia. Skrzeplina związana z urządzeniem wystąpiła po zabiegu u 5 pacjentów.

W drugiej pracy analizie poddano grupę pacjentów, którzy mieli kontrolne badanie TEE po skutecznym zabiegu, a szczególną uwagę skupiono na pacjentach, u których stwierdzono DRT. Jak wspomniano powyżej, DRT stwierdzono u 5 pacjentów, których porównano z resztą populacji w celu określenia predyktorów wystąpienia skrzepliny. Udało się stwierdzić, że istotnie statystycznie częściej DRT wystąpiła u pacjentów młodszych (67.4 vs. 75; $p = 0.045$), z niższą frakcją wyrzutową [40% (23.5-45.5) vs. 55% (48-60); $p = 0.005$], z niższą prędkością opróżniania LAA [25

cm/s (17.5-27) vs. 53 cm/s (26.5-78); $p = 0.009$] oraz z głębiej implantowanym urządzeniem [18 mm (14-20.5) vs. 8 mm (5-11); $p < 0.001$]. Wszystkie skrzepliny uległy całkowitej rezolucji po leczeniu LMWH, co zostało potwierdzone kontrolnym TEE. W trakcie leczenia LMWH nie wystąpiło żadne zdarzenie niepożądane.

W trzeciej pracy przeprowadzono szczegółową analizę LAAC z wykorzystaniem urządzenia WATCHMAN. Przedstawiono rodzaje urządzenia oraz ich różnice. W publikacji zebrano i podsumowano dane dotyczące skuteczności i bezpieczeństwa omawianej terapii. Ponadto na podstawie zebranych danych omówiono różne formy farmakoterapii pozabiegowej, oraz ewentualne powikłania zabiegu i sposoby ich leczenia. Z aktualnego piśmiennictwa wynika, że metoda LAAC z wykorzystaniem urządzenia WATCHMAN jest bezpieczną i skuteczną alternatywą dla OAC u pacjentów z przeciwwskazaniami do długotrwałej terapii przeciwkrzepliwej. Przedstawione zestawienie wielu wyników badań i rejestrów dotyczące leczenia przeciwzakrzepowego po zabiegu jest szczególnie istotne z uwagi na fakt, że dotychczas nie przedstawiono jednoznacznych zaleceń odnośnie takiego leczenia. Eksperci podkreślają, że u każdego chorego wymagana jest indywidualizacja leczenia. Powyższe podsumowanie może stanowić użyteczne narzędzie w codziennej praktyce klinicznej.

Najważniejsze wnioski:

- Zabieg LAAC z wykorzystaniem urządzenia WATCHMAN wydaje się być skuteczną i bezpieczną metodą prewencji udaru mózgu u pacjentów z niezastawkowym AF, a bezpieczeństwo metody rośnie wraz z doświadczeniem operatora.
- Podwójne leczenie przeciwplatekcyjne po implantacji okludera WATCHMAN wydaje się być skuteczne i bezpieczne w grupie chorych z wysokim ryzykiem zakrzepowo-zatorowym i wysokim ryzykiem krwawienia. Większe, wieloośrodkowe, randomizowane badania są potrzebne w celu potwierdzenia tych wyników.

- Istnieją czynniki związane z pacjentem oraz techniką zabiegu, które mają wpływ na powstanie DRT po skutecznej implantacji okludera WATCHMAN. W ramach indywidualizacji leczenia, uwzględnienie predyktorów wystąpienia DRT wydaje się być słuszne przy doborze odpowiedniej farmakoterapii pozabiegowej.

8. Piśmiennictwo.

1. Sagris M, Vardas EP, Theofilis P, Antonopoulos AS, Oikonomou E, Tousoulis D. Atrial Fibrillation: Pathogenesis, Predisposing Factors, and Genetics. *Int J Mol Sci*. 2021 Dec 21;23(1):6.
2. Rogers PA, Bernard ML, Madias C, Thihalolipavan S, Mark Estes NA 3rd, Morin DP. Current Evidence-Based Understanding of the Epidemiology, Prevention, and Treatment of Atrial Fibrillation. *Curr Probl Cardiol*. 2018 Jun;43(6):241-283.
3. Kornej J, Börschel CS, Benjamin EJ, Schnabel RB. Epidemiology of Atrial Fibrillation in the 21st Century: Novel Methods and New Insights. *Circ Res*. 2020 Jun 19;127(1):4-20.
4. Van Gelder IC, Rienstra M, Bunting KV, Casado-Arroyo R, Caso V, Crijns HJGM, De Potter TJR, Dwight J, Guasti L, Hanke T, Jaarsma T, Lettino M, Løchen ML, Lumbers RT, Maesen B, Mølgaard I, Rosano GMC, Sanders P, Schnabel RB, Suwalski P, Svennberg E, Tamargo J, Tica O, Traykov V, Tzeis S, Kotecha D; ESC Scientific Document Group. 2024 ESC Guidelines for the management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS). *Eur Heart J*. 2024 Sep 29;45(36):3314-3414.
5. Merella P, Lorenzoni G, Delitala AP, Sechi F, Decandia F, Viola G, Berne P, Deiana G, Mazzone P, Casu G. Left Atrial Appendage Occlusion in High Bleeding Risk Patients. *J Interv Cardiol*. 2019 Feb 18;2019:6704031.
6. Magdi M, Renjithal SLM, Mubasher M, Mostafa MR, Lathwal Y, Mukuntharaj P, Mohamed S, Alweis R, Tan BE, Baibhav B. The WATCHMAN device and post-implantation anticoagulation management. A review of key studies and the risk of device-related thrombosis. *Am J Cardiovasc Dis*. 2021 Dec 15;11(6):714-722.
7. Scheitz JF, Nolte CH, Doehner W, Hachinski V, Endres M. Stroke-heart syndrome: clinical presentation and underlying mechanisms. *Lancet Neurol*. 2018 Dec;17(12):1109-1120.

8. Sposato LA, Chaturvedi S, Hsieh CY, Morillo CA, Kamel H. Atrial Fibrillation Detected After Stroke and Transient Ischemic Attack: A Novel Clinical Concept Challenging Current Views. *Stroke*. 2022 Mar;53(3):e94-e103.
9. Kamel H, Okin PM, Elkind MS, Iadecola C. Atrial Fibrillation and Mechanisms of Stroke: Time for a New Model. *Stroke*. 2016 Mar;47(3):895-900.
10. Hart RG, Pearce LA, Aguilar MI. Meta-analysis: antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation. *Ann Intern Med*. 2007 Jun 19;146(12):857-67.
11. Potpara T, Grygier M, Häusler KG, Nielsen-Kudsk JE, Berti S, Genovesi S, Marijon E, Boveda S, Tzikas A, Boriani G, Boersma LVA, Tondo C, De Potter T, Lip GYH, Schnabel RB, Bauersachs R, Senzolo M, Basile C, Bianchi S, Osmancik P, Schmidt B, Landmesser U, Döhner W, Hindricks G, Kovac J, Camm AJ. Practical guide on left atrial appendage closure for the non-implanting physician: an international consensus paper. *Europace*. 2024 Mar 30;26(4):euae035.
12. Ruff CT, Giugliano RP, Braunwald E, Hoffman EB, Deenadayalu N, Ezekowitz MD, Camm AJ, Weitz JI, Lewis BS, Parkhomenko A, Yamashita T, Antman EM. Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials. *Lancet*. 2014 Mar 15;383(9921):955-62.
13. Blackshear JL, Odell JA. Appendage obliteration to reduce stroke in cardiac surgical patients with atrial fibrillation. *Ann Thorac Surg*. 1996 Feb;61(2):755-9.
14. Holmes DR Jr, Alkhouli M. The History of the Left Atrial Appendage Occlusion. *Card Electrophysiol Clin*. 2020 Mar;12(1):1-11.
15. Cresti A, García-Fernández MA, Sievert H, Mazzone P, Baratta P, Solari M, Geyer A, De Sensi F, Limbruno U. Prevalence of extra-appendage thrombosis in non-valvular atrial fibrillation and atrial flutter in patients undergoing cardioversion: a large transoesophageal echo study. *EuroIntervention*. 2019 Jun 12;15(3):e225-e230.

16. Holmes DR, Reddy VY, Turi ZG, Doshi SK, Sievert H, Buchbinder M, Mullin CM, Sick P; PROTECT AF Investigators. Percutaneous closure of the left atrial appendage versus warfarin therapy for prevention of stroke in patients with atrial fibrillation: a randomised non-inferiority trial. *Lancet*. 2009 Aug 15;374(9689):534-42.
17. Holmes DR Jr, Kar S, Price MJ, Whisenant B, Sievert H, Doshi SK, Huber K, Reddy VY. Prospective randomized evaluation of the Watchman Left Atrial Appendage Closure device in patients with atrial fibrillation versus long-term warfarin therapy: the PREVAIL trial. *J Am Coll Cardiol*. 2014 Jul 8;64(1):1-12.
18. Reddy VY, Doshi SK, Kar S, Gibson DN, Price MJ, Huber K, Horton RP, Buchbinder M, Neuzil P, Gordon NT, Holmes DR Jr; PREVAIL and PROTECT AF Investigators. 5-Year Outcomes After Left Atrial Appendage Closure: From the PREVAIL and PROTECT AF Trials. *J Am Coll Cardiol*. 2017 Dec 19;70(24):2964-2975.
19. Osmancik P, Herman D, Neuzil P, Hala P, Taborsky M, Kala P, Poloczek M, Stasek J, Haman L, Branny M, Chovancik J, Cervinka P, Holy J, Kovarnik T, Zemanek D, Havranek S, Vancura V, Peichl P, Tousek P, Lekesova V, Jarkovsky J, Novackova M, Benesova K, Widimsky P, Reddy VY; PRAGUE-17 Trial Investigators. 4-Year Outcomes After Left Atrial Appendage Closure Versus Nonwarfarin Oral Anticoagulation for Atrial Fibrillation. *J Am Coll Cardiol*. 2022 Jan 4;79(1):1-14.
20. Boersma LV, Schmidt B, Betts TR, Sievert H, Tamburino C, Teiger E, Pokushalov E, Kische S, Schmitz T, Stein KM, Bergmann MW; EWOLUTION investigators. Implant success and safety of left atrial appendage closure with the WATCHMAN device: peri-procedural outcomes from the EWOLUTION registry. *Eur Heart J*. 2016 Aug;37(31):2465-74.
21. Doshi SK, Kar S, Sadhu A, Horton R, Osorio J, Ellis C, Stone J Jr, Shah M, Dukkipati SR, Adler S, Nair DG, Kim J, Wazni O, Price MJ, Holmes DR Jr, Shipley R, Christen T, Allocco DJ, Reddy VY; PINNACLE FLX investigators [Link]. Two-Year Outcomes With a

- Next-Generation Left Atrial Appendage Device: Final Results of the PINNACLE FLX Trial. *J Am Heart Assoc.* 2023 Feb 21;12(4):e026295.
22. Waranugraha Y, Lin LY, Tsai CT. Head-to-head comparison between left atrial appendage occlusion and non-vitamin K oral anticoagulants in non-valvular atrial fibrillation patients: A systematic review and meta-analysis study. *Trends Cardiovasc Med.* 2024 May;34(4):225-233.
 23. Shrestha B, Poudel B, Poudel D, Diaz Fraga J. National Yearly Trend of Utilization and Procedural Complication of the Watchman Device in the United States. *Cureus.* 2022 Jun 1;14(6):e25567.
 24. Boriani G, Proietti M, Laroche C, Fauchier L, Marin F, Nabauer M, Potpara T, Dan GA, Kalarus Z, Tavazzi L, Maggioni AP, Lip GYH; EORP-AF Long-Term General Registry Investigators. Association between antithrombotic treatment and outcomes at 1-year follow-up in patients with atrial fibrillation: the EORP-AF General Long-Term Registry. *Europace.* 2019 Jul 1;21(7):1013-1022.
 25. Glikson M, Wolff R, Hindricks G, Mandrola J, Camm AJ, Lip GYH, Fauchier L, Betts TR, Lewalter T, Saw J, Tzikas A, Sternik L, Nietlispach F, Berti S, Sievert H, Bertog S, Meier B; ESC Scientific Document Group. EHRA/EAPCI expert consensus statement on catheter-based left atrial appendage occlusion - an update. *Europace.* 2020 Feb 1;22(2):184.
 26. Freeman JV, Higgins AY, Wang Y, Du C, Friedman DJ, Daimee UA, Minges KE, Pereira L, Goldsweig AM, Price MJ, Reddy VY, Gibson D, Doshi SK, Varosy PD, Masoudi FA, Curtis JP. Antithrombotic Therapy After Left Atrial Appendage Occlusion in Patients With Atrial Fibrillation. *J Am Coll Cardiol.* 2022 May 10;79(18):1785-1798.
 27. Garg J, Shah S, Shah K, Turagam MK, Tzou W, Natale A, Lakkireddy D. Direct Oral Anticoagulant Versus Warfarin for Watchman Left Atrial Appendage Occlusion-Systematic Review: Electram Investigators. *JACC Clin Electrophysiol.* 2020 Dec 14;6(13):1735-1737.

28. Patti G, Sticchi A, Verolino G, Pasceri V, Vizzi V, Brscic E, Casu G, Golino P, Russo V, Rapacciuolo A, Boccuzzi G, Mangieri A, Pagnotta PA, Colombo A; A list of study collaborators can be found in the Appendix. Safety and Efficacy of Single Versus Dual Antiplatelet Therapy After Left Atrial Appendage Occlusion. *Am J Cardiol*. 2020 Nov 1;134:83-90.
29. Søndergaard L, Wong YH, Reddy VY, Boersma LVA, Bergmann MW, Doshi S, Kar S, Sievert H, Wehrenberg S, Stein K, Holmes DR Jr. Propensity-Matched Comparison of Oral Anticoagulation Versus Antiplatelet Therapy After Left Atrial Appendage Closure With WATCHMAN. *JACC Cardiovasc Interv*. 2019 Jun 10;12(11):1055-1063.
30. Freeman JV, Varosy P, Price MJ, Slotwiner D, Kusumoto FM, Rammohan C, Kavinsky CJ, Turi ZG, Akar J, Koutras C, Curtis JP, Masoudi FA. The NCDR Left Atrial Appendage Occlusion Registry. *J Am Coll Cardiol*. 2020 Apr 7;75(13):1503-1518.
31. Cruz-González I, Korsholm K, Trejo-Velasco B, Thambo JB, Mazzone P, Rioufol G, Grygier M, Möbius-Winkler S, Betts T, Meincke F, Sandri M, Schmidt B, Schmitz T, Nielsen-Kudsk JE. Procedural and Short-Term Results With the New Watchman FLX Left Atrial Appendage Occlusion Device. *JACC Cardiovasc Interv*. 2020 Dec 14;13(23):2732-2741.
32. Reddy VY, Doshi SK, Sievert H, Buchbinder M, Neuzil P, Huber K, Halperin JL, Holmes D; PROTECT AF Investigators. Percutaneous left atrial appendage closure for stroke prophylaxis in patients with atrial fibrillation: 2.3-Year Follow-up of the PROTECT AF (Watchman Left Atrial Appendage System for Embolic Protection in Patients with Atrial Fibrillation) Trial. *Circulation*. 2013 Feb 12;127(6):720-9.
33. Bergmann MW, Betts TR, Sievert H, Schmidt B, Pokushalov E, Kische S, Schmitz T, Meincke F, Stein KM, Boersma LVA, Ince H. Safety and efficacy of early anticoagulation drug regimens after WATCHMAN left atrial appendage closure: three-month data from the

- EWOLUTION prospective, multicentre, monitored international WATCHMAN LAA closure registry. *EuroIntervention*. 2017 Sep 20;13(7):877-884.
34. Korsholm K, Nielsen KM, Jensen JM, Jensen HK, Andersen G, Nielsen-Kudsk JE. Transcatheter left atrial appendage occlusion in patients with atrial fibrillation and a high bleeding risk using aspirin alone for post-implant antithrombotic therapy. *EuroIntervention*. 2017 Apr 20;12(17):2075-2082.
 35. Kar S, Doshi SK, Sadhu A, Horton R, Osorio J, Ellis C, Stone J Jr, Shah M, Dukkipati SR, Adler S, Nair DG, Kim J, Wazni O, Price MJ, Asch FM, Holmes DR Jr, Shipley RD, Gordon NT, Allocco DJ, Reddy VY; PINNACLE FLX Investigators. Primary Outcome Evaluation of a Next-Generation Left Atrial Appendage Closure Device: Results From the PINNACLE FLX Trial. *Circulation*. 2021 May 4;143(18):1754-1762.
 36. Paitazoglou C, Bergmann MW, Ince H, Kische S, Romanov A, Schmitz T, Schmidt B, Gori T, Meincke F, Protopopov AV, Betts T, Vireca E, Wohlmuth P, Boersma L; theEWOLUTION Investigators. True Efficacy of LAA Closure: Patient Outcomes on Long-term Single-Antiplatelet or No Therapy: Insights From the EWOLUTION Registry. *J Invasive Cardiol*. 2022 May;34(5):E348-E355.
 37. Simard T, Jung RG, Lehenbauer K, Piayda K, Pracoń R, Jackson GG, Flores-Umanzor E, Faroux L, Korsholm K, Chun JKR, Chen S, Maarse M, Montrella K, Chaker Z, Spoon JN, Pastormerlo LE, Meincke F, Sawant AC, Moldovan CM, Qintar M, Aktas MK, Branca L, Radinovic A, Ram P, El-Zein RS, Flautt T, Ding WY, Sayegh B, Benito-González T, Lee OH, Badejoko SO, Paitazoglou C, Karim N, Zaghloul AM, Agrawal H, Kaplan RM, Alli O, Ahmed A, Suradi HS, Knight BP, Alla VM, Panaich SS, Wong T, Bergmann MW, Chothia R, Kim JS, Pérez de Prado A, Bazaz R, Gupta D, Valderrabano M, Sanchez CE, El Chami MF, Mazzone P, Adamo M, Ling F, Wang DD, O'Neill W, Wojakowski W, Pershad A, Berti S, Spoon D, Kawsara A, Jabbour G, Boersma LVA, Schmidt B, Nielsen-Kudsk JE, Rodés-Cabau J, Freixa X, Ellis CR, Fauchier L, Demkow M, Sievert H, Main ML, Hibbert

- B, Holmes DR Jr, Alkhouli M. Predictors of Device-Related Thrombus Following Percutaneous Left Atrial Appendage Occlusion. *J Am Coll Cardiol*. 2021 Jul 27;78(4):297-313.
38. Pracon R, Bangalore S, Dzielinska Z, Konka M, Kepka C, Kruk M, Kaczmarska-Dyrda E, Petryka-Mazurkiewicz J, Bujak S, Solecki M, Pskit A, Dabrowska A, Sieradzki B, Plonski A, Ruzyllo W, Witkowski A, Demkow M. Device Thrombosis After Percutaneous Left Atrial Appendage Occlusion Is Related to Patient and Procedural Characteristics but Not to Duration of Postimplantation Dual Antiplatelet Therapy. *Circ Cardiovasc Interv*. 2018 Mar;11(3):e005997.

9. Opinia Komisji Bioetycznej lub Etycznej.

Badanie retrospektywne - nie dotyczy.

10. Oświadczenia współautorów.

Warszawa, 20.12.2024 r.

prof. dr hab. n. med. Agnieszka Kapłon-Cieślicka

OŚWIADCZENIE

Jako współautor pracy pt. "Safety and efficacy of percutaneous atrial appendage closure followed by antiplatelet therapy in a high-risk population: single-center experience with a WATCHMAN device." oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji stanowi: opracowanie koncepcji i przygotowanie manuskryptu.

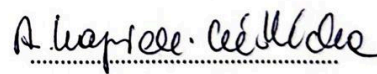
Mój udział procentowy w przygotowaniu publikacji określám jako 1%.

Wkład Jakuba Maksyma w powstanie publikacji określám jako 65%,

obejmował on: opracowanie koncepcji, przegląd piśmiennictwa, stworzenie bazy danych, analizę zebranych danych, interpretację wyników i sformułowanie wniosków, przygotowanie manuskryptu.

Jednocześnie wyrażam zgodę na wykorzystanie w/w pracy jako część rozprawy doktorskiej lek.

Jakuba Maksyma



(podpis oświadczającego)

Warszawa, 20.12.2024 r.

dr hab. n. med. Piotr Scisło

OŚWIADCZENIE

Jako współautor pracy pt. "Safety and efficacy of percutaneous atrial appendage closure followed by antiplatelet therapy in a high-risk population: single-center experience with a WATCHMAN device." oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji stanowi: opracowanie koncepcji i przygotowanie manuskryptu.

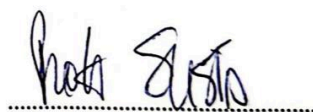
Mój udział procentowy w przygotowaniu publikacji określłam jako 1%.

Wkład Jakuba Maksyma w powstanie publikacji określłam jako 65%,

obejmował on: opracowanie koncepcji, przegląd piśmiennictwa, stworzenie bazy danych, analizę zebranych danych, interpretację wyników i sformułowanie wniosków, przygotowanie manuskryptu.

Jednocześnie wyrażam zgodę na wykorzystanie w/w pracy jako część rozprawy doktorskiej lek.

Jakuba Maksyma



(podpis oświadczającego)

Warszawa, 20.12.2024 r.

prof. dr hab. n. med. Zenon Huczek

OŚWIADCZENIE

Jako współautor pracy pt. "Safety and efficacy of percutaneous atrial appendage closure followed by antiplatelet therapy in a high-risk population: single-center experience with a WATCHMAN device." oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji stanowi: opracowanie koncepcji i przygotowanie manuskryptu.

Mój udział procentowy w przygotowaniu publikacji określám jako 1%.

Wkład Jakuba Maksyma w powstanie publikacji określám jako 65%,

obejmował on: opracowanie koncepcji, przegląd piśmiennictwa, stworzenie bazy danych, analizę zebranych danych, interpretację wyników i sformułowanie wniosków, przygotowanie manuskryptu.

Jednocześnie wyrażam zgodę na wykorzystanie w/w pracy jako część rozprawy doktorskiej lek. Jakuba Maksyma



(podpis oświadczającego)

Warszawa, 20.12.2024 r.

dr hab. n. med. Michał Marchel

OŚWIADCZENIE

Jako współautor pracy pt. "Safety and efficacy of percutaneous atrial appendage closure followed by antiplatelet therapy in a high-risk population: single-center experience with a WATCHMAN device." oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji stanowi: opracowanie koncepcji i przygotowanie manuskryptu.

Mój udział procentowy w przygotowaniu publikacji określam jako 1%.

Wkład Jakuba Maksyma w powstanie publikacji określam jako 65%,

obejmował on: opracowanie koncepcji, przegląd piśmiennictwa, stworzenie bazy danych, analizę zebranych danych, interpretację wyników i sformułowanie wniosków, przygotowanie manuskryptu.

Jednocześnie wyrażam zgodę na wykorzystanie w/w pracy jako część rozprawy doktorskiej lek Jakuba Maksyma

dr hab. n. med. MICHAŁ MARCHEL
specjalista chorób wewnętrznych
KARDIOLOG
18821/22

(podpis oświadczającego)

Warszawa, 20.12.2024 r.

dr hab. n. med. Radosław Piątkowski

OŚWIADCZENIE

Jako współautor pracy pt. "Safety and efficacy of percutaneous atrial appendage closure followed by antiplatelet therapy in a high-risk population: single-center experience with a WATCHMAN device." oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji stanowi: opracowanie koncepcji i przygotowanie manuskryptu.

Mój udział procentowy w przygotowaniu publikacji określłam jako 1%.

Wkład Jakuba Maksyma w powstanie publikacji określłam jako 65%,

obejmował on: opracowanie koncepcji, przegląd piśmiennictwa, stworzenie bazy danych, analizę zebranych danych, interpretację wyników i sformułowanie wniosków, przygotowanie manuskryptu.

Jednocześnie wyrażam zgodę na wykorzystanie w/w pracy jako część rozprawy doktorskiej lek.

Jakuba Maksyma



(podpis oświadczającego)

Warszawa, 20.12.2024 r.

prof. dr hab. n. med. Janusz Kochman

OŚWIADCZENIE

Jako współautor pracy pt. "Safety and efficacy of percutaneous atrial appendage closure followed by antiplatelet therapy in a high-risk population: single-center experience with a WATCHMAN device." oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji stanowi: opracowanie koncepcji i przygotowanie manuskryptu.

Mój udział procentowy w przygotowaniu publikacji określám jako 1%.

Wkład Jakuba Maksyma w powstanie publikacji określám jako 65%,

obejmował on: opracowanie koncepcji, przegląd piśmiennictwa, stworzenie bazy danych, analizę zebranych danych, interpretację wyników i sformułowanie wniosków, przygotowanie manuskryptu.

Jednocześnie wyrażam zgodę na wykorzystanie w/w pracy jako część rozprawy doktorskiej lek. Jakuba Maksyma

Prof. dr hab. n. med. Janusz Kochman
Specjalista chorób wewnętrznych
KARDIOLOG
1716459

.....
(podpis oświadczającego)

Warszawa, 20.12.2024 r.

prof. dr hab. n. med. Grzegorz Opolski

OŚWIADCZENIE

Jako współautor pracy pt. "Safety and efficacy of percutaneous atrial appendage closure followed by antiplatelet therapy in a high-risk population: single-center experience with a WATCHMAN device." oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji stanowi: opracowanie koncepcji i przygotowanie manuskryptu.

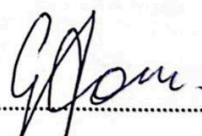
Mój udział procentowy w przygotowaniu publikacji określam jako 1%.

Wkład Jakuba Maksyma w powstanie publikacji określam jako 65%,

obejmował on: opracowanie koncepcji, przegląd piśmiennictwa, stworzenie bazy danych, analizę zebranych danych, interpretację wyników i sformułowanie wniosków, przygotowanie manuskryptu.

Jednocześnie wyrażam zgodę na wykorzystanie w/w pracy jako część rozprawy doktorskiej lek.

Jakuba Maksyma

.....

(podpis oświadczającego)

Warszawa, 20.12.2024 r.

prof. dr hab. n. med. Marcin Grabowski

OŚWIADCZENIE

Jako współautor pracy pt. "Safety and efficacy of percutaneous atrial appendage closure followed by antiplatelet therapy in a high-risk population: single-center experience with a WATCHMAN device." oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji stanowi: opracowanie koncepcji i przygotowanie manuskryptu.

Mój udział procentowy w przygotowaniu publikacji określam jako 1%.

Wkład Jakuba Maksyma w powstanie publikacji określam jako 65%,

obejmował on: opracowanie koncepcji, przegląd piśmiennictwa, stworzenie bazy danych, analizę zebranych danych, interpretację wyników i sformułowanie wniosków, przygotowanie manuskryptu.

Jednocześnie wyrażam zgodę na wykorzystanie w/w pracy jako część rozprawy doktorskiej lek.

Jakuba Maksyma

KIEROWNIK
Klinika Kardiologii
Centralny Szpital Kliniczny UCK WUM
prof. dr hab. n. med. Marcin Grabowski

(podpis oświadczającego)

Warszawa, 20.12.2024 r.

dr hab. n. med. Tomasz Mazurek

OŚWIADCZENIE

Jako współautor pracy pt. "Safety and efficacy of percutaneous atrial appendage closure followed by antiplatelet therapy in a high-risk population: single-center experience with a WATCHMAN device." oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji stanowi: opracowanie koncepcji, interpretację wyników i sformułowanie wniosków, przygotowanie manuskryptu.

Mój udział procentowy w przygotowaniu publikacji określłam jako 27%.

Wkład Jakuba Maksyma w powstanie publikacji określłam jako 65%,

obejmował on: opracowanie koncepcji, przegląd piśmiennictwa, stworzenie bazy danych, analizę zebranych danych, interpretację wyników i sformułowanie wniosków, przygotowanie manuskryptu.

Jednocześnie wyrażam zgodę na wykorzystanie w/w pracy jako część rozprawy doktorskiej lek. Jakuba Maksyma

dr hab. n. med. Tomasz Mazurek
specjalista chorób wewnętrznych
KARDIOLOG

(podpis oświadczającego)

Warszawa, 20.12.2024 r.

dr hab. n. med. Piotr Scisło

OŚWIADCZENIE

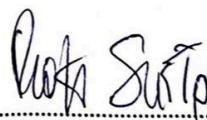
Jako współautor pracy pt. "Incidence and predictors of device-related thrombus after left atrial appendage closure with Watchman device." oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji stanowi: opracowanie koncepcji i przygotowanie manuskryptu.

Mój udział procentowy w przygotowaniu publikacji określam jako 1%.

Wkład Jakuba Maksyma w powstanie publikacji określam jako 70%,

obejmował on: opracowanie koncepcji, przegląd piśmiennictwa, stworzenie bazy danych, analizę zebranych danych, interpretację wyników i sformułowanie wniosków, przygotowanie manuskryptu.

Jednocześnie wyrażam zgodę na wykorzystanie w/w pracy jako część rozprawy doktorskiej lek. Jakuba Maksyma



(podpis oświadczającego)

Warszawa, 20.12.2024 r.

prof. dr hab. n. med. Agnieszka Kapłon-Cieślicka

OŚWIADCZENIE

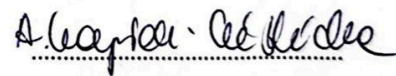
Jako współautor pracy pt. "Incidence and predictors of device-related thrombus after left atrial appendage closure with Watchman device." oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji stanowi: opracowanie koncepcji i przygotowanie manuskryptu.

Mój udział procentowy w przygotowaniu publikacji określłam jako 1%.

Wkład Jakuba Maksyma w powstanie publikacji określłam jako 70%,

obejmował on: opracowanie koncepcji, przegląd piśmiennictwa, stworzenie bazy danych, analizę zebranych danych, interpretację wyników i sformułowanie wniosków, przygotowanie manuskryptu.

Jednocześnie wyrażam zgodę na wykorzystanie w/w pracy jako część rozprawy doktorskiej lek. Jakuba Maksyma



(podpis oświadczającego)

Warszawa, 20.12.2024 r.

prof. dr hab. n. med. Zenon Huczek

OŚWIADCZENIE

Jako współautor pracy pt. "Incidence and predictors of device-related thrombus after left atrial appendage closure with Watchman device." oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji stanowi: opracowanie koncepcji i przygotowanie manuskryptu.

Mój udział procentowy w przygotowaniu publikacji określam jako 1%.

Wkład Jakuba Maksyma w powstanie publikacji określam jako 70%,

obejmował on: opracowanie koncepcji, przegląd piśmiennictwa, stworzenie bazy danych, analizę zebranych danych, interpretację wyników i sformułowanie wniosków, przygotowanie manuskryptu.

Jednocześnie wyrażam zgodę na wykorzystanie w/w pracy jako część rozprawy doktorskiej lek. Jakuba Maksyma



(podpis oświadczającego)

Warszawa, 20.12.2024 r.

dr hab. n. med. Michał Marchel

OŚWIADCZENIE

Jako współautor pracy pt. "Incidence and predictors of device-related thrombus after left atrial appendage closure with Watchman device." oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji stanowi: opracowanie koncepcji i przygotowanie manuskryptu.

Mój udział procentowy w przygotowaniu publikacji określam jako 1%.

Wkład Jakuba Maksyma w powstanie publikacji określam jako 70%,

obejmował on: opracowanie koncepcji, przegląd piśmiennictwa, stworzenie bazy danych, analizę zebranych danych, interpretację wyników i sformułowanie wniosków, przygotowanie manuskryptu.

Jednocześnie wyrażam zgodę na wykorzystanie w/w pracy jako część rozprawy doktorskiej lek. Jakuba Maksyma

dr hab. n. med. MICHAŁ MARCHEL
specjalista chorób wewnętrznych
KARDIOLOG
1882122

.....
(podpis oświadczającego)

Warszawa, 20.12.2024 r.

prof. dr hab. n. med. Janusz Kochman

OŚWIADCZENIE

Jako współautor pracy pt. "Incidence and predictors of device-related thrombus after left atrial appendage closure with Watchman device." oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji stanowi: opracowanie koncepcji i przygotowanie manuskryptu.

Mój udział procentowy w przygotowaniu publikacji określam jako 1%.

Wkład Jakuba Maksyma w powstanie publikacji określam jako 70%,

obejmował on: opracowanie koncepcji, przegląd piśmiennictwa, stworzenie bazy danych, analizę zebranych danych, interpretację wyników i sformułowanie wniosków, przygotowanie manuskryptu.

Jednocześnie wyrażam zgodę na wykorzystanie w/w pracy jako część rozprawy doktorskiej lek. Jakuba Maksyma

Prof. dr hab. n. med. Janusz Kochman
Specjalista chorób wewnętrznych
KARDIOLOG
7716450

.....
(podpis oświadczającego)

Warszawa, 20.12.2024 r.

dr n. med. Karol Zbroński

OŚWIADCZENIE

Jako współautor pracy pt. "Incidence and predictors of device-related thrombus after left atrial appendage closure with Watchman device." oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji stanowi: opracowanie koncepcji i przygotowanie manuskryptu.

Mój udział procentowy w przygotowaniu publikacji określłam jako 1%.

Wkład Jakuba Maksyma w powstanie publikacji określłam jako 70%,

obejmował on: opracowanie koncepcji, przegląd piśmiennictwa, stworzenie bazy danych, analizę zebranych danych, interpretację wyników i sformułowanie wniosków, przygotowanie manuskryptu.

Jednocześnie wyrażam zgodę na wykorzystanie w/w pracy jako część rozprawy doktorskiej lek. Jakuba Maksyma



(podpis oświadczającego)

Warszawa, 20.12.2024 r.

prof. dr hab. n. med. Grzegorz Opolski

OŚWIADCZENIE

Jako współautor pracy pt. "Incidence and predictors of device-related thrombus after left atrial appendage closure with Watchman device." oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji stanowi: opracowanie koncepcji i przygotowanie manuskryptu.

Mój udział procentowy w przygotowaniu publikacji określam jako 1%.

Wkład Jakuba Maksyma w powstanie publikacji określam jako 70%,

obejmował on: opracowanie koncepcji, przegląd piśmiennictwa, stworzenie bazy danych, analizę zebranych danych, interpretację wyników i sformułowanie wniosków, przygotowanie manuskryptu.

Jednocześnie wyrażam zgodę na wykorzystanie w/w pracy jako część rozprawy doktorskiej lek. Jakuba Maksyma



(podpis oświadczającego)

Warszawa, 20.12.2024 r.

prof. dr hab. n. med. Marcin Grabowski

OŚWIADCZENIE

Jako współautor pracy pt. "Incidence and predictors of device-related thrombus after left atrial appendage closure with Watchman device." oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji stanowi: opracowanie koncepcji i przygotowanie manuskryptu.

Mój udział procentowy w przygotowaniu publikacji określam jako 1%.

Wkład Jakuba Maksyma w powstanie publikacji określam jako 70%,

obejmował on: opracowanie koncepcji, przegląd piśmiennictwa, stworzenie bazy danych, analizę zebranych danych, interpretację wyników i sformułowanie wniosków, przygotowanie manuskryptu.

Jednocześnie wyrażam zgodę na wykorzystanie w/w pracy jako część rozprawy doktorskiej lek.

Jakuba Maksyma

KIEROWNIK
Klinika Kardiologii
Centralny Szpital Kliniczny UCK WUM

.....prof. dr hab. n. med. Marcin Grabowski

(podpis oświadczającego)

Warszawa, 20.12.2024 r.

dr hab. n. med. Tomasz Mazurek

OŚWIADCZENIE

Jako współautor pracy pt. "Incidence and predictors of device-related thrombus after left atrial appendage closure with Watchman device." oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji stanowi: opracowanie koncepcji, interpretację wyników i sformułowanie wniosków, przygotowanie manuskryptu.

Mój udział procentowy w przygotowaniu publikacji określam jako 22 %.

Wkład Jakuba Maksyma w powstanie publikacji określam jako 70%,

obejmował on: opracowanie koncepcji, przegląd piśmiennictwa, stworzenie bazy danych, analizę zebranych danych, interpretację wyników i sformułowanie wniosków, przygotowanie manuskryptu.

Jednocześnie wyrażam zgodę na wykorzystanie w/w pracy jako część rozprawy doktorskiej lek.

Jakuba Maksyma

dr hab. n. med. Tomasz Mazurek
specjalista chorób wewnętrznych
KARDIOLOG
.....8479996.....

(podpis oświadczającego)

Warszawa, 20.12.2024 r.

prof. dr hab. n. med. Marcin Grabowski

OŚWIADCZENIE

Jako współautor pracy pt. "Percutaneous left atrial appendage closure with the Watchman device: a systematic review." oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji stanowi: opracowanie koncepcji i przygotowanie manuskryptu.

Mój udział procentowy w przygotowaniu publikacji określłam jako 1%.

Wkład Jakuba Maksyma w powstanie publikacji określłam jako 70%,

obejmował on: opracowanie koncepcji, przegląd piśmiennictwa, stworzenie bazy danych, analizę zebranych danych, interpretację wyników i sformułowanie wniosków, przygotowanie manuskryptu.

Jednocześnie wyrażam zgodę na wykorzystanie w/w pracy jako część rozprawy doktorskiej lek. Jakuba Maksyma

KIEROWNIK
Klinika Kardiologii
Centralny Szpital Kliniczny UCK WUM
prof. dr hab. n. med. Marcin Grabowski

(podpis oświadczającego)

Warszawa, 20.12.2024 r.

dr hab. n. med. Tomasz Mazurek

OŚWIADCZENIE

Jako współautor pracy pt. "Percutaneous left atrial appendage closure with the Watchman device: a systematic review." oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji stanowi: opracowanie koncepcji, przygotowanie manuskryptu.

Mój udział procentowy w przygotowaniu publikacji określłam jako 19 %.

Wkład Jakuba Maksyma w powstanie publikacji określłam jako 80%,

obejmował on: opracowanie koncepcji, przegląd piśmiennictwa, analizę zebranych danych, sformułowanie wniosków, przygotowanie manuskryptu.

Jednocześnie wyrażam zgodę na wykorzystanie w/w pracy jako część rozprawy doktorskiej lek.

Jakuba Maksyma

dr hab. n. med. Tomasz Mazurek
Specjalista chorób wewnętrznych
KARDIOLOG
8479996

(podpis oświadczającego)