lek. Monika Maria Gawałko

Migotanie przedsionków i wybrane choroby współistniejące

Rozprawa na stopień doktora nauk medycznych i nauk o zdrowiu
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1. Wykaz stosowanych skrótów

AF, *atrial fibrillation* = migotanie przedsionków

CAD*, coronary artery disease* = choroba wieńcowa

DAPT*, dual antiplatelet therapy* = podwójna terapia przeciwpłytkowa

ESC, *European Society of Cardiology* = Europejskie Towarzystwo Kardiologiczne

HF, *heart failure* = niewydolność serca

ICS*, ischemic stroke* = udar niedokrwienny mózgu

LAAV, *left atrial appendage emptying velocity* = prędkośc opróżniana uszka lewego przedsionka

OAC*, oral anticoagulation* = doustna terapia przeciwkrzepliwa

NOAC*, non-vitamin K oral anticoagulants* = doustny antykoagulant niebędący antagonistą witaminy K

PAD*, peripheral artery disease* = choroba tętnic obwodowych

TEE, *transoesophageal echocardiography* = echokardiografia przezprzełykowa

VD, *vascular disease* = choroba naczyniowa

VKA, *vitamin K antagonist* = antagonista witaminy K

2. Streszczenie w języku polskim

Zgodnie z wytycznymi Europejskiego Towarzystwa Kardiologicznego (*European Society of Cardiology*, ESC) z 2020 roku, rozpoznawanie i leczenie czynników ryzyka sercowo-naczyniowego i chorób współistniejących to jeden z trzech głównych filarów terapii migotania przedsionków (*atrial fibrillation*, AF). W Polsce brakuje dużych, wieloośrodkowych badań dotyczących wpływu chorób współistniejących na obraz kliniczny, ryzyko zakrzepowo-zatorowe i leczenie pacjentów z AF.

Celem niniejszej pracy była ocena częstości występowania wybranych chorób współistniejących – niewydolności serca (*heart failure*, HF) i choroby naczyniowej (*vascular disease*, VD) – u pacjentów z AF, charakterystyka kliniczna tych chorych i ocena stosowanej farmakoterapii, a także analiza zależności między ryzykiem wystąpienia skrzepliny w uszku lewego przedsionku, jego czynnością mechaniczną a chorobami współistniejącymi u pacjentów z AF.

Publikacja 1: VD u pacjentów z AF

W ramach prospektywnego, międzynarodowego rejestru EORP-AF Long-Term General Registry włączono 701 polskich pacjentów z AF. Chorobę naczyniową (VD), zdefiniowaną jako choroba wieńcowa (*coronary artery disease*, CAD) i/lub choroba tętnic obwodowych (*peripheral artery disease*, PAD) stwierdzono u 44% pacjentów z AF (tylko CAD u 31%, tylko PAD u 7.2%, współistnienie CAD i PAD u 5.9%). Występowanie VD było niezależnie związane ze starszym wiekiem, cukrzycą, hipercholesterolemią i HF. Wśród pacjentów z AF i VD, 96% było leczonych przeciwzakrzepowo (wśród nich potrójną terapię przeciwzakrzepową otrzymywało 11% chorych, podwójną terapię przeciwzakrzepową – 14%, doustne leczenie przeciwkrzepliwe [*oral anticoagulation*, OAC] – 63%, a leczenie przeciwpłytkowe – 8.6%) a 4.1% nie otrzymywało żadnej formy leczenia przeciwzakrzepowego. Stosowanie potrójnej terapii przeciwzakrzepowej było związane ze zwiększonym ryzykiem poważnych zdarzeń niepożądanych, w tym zgonu z jakiejkolwiek przyczyny, w porównaniu z pacjentami stosującymi tylko OAC lub OAC i jeden lek przeciwpłytkowy.

Publikacja 2: HF u pacjentów z AF

Do prospektywnego, wieloośrodkowego rejestru POL-AF włączono 3999 pacjentów z AF hospitalizowanych w 10 polskich ośrodkach kardiologicznych. Ponad 70% pacjentów miało rozpoznanie HF, z czego połowa – HF z zachowaną frakcją wyrzutową. Pacjenci ze

współistniejącą HF byli starsi, obciążeni większą liczbą chorób współistniejących i dwukrotnie częściej mieli utrwalone AF (34%) niż pacjenci bez HF (15%). Niemal jedna piąta pacjentów z AF i współistniejącą HF miała wywiad przebytego zdarzenia zakrzepowo-zatorowego. Mimo wskazań klasy I do OAC u 98% pacjentów z AF i współistniejącą HF, aż 16% z nich nie było leczonych przeciwkrzepliwie przed przyjęciem do szpitala. Do predyktorów nieprzyjmowania OAC przed przyjęciem do szpitala u pacjentów z AF i HF należały wiek powyżej ≥75 lat, przebyte zdarzenia krwotoczne, niedokrwistość i terapia przeciwpłytkowa. Spośród pacjentów z AF i HF nieleczonych przeciwkrzepliwie przed przyjęciem do szpitala, 63% otrzymało OAC (najczęściej apiksaban) przy wypisie. Aż 15% pacjentów z rozpoznaną HF z zachowaną frakcją wyrzutową otrzymało przy wypisie leki antyarytmiczne klasy I.

Publikacja 3: Choroby współistniejące a czynność mechaniczna uszka lewego przedsionka w AF

W ramach retrospektywnego, dwuośrodkowego rejestru włączono 1476 pacjentów z AF poddanych przezprzełykowemu badaniu echokardiograficznemu (*transesophageal echocardiography*, TEE) przed kardiowersją elektryczną AF lub ablacją podłoża AF. W trakcie TEE oceniano obecność skrzepliny w lewym przedsionku oraz czynność mechaniczną uszka lewego przedsionka przy pomocy pomiaru prędkości jego opróżniania (*left atrial appendage emptying velocity*, LAAV). Pacjenci zostali podzieleni na dwie grupy: z LAAV obniżoną <20 cm/s oraz z LAAV ≥20 cm/s. Częstość występowania skrzepliny w uszku lewego przedsionka była ponad czterokrotnie większa u pacjentów z obniżoną LAAV w porównaniu do pacjentów z LAAV ≥20 cm/s (20% vs 4.6%). W wieloczynnikowej analizie regresji logistycznej, nie-napadowe AF, HF i wiek ≥65 lat były predyktorami zarówno wystąpienia skrzepliny w uszku lewego przedsionka, jak i obniżonej LAAV, natomiast dysfunkcja nerek była predyktorem skrzepliny w lewym przedsionku, ale nie obniżonej LAAV.

Podsumowanie

W pracy wykorzystane zostały dane z dużych rejestrów wieloośrodkowych, co pozwala na wiarygodną ocenę rzeczywistego obrazu klinicznego współczesnych polskich pacjentów z AF. Niemal 44% chorych z AF ma współistniejącą VD, co wiąże się ze stosowaniem potrójnej terapii przeciwzakrzepowej u 11% z nich. Jednocześnie, stosowanie potrójnej terapii przeciwzakrzepowej było związane z wyższym ryzykiem zdarzeń

niepożądanych, w tym zgonu z dowolnej przyczyny. Ponadto wykazano, że u hospitalizowanych pacjentów z AF, HF występuje znacznie częściej niż to dotychczas raportowano, bo aż u 71% pacjentów, co wynika zapewne z objęcia analizą także chorych z HF z zachowaną frakcją wyrzutową. Mimo wskazań klasy I do OAC u 98% pacjentów z AF i towarzyszącą HF, aż jeden na sześciu chorych nie był leczony przeciwkrzepliwie przed przyjęciem do szpitala. Podobnie, jeden na sześciu pacjentów z HF z zachowaną frakcją wyrzutową otrzymywał leki antyarytmiczne klasy I, pomimo rozpoznania strukturalnej choroby serca. Powyższe wyniki pokazują rozbieżność między codzienną praktyką kliniczną a obowiązującymi wytycznymi. U pacjentów z AF, HF zwiększa ryzyko powstania skrzepliny w uszku lewego przedsionka m.in. poprzez upośledzenie jego czynności mechanicznej i związane z tym zaburzenia przepływu krwi, natomiast choroba nerek zwiększa ryzyko powstania skrzepliny w lewym przedsionku w mechanizmach innych niż zastój krwi.

3. Streszczenie w języku angielskim

Title: Atrial fibrillation and selected comorbidities

Screening and treatment of cardiovascular risk factors and comorbidities is one of the three main pillars of the treatment of AF. In Poland, there is a lack of multi-center, large-scale studies on the impact of comorbidities on the clinical picture, including the risk of thromboembolic events, as well as on the applied AF treatment. The aim of this study is to characterize, evaluate the pharmacotherapy in patients with AF and selected comorbidities, including heart failure (HF) and vascular disease (VD) as well as to analyze the relationship between the risk of a thrombus in the left atrial appendix, its mechanical function and comorbidities in patients with AF.

Publication 1: VD in patients with AF

Within the prospective international EORP-AF Long-Term General Registry, 701 Polish patients with AF were included. VD, defined as coronary artery disease (CAD) and/or peripheral artery disease (PAD), was found in 44% of patients with AF (CAD in 31%, PAD in 7.2%, CAD and PAD coexistence - in 5.9%). The occurrence of VD was independently associated with older age, diabetes, hypercholesterolaemia, and HF. Among patients with AF and VD, 96% were treated with antithrombotic treatment (triple antithrombotic therapy in 11%, dual antithrombotic therapy in 14%, oral anticoagulation [OAC] in 63% and antiplatelet therapy in 8.6%) and 4.1% of patients were not receiving ant form of antithrombotic treatment. Concomitant triple antithrombotic therapy was associated with an increased risk of major adverse events, including all-cause death, compared with patients using OAC alone or OAC and single antiplatelet agent.

Publication 2: HF in patients with AF

The prospective, multicenter registry POL-AF included 3999 patients with AF hospitalized in 10 Polish cardiology centers. Over 70% of patients had HF, half of them, HF with a preserved ejection fraction. Patients with concomitant HF were older, had more comorbidities, and had permanent AF twice as often (34%) than patients without HF (15%). Almost one fifth of patients with AF and coexisting HF had a history of a thromboembolic event. Despite class I indications for OAC in 98% of patients with AF and HF, as many as 16% of them did not receive OAC treatment on hospital admission. Predictors for not prescribing OAC at hospital admission included older age ($\geq$ 75 years), prior hemorrhagic events, anemia and antiplatelet therapy. Of patients with AF and HF not treated with OAC

prior to admission to hospital, 63% received OAC (most commonly apixaban) at discharge. As many as 15% of patients diagnosed with HF with preserved ejection fraction received class I antiarrhythmic drugs at discharge.

Publication 3: Comorbidities and mechanical function of the left atrial appendage in AF

A retrospective, two-center registry enrolled 1476 patients with AF who underwent transesophageal echocardiography (TEE) prior to AF ablation or electrical cardioversion. During TEE, the presence of a thrombus in the left atrium and the mechanical function of the left atrial appendage were assessed by measuring the velocity of its emptying (left atrial appendage emptying velocity, LAAV). Patients were divided according to the value of left atrial appendage velocity (LAAV <20 cm/s and ≥ 20 cm/s). The incidence of thrombus in the left atrial appendix was almost four times higher in patients with decreased LAAV compared to those with LAAV ≥ 20 cm/s (20% vs 4.6%). In multivariate logistic regression, non-paroxysmal AF, HF and age ≥ 65 years were predictors of both left atrial appendage thrombus and decreased LAAV, while renal dysfunction was a predictor of left atrial thrombus but not decreased LAAV.

Summary

The study used data from large multicentre registries, including Polish patients with AF. The collected data allow for a reliable assessment of the actual clinical picture of contemporary Polish patients with AF. Almost 44% of patients with AF have coexisting VD, which is associated with the use of triple anticoagulant therapy in 11% of them. At the same time, the use of triple anticoagulation therapy was associated with a higher risk of adverse events, including death from any cause. Moreover, it has been shown that in hospitalized patients with AF, HF occurs much more often than previously reported, in as many as 71% of patients, which is probably due to the analysis of patients with HF with a preserved ejection fraction. Despite class I indications for OAC in 98% of patients with AF and accompanying HF, as many as one in six patients was not treated with OAC prior to admission to the hospital. Similarly, one in six HF patients with a preserved ejection fraction received class I antiarrhythmic drugs despite a diagnosis of structural heart disease. The above results show a discrepancy between daily clinical practice and current guidelines. In patients with AF, HF increases the risk of thrombus formation in the left atrial appendage, by impaired mechanical function and related disturbances in blood flow, while kidney disease increases the risk of thrombus formation in the left atrium by mechanisms other than blood stasis.

4. Wstęp

4.1. Migotanie przedsionków – rozpowszechnienie i znaczenie kliniczne

Migotanie przedsionków (*atrial fibrillation*, AF) jest najczęstszym utrwalonym zaburzeniem rytmu serca wśród dorosłych. Pomimo znacznych postępów w zakresie diagnostyki i leczenia, w tym doustnej terapii przeciwkrzepliwej (*oral anticoagulation*, OAC), AF pozostaje jednym z najbardziej istotnych problemów klinicznych we współczesnej kardiologii. Częstość występowania AF zwiększa się z wiekiem, wynosząc od 2% w grupie wiekowej poniżej 65 roku życia do 9% u osób starszych (1). Szacuje się, że w Polsce AF dotyczy blisko 600 000 osób, a prognozy epidemiologiczne wskazują na podwojenie tej liczby w ciągu następnych dwóch dekad w związku ze starzeniem się populacji (2).

Występowanie AF wiąże się ze wzrostem śmiertelności: 2-krotnym u kobiet i 1,5-krotnym u mężczyzn (3). Najbardziej poważnym i niebezpiecznym powikłaniem AF jest udar niedokrwienny mózgu (*ischemic stroke,* ICS) (3). W trakcie epizodu AF, szybka i nieskoordynowana czynność elektryczna przedsionków skutkuje upośledzeniem ich funkcji skurczowej, powodując zwolnienie prędkości przepływu krwi w niektórych obszarach przedsionków, co sprzyja formowaniu się materiału zakrzepowego (4). AF stanowi 45-60% przyczyn ICS występującego na podłożu zatoru pochodzenia sercowego (5). Uważa się, że w ponad 90% materiał zakrzepowo-zatorowy pochodzi z uszka lewego przedsionka (6). Współczesne badania pokazują, że u 20–30% pacjentów z ICS, AF rozpoznano przed, w trakcie, lub na krótko po tym incydencie (7). W Europie z powodu ICS rocznie umiera 650 000 chorych, a częstość występowania ICS rośnie z wiekiem. ICS w następstwie AF ma gorsze rokowanie w porównaniu do ICS o innej etiologii. Szacuje się, że ICS jest trzecią co do częstości przyczyną zgonów na świecie i pierwszą co do częstości przyczyną długoterminowej, poważnej niesprawności, co sprawia, że jest to nie tylko bardzo istotny problem kliniczny, ale również społeczny i ekonomiczny. Ryzyko wystąpienia ICS u chorych z AF jest nawet 6-krotnie wyższe niż w grupie chorych bez tej arytmii. Nawet krótki, bezobjawowy epizod AF, trwający 5-6 min, może prawie 3-krotnie zwiększyć ryzyko wystąpienia ICS, a ponad 2-krotnie ryzyko zgonu (4). ICS nie jest jedynym istotnym klinicznie powikłaniem AF. U pacjentów z AF często stwierdza się zmiany w istocie białej mózgu, zaburzenia czynności poznawczych, pogorszenie jakości życia oraz obniżony nastrój (8), a każdego roku jest hospitalizowanych 10-40% pacjentów z AF (9).

W Polsce brakuje wieloośrodkowych, dużych liczebnie badań dotyczących charakterystyki klinicznej i farmakoterapii pacjentów z AF i częstymi chorobami współistniejącymi, takimi jak niewydolność serca (*heart failure*, HF) czy choroba

naczyniowa (*vascular disease,* VD), obejmującą chorobę wieńcową (*coronary artery disease,* CAD) i chorobę tętnic obwodowych (*peripheral artery disease*, PAD).

4.2. Migotanie przedsionków a choroba wieńcowa i choroba tętnic obwodowych

Choroba wieńcowa (CAD) i PAD to częste schorzenia współistniejące z AF, występujące nawet do 30% pacjentów z AF (10, 11). Wcześniejsze badania wykazały, że współistnienie PAD z CAD zwiększa ryzyko zdarzeń sercowo-naczyniowych i zgonu (12). W badaniu CHARISMA (*Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance*) wykazano, że u pacjentów z rozpoznaną chorobą więcej niż jednego łożyska naczyniowego (przebyty zawał serca, udar mózgu lub PAD) śmiertelność jest dwukrotnie wyższa niż u pacjentów z izolowaną VD (15% vs 7,7%) (13). Dodatkowo, w badaniu przeprowadzonym na 2424 pacjentach z CAD, wykazano, że częstość nowo zdiagnozowanej bezobjawowej PAD wynosi 14% i wiąże się z 2,4-krotnie wyższą śmiertelnością (14). Stąd też u pacjentów z AF ze współistniejącymi CAD i PAD można spodziewać się znacznie zwiększonego ryzyka sercowo-naczyniowego. Niemniej jednak istnieją ograniczone dane dotyczące rokowania pacjentów z AF z towarzyszącą PAD i/lub CAD. Ponadto obecność VD utrudnia wybór strategii leczenia przeciwzakrzepowego u pacjentów z AF. Chociaż w porównaniu do poprzednich wytycznych, obecnie zaleca się krótszy czas trwania potrójnej terapii przeciwzakrzepowej (OAC w skojarzeniu z podwójną terapią przeciwpłytkową (*dual antiplatelet therapy*, DAPT)) u pacjentów z AF po ostrym zespole wieńcowym i/lub przezskórnej interwencji wieńcowej (15), trwa dyskusja dotycząca optymalnego czasu trwania tej terapii w poszczególnych podgrupach chorych. Wybór strategii leczenia przeciwzakrzepowego u pacjentów z AF po ostrym zespole wieńcowym i/lub angioplastyce wieńcowej dodatkowo komplikuje coraz bogatsze armamentarium dostępnych OAC (antagoniści witaminy K [*vitamin K antagonists*, VKA] *vs* OAC nie będące antagonistami witaminy K [*non-vitamin K oral anticoagulants*, NOAC]): dabigatran, riwaroksaban, apiksaban, edoksaban) i antagonistów receptora P2Y12 (klopidogrel, tikagrelor, prasugrel) z dużą liczbą możliwych skojarzeń tych leków. Z kolei u pacjentów z AF i przewlekłym zespołem wieńcowym, w odległym czasie po ostrym zespole wieńcowym lub angioplastyce wieńcowej, zaleca się stosowanie jedynie OAC. Na podstawie rejestru duńskiego wykazano, że skojarzona terapia lekiem przeciwpłytkowym i warfaryną u pacjentów z AF i przewlekłym zespołem wieńcowym wiąże się ze zwiększonym ryzykiem krwawienia w porównaniu z monoterapią warfaryną, bez dodatkowej korzyści w zakresie zmniejszenia ryzyka zakrzepowo-zatorowego lub sercowo-naczyniowego (16). Wyniki te

potwierdzono w badaniu ORBIT-AF II (*Outcomes Registry for Better Informed Treatment of Atrial Fibrillation II*) (10), w którym dodatkowo stwierdzono niższe ryzyko krwawienia wśród pacjentów leczonych NOAC względem pacjentów przyjmujących warfarynę. W ostatnio opublikowanej analizie danych z rejestru duńskiego wykazano, że u pacjentów z AF po zawale serca i/lub przezskórnej interwencji wieńcowej zastosowanie NOAC w skojarzeniu z DAPT wiązało się ze znaczną redukcją ryzyka krwawienia przy podobnej skuteczności przeciwzakrzepowej w porównaniu z warfaryną w połączeniu z DAPT (17). Podobne wyniki uzyskano również w badaniu PIONEER AF-PCI trial (*Open-Label, Randomized, Controlled, Multicenter Study Exploring Two Treatment Strategies of Rivaroxaban and a Dose-Adjusted Oral Vitamin K Antagonist Treatment Strategy in Subjects with Atrial Fibrillation who Undergo Percutaneous Coronary Intervention*) (18). Mimo coraz liczniejszych danych z badań klinicznych, wybór optymalnej strategii leczenia przeciwzakrzepowego u indywidualnego pacjenta z AF i chorobą naczyniową pozostaje trudny i wymaga wyważenia pomiędzy ryzykiem zdarzeń zakrzepowo-zatorowych a ryzykiem powikłań krwotocznych. Znajomość aktualnej częstości występowania VD u pacjentów z AF i rokowania długoterminowego tych chorych oraz analiza schematów leczenia przeciwzakrzepowego w tej populacji może w znaczący sposób poprawić prowadzenie terapii.

4.3. Migotanie przedsionków a niewydolność serca

HF i AF to dwa często współistniejące schorzenia kardiologiczne, które mogą wywoływać i nasilać się wzajemnie za pośrednictwem zbliżonych mechanizmów patofizjologicznych i czynników ryzyka (3, 19). Dotychczasowe dane wskazują, że HF współistnieje u ponad 50% pacjentów z AF (20), a częstość występowania pierwszych objawów HF w ciągu 12 miesięcy od rozpoznania AF wynosi od 8% do 24% w okresie kolejnych 5 lat (21). Pomimo postępów w leczeniu, hospitalizowani pacjenci z AF i HF pozostają w grupie wysokiego ryzyka wystąpienia zdarzeń niepożądanych, w tym zgonu i ponownych hospitalizacji (22). W polskiej części Pilotażowego Rejestru HF Europejskiego Towarzystwa Kardiologicznego (*European Society of Cardiology*, ESC) niemal 50% pacjentów z HF i współistniejącym AF doświadczyło rehospitalizacji lub zmarło w pierwszym roku obserwacji (23). Wyniki te z jednej strony sugerują, że opieka ambulatoryjna w Polsce może być niewystarczająca, a z drugiej strony obrazują istotną rolę rejestrów, które analizują dane rzeczywistych (tzw. „real-life") pacjentów i umożliwiają ocenę czynników ryzyka z dobraniem odpowiedniego planu leczenia. Podstawowym problemem terapeutycznym u chorego z AF i współistniejącym HF, poza leczeniem przeciwkrzepliwym,

jest wybór strategii utrzymania rytmu zatokowego lub kontroli częstości rytmu komór (3). Dotychczasowe badania nie przyniosły jednoznacznego rozstrzygnięcia w kwestii wyboru optymalnej strategii leczenia AF u chorych z HF. W historycznych już, wieloośrodkowych badaniach, takich jak AFFIRM (*Atrial Fibrillation Follow-up Investigation of Rhythm Management*) (24) czy AF-CHF (*Atrial Fibrillation and Congestive Heart Failure*) (25) nie wykazano różnic między obiema strategiami pod kątem umieralności ani częstości powikłań sercowo-naczyniowych. Niemniej jednak, w analizach post-hoc przedstawiono dowody na przewagę strategii utrzymania rytmu zatokowego, wskazując, że osoby z HF z przywróconym i utrzymanym rytmem zatokowym cechuje lepsze rokowanie i poprawa wydolności fizycznej (26). Co więcej, niedawno opublikowane badanie CASTLE-AF (*Catheter Ablation versus Standard Conventional Therapy in Patients with Left Ventricular Dysfunction and Atrial Fibrillation*) wykazało, że u pacjentów z HF, wykonanie zabiegu ablacji podłoża AF wiązało się ze znacznie niższym ryzykiem zgonu z jakiejkolwiek przyczyny lub rehospitalizacji z powodu zaostrzenia HF w porównaniu do chorych poddanych optymalnej terapii farmakologicznej (27).

Istnieją znaczne różnice w odniesieniu do patofizjologii, obrazu klinicznego (w tym częstości występowania AF) i skuteczności leczenia HF w zależności od jej fenotypu (HF z obniżoną, pośrednią lub zachowaną frakcją wyrzutową). Ponadto ustalenie rozpoznania HF z zachowaną bądź pośrednią frakcją wyrzutową wśród pacjentów z AF jest trudniejsze, ponieważ u tych chorych podwyższenie stężenia peptydów natriuretycznych i powiększenie lewego przedsionka (które stanowią kryteria diagnostyczne HF z zachowaną lub pośrednią frakcją wyrzutową), może być związane z arytmią (3).

W świetle powyższych rozważań, istotne wydaje się przedstawienie charakterystyki klinicznej pacjentów z AF z towarzyszącą HF (zarówno z obniżoną, pośrednią, jak i zachowaną frakcją wyrzutową) z uwzględnieniem stosowanego leczenia (w tym terapii antyarytmicznej i przeciwzakrzepowej). Dane te mogłyby umożliwić zrozumienie rzeczywistej skali problemu i faktycznego obrazu klinicznego polskich pacjentów z AF i współistniejącą HF, a w konsekwencji także poprawę terapii.

4.4. Czynności mechaniczna uszka lewego przedsionka a ryzyko zakrzepowo-zatorowe

Tworzenie się skrzepliny w lewym przedsionku jest głównym mechanizmem odpowiedzialnym za zdarzenia zakrzepowo-zatorowe u pacjentów z AF, przy czym w ponad 90% przypadków skrzeplina zlokalizowana jest w uszku lewego przedsionka (28-30). Do

powstania skrzepliny dochodzi zgodnie z zasadami triady Virchowa, obejmującej zaburzenia przepływu krwi, dysfunkcję śródbłonka oraz stan nadkrzepliwości. Prędkość opróżniana uszka lewego przedsionka (*left atrial appendage emptying velocity,* LAAV) jest najczęściej stosowanym parametrem, służącym do oceny funkcji mechanicznej uszka lewego przedsionka u pacjentów z AF (31-33)]. U zdrowych osób LAAV mieści się w zakresie od 50 ± 6 cm/s do 83 ± 25 cm/s (31-33). Prędkości poniżej 40 cm/s, a zwłaszcza poniżej 20 cm/s, wiążą się z zastojem krwi (pierwszy element triady Virchowa), wyższym ryzykiem powstania skrzepliny w uszku lewego przedsionka i większą częstością zdarzeń zakrzepowo-zatorowych, w tym udaru niedokrwiennego mózgu (31, 34, 35). W badaniu Bernhardta i wsp., u 42% pacjentów z AF i udarem mózgu stwierdzono LAAV poniżej 20 cm/s, a tylko 6% pacjentów z AF z LAAV poniżej 20 cm/s nie miało udaru mózgu (36). Ponadto pacjenci, u których skrzeplina w uszku lewego przedsionka utrzymywała się po leczeniu przeciwkrzepliwym, mieli niższe wartości LAAV niż ci, u których skrzeplina uległa rezolucji w wyniku leczenia. Reasumując, obniżona LAAV, zdefiniowana jako prędkość mniejsza niż 20 cm/s, jest znanym predyktorem wystąpienia skrzepliny w uszku lewego przedsionka u pacjentów z AF i jako element triady Virchowa stanowi patomechanizm, który potencjalnie tłumaczy związek niektórych stanów klinicznych i chorób współistniejących ze zwiększonym ryzykiem zdarzeń zakrzepowo-zatorowych w AF. Istotne wydaje się zatem ustalenie, które ze znanych klinicznych czynników ryzyka udaru niedokrwiennego u pacjentów z AF są związane z powstaniem skrzepliny w uszku lewego przedsionka na drodze zmniejszenia LAAV.

4.5. Przestrzeganie wytycznych leczenia migotania przedsionków

Wyniki niedawno opublikowanego międzynarodowego, prospektywnego, obserwacyjnego rejestru EORP-AF Pilot (*EURObservational Research Programme — Atrial Fibrillation General Registry Pilot Phase*) pokazują, że przestrzeganie zaleceń ESC dotyczących farmakoterapii AF, a w szczególności leczenia przeciwzakrzepowego, nie jest zadawalające (37). Jedynie 78% pacjentów z AF było leczonych OAC mimo istniejących bezwzględnych wskazań do ich stosowania, a ponad połowa pacjentów z AF i CHA_2DS_2-VASc wynoszącym 0 punktów otrzymywała OAC pomimo braku wskazań (37). Jeszcze mniej zadawalające były wyniki uzyskane w kohorcie 419 polskich pacjentów z rejestru EORP-AF. Stosowanie OAC zgodnie z wytycznymi ESC było rzadsze niż u pacjentów z pozostałych krajów europejskich (61% vs 79%; p <0,01), natomiast porównywalnie często przepisywano OAC mimo braku wskazań (67% vs 69%; p >0,99) (2). W porównaniu do

innych krajów europejskich, w populacji polskiej zaobserwowano częstsze wykorzystanie ablacji przezskórnej celem uzyskania kontroli rytmu (szczególnie wśród osób młodych, kobiet, pacjentów z niewydolnością serca z objawami w klasie NYHA ≥2) oraz częstsze przepisywanie β-adrenolityków i niedihydropirydynowych antagonistów kanałów wapniowych, natomiast rzadziej stosowano amiodaron i digoksynę (2).

Wciąż jednak brakuje w Polsce badań dotyczących przestrzegania zaleceń terapii AF przeprowadzonych na większej liczebnie, bardziej reprezentatywnej grupie pacjentów. Istotna jest również ocena stosowanego leczenia w subpopulacjach pacjentów z AF i najczęstszymi chorobami towarzyszącymi, takimi jak HF i VD, zwłaszcza, że ich współistnienie wpływa na wartość szacowanego ryzyka zakrzepowo-zatorowego, a przez to determinuje wskazania do OAC. Dane dotyczące stopnia przestrzegania wytycznych w warunkach polskich mogą umożliwić wdrożenie działań poprawiających prowadzenie terapii AF, co może w znaczący sposób przełożyć się na przebieg choroby oraz ryzyko jej powikłań.

4.6. Uzasadnienie wyboru tematu pracy

Wzrastająca częstość występowania AF i jego poważne konsekwencje kliniczne wiążą się z wysoką chorobowością i istotnymi kosztami dla opieki zdrowotnej oraz gorszym rokowaniem w tej grupie chorych. Dlatego istotne jest pozyskiwanie i analiza aktualnych danych dotyczących charakterystyki klinicznej, farmakoterapii i rokowania polskich pacjentów z AF. Szczególną, niewystarczająco przebadaną populacją pacjentów z AF są chorzy z AF i schorzeniami towarzyszącymi, w tym HF i VD. Zgodnie z aktualnymi wytycznymi ESC, optymalizacja leczenia chorób współistniejących i kontrola czynników ryzyka sercowo-naczyniowego jest jednym z trzech głównych filarów terapii AF (C - „*Cardiovascular and Comorbidity optimization*" w zintegrowanej ścieżce ABC z wytycznych ESC z 2020 roku) (3). W niedawno opublikowanym badaniu randomizowanym terapia celowana schorzeń podstawowych znacząco zwiększyła prawdopodobieństwo utrzymania rytmu zatokowego u pacjentów z przetrwałym AF i HF (38). Kontrola czynników ryzyka i chorób współistniejących ma istotny wpływ na prawdopodobieństwo rozwoju AF, a u pacjentów z już rozpoznanym AF - na stopień nasilenia objawów, ryzyko zakrzepowo-zatorowe i rokowanie odległe (3). Obecność chorób towarzyszących modyfikuje terapię AF, w tym wybór strategii leczenia przeciwzakrzepowego czy antyarytmicznego (3). Uzasadnia to analizę danych rejestrowych pod kątem najczęściej występujących chorób towarzyszących i sposobu ich leczenia u chorych z AF. Duże znaczenie praktyczne ma również weryfikacja przestrzegania wytycznych ESC w warunkach polskich. Dodatkowo, istotne poznawczo jest

ustalenie, które z chorób współistniejących, będących czynnikami ryzyka udaru niedokrwiennego u pacjentów z AF, są związane z powstaniem skrzepliny w uszku lewego przedsionka na drodze upośledzenia jego funkcji mechanicznej.

Większość dostępnych danych dotyczących AF pochodzi z randomizowanych badań klinicznych, obejmujących stosunkowo wąskie grupy pacjentów, spełniających kryteria włączenia do badania. Częstość występowania istotnych chorób towarzyszących w tych kohortach jest mniejsza w porównaniu do populacji ogólnej chorych z AF (39). Ma to tym większe znaczenie, że AF dotyczy przede wszystkim osób w wieku podeszłym, z licznymi schorzeniami towarzyszącymi. Główną zaletą rejestrów jest ich obserwacyjny charakter pozwalający na uwzględnienie w badaniu niewyselekcjonowanej grupy pacjentów z codziennej praktyki klinicznej.

5. Założenia i cele pracy

Głównym celem pracy była ocena częstości występowania wybranych chorób współistniejących, HF i VD, u polskich pacjentów z AF oraz charakterystyka kliniczna tych chorych.

Szczegółowe cele badania obejmowały:

- ocenę częstości występowania manifestacji klinicznych VD (CAD i PAD) oraz poszczególnych typów HF (HF z obniżoną, pośrednią i zachowaną frakcją wyrzutową) w populacji pacjentów z AF,
- porównanie charakterystyki klinicznej pacjentów z i bez VD oraz z i bez HF,
- ocenę stosowanej farmakoterapii, w tym w szczególności leczenia przeciwzakrzepowego u pacjentów z AF i współistniejącą VD lub HF,
- ocenę zgodności stosowanej farmakoterapii z obowiązującymi wytycznymi ESC dotyczącymi postępowania u pacjentów z AF,
- ocenę zależności między obecnością skrzepliny w uszku lewego przedsionka, jego czynnością mechaniczną a współistnieniem chorób towarzyszących u pacjentów z AF.

6. Materiał i metody

W ramach niniejszej rozprawy doktorskiej analizą zostały objęte dane pochodzące z:

1) polskiej części prospektywnego, międzynarodowego rejestru EORP-AF (*EURObservational Research Programme - Atrial Fibrillation*) Long-Term General Registry,

2) polskiego, prospektywnego rejestru wieloośrodkowego POL-AF (*POLish Atrial Fibrillation registry*),

3) polskiego, retrospektywnego rejestru dwuośrodkowego.

We wszystkich tych rejestrach zajmowałam się rekrutacją pacjentów, analizą dostępnej dokumentacji medycznej i uzupełnianiem baz danych.

Dalsze szczegóły dotyczące metodologii każdego z badań przedstawiono w załączonych publikacjach.

7. Publikacje wchodzące w skład cyklu prac

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Vascular disease in patients with atrial fibrillation. A report from Polish participants in the EORP-AF General Long-Term Registry

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Abstract

Aims: This study aimed to (1) define the prevalence of vascular disease (VD; coronary (CAD) and/or peripheral artery disease (PAD)) and associated risk factors in patients with atrial fibrillation (AF); (2) establish the relationship of VD and associated treatment patterns on adverse events in AF.

Methods: Data from 701 Polish AF patients enrolled in the EORP-AF General Long-Term Registry in the years 2013-2016 were included in this analysis. During the one-year follow-up, the occurrence of major adverse events (MAE; all-cause death, thromboembolic event, myocardial infraction) and its components was evaluated.

Results: VD was recorded in 293 (44%) patients and based on multivariate logistic analysis was associated with age >75, diabetes, hypercholesterolemia, heart failure (HF). There was no significant difference in rates of MAE between patients with and without VD based on Fisher's exact test (8.8% vs 5.7%, $P = .16$), as well as between patients with concomitant CAD and PAD, PAD and CAD alone based on the Chi-square test (21% vs 7.5% vs 6.7%; $P = .09$). A higher risk of MAE was associated with HF, chronic kidney disease (in all study group), age >75, HF, diabetes (VD group),chronic obstructive pulmonary disease (non-VD group) based on the multivariate logistic analysis. Relative to patients with VD on vitamin K antagonists (VKA), those treated with non-VKA-oral anticoagulants (NOAC) had lower absolute rate of MAE according to Fisher's exact test (1.4% vs 10%, $P = .02$) but similar risks for thromboembolic and hemorrhagic events. The concomitant use of triple therapy was associated with increased risk of MAE as compared with those on OAC alone or dual therapy based on the Chi-square test (20% vs 4.8%, 3.2%, $P = .02$).

Conclusion: VD was prevalent in almost two-fifths of AF patients. The incidence of MAE was higher in patients with VD on VKA (vs NOAC) and on triple therapy (vs dual therapy, OAC alone) within one-year follow-up.

1 | INTRODUCTION

Coronary artery disease (CAD) and peripheral artery disease (PAD) are common comorbidities, occurring up to 30% of patients with atrial fibrillation (AF).[1,2] The coexistence of PAD with CAD increases the risk of cardiovascular events and mortality amongst AF patients.[3,4] As the presence of vascular disease (VD) is included in the guideline-recommended thromboembolic risk stratification (CHA2DS2-VASc score) and current European Society of Cardiology (ESC) guidelines recommend that oral anticoagulation (OAC) should be considered in AF patients even with only one non-sex stroke risk factor (Class IIa recommendations), most of the patients with AF and CAD and/or PAD are eligible for anticoagulant therapy.[5,6]

Despite increasing data from clinical trials, the selection of the optimal anticoagulant strategy for an individual patient with AF and VD remains difficult and requires a balance between the risk of thromboembolic events and the risk of hemorrhagic complications. The EURObservational Research Programme Atrial Fibrillation (EORP-AF) General Long-Term Registry is a prospective multi-national survey conducted by the ESC in 250 centres from 27 European countries to determine clinical features, treatment patterns and outcomes amongst patients with AF managed by cardiologists.[7]

The objective of the present study was to analyse the Polish part of the EORP-AF General Long-Term Registry. We aimed to (1) define the prevalence of VD (ie, CAD and/or PAD) in patients with AF and describe its associated risk factors; and (2) establish the relationship of VD and associated treatment patterns on adverse events in AF.

What is known

- In atrial fibrillation (AF), vascular disease (VD) is frequently reported.
- The presence of VD is associated with poor prognosis in AF patients

What is new

- Concomitant VD increased risk of major adverse events (MAE) and its components
- Vitamin K antagonists and triple therapy are associated with an increased MAE rate.

2 | METHODS

2.1 | Study population

The cohort analysed in this study was derived from EORP-AF General Long-Term Registry. The rationale design and methods of the registry have been previously published.[7,8] Briefly, EORP-AF General Long-Term Registry is a prospective, observational, international registry of patients with AF. Eligible patients were required to be 18 years of age with electrographically documented AF. Moreover, eligible patients had to be able to adhere to local follow-up every 12 months during a three-year period. An electronic case report form (eCRF) was used to collect information on patient demographics, medical history, medications, vital signs, laboratory data, and imaging and electrocardiographic parameters.

For the purpose of this study, we only included patients with AF and data on CAD, and PAD, from Poland. Only the baseline and one-year follow-up visit was analysed to avoid a significant loss to follow-up patients that number increased with the years of follow-up. The registry was approved by local ethical review boards according to the regulations of each participating country. The study was performed according to the European Union Note for Guidance on Good Clinical Practice CPMP/ECH/135/95 and the Declaration of Helsinki. A signed, informed consent was obtained from each patient after providing detailed information on the registry.[7]

2.2 | Definitions

"Vascular disease" was defined as any the presence of CAD and PAD. The presence of CAD was defined by a positive history of any of the following: stable CAD, myocardial infraction (MI), percutaneous coronary interventions (PCI), coronary artery bypass grafting (CABG). PAD was defined as any the presence of the following: intermittent claudication, previous surgery, percutaneous intervention or thrombosis of abdominal or thoracic aorta, lower extremity vessels and aortic plaque. This assessment was performed by any physician during the clinical assessment and/or by searching through medical records, if available. The presence or absence of CAD and PAD was recorded in the eCRF of the registry, but with no further details on its clinical manifestations. Types of AF were defined as follows: (a) first detected AF, (b) paroxysmal AF, (c) persistent AF including long-standing persistent AF, (d) permanent AF. Thromboembolic risk was defined according to the CHA2DS2-VASc score and bleeding risk was assessed based on the HAS-BLED score.[6] Single antiplatelet therapy (SAPT) was defined as the current use of any one of the following: aspirin, clopidogrel, prasugrel, or ticagrelor. Dual APT (DAPT) was defined as the current use of aspirin plus either clopidogrel, ticlopidine, prasugrel, or ticagrelor. The current study assessed adherence of cardiologists to 2012 ESC recommendations as a study was conducted in years 2013-2016.[9]

2.3 | Primary and secondary endpoints

During the pre-specified one-year follow-up period, the occurrence of major adverse events (MAE) was evaluated. Based on the study protocol, MAE recorded were as follows: all-cause death and any thromboembolic event (TE) (defined as the occurrence of any stroke, transient ischemic attack (TIA), peripheral or pulmonary embolism), MI. As secondary outcomes, individual components of MAE,

hemorrhagic events (HE) and hospitalisation related to cardiovascular, TE or HE were also evaluated in the analysis.

2.4 | Statistical analysis

Categorical variables were presented as counts and frequencies, and continuous variables were presented as median values with interquartile ranges (IQR). Differences between groups were appropriately assessed using Fisher's exact test (two groups comparison) or chi-squared test (three groups comparison) for categorical variables and the Mann-Whitney U test (non-parametric; two groups comparison) or Kruskal-Wallis test (non-parametric; three groups comparison) for continuous variables. Shapiro-Wilk test was used for testing the normality of data.

A regression analysis was performed to establish the demographic and clinical factors significantly associated with the presence of VD in all study group. All variables considered of clinical relevance (listed in Table S1) underwent a univariate analysis and those predictors with a level significance of $P < .10$ were inserted into a multivariate logistic model. Kaplan-Meier analysis was used to establish the relation of VD to all-cause death and differences in survival were analysed using the log-rank test.

A regression analysis was performed to establish the demographic and clinical factors significantly associated with the presence of MAE in all study group, patients with VD and patients without VD. All variables considered of clinical relevance (listed in Table S1) underwent a univariate analysis and those predictors with a level significance of $P < .10$ were inserted into a multivariate logistic model.

All variables with a $P < .10$ in univariate analysis for the association to MAE in all study group were inserted in the stepwise multivariate logistic model along with VD. Additional stepwise models were then performed inserting in any model a specific class of drugs with a known role in cardiovascular prevention such as antiplatelets, OAC, statins, angiotensin-converting enzyme (ACE) inhibitors and calcium-channel blockers (CCB).

A two-sided $P < .05$ was considered statistically significant. All analyses were performed using StatsModels: Statistic in Python - v0.10.1 documentation.

3 | RESULTS

3.1 | Baseline characteristic of all study group

The EORP-AF General Long-Term Registry enrolled 701 patients with AF from 2013 to 2016 at 25 cardiology centres within Poland. Of these, 663 patients had data on CAD and PAD, therefore, included in the present analysis (Figure S1): 32% patients were diagnosed with paroxysmal AF, 29%—with persistent AF and 33%—with permanent AF). A high thromboembolic risk (CHA2DS2-VASc score ≥2) was recorded in 79%, while a high risk for bleeding (HAS-BLED score ≥3) was documented in 16% (Table 1).

Of the whole cohort, 17% of patients were treated at least with one antiplatelet drug, while OAC was used in 589 (89%) AF patients (Table 1). Overall, 395 (60%) patients were treated with a statin (Table S2).

3.2 | Baseline characteristic of patients with and without VD

VD was recorded in 293 patients (44%). Baseline clinical characteristics in patients with and without VD are summarised in Table 1, while detailed characteristics in the subgroup of patients with VD (CAD, PAD and CAD + PAD) are summarised in Table S3. Patients with VD were older, more prevalent permanent AF, hypertension, diabetes mellitus, hypercholesterolemia, heart failure (HF), chronic kidney disease (CKD). On echocardiography, patients with VD were characterised by lower ejection fraction, heart cavities enlargement and left ventricular hypertrophy as compared with those without VD. Laboratory tests showed lower estimated glomerular filtration rate and cholesterol values amongst the VD group.

As expected, patients with VD had higher CHA2DS2-VASc and HAS-BLED scores than patients without VD. At follow-up, TE were recorded in 13% (vs 11% in those without VD, $P = .40$) and HE in 9.9% (vs 6.0%, $P = .06$).

In patients treated with OAC (n = 589), the temporal trend of treatment patterns was assessed by the year of patient enrollment (Figure S2). In both groups (VD and non-VD group), the prescription rate of non-vitamin K antagonist oral anticoagulants (NOAC) increased in parallel with decreasing rates of vitamin K antagonists (VKA) over time.

Patients with VD were more commonly treated with antiplatelet drugs, usually acetylsalicylic acid, than those without (29% vs 3.8%, $P < .01$). Similarly, clopidogrel (19% vs 1.4%, $P < .01$), ACE inhibitors (66% vs 46%, $P < .01$), aldosterone receptor antagonists (41% vs 27%, $P < .01$), diuretics (67% vs 48%, $P < .01$) and statins (76% vs 48%, $P < .01$) were more used in VD patients (Table S2).

On multivariate logistic analysis (Table 2), age >75 (odd ratio (OR) 2.47, 95% confidence interval (CI) 1.66-3.68, $P < .01$), diabetes mellitus (OR 2.14, 95% CI 1.46-3.16, $P < .01$), hypercholesterolemia (OR 1.95, 95% CI 1.37-2.76, $P < .01$) and HF (OR 2.36, 95% CI 1.64-3.38, $P < .01$) were significantly associated with the presence of VD. Of note, the presence of AF type, hypertension, CKD, HE was associated with VD on univariate but not multivariate analysis.

3.3 | Major adverse events and survival analysis

Follow-up data were available for a total of 497 (75%) patients (Figure S1). Of the whole cohort available at the pre-specified one-year follow-up, 35 (7.0%) patients had an MAE (including 28 patients (5.6%) who died). In the 215 patients with VD, there were 19 (8.8%) MAE, as summarised in the following: all-cause deaths in 15 (7.0%),

TABLE 1 Baseline characteristics of patients with and without vascular disease

Characteristics	Overall (n = 663)	No vascular disease (n = 370)	Vascular disease (n = 293)	*P*
Demographics				
Age, y	67 [61-75]; n = 661	65 [58-71]; n = 369	71 [65-77]; n = 292	<0.01
Gender, females	277 (42%)	158 (44%)	119 (41%)	0.59
BMI, kg/m^2	29 [26-32]; n = 622	28 [26-31]; n = 348	29 [26-32]; n = 274	0.07
Atrial fibrillation [n (%)]				
AF first detected	41 (6.2%); n = 662	24 (6.5%); n = 369	17 (5.8%)	0.72
AF paroxysmal	211 (32%); n = 662	128 (35%); n = 369	83 (28%)	0.09
AF persistent/long-standing persistent	191 (29%); n = 662	113 (31%); n = 369	78 (27%)	0.27
AF permanent	219 (33%); n = 662	104 (28%); n = 369	115 (39%)	<0.01
Medical history [n (%)]				
Hypertension	388 (59%); n = 661	196 (53%)	192 (66%); n = 291	<0.01
Heart failure	333 (50%);	143 (39%)	190 (65%)	<0.01
Thromboembolic events	79 (11%); n = 662	40 (11%); n = 369	38 (13%)	0.40
Haemorrhagic events	55 (8.0%); n = 662	22 (6.0%); n = 369	29 (9.9%)	0.06
Diabetes mellitus	186 (28%); n = 657	69 (19%); n = 365	117 (40%); n = 292	<0.01
CKD	108 (16%)	48 (13%)	58 (20%)	0.02
Hypercholesterolemia	320 (48%); n = 647	150 (42%); n = 358	170 (59%) n = 289	<0.01
Smoking (former/current)	210 (32%); n = 640	112 (31%); n = 358	98 (35%) n = 282	0.38
COPD	43 (6.5%); n = 662	19 (5.1%)	24 (8.2%) n = 292	0.11
Liver disease	11 (1.7%); n = 662	4 (1.1%); n = 369	7 (2.4%)	0.19
Thromboembolic/bleeding risk scores				
CHA2DS2-VASc	3 [2-4]	2 [1-3]	4 [3-5]	<0.01
HAS-BLED	1 [1-2]	1 [0-2]	2 [1-3]	<0.01
Echocardiography findings				
LVEF, %	50 [39-60]; n = 537	55 [44-60]; n = 284	49 [35-55]; n = 253	<0.01
LAD, cm	46 [42-51]; n = 550	46 [41-50]; n = 291	47 [43-51]; n = 259	0.02
LVEDD, cm	52 [47-57]; n = 551	51 [47-56]; n = 293	53 [48-58]; n = 258	0.04
LVH, n [%]	125 (18%); n = 557	49 (17%); n = 294	69 (26%); n = 263	<0.01
Laboratory data				
eGFR, ml/min/1.72 m^2	69 [57-82]; n = 621	70 [60-85]; n = 343	67 [53-78]; n = 278	<0.01
Cholesterol, mg/dl	163 [135-195]; n = 444	170 [140-201]; n = 221	154 [130-188]; n = 223	<0.01
Haemoglobin, g/dl	14 [13-15]; n = 629	14 [13-15]; n = 348	14 [13-15]; n = 281	0.10
Antithrombotic therapy [n (%)]				
OAC	589 (89%); n = 662	334 (90%)	255 (87%); n = 292	0.23
VKA	352 (53%); n = 662	194 (52%)	158 (54%); n = 292	0.67
NOAC	237 (36%); n = 662	140 (38%)	97 (33%); n = 292	0.22
Dabigatran	152 (23%); n = 662	97 (26%)	55 (19%); n = 292	0.03
Rivaroxaban	85 (13%); n = 662	43 (12%)	42 (14%); n = 292	0.29
Antiplatelet therapy	111 (17%); n = 662	14 (3.8%)	97 (33%); n = 292	<0.01

Note: Number provided after the semicolon indicates the total number of patients available for that variable. Fisher's exact test was used to compare categorical variables and Mann-Whitney U test was used to compare continuous variables.

Abbreviations: AF, atrial fibrillation; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; LAD, left atrium diameter; LVEF, left ventricular ejection fraction; NOAC, non-vitamin K antagonist oral anticoagulants; OAC, oral anticoagulation; VKA, vitamin K antagonists

TABLE 2 Univariate and multivariate logistic analyses for clinical determinants of the presence of vascular disease

	Univariate analysis			Multivariate analysis		
Variable	**OR**	**95% CI**	***P***	**OR**	**95% CI**	***P***
Age >75 years	1.59	1.41-1.80	**<.01**	2.47	1.66-3.68	**<.01**
AF paroxysmal	0.75	0.53-1.04	**.09**	1.03	0.68-1.58	.99
AF permanent	1.65	1.19-2.29	**<.01**	1.05	0.69-1.62	.76
Hypertension	1.72	1.25-0.236	**<.01**	1.32	0.92-1.90	.50
Diabetes mellitus	2.87	2.02-4.08	**<.01**	2.14	1.46-3.16	**<.01**
Hypercholesterolemia	1.98	1.45-2.71	**<.01**	1.95	1.37-2.76	**<.01**
Heart failure	2.93	2.13-4.03	**<.01**	2.36	1.64-3.38	**<.01**
CKD	1.66	1.09-2.51	**.02**	0.94	0.58-1.50	.43
Haemorrhagic events	1.73	0.97-3.08	**.06**	1.44	0.77-2.72	.27

Note: Multivariate logistic analysis, which included variables showing a significant difference in the univariate analysis ($P < .10$).

Abbreviations: AF, atrial fibrillation; CI, confidence interval; CKD, chronic kidney disease; OR, odd ratio.

any TE in 1 (0.5%), MI in 4 (1.9%). In the 282 patients without VD, 16 (5.7%) MAE occurred as follows: all-cause death in 13 (4.6%), any TE in 1 (0.4%), MI in 3 (1.1%) (Table 3).

Despite a higher rate of MAE and its components, HE in patients with VD as compared with those without, the differences did not reach statistical significance. On Kaplan-Meier survival analysis for all-cause death, patients with VD had a non-significantly higher risk for all-cause death than patients without VD (Figure S3).

In multivariate analysis, independent predictors for MAE occurrence were HF (OR 3.83, 95% CI 1.39-10.57, $P = .01$), CKD (OR 2.27, 95% CI 1.02-5.06, $P = .04$) in whole study group, age >75 years (OR 3.09, 95% CI 1.07-8.97, $P = .04$), diabetes mellitus (HR 4.00, 95% CI 1.28-12.52, $P = .02$), HF (OR 8.93, 95% CI 1.13-70.81, $P = .04$) amongst the VD group and only chronic obstructive pulmonary disease (COPD) in non-VD group (OR 6.55, 95% CI 1.44-29.79, $P = .02$) (Table 4).

Variables significantly associated with MAE on univariate analysis in all study group were entered into the multivariate models along with VD (Table S4). In model 1, HF (OR 4.08, 95% CI 1.45-11.48, $P < .01$) and CKD (OR 2.25, 95% CI 1.01-5.03, $P < .05$) were independently associated with the occurrence of MAE, but VD was not independently associated with MAE. In model 2, which included pharmacological therapy with any antiplatelet drug, the HF (OR 4.05, 95% CI 1.44-11.39, $P < .01$), COPD (OR 3.00, 95% CI 1.06-8.44, $P = .04$), CKD (OR 2.39, 95% CI 1.06-5.37, $P = .04$) and any antiplatelet drug (OR 3.16, 95% CI 1.24-8.03, $P = .02$) were independently associated with MAE. Other multivariate models were compiled inserting one variable at a time, successively, pharmacological therapy with any OAC in model 3, statins in model 4, ACE inhibitors in model 5 and CCB in model 6. In all models (from 3 to 6), HF and CKD were independently associated with MAE and additionally, OAC (OR 0.32, 95% CI 0.12-0.84, $P = .02$) in model 3. When considering all the drugs together in model 7, HF (OR 4.28, 95% CI 1.51-12.15, $P < .01$), CKD (OR 2.35, 95% CI 1.03-5.38, $P = .04$) and antiplatelets drugs (OR 3.08, 95% CI 1.11-8.5, $P = .03$) were associated with the occurrence of MAE.

3.4 | Antithrombotic treatment in patient with VD

In AF patients with concomitant VD who were treated with OAC (n = 186), clinical outcomes (MAE and its components, HE and all-cause hospitalisation) were compared according to the status (presence or absence) of antiplatelet therapy (Table 5). The risk of both MAE and all-cause death was significantly higher amongst patients treated with VKA as compared with those on NOAC (10% vs 1.4%, $P = .02$; 7.8% vs 0%, $P = .02$). Moreover, the rate of MAE and all-cause death was higher amongst patients on triple therapy (DAPT + OAC) as compared with those who were on dual therapy (SAPT + OAC) or OAC alone (20% vs 3.2%, 4.8%, $P = .02$; 16% vs 3.2%, 3.1%, $P = .01$).

Time from most recent MI or PCI until enrolment is summarised in Table S5. A total of 32 patients were receiving DAPT in addition to OAC ("triple therapy") and of these, 6 (19%) were taking DAPT for >1 month despite high bleeding risk (HAS-BLED score >3), 3 (9.4%) with low bleeding risk (HAS-BLED score <3) were taking DAPT for >12 or did not have a history of MI and/or PCI. As a result, the use of DAPT was considered as inappropriate in 9 (28%) of patients receiving DAPT and OAC. A total of 40 patients were receiving dual therapy (SAPT with OAC) and of these patients, 28 (70%) was considered as inappropriate as they were receiving dual therapy within >12 months (HAS-BLED score >3) or within <1 month/>12 month (HAS-BLED score <3) or did not have a history of MI and/or PCI. Amongst patients on OAC alone (n = 183), 12 (6.6%) were treated inappropriately as they received OAC alone within <12 months from MI/PCI.

4 | DISCUSSION

The analysis of Polish participants of the EORP-AF General Long-Term registry provides an important view on patients with AF and concomitant VD. The major findings of the present study are as follows. First, VD was prevalent in almost two-fifths of patients with

TABLE 3 Clinical outcomes by vascular disease status and subgroup analysis

Variable	No vascular disease (n = 282)	Vascular disease (n = 215)				p1	p2
		Overall	CAD (n = 161)	PAD (n = 30)	CAD + PAD (n = 24)		
MAE	16 (5.7%)	19 (8.8%)	12 (7.5%)	2 (6.7%)	5 (21%)	0.16	0.09
All-cause death	13 (4.6%)	15 (7.0%)	9 (5.6%)	2 (6.7%)	4 (17%)	0.26	0.14
Myocardial infraction	3 (1.1%)	4 (1.9%)	3 (1.9%)	0 (0%)	1 (4.2%)	0.45	0.48
Thromboembolic events	1 (0.4%)	1 (0.5%)	1 (0.6%)	0 (0%)	0 (0%)	0.84	0.86
Haemorrhagic events	2 (0.8%)	5 (2.3%)	2 (1.2%)	1 (3.3%)	2 (8.3%)	0.12	0.06
All-cause hospitalisation	61 (22%)	59 (27%)	42 (26%)	10 (33%)	7 (29%)	0.10	0.53

Note: p1 value for the difference between patients with and without vascular disease. p2 value for the difference between patients with CAD, PAD and CAD + PAD. Fisher's exact test was used to compare categorical variables between patients with and without vascular disease. Chi-square test was used to compare categorical variables between patients with CAD, PAD and CAD + PAD.

Abbreviations: CAD, coronary artery disease; MAE, major adverse event; PAD, peripheral artery disease.

TABLE 4 Univariate and multivariate logistic analyses for clinical predictors of major adverse events amongst all study group (A), vascular disease group (B), non-vascular disease group (C)

Variable	Univariate analysis			Multivariable analysis		
	OR	95% CI	*P*	OR	95% CI	*P*
A. All study group						
Age >75 years	3.05	1.52-6.12	**<0.01**	1.86	0.86-4.04	0.11
AF permanent	3.17	1.57-6.41	**<0.01**	1.74	0.81-3.76	0.16
Diabetes mellitus	2.87	1.43-5.76	**<0.01**	1.59	0.74-3.42	0.24
Heart Failure	6.62	2.52-17.27	**<0.01**	3.83	1.39-10.57	**0.01**
COPD	5.08	1.99-12.97	**<0.01**	2.75	0.98-7.76	0.056
CKD	4.06	2.00-8.24	**<0.01**	2.27	1.02-5.06	**0.04**
Hemorrhagic events	2.86	1.17-7.00	**0.02**	1.98	0.74-5.27	0.17
B. Vascular disease group						
Age >75 years	3.46	1.30-9.21	**0.01**	3.09	1.07-8.97	**0.04**
Diabetes mellitus	4.35	1.50-12.59	**<0.01**	4.00	1.28-12.52	**0.02**
Heart failure	10.50	1.37-80.36	**0.02**	8.93	1.13-70.81	**0.04**
CKD	3.17	1.21-8.31	**0.02**	1.54	0.52-4.62	0.44
C. Non-vascular disease group						
AF permanent	4.39	1.54-12.52	**<0.01**	3.51	0.97-12.65	0.06
Heart failure	5.32	1.67-16.97	**<0.01**	2.43	0.63-9.33	0.20
COPD	10.41	2.74-39.49	**<0.01**	6.55	1.44-29.79	**0.02**
Smoking	2.43	0.85-6.94	**0.09**	3.05	0.86-10.79	0.08
CKD	4.96	1.73-14.16	**<0.01**	3.03	0.85-10.84	0.09
Haemorrhagic events	3.74	0.96-14.56	**0.06**	2.03	0.40-10.38	0.40

Note: Multivariate logistic analysis, which included variables showing a significant difference in the univariate analysis ($P < .10$).

Abbreviations: AF, atrial fibrillation; CI, confidence interval; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; OR, odd ratio.

AF and was related to various atherosclerotic risk factors. Second, the overall use of OAC was high, 89% and comparable between patients with and without VD. In addition, the use of NOAC increased over time in parallel with decreased VKA use regardless of VD status. Third, the incidence of MAE and its components was numerically higher in patients with VD than in those without. Moreover, patients with concomitant CAD and PAD had numerically higher mortality than those with PAD and CAD alone. Fourth, relative to patients with VD on NOAC, those treated with VKA had higher absolute rate of MAE but similar risks for TE and HE. Finally,

in AF patients with VD, the concomitant use of antiplatelet therapy was associated with increased risk of MAE, its components and HE.

Reports on the prevalence of VD and its components have been contradictory. Reported PAD prevalence in the AF population, varies from 4.1% to as high as 16.8%,[10] whereas CAD prevalence varies from 17.0% to 46.5%.[11] Compared with our results, in the whole EORP-AF General Long-Term registry, the prevalence of CAD and PAD was 29.3% and 8.1%, respectively.[7] With reference to VD, Olesen et al found a prevalence of 17.5% in the Danish AF population,[13] while Pastori et al reported a prevalence of 27.7% in Italian AF patients.[2] The Outcomes Registry for Better Informed Treatment of Atrial Fibrillation II (ORBIT-AF II) reported that almost one-third of patients with new-onset AF had VD.[1]

In our study, 10.4%, 37% and 44% of AF patients were recognised with PAD, CAD and VD, respectively. The wide difference between those previous reports and our data according to VD prevalence may reflect the nature of the study itself. In studies based on ICD codes,[12] reporting could be affected by selection bias or wrong coding, while randomised controlled trials are a highly selected cohort that may overestimate of VD prevalence. Moreover, randomised trials suffer from selection bias and thus underestimate the prevalence of many comorbidities.

Amongst the clinical factors identified in our study as associated with VD, age, hypercholesterolemia, HF and diabetes mellitus have been previously identified as risk factors both in the general population[13] and in AF patients.[1,14-16] Of note, HF and diabetes mellitus were independent predictors of MAE amongst patients with VD. This close association with HF and previous history of clinically evident atherosclerotic disease (diabetes mellitus) for both occurrence of VD and MAE amongst AF patients, reemphasises that all these factors may be intimately related, perhaps also from a pathophysiological perspective.[17]

Various studies involving AF patients have documented a higher risk of all-cause death in those AF patients with concomitant VD. Based on the Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilisation, Management and Avoidance (CHARISMA) study, the composite of cardiovascular death, MI or stroke is twice as likely in patients with more than one VD (MI, stroke or PAD) than in those with isolated VD (14.7% vs 7.7%, $P < .001$).[18] In the recent study by Pastori et al, the rate of cardiovascular events (MI, cardiac revascularisation, cardiovascular death, TIA) progressively increased from 2.4%/year in patients without PAD and CAD, to 5.6%/year and 6.1%/year in those with PAD and CAD alone, respectively, to 8.1%/year in patients with concomitant PAD and CAD. Indeed, as compared with a group of patients without CAD and PAD, those with concomitant CAD and PAD were characterised by a 2.4-fold higher risk of cardiovascular events.[2] This higher risk of major adverse cardiovascular and neurological events was also evident from the ORBIT-AF II study, amongst patients with as compared with those without VD. Similar to our study, there were no statistically significant differences in TE between patients with VD and those without (1.75% vs 1.07%, $P = .787$).[1] A subanalysis of the Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET-AF) trial also reported similar rates of TE within anticoagulated patients with polyvascular disease (any combination of two or more: CAD, PAD, carotid artery disease) as compared with dose with single-bed VD and without VD.[19]

Hence, VD may produce a very small independent effect (<15% increase in risk) in the NOAC era.[20] In our study, for example, VD was not associated with increased risk of HE, consistent with previous studies.[1,19] The limited proportion of patients who had both CAD and PAD in our study population may have resulted in a non-significant difference in major bleeding between those with and without VD.

When reviewing the relationship between AF, PAD and all-cause death, the available evidence seems conflicting. Despite documented a higher risk (varying from 1.3- to 2.5-fold) of the primary

TABLE 5 Clinical outcomes by anticoagulant type and antithrombotic strategy in patients with concomitant atrial fibrillation and vascular disease

	By type of OAC			By antithrombotic strategy					
					OAC + AP (n = 56)				
Variable	VKA (n = 115)	NOAC (n = 71)	*P*	OAC alone (n = 130)	Overall (n = 56)	OAC + SAPT (n = 31)	OAC + DAPT (n = 25)	p1	p2
MAE	11 (10%)	1 (1.4%)	**.02**	6 (4.8%)	6 (11%)	1 (3.2%)	5 (20%)	0.14	0.02
All-cause death	9 (7.8%)	0 (0%)	**.02**	4 (3.1%)	5 (8.9%)	1 (3.2%)	4 (16%)	0.09	0.01
Myocardial infraction	3 (2.8%)	1 (1.4%)	.55	2 (1.6%)	2 (3.6%)	0 (0%)	2 (8.0%)	0.39	0.07
Thromboembolic events	0 (0%)	0 (0%)	1.00	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1.00	1.00
Haemorrhagic events	3 (2.8%)	2 (2.9%)	.98	2 (1.6%)	3 (5.4%)	1 (3.2%)	2 (8.0%)	0.14	0.17
All-cause hospitalise-tion	31 (29%)	22 (31%)	.70	37 (30%)	16 (29%)	7 (23%)	9 (36%)	0.98	0.42

Note: p1 value for the difference between patients with OAC alone and OAC + AP. p2 value for the difference between patients with OAC alone, OAC + SAPT and OAC + DAPT. Fisher's exact test was used to compare categorical variables between patients with OAC alone and OAC + AP. Chi-square test was used to compare categorical variables between patients with OAC alone, OAC + SAPT and OAC + DAPT.

Abbreviations: AP, antiplatelets; MAE, major adverse event; NOAC, non-vitamin K antagonist oral anticoagulants; OAC, oral anticoagulation; VKA, vitamin K antagonists.

end-point of stroke, thromboembolism or death in patients with coexist PAD and AF,[16] in various studies this risk is often not independent of other risk factors[21-23] and some studies have suggested no interaction between the presence of PAD and worse clinical outcomes amongst AF patients.[24,25]

Our study also shows that pharmacological therapy with OAC was inversely associated with MAE and the use of antiplatelet therapies increased the risk of MAE. It has largely been assumed that the combination of antiplatelet and OAC therapy increases a patient's risk of bleeding (from 2% in DAPT alone to 14% with the addition of OAC).[26] Therefore, the selection of the optimal anticoagulant strategy for an individual patient with AF and VD remains difficult and requires a balance between the risk of TE and HE. Similar to previous reports, the use of NOAC increased over time in parallel with the decrease in VKA therapy in our study cohort.[1,27] The combination of antiplatelet drug and VKA in patients with AF and CAD was associated with an increased bleeding risk compared with VKA monotherapy, without the added benefit of reducing the risk of thromboembolism or cardiovascular risk.[28] These results were confirmed in the ORBIT-AF II study,[1] which additionally found a lower bleeding rate amongst patients treated with NOAC compared with patients treated with VKA. The use of NOAC in combination with DAPT was associated with a significant reduction in the risk of bleeding with similar anticoagulant efficacy compared with VKA in combination with DAPT.[29-31]

4.1 | Limitations

EORP-AF General Long-Term registry was a European cardiologist-based registry, so this could have led to an overestimate of VD prevalence. Conversely, this could have resulted in the enrolment of patients with more severe conditions that could have reduced the influence of VD on event rates. Moreover, the relatively short follow-up period and missing follow-up data in 25% of patients could have limited the influence of VD in determining MAE. As the sample size is quite moderate, there are potential biases not adequately resolved. Consequently, our data should be considered carefully when trying to extend our conclusions to the general AF population.

5 | CONCLUSIONS

VD was prevalent in almost two-fifths of AF patients. The incidence of MAE was numerically higher in patients with VD on VKA (vs NOAC) and on triple therapy (vs dual therapy, OAC alone) within a one-year follow-up.

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CONFLICT OF INTEREST

Monika Gawałko declares that she has no conflict of interest. Piotr Lodziński has received a speaker honorarium from Bayer, Boehringer Ingelheim, Pfizer. Monika Budnik declares that she has no conflict of interest. Agata Tymińska has received a speaker honorarium from Novartis, Boehringer Ingelheim. Anna Wancerz declares that she has no conflict of interest. Krzysztof Ozierański has received a speaker honorarium from Novartis, Boehringer Ingelheim, Orion Pharma. Agnieszka Kapłon-Cieślicka has received a speaker honorarium and travel grants from Bayer, Boehringer Ingelheim, MSD, Pfeizer. Marcin Grabowski declares that he has no conflict of interest. Grzegorz Opolski has received a speaker honorarium from Bayer, Boehringer Ingelheim, Pfizer. Radosław Lenarczyk declares that he has no conflict of interest. Zbigniew Kalarus declares that he has no conflict of interest. Gregory YH Lip is a consultant for Bayer/Janssen, BMS/Pfizer, Medtronic, Boehringer Ingelheim, Novartis, Verseon, Daiichi-Sankyo and speaker for Bayer, BMS/Pfizer, Medtronic, Boehringer Ingelheim and Daiichi-Sankyo. No fees are directly received personally. Paweł Balsam has received a speaker honorarium from Bayer, Boehringer Ingelheim, Pfizer.

ETHICAL APPROVAL

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

INFORMED CONSENT

Informed consent was obtained from all individual participants included in the study.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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Supplementary material online

Table S1. A list of candidate predictor variables.

Demographic variables	Variables regarding AF	Clinical variables
Age 65-74 years Age≥75 years Female gender	AF first detected AF paroxysmal AF permanent AF persistent/long-standing persistent	CKD Coronary artery disease COPD Diabetes mellitus Heart failure Haemorrhagic events Hypercholesterolemia Hypertension Liver disease Peripheral artery disease Smoking Thromboembolic events Vascular disease

AF, atrial fibrillation; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease;

Table S2. Treatment patterns by vascular disease

Characteristics	Overall (n=663)	No vascular disease (n=370)	Vascular disease (n=293)	p
Antiplatelet therapy				
None	552 (83%); *n=662*	356 (96%)	196 (67%); *n=292*	**<0.01**
SAPT	63 (9.5%); *n=662*	9 (2.4%)	54 (19%); *n=292*	**<0.01**
DAPT	48 (7.2%); *n=662*	5 (1.4%)	43 (15%); *n=292*	**<0.01**
Type of antiplatelet agents				
Aspirin	98 (15%); *n=662*	14 (3.8%)	84 (29%); *n=292*	**<0.01**
Clopidogrel	61 (9.2%); *n=662*	5 (1.4%)	56 (19%); *n=292*	**<0.01**
Antithrombotic strategy				
None	40 (6.0%); *n=662*	28 (7.6%)	12 (4.1%); *n=292*	0.06
Antiplatelet alone	33 (5.0%); *n=662*	8 (2.2%)	25 (8.6%); *n=292*	**<0.01**
OAC alone	511 (77%); *n=662*	328 (89%)	183 (63%); *n=292*	**<0.01**
OAC +SAPT	43 (6.5%); *n=662*	3 (0.8%)	40 (14%); *n=292*	**<0.01**
OAC + DAPT	35 (5.3%); *n=662*	3 (0.8%)	32 (11%); *n=292*	**<0.01**
Other treatment				
ACE inhibitors	361 (55%); *n=658*	170 (46%); *n=368*	191 (66%); *n=290*	**<0.01**
ARB	117 (18%); *n=658*	62 (17%); *n=368*	55 (19%); *n=290*	0.48
Beta-blockers	531 (81%);	278 (76%);	253 (87%);	**<0.01**

	n=658	*n=368*	*n=290*	
Diuretics	373(57%); *n=658*	178 (48%); *n=368*	195 (67%); *n=290*	**<0.01**
ARA	216 (33%); *n=658*	98 (27%); *n=368*	118 (41%); *n=290*	**<0.01**
DHP-CCB	106 (16%); *n=658*	53 (14%); *n=368*	53 (18%); *n=290*	0.18
Non-DHP-CCB	11 (1.7%); *n=658*	5 (1.4%); *n=368*	6 (2.1%); *n=290*	0.48
Statin	395 (60%); *n=658*	175 (48%); *n=368*	220 (76%); *n=290*	**<0.01**

Number provided after the semicolon indicates the total number of patients available for that variable. Fisher's exact test was used to compare categorical variables.

ACE, angiotensin-converting enzyme; ARA, aldosterone receptor antagonists, ARB, Angiotensin II receptor blockers, CCB, calcium channel blockers, DAPT, dual antiplatelet therapy; DHP, dihydropyridine; OAC, oral anticoagulation; SAPT, single antiplatelet therapy

Table S3. Subgroup analysis of patients with vascular disease.

Characteristics	CAD (n=206)	PAD (n=48)	CAD+PAD (n=39)	p
Vascular disease				
Angina	77 (37%)	NA	17 (44%)	NA
Prior MI	97 (47%)	NA	21 (54%)	NA
Prior CABG	22 (11%)	NA	7 (18%)	NA
Prior PCI	92 (45%)	NA	16 (41%)	NA
Aortic plaque	NA	28 (58%)	25 (64%)	NA
Demographics				
Age, years	71 [65-76]; *n=205*	71 [64-77]	71 [66-79]	0.67
Gender, females	76 (37%)	25 (52%)	18 (46%)	0.12
BMI, kg/m2	29 [26-32]; *n=193*	29 [27-33]; *n=44*	29 [26-33]; *n=37*	0.68
Atrial fibrillation				
AF first detected	10 (4.9%)	3 (6.2%)	4 (10%)	0.41
AF paroxysmal	68 (33%)	9 (19%)	6 (15%)	**0.02**
AF persistent/long-standing persistent	55 (27%)	18 (38%)	5 (13%)	**0.04**
AF permanent	73 (35%)	18 (18%)	24 (62%)	**<0.01**
Medical history				
Hypertension	135 (66%); *n=205*	29 (62%); *n=47*	28 (72%)	0.62
Heart failure	126 (61%)	32 (67%)	32 (82%)	**0.04**
Thromboembolic events	17 (8.3%)	12 (25%)	9 (23%)	**<0.01**
Haemorrhagic events	16 (7.8%)	6 (13%)	7 (18%)	0.12
Diabetes mellitus	75 (37%); *n=205*	20 (42%)	22 (56%)	0.07
CKD	43 (21%)	10 (21%)	5 (13%)	0.53
Hypercholesterolemia	120 (59%);	28 (58%)	22 (58%);	0.99

	n=202		*n=38*	
Smoking (former/current)	70 (35%); n=201	20 (44%); *n=44*	8 (22%); *n=37*	0.10
COPD	18 (8.7%); *=205*	3 (6.2%)	3 (7.9%)	0.85
Liver disease	4 (1.9%)	2 (4.2%)	1 (2.6%)	0.66
Thromboembolic / bleeding risk scores				
CHA2DS2-VASc	4 [3-5]	5 [4-6]	5 [4-6]	**<0.01**
HAS-BLED	2 [1-2]	2 [1-2]	2 [1-3]	0.21
Echocardiography findings				
LVEF, %	45 [34-55]; *n=178*	55 [45-60]; *n=40*	47 [38-50]; *n=35*	**0.03**
LAD, cm	46 [43-51]; *n=183*	47 [43-50]; *n=41*	48 [44-53]; *n=35*	0.42
LVEDD, cm	53 [48-58]; *n=182*	51 [47-59]; *n=41*	53 [47-58]; *n=35*	0.82
LVH, n [%]	46 (25%); *n=184*	13 (31%); *n=42*	10 (27%) *; n=37*	0.95
Laboratory data				
eGFR, ml/min/1,72m2	68 [55-80]; *n=195*	63 [48-72]; *n=45*	68 [48-77]; *n=38*	0.12
Cholesterol, mg/dl	153 [129-187]; *n=157*	148 [130-181]; *n=33*	155 [132-194]; *n=33*	0.88
Hemoglobin, g/dl	14 [13-15]; *n=199*	13 [12-14]; *n=45*	13 [12-14]; *n=37*	**0.04**
Anticoagulant therapy				
OAC	180 (88%); *n=205*	40 (83%)	35 (90%)	0.63
VKA	110 (54%); *n=205*	23 (48%)	25 (64%)	0.31
NOAC	70 (34%); *n=205*	17 (35%)	10 (26%)	0.55

- dabigatran	38 (19%); *n=205*	11 (23%)	6 (15%)	0.66
- rivaroxaban	32 (16%); *n=205*	6 (13%)	4 (10%)	0.63
Antiplatelet therapy				
None	133 (65%); *n=205*	41(85%)	21 (54%)	**<0.01**
SAPT	40 (20%); *n=205*	7 (15%)	7 (18%)	0.73
DAPT	32 (16%); *n=205*	0 (0%)	11 (28%)	**<0.01**
Antithrombotic strategy				
None	8 (3.9%); *n=205*	4 (8.3%)	0 (0%)	0.15
Antiplatelet alone	17 (8.3%); *n=205*	4 (8.3%)	4 (10%)	0.92
OAC alone	125 (61%); *n=205*	37 (77%)	21 (54%)	0.055
OAC +SAPT	30 (15%); *n=205*	3 (6.2%)	7 (18%)	0.22
OAC + DAPT	25 (12%); *n=205*	0 (0%)	7 (18%)	**0.02**
Other treatment				
ACE inhibitors	135 (66%); *n=205*	24 (52%); *n=46*	32 (82%)	**0.02**
ARB	40 (20%); *n=205*	12 (26%); *n=46*	3 (7.7%)	0.09
Beta-blockers	179 (87%); *n=205*	40 (87%); *n=46*	34 (87%)	1.00
Diuretics	138 (67%); *n=205*	30 (65%); *n=46*	27 (69%)	0.93
ARA	83 (41%); *n=205*	19 (41%); *n=46*	16 (41%)	0.99

DHP-CCB	36 (18%); *n=205*	7 (15%); *n=46*	10 (26%)	0.41
Non-DHP-CCB	4 (2.0%); *n=205*	1 (2.2%); *n=46*	1 (2.6%)	0.97
Statins	165 (81%); *n=205*	23 (50%); *n=46*	32 (82%)	**<0.01**

Number provided after the semicolon indicates the total number of patients available for that variable. Chi-square test was used to compare categorical variables and Kruskal-Wallis test was used to compare continuous variables.

ACE, angiotensin-converting enzyme; AF, atrial fibrillation; ARA, aldosterone receptor antagonists, ARB, angiotensin II receptor blockers; CABG, coronary artery bypass grafting; CAD, coronary artery disease; CCB, calcium channel blockers; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; DAPT, dual antiplatelet therapy; DHP, dihydropyridine; eGFR, estimated glomerular filtration rate; LAD, left atrium diameter; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NOAC, non-vitamin K antagonist oral anticoagulants; OAC, oral anticoagulation; PAD, peripheral artery disease; SAPT, single antiplatelet therapy; VKA, vitamin K antagonists

Table S4. Multivariate models for major adverse events.

Variable	Multivariate analysis		
	OR	**95% CI**	**p**
Model 1			
Vascular disease	0.74	0.34-1.65	0.47
Age ≥75 years	2.06	0.93-4.56	0.07
AF permanent	1.65	0.76-3.58	0.21
Diabetes	1.74	0.79-3.85	0.17
Heart failure	4.08	1.45-11.48	**<0.01**
COPD	2.70	0.95-7.64	0.06
CKD	2.25	1.01-5.03	**<0.05**
Haemorrhagic events	2.17	0.81-5.80	0.12
Model 2			
Vascular disease	0.47	0.18-1.18	0.11
Age ≥75 years	0.95	0.88-4.34	0.10
AF permanent	1.70	0.78-3.69	0.18
Diabetes	1.68	0.75-3.74	0.21
Heart failure	4.05	1.44-11.39	**<0.01**
COPD	3.00	1.06-8.44	**0.04**
CKD	2.39	1.06-5.37	**0.04**
Haemorrhagic events	1.90	0.69-5.23	0.21
Any antiplatelets	3.16	1.24-8.03	**0.02**
Model 3			
Vascular disease	0.70	0.31-1.59	0.40
Age ≥75 years	1.87	0.84-4.18	0.13
AF permanent	1.78	0.82-3.90	0.15
Diabetes	1.64	0.73-3.67	0.23
Heart failure	4.23	1.50-11.95	**<0.01**
COPD	2.45	0.85-7.08	0.10
CKD	2.30	1.02-5.20	**<0.05**
Haemorrhagic events	1.59	0.55-4.53	0.39
Any OAC	0.32	0.12-0.84	**0.02**

Model 4			
Vascular disease	0.75	0.32-1.78	0.52
Age ≥75 years	2.14	0.96-4.78	0.07
AF permanent	1.54	0.70-3.39	0.28
Diabetes	1.65	0.73-3.70	0.23
Heart failure	3.96	1.40-11.22	**0.01**
COPD	2.77	0.96-8.02	0.06
CKD	2.42	1.07-5.46	**0.03**
Haemorrhagic events	2.25	0.83-6.08	0.11
Statins	0.90	0.39-2.07	0.80
Model 5			
Vascular disease	0.72	0.32-1.64	0.44
Age (per years)	2.21	0.99-4.93	0.05
AF permanent	1.58	0.72-3.47	0.25
Diabetes	1.65	0.74-3.72	0.22
Heart failure	4.03	1.42-11.46	**<0.01**
COPD	2.69	0.91-7.89	0.07
CKD	2.38	1.06-5.34	**0.04**
Haemorrhagic events	2.25	0.83-6.07	0.11
ACE inhibitors	0.86	0.39-1.89	0.71
Model 6			
Vascular disease	0.71	0.32-1.59	0.41
Age ≥75 years	2.12	0.95-4.74	0.07
AF permanent	1.57	0.72-3.43	0.26
Diabetes	1.65	0.73-3.69	0.23
Heart failure	3.88	1.39-10.87	**0.01**
COPD	2.79	0.98-8.00	0.06
CKD	2.37	1.05-5.35	**0.04**
Haemorrhagic events	2.24	0.83-6.04	0.11
CCB	0.96	0.36-2.54	0.94
Model 7			
Vascular disease	0.40	0.15-1.09	0.07
Age ≥75 years	2.13	0.94-4.82	0.07

AF permanent	1.62	0.73-3.58	0.24
Diabetes	1.59	0.70-3.63	0.27
Heart failure	4.28	1.51-12.15	**<0.01**
COPD	2.82	0.94-8.44	0.06
CKD	2.35	1.03-5.38	**0.04**
Haemorrhagic events	1.72	0.59-5.07	0.32
Any antiplatelets	3.08	1.11-8.51	**0.03**
Any OAC	0.56	0.19-1.68	0.30
Statins	0.99	0.41-2.41	0.99
ACE inhibitors	0.84	0.36-1.92	0.68
CCB	1.01	0.37-2.80	0.99

ACE, angiotensin-converting enzyme; AF, atrial fibrillation; ARA, aldosterone receptor antagonists, CCB, calcium channel blockers; CI, confidence interval; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; HR, hazard ratio; OAC, oral anticoagulation

Table S5. Time from most recent myocardial infraction or percutaneous coronary intervention until enrolment and appropriateness of anticoagulation in patients with vascular disease.

Variable	**Triple therapy (n=32)**		**Dual therapy (n=40)**		**OAC alone (n=183)**	
	HASBLED score ≥ 3 **(n=11)**	*HASBLED score < 3* **(n=21)**	*HASBLED score ≥ 3* **(n=18)**	*HASBLED score < 3* **(n=22)**	*HASBLED score ≥ 3* **(n=37)**	*HASBLED score < 3* **(n=146)**
Time from most recent MI/PCI until enrollment						
<1 month	5 (45%)	15 (71%)	3 (17%)	3 (14%)	7 (19%)	0 (0%)
1-12months	5 (45%)	3 (14%)	3 (17%)	6 (27%)	2 (5.4%)	3 (2.0%)
>12months	1 (5.7%)	1 (4.8%)	5 (28%)	5 (23%)	11 (30%)	50 (34%)
no prior MI/PCI	0 (0%)	2 (10%)	7 (39%)	8 (36%)	17 (46%)	93 (64%)
Type of CAD						
prior MI	9 (82%)	10 (52%)	8 (73%)	12 (86%)	9 (45%)	45 (85%)
prior PCI	9 (82%)	16 (84%)	7 (64%)	12 (86%)	8 (40%)	39 (74%)
Appropriateness of anticoagulation strategy						
No	6 (55%)	3 (14%)	12 (67%)	16 (73%)	9 (24%)	3 (2.1%)
Yes	5 (45%)	18 (86%)	6 (33%)	6 (27%)	28 (76%)	143 (98%)

Patients were deemed “appropriate”, if patients met any of the following criteria:

1) triple therapy if most recent PCI/MI was within 1 month of enrollment, among those with high bleeding score (HASBLED score ≥ 3),

2) triple therapy if most recent PCI/MI was within 12 months (in this study instead of 6 months, we deemed appropriate 12 months in connection with the design of the case form report), among those with low bleeding score (HASBLED score < 3),

3) dual therapy if most recent PCI/MI was within 12 months of enrollment, among those with low bleeding score (HASBLED score ≥ 3),

4) dual therapy if most recent PCI/MI was within 1-12 months of enrollment, among those with high bleeding score (HASBLED score < 3),

5) OAC alone therapy if most recent PCI/MI was within >12 months

CAD, coronary artery disease; DAPT, dual antiplatelet therapy; MI, myocardial infarction; NOAC, non-vitamin K antagonist oral anticoagulants; PCI, percutaneous coronary intervention; VKA, vitamin K antagonists

Table S6. Participating centers, investigators, and data collection officers.

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25. **Zakopane:** A. Orzechowska, M. Szpot, M. Staszel,

Figure S1. Study patients' flow chart.

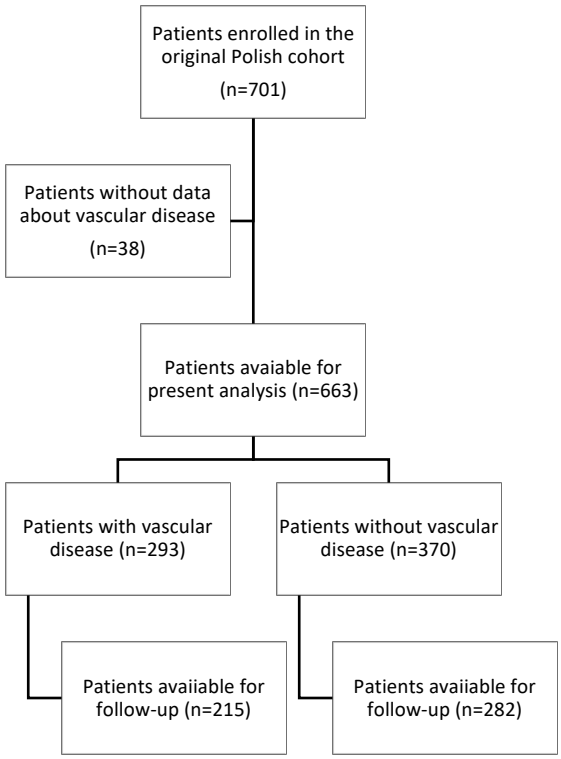
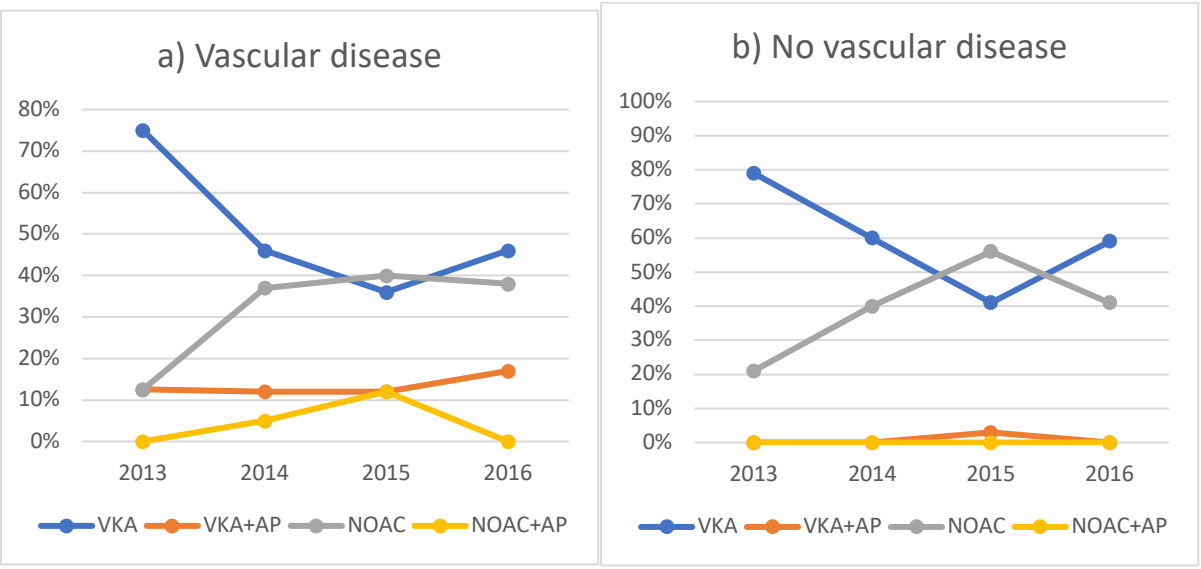


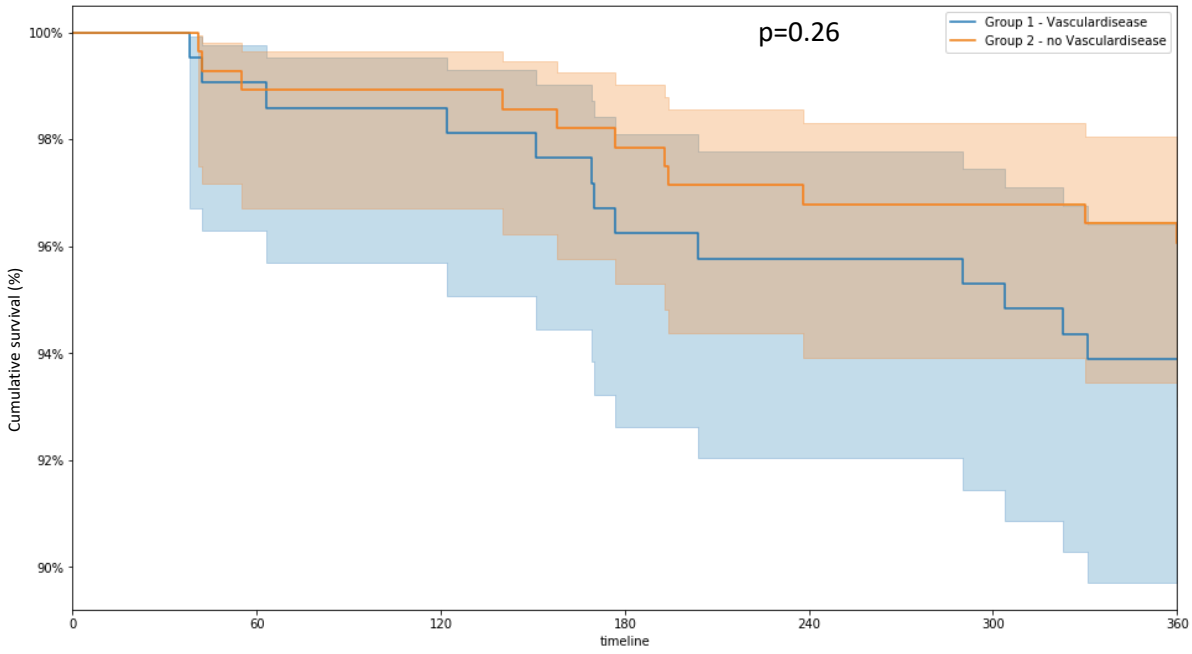
Figure S2. Temporal trend of treatment patterns in atrial fibrillation patients with and without concomitant vascular disease.



Temporal trends of treatment patterns in patients who were anticoagulated are shown by presence (a) or absence (b) of vascular disease. Trend tests showed no statistical significance in all groups expect for VKA alone in patients without vascular disease (p for trend = 0.01) and NOAC alone in patients without vascular disease (p for trend = 0.04).

AP, antiplatelet therapy; NOAC, non-vitamin K antagonist oral anticoagulants; VKA, vitamin K antagonist

Figure S3. Kaplan–Meier curve for all-cause death according to the presence of vascular disease.



Number of subjects at risk							
[days]	0	60	120	180	240	300	360
Vascular disease	213*	211	210	205	204	203	200
No vascular disease	280*	277	277	274	271	271	269

* 2 patients less in each group due to missing date of death

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Article

Characteristics and Treatment of Atrial Fibrillation with Respect to the Presence or Absence of Heart Failure. Insights from the Multicenter Polish Atrial Fibrillation (POL-AF) Registry

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Abstract: Background: We aimed to assess characteristics and treatment of AF patients with and without heart failure (HF). Methods: The prospective, observational Polish Atrial Fibrillation (POL-AF) Registry included consecutive patients with AF hospitalized in 10 Polish cardiology centers in 2019–2020. Results: Among 3999 AF patients, 2822 (71%) had HF (AF/HF group). Half of AF/HF patients had preserved ejection fraction (HFpEF). Compared to patients without HF (AF/non–HF), AF/HF patients were older, more often male, more often had permanent AF, and had more comorbidities. Of AF/HF patients, 98% had class I indications to oral anticoagulation (OAC). Still, 16% of patients were not treated with OAC at hospital admission, and 9%—at discharge (regardless of the presence of HF and its subtypes). Of patients not receiving OAC upon admission, 61% were prescribed OAC (most often apixaban) at discharge. AF/non–HF patients more often converted from AF at admission to sinus rhythm at discharge compared to AF/HF patients (55% vs. 30%), despite cardioversion performed as often in both groups. Class I antiarrhythmics were more often prescribed in AF/non–HF than in AF/HF group (13% vs. 8%), but still as many as 15% of HFpEF patients received them. Conclusions: Over 70% of hospitalized AF patients have coexisting HF. A significant number of AF patients does not receive the recommended OAC.

Keywords: atrial fibrillation; anticoagulation; heart failure

1. Introduction

Atrial fibrillation (AF) and heart failure (HF) are two colliding epidemics affecting approximately 1–2% of the world population [1], and resulting in significant morbidity and mortality [2,3]. HF affects overall more than 50% of patients with AF, whilst the prevalence of AF increases proportionally with the severity of the HF, reaching as much as over 50% of patients in New York Heart Association (NYHA) functional class IV [4]. HF and AF can cause and exacerbate each other through jointly shared risk factors, pathophysiology and mechanisms such as structural cardiac remodeling, activation of neurohormonal mechanisms, and rate-related impairment of left ventricular (LV) function [2].

The general approach to AF management does not differ between HF and other patients, with anticoagulation as the basis of treatment [2]. However, when it comes to maintenance of sinus rhythm and rate control, the matter becomes more complicated and the decision to adopt a treatment strategy depends on the patient's age, HF etiology (tachycardia-related cardiomyopathy), AF duration and symptomatology, other coexisting cardiac and non-cardiac diseases and conditions, left atrial dimensions, anticipated adverse effects of antiarrhythmic drugs (AADs), and patient's preferences [2].

There are significant differences in terms of pathophysiology, clinical features, and effectiveness of HF treatment depending on its phenotype i.e., HF with reduced ejection fraction (HFrEF), mid-range EF (HFmrEF), or preserved EF (HFpEF). In addition, diagnosis of HFpEF and HFmrEF in patients with AF is more challenging because elevation of natriuretic peptide levels and enlargement of the left atrium (which are diagnostic criteria for both HFmrEF and HFpEF) may be also associated with AF alone [2].

The aim of the study was to assess prevalence, clinical characteristics, and treatment of HF and its subtypes in hospitalized patients with AF.

2. Materials and Methods

2.1. Study Population

The POL-AF Registry (NCT04419012) was a prospective, observational study enrolling AF patients hospitalized in 10 cardiology departments (eight academic centers and two territorial centers) in Poland. Details on the study design and main results have been reported elsewhere [5,6]. Briefly, consecutive hospitalized patients in cardiology centers diagnosed with AF, except those admitted for AF ablation (in centers with electrotherapy labs), were included in the registry. Importantly, AF was not required to be the primary diagnosis and/or primary reason for index hospitalization, as the study included all hospitalized patients with AF diagnosis (except those admitted for AF ablation) to represent a broad spectrum of real-life AF patients. Patients with AF diagnosed upon hospital admission or during hospitalization were also included in the registry. Patients' recruitment process started in January 2019 and lasted 12 months or longer, i.e., until the inclusion of 300 consecutive AF patients at each participating center (with the last patient enrolled in March 2020). Patients hospitalized several times during the study period were entered in the database under the same number.

Diagnosis of AF and HF were made by attending physicians in accordance with the European Society of Cardiology (ESC) guidelines [7,8] In the current analysis, patients were categorized as having HF if they had a previous diagnosis of HF (classified as "previous HF diagnosis") or were classified by the investigators as having HF with symptoms in NYHA class II, III, or IV during index hospitalization (classified as "HF de novo"). The methodology was similar to the one applied in previous studies [9–16]. Patients with HF and LV EF of <40%, 40–49%, and >50% were included in the HFrEF, HFmrEF, and HFpEF groups, respectively.

The study was approved by the Ethics Committee of the Swietokrzyska Medical Chamber in Kielce (104/2018). The Ethics Committee waived the requirement of obtaining informed consent from the patients.

2.2. Data Collection

Data in the POL-AF Registry was gathered prospectively and included: demographics, medical history, electrocardiograms, results of laboratory tests (values on hospital admission), echocardiography, pharmacotherapy before hospital admission, and recommended at discharge.

2.3. Statistical Analysis

All continuous variables were tested for normality with the Kolmogorov–Smirnov test. Variables with normal distribution were expressed as mean ± standard deviation (SD). Nonparametric variables were expressed as median and interquartile range (IQR), and categorical variables as counts (*n*) with percentages (%). Fisher's exact test (two group comparison) or chi-square test (three or more group comparison) were used to compare categorical variables. Differences in continuous parameters were compared using the Mann–Whitney U test (two group comparison) and the Kruskal–Wallis test (three groups comparison) in case of nonparametric variables and unpaired *t*-test (two group comparison) or ANOVA (three groups comparison) in case of parametric variables. To determine predictors of non-prescription of oral anticoagulation (OAC) in AF/non–HF and AF/HF groups, multiple logistic regression analysis, using the stepwise forward procedure, was performed, including following variables: age ≥ 75 years, female sex (vs. male), LV EF < 50% (for the AF/HF group), hypertension, vascular disease (including those hospitalized for acute coronary syndrome for the analysis at discharge), diabetes, previous stroke, previous hemorrhagic events, renal dysfunction (chronic kidney dysfunction for the analysis at hospital admission, and glomerular filtration rate (GFR) < 60 mL/min/1.73m^2 for the analysis at discharge), liver disease, anemia (hemoglobin < 12 g/dL for women and <13 g/dL for men), antiplatelet therapy (at hospital admission and at hospital discharge for admission and discharge analyses, respectively), alcohol overconsumption, and chronic treatment with nonsteroidal anti-inflammatory drugs (NSAIDs). A two-sided *p* value of 0.05 was considered statistically significant. For database management and statistical analysis, we used SAS Institute Inc. 2015. SAS/IML® 14.1 User's Guide (SAS Institute Inc. Cary, NC, USA).

3. Results

3.1. Study Population

Overall, 3999 patients were enrolled in the POL-AF Registry. A total of 3396 patients (85%) were enrolled in academic centers and 603 patients (15%)—in territorial centers. Among them, 2822 (71%) had a diagnosis of HF, that was confirmed by previous documentation in 2621 (93%) and was first made during index hospitalization in 201 (7.1%) patients (Table 1). Of those, 950 (34%) had HFrEF, 417 (15%)—HFmrEF, 1359 (48%)—HFpEF and for 96 (3.4%) there were no information on LV EF and/or HF subtype in the registry database (Figure 1).

Table 1. Baseline characteristics of hospitalized atrial fibrillation patients depending on presence or absence of heart failure and its subtypes.

Variable	AF/non–HF (*n* = 1177)	AF/HF (*n* = 2822)	*p* [1]	AF/HF with Known EF (*n* = 2726)			*p* [2]
				HFrEF (*n* = 950)	HFmrEF (*n* = 417)	HFpEF (*n* = 1359)	
Demographics							
Age (years)	70.0 (64.0–78.0)	74.0 (66.0–82.0)	<0.01	71 (63–80)	76 (61–83)	75 (67–82)	<0.01
Females (%)	540 (50%)	1164 (41%)	<0.01	269 (29%)	163 (40%)	629 (50%)	<0.01
BMI (kg/m^2)	28.6 (26.0–31.3) *n* = 677	28.4 (25.6–32.4) *n* = 2065	0.54	28.1 (25.2–32.2) *n* = 633	29.0 (25.8–32.8) *n* = 308	28.6 (25.7–32.4) *n* = 1087	0.40

Table 1. *Cont.*

Variable	AF/non–HF (*n* = 1177)	AF/HF (*n* = 2822)	p [1]	AF/HF with Known EF (*n* = 2726)			p [2]
				HFrEF (*n* = 950)	HFmrEF (*n* = 417)	HFpEF (*n* = 1359)	
Primary reason of index hospital admission							
AF without any procedures	159 (14%)	93 (3.3%)	<0.01	19 (2.0%)	13 (3.1%)	57 (4.2%)	0.01
DC cardioversion for AF	267 (23%)	626 (22%)	0.74	105 (11%)	78 (19%)	438 (32%)	<0.01
HF decompensation	NA	806 (29%)	NA	380 (40%)	118 (28%)	296 (22%)	<0.01
Elective CIED * implantation/replacement	130 (11%)	230 (8.2%)	<0.01	92 (9.7%)	36 (8.6%)	94 (6.9%)	0.053
ACS	45 (3.8%)	202 (7.2%)	<0.01	80 (8.4%)	45 (11%)	73 (5.4%)	<0.01
Elective PCI	91 (7.7%)	292 (10%)	0.01	101 (11%)	50 (12%)	122 (9.0%)	0.15
Non-AF-ablation	78 (6.6%)	132 (4.7%)	0.02	34 (3.6%)	18 (4.3%)	76 (5.6%)	0.07
Other	388 (33%)	441 (16%)	<0.01	139 (15%)	59 (14%)	203 (15%)	0.92
AF type							
AF paroxysmal	664 (56%)	1259 (45%)	<0.01	352 (37%)	149 (36%)	719 (53%)	<0.01
AF persistent	337 (29%)	596 (21%)	<0.01	204 (22%)	103 (25%)	277 (20%)	0.17
AF permanent	176 (15%)	967 (34%)	<0.01	394 (42%)	165 (40%)	363 (26%)	<0.01
AF history							
Prior AF history	1043 (89%)	2654 (94%)	<0.01	893 (94%)	379 (91%)	1287 (95%)	0.02
Prior DC cardioversion for AF	211 (18%)	709 (25%)	<0.01	146 (15%)	93 (22%)	460 (34%)	<0.01
Prior AF-ablation	104 (8.8%)	160 (5.7%)	<0.01	44 (4.6%)	23 (5.5%)	90 (6.6%)	0.13
EHRA I	288 (38%) *n* = 753	1067 (53%) *n* = 2027	<0.01	292 (45%) *n* = 652	139 (48%) *n* = 291	602 (59%) *n* = 1023	<0.01
EHRA II	353 (47%) *n* = 753	614 (30%) *n* = 2027	<0.01	228 (35%) *n* = 652	96 (33%) *n* = 291	265 (26%) *n* = 1023	<0.01
-EHRA IIa	148 (20%) *n* = 753	246 (12%) *n* = 2025	<0.01	84 (13%) *n* = 652	44 (15%) *n* = 290	108 (11%) *n* = 1022	0.07
-EHRA IIb	113 (15%) *n* = 753	223 (11%) *n* = 2025	<0.01	70 (11%) *n* = 652	37 (13%) *n* = 290	114 (11%) *n* = 1022	0.66
EHRA III	96 (12%) *n* = 753	281 (14%) *n* = 2027	0.50	101 (15%) *n* = 652	46 (16%) *n* = 291	133 (13%) *n* = 1023	0.26
EHRA IV	16 (2.1%) *n* = 753	65 (3.2%) *n* = 2027	0.16	31 (4.8%) *n* = 652	10 (3.4%) *n* = 291	23 (2.3%) *n* = 1023	0.02
HF							
Previous HF diagnosis	NA	2621 (93%)	NA	936 (99%)	394 (94%)	1214 (89%)	<0.01
HF de novo	NA	201 (7.1%)	NA	14 (1.5%)	23 (5.5%)	145 (11%)	<0.01
NYHA I/II at admission	NA	1473 (55%) *n* = 2665	NA	327 (37%) *n* = 889	207 (53%) *n* = 392	886 (68%) *n* = 1301	<0.01
NYHA III at admission	NA	859 (32%) *n* = 2665	NA	398 (45%) *n* = 889	138 (35%) *n* = 392	304 (23%) *n* = 1301	<0.01

Table 1. *Cont.*

Variable	AF/non–HF (*n* = 1177)	AF/HF (*n* = 2822)	*p* [1]	AF/HF with Known EF (*n* = 2726)			*p* [2]
				HFrEF (*n* = 950)	HFmrEF (*n* = 417)	HFpEF (*n* = 1359)	
NYHA IV at admission	NA	190 (7.1%) *n* = 2665	NA	115 (13%) *n* = 889	25 (6.4%) *n* = 392	45 (3.5%) *n* = 1301	<0.01
Comorbidities							
Hypertension	937 (80%)	2407 (85%)	<0.01	761 (80%)	349 (84%)	1216 (90%)	<0.01
Vascular disease	434 (37%)	1811 (64%)	<0.01	660 (69%)	291(70%)	798 (59%)	<0.01
Previous stroke	120 (10%)	380 (13%)	<0.01	133 (14%)	58 (14%)	171 (13%)	0.60
Thromboembolic events	151 (13%)	508 (18%)	<0.01	167 (18%)	66 (16%)	254 (19%)	0.39
Hemorrhagic events	58 (4.9%)	193 (6.8%)	0.02	68 (7.2%)	30 (7.2%)	85 (6.3%)	0.63
Diabetes mellitus	319 (27%)	1047 (37%)	<0.01	397 (42%)	158 (38%)	450 (33%)	<0.01
Chronic kidney disease	138 (12%)	891 (32%)	<0.01	346 (36%)	126 (30%)	384 (29%)	<0.01
Smoking (current/former)	256 (23%) *n* = 1098	795 (30%) *n* = 2677	<0.01	332 (37%) *n* = 904	106 (27%) *n* = 391	322 (25%) *n* = 1296	<0.01
Alcohol overconsumption (≥8 drinks/week)	21 (1.9%) *n* = 1107	129 (4.8%) *n* = 2701	<0.01	68 (7.5%) *n* = 906	13 (3.3%) *n* = 395	44 (3.4%) *n* = 1312	<0.01
Liver disease	46 (3.9%)	215 (7.6%)	<0.01	103 (11%)	31 (7.4%)	74 (5.5%)	<0.01
Thyroid disease	205 (17%)	522 (19%)	0.44	159 (17%)	91 (22%)	257 (19%)	0.08
COPD/asthma	67 (5.7%)	381 (14%)	<0.01	136 (14%)	49 (12%)	182 (13%)	0.44
CIED therapy *	162 (14%)	717 (25%)	<0.01	343 (36%)	95 (23%)	255 (19%)	<0.01

[1] *p* value for difference between patients with and without heart failure. [2] *p* value for difference between heart failure patients with reduced, mid-range, and preserved ejection fraction. * defined as use of pacemaker, implantable cardioverter-defibrillator and/or cardiac resynchronization therapy. Abbreviations: AF, atrial fibrillation; BMI, body mass index; CAD, coronary artery disease; CIED; cardiac implantable electronic device; COPD, chronic obstructive pulmonary disease; DC, direct current; EHRA, European Heart Rhythm Association; HF, heart failure; HFmEF, heart failure with mild-range ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; NA, non-applicable; NYHA, New York Heart Association; PAD, peripheral artery disease.

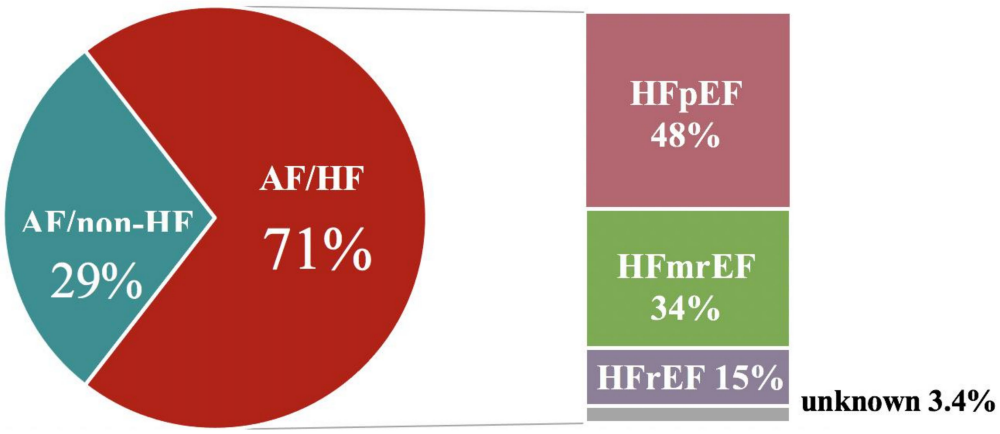

Figure 1. Frequency of heart failure and its subtypes in hospitalized atrial fibrillation patients. Abbreviations: AF, atrial fibrillation; HF, heart failure; HFmEF, heart failure with mild-range ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction.

3.2. Atrial Fibrillation Patients with and without Heart Failure

Clinical and laboratory characteristics of the study groups are presented in Tables 1, 2 and S1

Table 2. Thromboembolic and bleeding risk of hospitalized atrial fibrillation patients depending on presence or absence of heart failure and its subtypes.

Variable	AF/non–HF (*n* = 1177)	AF/HF (*n* = 2822)	*p* [1]	AF/HF with Known EF (*n* = 2726)			*p* [2]
				HFrEF (*n* = 950)	HFmrEF (*n* = 417)	HFpEF (*n* = 1359)	
CHA2DS2-VASc score	3 (2–4) 3.2 ± 1.7	5 (4–6) 4.9 ± 1.6	<0.01	5 (4–6) 4.7 ± 1.7	5 (4–6) 5.0 ± 1.6	5 (4–6) 5.0 ± 1.5	<0.01
No indications to OAC [3]	89 (7.6%)	0 (0%)	<0.01	0 (0%)	0 (0%)	0 (0%)	1.00
Class IIa indications to OAC [4]	174 (15%)	61 (2.2%)	<0.01	36 (3.8%)	5 (1.2%)	18 (1.3%)	<0.01
Class I indications to OAC [5]	914 (78%)	2761 (98%)	<0.01	914 (96%)	412 (99%)	1341 (99%)	<0.01
HAS-BLED score	2 (1–2) 1.9 ± 0.9	2 (2–3) 2.2 ± 0.9	<0.01	2 (2–3) 2.2 ± 1.0	2 (2–3) 2.3 ± 0.9	2 (2–3) 2.2 ± 0.9	0.03

[1] *p* value for difference between patients with and without heart failure.[2] *p* value for difference between heart failure patients with reduced, mid-range and preserved ejection fraction.[3] CHA2DS2-VASc score 0 for men and 1 for women.[4] CHA2DS2-VASc score 1 for men and 2 for women.[5] CHA2DS2-VASc score $\geq$ 2 for men and $\geq$ 3 for women. Abbreviations: See Table 1; OAC, oral anticoagulation.

In patients with AF and no HF (AF/non–HF), median age was 70 years, half were female, 56% had paroxysmal AF, 80% had hypertension, 37% had vascular disease, 13% had previous thromboembolic events, 5% had previous hemorrhagic events, and the median CHA_2DS_2-VASc score was 3, with 78% of patients with class I indications to OAC. Compared to AF/non–HF patients, those with both AF and HF diagnosis (AF/HF) were older (median age 74 years), more often male, more often had permanent AF (34% vs. 15%), and had an even higher prevalence of comorbidities, including hypertension, vascular disease, diabetes, and previous thromboembolic (18%) and hemorrhagic events (7%), hence were at higher thromboembolic risk based on the CHA_2DS_2-VASc score (5 points), with 98% of patients with class I indications to OAC.

The most common primary reason for index hospitalization in AF/non–HF patients was direct current cardioversion (23%). The most common primary reason for index hospitalization in the AF/HF group was HF decompensation (29%). Direct current cardioversion in AF/HF was as commonly performed as in AF/non–HF (22% vs. 23%, $p = 0.74$) (Table 1).

At hospital admission, 66% of AF/non–HF and 76% of AF/HF patients were in AF. If in AF at hospital admission, AF/non–HF patients more often converted to sinus rhythm at discharge as compared to AF/HF patients (55% vs. 30%, $p < 0.05$), given higher prevalence of permanent AF in AF/HF group. Irrespective of HF, the majority of patients with sinus rhythm on an electrocardiogram at hospital admission remained in sinus rhythm at discharge (99% of AF/non–HF and 97% of AF/HF patients, $p > 0.05$) (Figure S1; Supplementary Materials online).

At hospital admission, 17% of AF/non–HF and 16% of AF/HF patients, did not receive any anticoagulation (Figure 2).

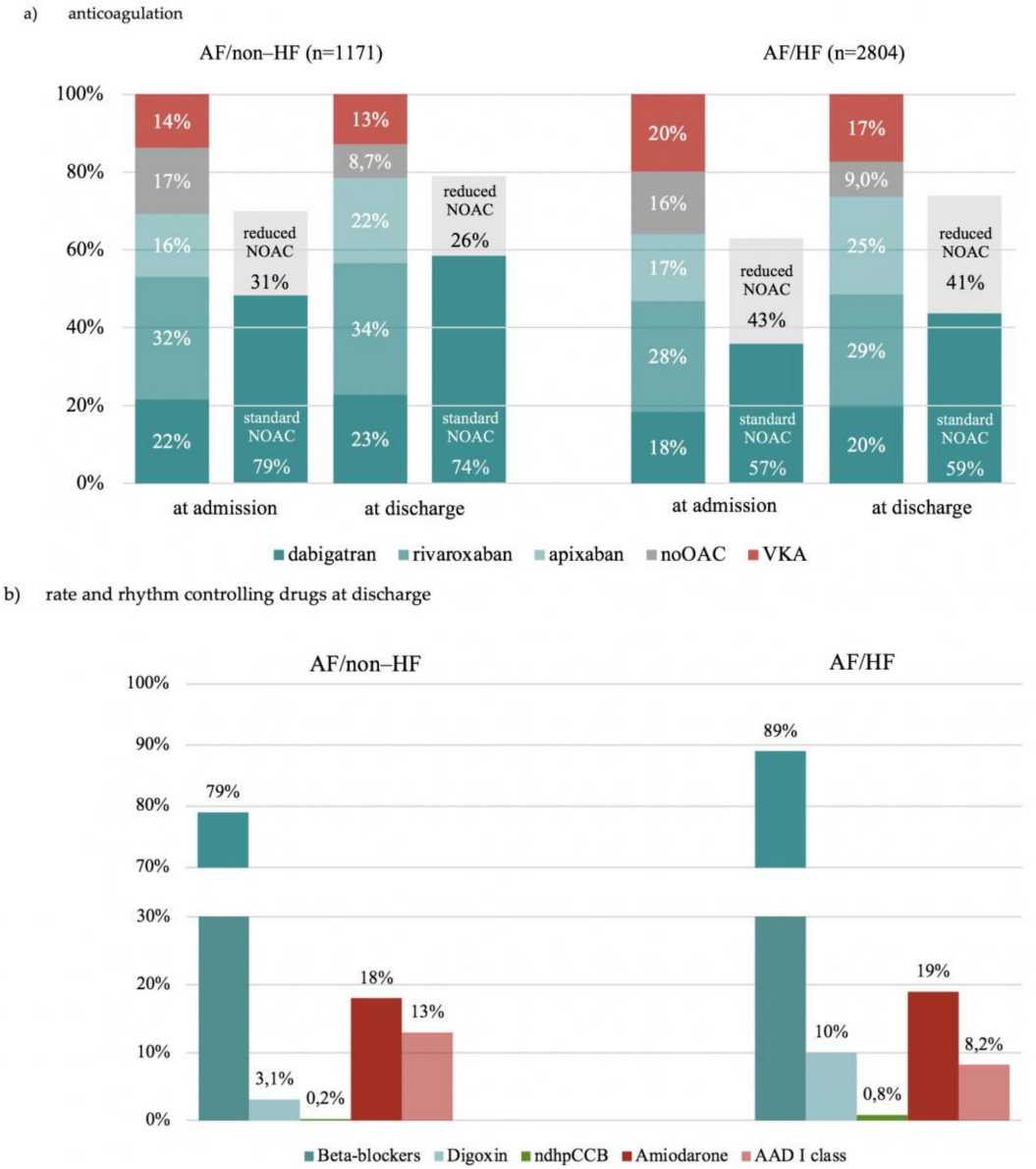

Figure 2. Pharmacotherapy of hospitalized atrial fibrillation patients depending on presence or absence of heart failure and its subtypes. (**a**) Differences between AF/non–HF vs. AF/HF group were statistically significant for all treatment subgroups ($p < 0.05$), except no OAC at baseline ($p = 0.64$), apixaban treatment at baseline ($p = 0.29$), and no OAC ($p = 1.00$) at discharge. Differences between AF/non–HF vs. AF/HF group regarding reduced and standard NOAC doses were statistically significant ($p < 0.05$). (**b**) Dronedarone was not prescribed in any of the groups. Differences in pharmacotherapy between AF/nonHF vs. AF/HF group were statistically significant ($p < 0.05$), except amiodarone treatment ($p = 0.53$). Abbreviations: See Table 1; AAD, antiarrhythmic drug; ndhpCCB, non-dihydropyridine calcium channel blockers, NOAC, non-vitamin K antagonist oral anticoagulant.

A total of 69% of such patients in the AF/non–HF group and 96% of such patients in the AF/HF group had class I indications to OAC (Figure S2, Supplementary Materials online). Of patients not receiving OAC upon hospital admission, 58% in the AF/non–HF group and 63% in the AF/HF group were prescribed OAC (most often apixaban) at hospital discharge (Table S2, Supplementary Materials online). Conversely, of AF/non–HF patients with no indications to OAC, almost three quarters received OAC at hospital admission (Table 3). Predictors of non-prescription of OAC in both groups are shown in Figure 3.

Table 3. (**A**) Proportion of patients receiving oral anticoagulation at hospital admission in relation to heart failure presence and indications to oral anticoagulation [2]. (**B**) Proportion of patients not receiving oral anticoagulants at hospital admission who received oral anticoagulation at discharge in relation to heart failure presence and indications to oral anticoagulation [2].

(A)	**No Indications to OAC**		**Class IIa Indications to OAC**		**Class I Indications to OAC**	
			AF/non–HF			
Overall	65 (74%)		135 (78%)		768 (85%)	
-HAS-BLED 0	59 (91%)		3 (2.2%)		1 (0.1%)	
-HAS-BLED 1–2	6 (9.2%)		131 (97%)		593 (77%)	
-HAS-BLED ≥3	0 (0%)		1 (0.7%)		174 (23%)	
			AF/HF			
Overall	NA		44 (72%)		2276 (84%)	
-HAS-BLED 0	NA		29 (66%)		15 (0.7%)	
-HAS-BLED 1–2	NA		15 (34%)		1540 (68%)	
-HAS-BLED ≥ 3	NA		0 (0%)		721 (32%)	
(B)	**No Indications to OAC**		**Class IIa Indications to OAC**		**Class I Indications to OAC**	
			AF/non–HF			
Overall	23 (26%)		39 (22%)		136 (15%)	
-HAS-BLED 0	19 (83%)		3 (7.7%)		1 (0.7%)	
-HAS-BLED 1–2	4 (17%)		35 (90%)		85 (63%)	
-HAS-BLED ≥3	0 (0%)		1 (2.6%)		50 (37%)	
	OAC at discharge	No OAC at discharge	OAC at discharge	No OAC at discharge	OAC at discharge	No OAC at discharge
Overall	10 (43%)	13 (57%)	23 (59%)	16 (41%)	80 (59%)	56 (41%)
-HAS-BLED 0	10 (100%)	9 (69%)	0 (0%)	3 (19%)	0 (0%)	1 (1.8%)
-HAS-BLED 1–2	0 (0%)	4 (31%)	22 (96%)	13 (81%)	57 (71%)	28 (50%)
-HAS-BLED ≥3	0 (0%)	0 (0%)	1 (4.3%)	0 (0%)	23 (29%)	27 (48%)
			AF/HF			
Overall	NA		17 (28%)		430 (16%)	
-HAS-BLED 0	NA		13 (76%)		3 (0.7%)	
-HAS-BLED 1–2	NA		3 (15%)		202 (47%)	
-HAS-BLED ≥3	NA		1 (5.9%)		225 (52%)	
	OAC at discharge	No OAC at discharge	OAC at discharge	No OAC at discharge	OAC at discharge	No OAC at discharge
Overall	NA	NA	13 (76%)	4 (24%)	268 (62%)	162 (38%)
-HAS-BLED 0	NA	NA	10 (77%)	3 (75%)	2 (0.7%)	1 (0.6%)
-HAS-BLED 1–2	NA	NA	2 (15%)	1 (25%)	137 (51%)	65 (40%)
-HAS-BLED ≥3	NA	NA	1 (7.7%)	0 (0%)	129 (48%)	96 (59%)

Class IIa indications to OAC: CHA_2DS_2-VASc 1 (if male), 2 (if female). Class I indications to OAC: CHA_2DS_2-VASc ≥2 (if male), ≥3 (if female). Differences in non-oral anticoagulation prescription at admission between AF/non–HF vs. AF/HF group were not statistically significant for both, class IIa ($p = 0.39$) and class I ($p = 0.50$) indications to oral anticoagulation. Differences in non-oral anticoagulation prescription at discharge between AF/non–HF vs. AF/HF group were not statistically significant for both, class IIa ($p = 0.54$) and class I ($p = 0.48$) indications to oral anticoagulation. Presented data included only patients with information on oral anticoagulation at hospital admission and at hospital discharge ($n = 3933$). Abbreviations: See Table 1.

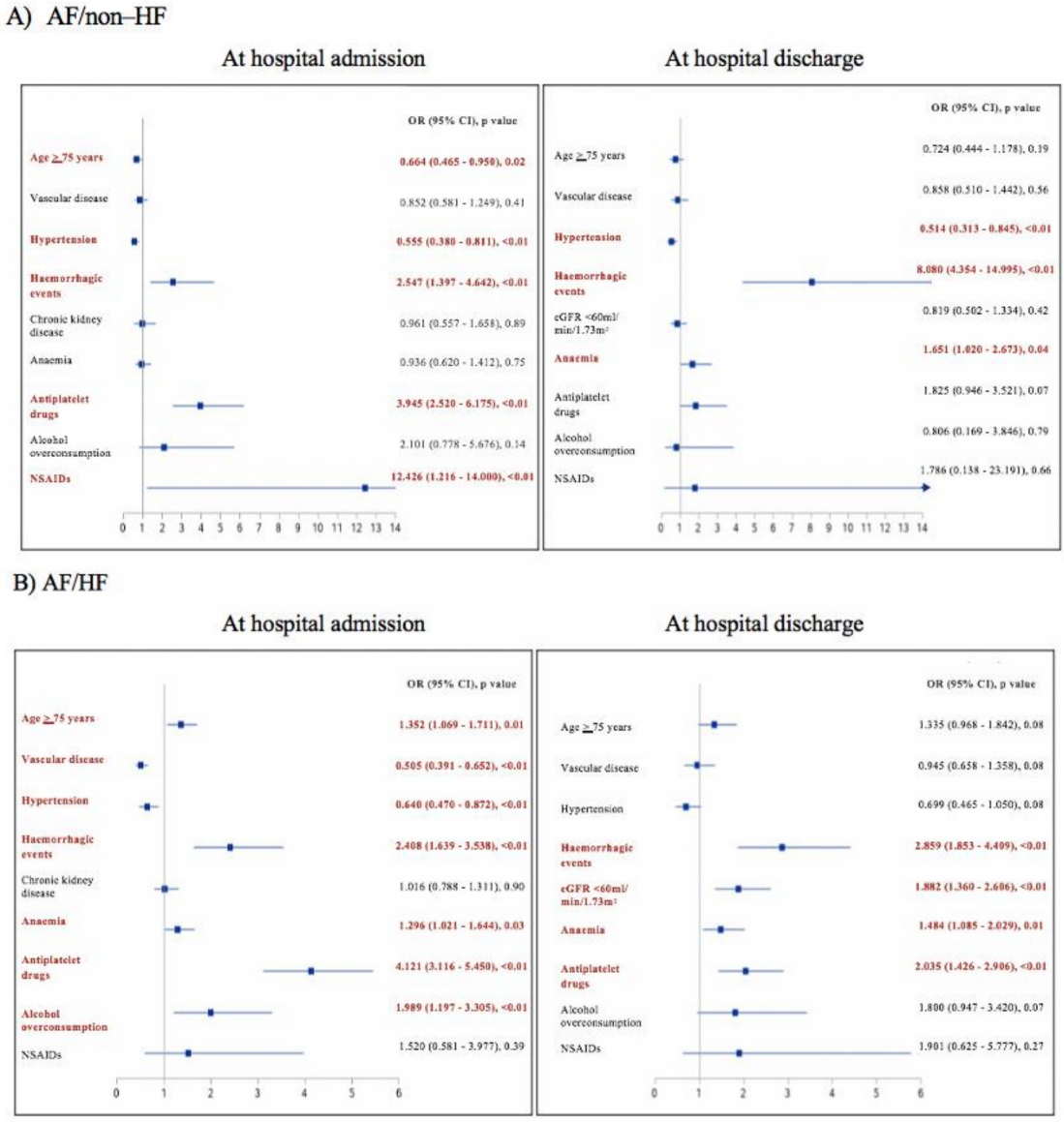

Figure 3. Predictors of non-prescription of oral anticoagulation in atrial fibrillation patients without heart failure (**A**) and with heart failure (**B**). Following variables were included in analysis: age ≥ 75 years, female sex (vs male), LV EF < 50% (for the AF/HF group), hypertension, vascular disease (including those hospitalized for acute coronary syndrome for the analysis at discharge), diabetes, previous stroke, previous hemorrhagic events, renal dysfunction (chronic kidney dysfunction for the analysis at hospital admission, and GFR < 60 mL/min/1.73 m^2 for the analysis at discharge), liver disease, anemia (hemoglobin < 12 g/dL for women and <13 g/dL for men), antiplatelet therapy (at hospital admission and at hospital discharge for admission and discharge analyses, respectively), alcohol overconsumption and chronic treatment with NSAIDs. Abbreviations: See Table 1; CI, coincidence interval; NSAIDs, non-steroidal anti-inflammatory drugs; OR, odds ratio.

Irrespective of the presence of HF, majority of patients were prescribed non-vitamin K antagonist OAC (NOAC) with a predominance of rivaroxaban (Figure 2a). However, apixaban was the type of OAC most frequently initiated during hospitalization in both AF/HF and AF/non–HF group. (Figure 2a; Table S2; Supplementary Materials online). Reduced NOAC doses were more often prescribed in AF/HF group both at baseline (43% vs. 31%) and at discharge (41% vs. 26%) as compared to AF/non–HF group (Figure 2a).

At hospital discharge, beta-blockers were the most commonly prescribed medications for rhythm/rate control in both groups (79% in AF/non–HF, and 89% in AF/HF group). Digoxin was more often prescribed in the AF/HF group (10% vs. 3.1%). Non-

dihydropyridine calcium channel blockers (CCB) were rarely prescribed in either group. Amiodarone was as frequently prescribed in both groups (18% and 19%). Class I antiarrhythmic drugs (AADs) were more often prescribed in AF/non–HF than in AF/HF group (13% vs. 8%) (Figure 2b). None of the patients received dronedarone.

Diuretics (73% vs. 45%), renin-angiotensin system (RAS) inhibitors (81% vs. 71%), and mineralocorticoid receptor antagonists (50% vs. 17%) were more often prescribed in AF/HF patients as compared to AF/non–HF patients (Figure S3; Supplementary Materials online).

3.3. Atrial Fibrillation Patients with Heart Failure Depending on Ejection Fraction

The comparison of clinical and laboratory characteristics of AF patients with HFrEF, HFmrEF and HFpEF are shown in Tables 1 and 2 and Table S1, respectively. Pharmacotherapy of those patients is presented in Figures S3 and S4 (Supplementary Materials online). All HF subgroups were most often prescribed rivaroxaban, with the exception of HFrEF patients at discharge who were more often prescribed apixaban. The frequency of apixaban prescription increased, and that of rivaroxaban decreased with decreasing LVEF. There were no other differences in terms of OAC treatment between HF subtypes (Figure S4a). Reduced doses of NOACs were more often prescribed in HFrEF at baseline (Figure S4b). Beta-blockers were the most commonly prescribed medications for rhythm/rate control in all groups, with no differences between HF subtypes. Digoxin and amiodarone were more often prescribed in the HFrEF group. Noteworthy, 15% of HFpEF were prescribed AADs class I (Figure S4c). No statistically significant difference was observed in prescription of RAS inhibitors between HF subgroups. Patients with HFrEF more often received diuretics and mineralocorticoid receptor antagonists, whereas patients with HFpEF were more often treated with CCBs as compared to other subgroups (Figure S3).

4. Discussion

The main advantage of registries is their observational character, which allows one to study real-world, unselected groups of patients encountered in everyday clinical practice. The POL-AF registry included AF patients hospitalized in cardiology centers and, thus, it does not reflect the characteristics of the general AF population. Still, given the large number of consecutive patients enrolled in the registry, irrespective of the reason for index hospitalization or the presence of AF at hospital admission, the POL-AF registry provides a reliable description of this specific AF subpopulation.

The most important findings of our study are as follows: (1) Over 70% of AF patients hospitalized in cardiology centers had coexisting HF, mostly HFpEF (2); due to advanced age and high comorbidity burden AF/HF patients had a high CHA_2DS_2-VASc score (median: 5 points); with 98% of patients with class I indications to OAC (3); however, at hospital admission, 16% of AF/HF patients did not receive any OAC (4); predictors of OAC non-prescription in patients with AF and HF included age $\geq$ 75 years, previous hemorrhagic events, renal dysfunction, anemia, antiplatelet therapy and alcohol overconsumption; and (5) 15% of AF patients with HFpEF were treated with class I AADs, despite a diagnosis of structural heart disease.

The prevalence of HF in the POL-AF population was higher than reported in previous studies [9–16]. This may be explained by the fact that the POL-AF registry included AF patients hospitalized in cardiology centers, as well as by the fact that previous studies reported mostly HF with moderately or severely reduced LV EF [15,16], while in POL-AF, HFpEF constituted half of all HF cases. This reflects the close relationship between HFpEF and AF, resulting not only from increased left atrial pressures in the course of HF, but also from shared risk factors of these two clinical entities. Consequently, the prevalence of AF in HFpEF is even higher than in HFrEF [17,18]. In the ESC-HF Long-Term registry, the prevalence of HFpEF in patients hospitalized for HF was 29%, while in our study, in AF/HF patients, it was much higher (48%), which further proves the strong association of AF with HFpEF [19,20]. The diagnosis of HFpEF in patients with AF may be problematic because of the difficulty in separating symptoms that are due to

HF from those due to AF [21]. Natriuretic peptides are elevated, and left atrial dilatation is common in AF regardless of concomitant HF [22,23]. This issue has been addressed in the recent consensus recommendation from the Heart Failure Association of the ESC, with higher cut-offs for HFpEF diagnosis for both left atrial volume index and natriuretic peptides in AF patients in the HFA-PEFF score [22]. On the other hand, AF is highly prevalent in HFpEF, even more prevalent than in HFrEF [17,18], and presence of AF was actually proven to predict HFpEF [24]. In the H2FPEF score, a modern score to predict HFpEF, derived from a population with HFpEF confirmed with a gold standard, i.e., invasive hemodynamic exercise testing, presence of AF is the strongest predictive factor for HFpEF [24]. High prevalence of AF in HFpEF patients results not only from a HF-related elevation in left atrial pressure, but also from a common pathophysiological background of both AF and HFpEF, which share the same risk factors, including older age, hypertension, obesity, metabolic syndrome and other cardiac and extra-cardiac comorbidities. Thus, high prevalence of HFpEF in the AF population in our study is not surprising, even if the finding is, itself, novel.

Our study performed a thorough analysis of patients with AF and HFmrEF. The ESC guidelines do not give specific recommendations for management of HFmrEF, but they suggest that, since patients with HFmrEF have mostly been included in trials of HFpEF, rather than HFrEF, they should be treated with the same management principle as patients with the former, until new evidence is available [7]. In current clinical practice, compared with HFrEF patients, fewer patients with HFpEF and HFmrEF appear to receive diuretics, beta-blockers, mineralocorticoid receptor antagonists, and RAS inhibitors [7,25]. However, in our study there was no difference in the number prescribed the aforementioned drugs between subgroups of HF except MRAs and diuretics. Further randomized clinical trials with long-term follow-up of this group are required before particular treatment strategies in AF patients with HFmrEF can be recommended.

Indeed, in the 7.1% of patients with "de novo" HF diagnosis, an unequivocal distinction between AF-related dyspnea and AF associated with HF may not be possible, especially in patients with HFpEF. However, the resolution of symptoms after conversion to sinus rhythm suggests AF-related dyspnea, while their persistence despite conversion to sinus rhythm (in patients fulfilling other HF diagnostic criteria) confirms correct HF diagnosis. As presented in Figure S1b, 55% of patients with AF at hospital admission converted to sinus rhythm during hospitalization, which might have helped their attending physicians in securing a correct HF diagnosis. Furthermore, 29% of HF patients were in sinus rhythm (and not AF) on hospital admission (Figure S1a), meaning that their symptoms on admission were attributable to HF, and not AF.

The background etiology and epidemiology differ between the particular types of HF and our results reflect previous observations [26–28]. Age and comorbidity burden were high even in the AF/non–HF group. AF/HF patients, as expected, had even more comorbidities. Median CHA_2DS_2-VASc scores were 3 and 5 in AF/non–HF and AF/HF groups, respectively. Despite the majority of patients with previous diagnosis of AF and class I indications to OAC, a significant proportion of patients in both groups did not receive OAC upon hospital admission. This is somewhat similar to the results of our previous study of AF patients admitted for AF direct current cardioversion or AF ablation in years 2012–2016, where also 17% of patients were not treated with any OAC, although it must be noted that these two populations were very different [29]. Low prescription of recommended OAC is complex and may compounded by many factors. In our study, predictors of OAC non-prescription in both AF/non–HF and AF/HF groups included age >75 years, previous hemorrhagic events, hypertension and antiplatelet therapy at hospital admission, and hemorrhagic events and anemia at hospital discharge. This variety of factors associated with OAC non-prescription is line with previous studies [30]. Future efforts to characterize reasons for non-prescription and determine whether educational or quality improvement interventions will increase OAC utilization in AF patients are warranted.

More than half of patients (61%) in the current study were ultimately discharged on OAC, mainly on apixaban. This could be explained by recent data implying superiority of apixaban over other NOACs. Compared to VKA, all NOACs are associated with fewer cardiovascular events, including myocardial infraction and stroke in patients with both AF and HF based on the recent study by Amin et al. [31]. The study reported that AF/HF patients prescribed NOAC had 36% lower odds of stroke/systemic embolism, 34% lower odds of major bleeding and 27% lower odds of major adverse cardiovascular events compared to VKA. Moreover, when apixaban users were compared to patients taking rivaroxaban and dabigatran, apixaban showed better results. Those patients had a 45% lower risk of bleeding and a 14% lower risk of major adverse cardiovascular events versus rivaroxaban, and corresponding risk reductions compared to dabigatran were 29% and 20% [31]. However, recent studies have shown inconclusive results regarding the superiority of one NOAC over others in subgroup populations including elderly patients (≥85-year-old) [32] or those with high prevalence of prescribed drugs interacting with NOAC pharmacokinetics [33].

In our study, RAS inhibitors were frequently used, irrespective of HF presence, which is not surprising given the high prevalence of coexisting hypertension, coronary artery disease, diabetes, and renal dysfunction in both AF/HF and AF/non–HF groups. This is in line with the most recent ESC AF guidelines [34], recommending comprehensive AF treatment consisting of three main pillars, anticoagulation (A), better symptom control (B), and comorbidities and risk factors control (C). High frequency of treatment with RAS inhibitors (concordant with the "C" element) suggests that this time the guidelines followed clinical practice, as our registry was conducted before the introduction of the 2020 ESC AF guidelines [34].

In the AF Follow-up Investigation of Rhythm Management (AFFIRM) trial, it was demonstrated that absence of HF favored the rate control strategy, but no differences were seen in patients with HF [35]. Further, Atrial Fibrillation and Congestive Heart Failure (AF-CHF) investigators indicated no differences between the rate and rhythm control strategy in AF patients with HF with regard to all-cause death, stroke and worsening HF, however AF hospitalization risk in the rhythm control group was higher than that in the rate control group [36]. On the other hand, catheter ablation was proved to improve quality of life, symptoms, and LV function [37] and reduce all-cause mortality and hospitalization [38] in other randomized control trials. A recent substudy of a meta-analysis comparing catheter ablation and rate control strategy, reported no differences in the composite of all-cause mortality and HF readmission between the two groups. However, when compared with rate control, catheter ablation was associated with improvement in LV function and health-related quality of life [39]. Still, superiority of rhythm over rate control still needs to be confirmed in large randomized controlled trials. In our study, beta-blockers were the most common rhythm/rate control drugs in both AF/non–HF and AF/HF patients. Beta-blockers are known to prolong life in HFrEF patients who are in sinus rhythm [40], however, their use has been questioned to improve prognosis in HFrEF and AF [41]. Still, in our study, most patients with AF and HFrEF were prescribed beta-blockers. Digoxin was rarely used, especially in AF/non–HF patients, even though many of them were elderly. This could be explained by heterogenous data regarding treatment with digoxin. Observational studies have associated digoxin use with excess mortality in AF patients [42–44]. However, recent metanalysis reported neutral effect on mortality and a lower rate of hospital admissions on digoxin treatment compared to placebo and emphasized that all reported adverse outcomes associated with digoxin were more likely due to selection and prescription biases rather than harm caused by digoxin [45]. Recent results from the Rate Control Therapy Evaluation in Permanent Atrial Fibrillation (RATE-AF) trial, confirmed safety of digoxin in AF/HF patients, where it was safer and more effective than beta-blockers [46]. Although amiodarone is associated with serious long-term side-effects [47,48], and is thus considered a second-line antiarrhythmic in AF patients without HF, almost one-fifth of AF/non–HF patients received amiodarone, which was as often as in the AF/HF group. In AF/non–HF

patients, amiodarone was prescribed more frequently than AADs class I. This may be to some extent explained by a high prevalence of coronary artery disease in those AF/non–HF patients (62% of patients prescribed amiodarone had coronary artery disease). In the AF/HF group, amiodarone might have also been prescribed for indications other than AF (such as ventricular arrhythmias). Finally, it is surprising that AADs class I were used in 8% of HF patients, including 15% of patients diagnosed with HFpEF, despite AADs class I being contraindicated in patients with known structural heart disease such as heart failure, hypertrophic cardiomyopathy and valvular heart disease [2,49]. The proportion of patients with HFpEF receiving contraindicated AADs class I was even higher in patients hospitalized in academic centers (16% vs. 5.3% in territorial centers, $p < 0.01$) However, our data must be interpreted in relation to the studied population, in which 85% were patients hospitalized in academic centers. This means that the percentage of patients not receiving OAC despite indications or receiving antiarrhythmics class I despite contraindications may be even higher in territorial hospitals, given the differences in characteristics and treatment between patients hospitalized in academic vs. territorial hospitals in the POL-AF registry (Table S3; Supplementary Materials online).

Limitations

The limitations of our study arise largely from the type of data analyzed (i.e., registry-derived). First, there was a certain proportion of data missing for some of the patients. Thus, we showed the number of patients for whom data were available in each table and figure. Second, only data predefined by the coordinators of the POL-AF registry were gathered in the database. Those did not include concentrations of natriuretic peptides or echocardiographic indices of LV diastolic function as well as HF etiology. Therefore, definitive verification of the pertinence of HFpEF diagnosis was not possible as well as definitively determining whether the patient had HF or AF first. However, the registry was conducted in academic and territorial centers with experience in managing multicenter registries and clinical trials, and investigators were requested to verify both AF and HF diagnosis in each patient according to the current guidelines [2,7]. Third, 85% of patients were enrolled in academic centers, which is important for data interpretation. Last, patients referred for catheter ablation for AF (pulmonary vein isolation) were excluded from the registry. Exclusion of patients referred for ablation was done in order to avoid selection bias, given that many academic cardiology centers perform catheter ablations, and AF patients admitted for ablation are mostly a specific group of young patients with no or few comorbidities. Given a high number of academic centers with an electrophysiology lab in the POL-AF registry, the number of young patients admitted for ablation would be high, and inclusion of such patients would artificially lower the age of the studied population and decrease the number of comorbidities as well as both thromboembolic and bleeding risks. This would then not properly reflect the characteristics of hospitalized AF patients who are mostly elderly with many comorbidities. Furthermore, patients referred for ablation are usually referred to an academic hospital from all over the region, while patients admitted for other elective procedures (such as cardioversion) or for acute reasons are mostly local residents of the area in which a given hospital (academic or territorial) is situated. On the other hand, it needs to be emphasized that the population of the POL-AF registry represents hospitalized patients with AF and not a general population of AF patients.

5. Conclusions

Herein, we performed a thorough analysis of patients with AF and HF subtypes including HFpEF, HFmrEF, and HFrEF. Almost all of the AF/HF patients had class I indications to OAC. Still, one in six AF patients did not receive OAC at hospital admission, irrespective of the presence of HF. Similarly, one in six HFpEF patients with AF was treated with class I AADs, despite a diagnosis of structural heart disease. Our study provides clinical characteristics and description of real-life treatment of AF/HF patients, showing some discrepancy between current guidelines and real-life practice.

Supplementary Materials: The following are available online at https://www.mdpi.com/2077-0383/10/7/1341/s1, Figure S1. Heart rhythm at hospital admission and its changes during hospitalization. Figure S2. Proportion of patients not receiving oral anticoagulation at hospital admission in relation to the presence or absence of heart failure and indications to oral anticoagulation. Figure S3. Prescription rate of heart failure medications in patients with and without heart failure (medication at discharge). Figure S4. Pharmacotherapy of hospitalized atrial fibrillation patients depending on the presence or absence of heart failure and its subtypes. Table S1. Laboratory and echocardiographic parameters of hospitalized atrial fibrillation patients depending on the presence or absence of heart failure and its subtypes. Table S2. Characteristics and treatment of patients receiving vs. not receiving oral anticoagulation at hospital admission. Table S3. Baseline characteristics of atrial fibrillation patients hospitalized in academic and territorial hospitals.

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Supplementary Materials

Table S1. Laboratory and echocardiographic parameters of hospitalized atrial fibrillation patients depending on presence or absence of heart failure and its subtypes.

Variable	AF/non–HF (n=1177)	AF/HF (n=2822)	p[1]	AF/HF with known EF (n=2726)			p[2]
				HFrEF (n=950)	HFmrEF (n=417)	HFpEF (n=1359)	
Laboratory tests							
Hemoglobin (g/dl)	13.7 [12.6-14.7] *n=1159*	13.1 [11.8-14.3] *n=2797*	**<0.01**	13.2 [11.8-14.4] *n=944*	13.1 [11.8-14.2] *n=415*	13.1 [11.9-14.2] *n=1342*	0.79
eGFR (ml/min/1.73m^2)	60.0 [53.0-78.5] *n=1121*	59.0 [44.0-75.0] *n=2776*	**<0.01**	56.8 [43.0-69.9] *n=938*	60.0 [45.0-79.9] *n=408*	60.0 [44.9-77.1] *n=1335*	**<0.01**
eGFR<60ml/ min/1.73m^2	701 (38%)	1407 (51%)	**<0.01**	522 (56%)	199 (49%)	639 (48%)	**<0.01**
Glucose (mg/dl)	101.0 [93.0-119.0] *n=915*	104 .0 [93.0-124.0] *n=2064*	0.08	105.0 [92.0-125.0] *n=709*	104.0 [95.0-124.0] *n=293*	103.0 [93.0-122.0] *n=992*	0.63
LDL (mg/dl)	93.0 [63.0-136.0] *n=727*	81.0 [58.0-113] *n=1749*	**<0.01**	81.2 [58.0-117.5] *n=620*	77.0 [56.0-104.0] *n=273*	83.0 [61.0-115.0] *n=814*	0.05
HDL (mg/dl)	48.0 [39.0-58.0] *n=726*	44.0 [36.0-54.0] *n=1754*	**<0.01**	43.7 [35.0-54.5] *n=621*	43.0 [34.4-52.2] *n=274*	45.0 [36.7-54.1] *n=817*	0.10
Triglycerides (mg/dl)	116.0 [62.9-167.0] *n=723*	106.3 [79.7-143.0] *n=1753*	**<0.01**	109.0 [81.0-153.1] *n=622*	107.0 [80.0-140.0] *n=275*	104.3 [76.2-138.0] *n=814*	0.05
Echocardiography parameters							
Left ventricular ejection fraction (%)	58.0 [55.0-60.0] *n=760*	50.0 [36.0-58.0] *n=2363*	**<0.01**	30.0 [25.0-37.0] *n=813*	45.0 [40.0-47.0] *n=367*	58.0 [55.0-60.0] *n=1183*	**<0.01**
Left atrial diameter (mm)	43.0 [40.0-47.0] *n=547*	48.0 [43.0-52.0] *n=2006*	**<0.01**	49.0 [45.0-54.0] *n=678*	48.0 [44.0-53.0] *n=299*	46.0 [42.0-51.0] *n=1028*	**<0.01**
Left atrial area (cm^2)	27 [23-32] *n=440*	29 [25-35] *n=1491*	**<0.01**	32 [28-38] *n=792*	29 [25-35] *n=477*	28 [24-33] *n=222*	**<0.01**
Left atrial volume index (ml/m^2)	43 [35-53] *n=210*	57 [44-75] *n=880*	**<0.01**	62 [51-79] *n=543*	51 [47-73] *n=223*	54 [42-73] *n=114*	**<0.01**
LVDD (mm)	49.0 [45.0-53.0] *n=707*	53.0 [48.0-59.0] *n=2250*	**<0.01**	59.0 [53.0-66.0] *n=770*	52.0 [48.0-57.0] *n=348*	50.0 [49.0-55.0] *n=1132*	**<0.01**
IVS (mm)	11.0 [10.0-13.0] *n=705*	11.0 [9.0-11.0] *n=2188*	0.50	11.0 [10.0-12.0] *n=731*	11.0 [10.0-12.0] *n=339*	11.0 [11.0-12.5] *n=1118*	**<0.01**

RVD (mm)	31.0 [28.0-34.0] *n=598*	32.0 [29.0-36.0] *n=1889*	**<0.01**	34.0 [31.0-39.0] *n=599*	32.0 [30.0-37.0] *n=299*	31.0 [28.0-34.0] *n=991*	**<0.01**
Aortic stenosis moderate/severe	34 (3.1%) *n=1098*	205 (7.5%) *n=2736*	**<0.01**	75 (8.1%) *n=921*	29 (7.1%) *n=407*	100 ((7.5%) *n=1332*	0.77
Mitral stenosis moderate/severe	37 (3.4%) *n=1098*	61 (2.2%) *n=2736*	**0.04**	32 (3.5%) *n=921*	9 (2.2%) *n=407*	18 (1.4%) *n=1331*	**<0.01**
Mechanical valve replacement	19 (1.6%) *n=1173*	116 (4.1%) *n=2817*	**<0.01**	35 (3.7%) *n=949*	22 (5.3%)	55 (4.1%)	0.39
- mitral valve replacement	12 (1.0%) *n=1176*	72 (2.6%) *n=2821*	**<0.01**	19 (2.0%)	15 (3.6%)	35 (2.6%)	0.22
- aortic valve replacement	9 (0.8%) *n=1174*	62 (2.2%) *n=2818*	**<0.01**	18 (1.9%) *n=949*	12 (2.9%)	29 (2.1%)	0.51

[1] p value for difference between patients with and without heart failure

[2] p value for difference between heart failure patients with reduced, mid-range and preserved ejection fraction

Abbreviations: AF, atrial fibrillation; eGFR, estimated glomerular filtration rate; HDL, high density lipoprotein; HF, heart failure; HFmEF, heart failure with mild-range ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; IVS, interventricular septum; LDL, low density lipoprotein; LVDD, left ventricular diastolic dimension; RVD, right ventricular dimension

Table S2. Characteristics and treatment of patients receiving vs not receiving oral anticoagulation at hospital admission.

Variable	AF/non–HF		p[1]	AF/HF		p[2]
	No OAC (n=200)	OAC (n=971)		No OAC (n=462)	OAC (n=2342)	
Demographics						
Age (years)	69 [61-77]	70 [64-79]	**0.02**	75 [68-83]	73 [66-81]	0.11
Females (%)	83 (42%)	453 (47%)	0.18	196 (42%)	962 (41%)	0.61
BMI (kg/m^2)	29 [26-32]	29 [26-31]	0.38	28 [25-32]	29 [26-32]	0.46
AF type						
AF paroxysmal	141 (70%)	522 (54%)	**<0.01**	224 (48%)	1029 (44%)	0.07
AF persistent	44 (22%)	291 (30%)	**0.03**	106 (23%)	488 (21%)	0.32
AF permanent	15 (7.5%)	158 (16%)	**<0.01**	132 (29%)	825 (35%)	**<0.01**
AF history						
Prior AF history	119 (60%)	919 (95%)	**<0.01**	352 (76%)	2285 (98%)	**<0.01**
Prior DC cardioversion for AF	19 (9.5%)	192 (20%)	**<0.01**	35 (7.6%)	674 (29%)	**<0.01**
Prior ablation for AF	8 (4.0%)	96 (9.9%)	**<0.01**	16 (3.5%)	144 (6.2%)	**0.02**
Comorbidities						
Hypertension	144 (72%)	788 (81%)	**<0.01**	374 (81%)	2019 (88%)	**<0.01**
CAD	66 (33%)	300 (31%)	0.56	260 (56%)	1385 (59%)	0.26
PAD	19 (9.5%)	86 (8.9%)	0.79	84 (18%)	385 (16%)	0.38
Valvular disease	78 (39%)	351 (36%)	0.47	282 (61%)	1518 (65%)	0.14
Previous stroke	20 (10%)	97 (10%)	1.00	49 (11%)	329 (14%)	0.052
Thromboembolic events	21 (11%)	127 (13%)	0.35	61 (13%)	444 (20%)	**<0.01**
Hemorrhagic events	21 (11%)	37 (3.8%)	**<0.01**	57 (12%)	136 (5.8%)	**<0.01**
Diabetes mellitus	47 (24%)	269 (28%)	0.26	173 (37%)	870 (37%)	0.92
Chronic kidney disease	21 (11%)	116 (12%)	0.63	153 (33%)	730 (31%)	0.41
Smoking (current/former)	49 (25%)	206 (23%)	0.58	135 (30%)	656 (30%)	0.91
Alcohol overconsumption (≥8 drinks/week)	7 (3.6%)	14 (1.5%)	0.08	29 (6.3%)	99 (4.5%)	0.09
Liver disease	12 (6.0%)	34 (3.5%)	0.11	44 (9.5%)	170 (7.3%)	0.10
Thyroid disease	27 (14%)	177 (18%)	0.12	73 (16%)	443 (19%)	0.13
COPD/asthma	11 (5.5%)	56 (5.8%)	1.00	59 (13%)	322 (14%)	0.60
Laboratory tests						
Hemoglobin (g/dl)	13.7 [12.4-15.0]	13.7 [12.6-14.6]	0.45	12.8 [11.3-14.1]	13.2 [12.0-14.3]	**<0.01**
eGFR (ml/min)	67 [56-90]	60 [52-76]	**<0.01**	57 [40-78]	60 [45-75]	**0.17**
Antiplatelet therapy at hospital admission						
Any antiplatelet therapy	45 (23%)	67 (6.9%)	**<0.01**	157 (34%)	322 (14%)	**<0.01**
Single antiplatelet therapy	34 (17%)	36 (3.7%)	**<0.01**	100 (22%)	206 (8.8%)	**<0.01**

Dual antiplatelet therapy	11 (5.5%)	31 (3.2%)	0.14	57 (12%)	116 (5.0%)	**<0.01**
Thromboembolic and bleeding risk						
CHA2DS2-VASc score	3 [2-4]	3 [2-4]	**<0.01**	5 [4-6]	5 [4-6]	**<0.01**
HAS-BLED score	2 [1-3]	2 [1-3]	0.73	3 [2-3]	2 [2-3]	**<0.01**
Oral anticoagulation at hospital discharge						
None	83 (42%) *n=198*	17 (1.8%) *n=968*	**<0.01**	166 (37%) *n=447*	71 (3.1%) *n=2320*	**<0.01**
VKA	7 (3.5%) *n=198*	144 (15%) *n=968*	**<0.01**	24 (5.2%)	464 (20%)	**<0.01**
rivaroxaban	41 (21%) *n=198*	356 (37%) *n=968*	**<0.01**	72 (16%)	726 (31%)	**<0.01**
dabigatran	16 (8.1%) *n=198*	250 (26%) *n=968*	**<0.01**	51 (11%)	501 (22%)	**<0.01**
apixaban	51 (26%) *n=198*	201 (21%) *n=968*	0.13	134 (30%)	558 (24%)	**0.01**
OAC transition						
VKA to NOAC	NA	15 (1.5%)	NA	NA	66 (2.8%)	NA
VKA to rivaroxaban	NA	1 (0.1%)	NA	NA	18 (0.8%)	NA
VKA to dabigatran	NA	3 (0.3%)	NA	NA	11 (0.5%)	NA
VKA to apixaban	NA	11 (1.1%)	NA	NA	37 (1.6%)	NA
NOAC* to VKA	NA	2 (0.2%)*	NA	NA	12 (0.5%)**	NA
Rivaroxaban to dabigatran	NA	2 (0.2%)	NA	NA	6 (0.3%)	NA
Rivaroxaban to apixaban	NA	4 (0.4%)	NA	NA	41 (1.8%)	NA
Dabigatran to rivaroxaban	NA	2 (0.2%)	NA	NA	3 (0.1%)	NA
Dabigatran to apixaban	NA	1 (0.1%)	NA	NA	16 (0.7%)	NA

[1] p value for difference between patients with and without heart failure

[2] p value for difference between heart failure patients with reduced, mid-range and preserved ejection fraction

*dabigatran

**dabigatran (0.1%), rivaroxaban (0.3%), apixaban (0.2%)

Abbreviations: AF, atrial fibrillation; BMI, body mass index; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; DC, direct current; eGFR, estimated glomerular filtration rate; EHRA, European Heart Rhythm Association; HF, heart failure; HFmEF, heart failure with mild-range ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; NA, non-applicable; NYHA, New York Heart Association; PAD, peripheral artery disease

Table S3. Baseline characteristics of atrial fibrillation patients hospitalized in academic and territorial hospital.

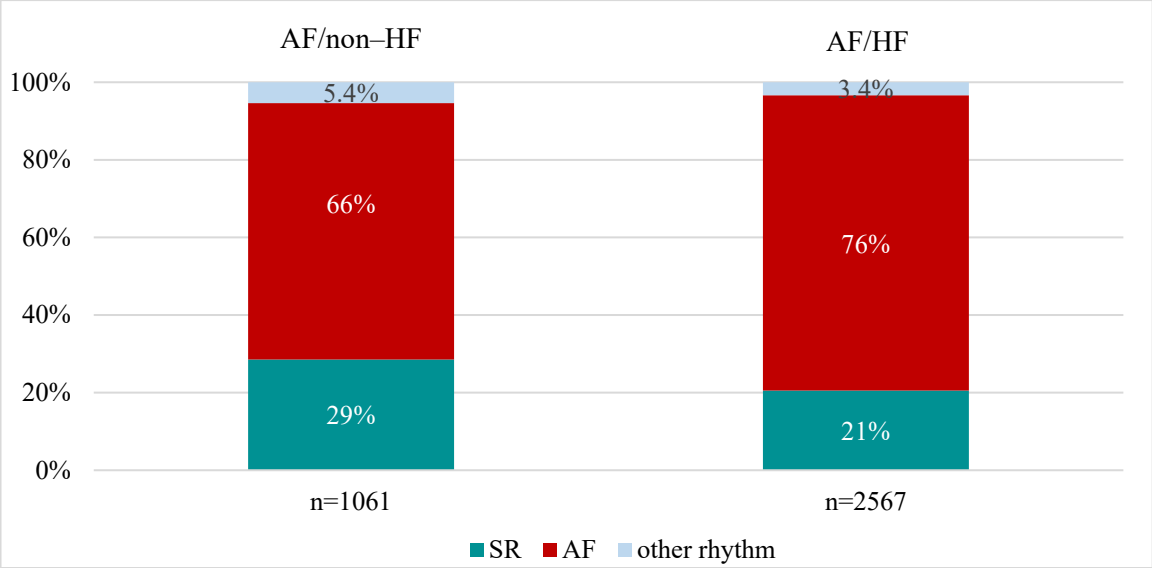
Variable	Patients from academic hospital (n=3396)	Patients from tertiary hospital (n=603)	p[1]
Demographics			
Age (years)	72 [65-81]	73 [67-82]	**0.01**
Females (%)	1427 (42%)	277 (46%)	0.07
BMI (kg/m^2)	28 [26-32] *n=2572*	29 [27-34] *n=170*	**<0.01**
Primary reason of index hospital admission			
AF without any procedures	190 (5.6%)	62 (10%)	**<0.01**
DC cardioversion for AF	793 (23%)	100 (17%)	**<0.01**
HF decompensation	581 (17%)	225 (37%)	**<0.01**
Elective CIED implantation/ replacement	298 (8.8%)	62 (10%)	0.25
ACS	236 (7.0%)	11 (1.8%)	**<0.01**
Elective PCI	374 (11%)	9 (1.5%)	**<0.01**
Non-AF-ablation	200 (5.9%)	10 (1.7%)	**<0.01**
Other	717 (21%)	112 (19%)	**<0.01**
AF type			
AF paroxysmal	1660 (49%)	263 (44%)	**0.02**
AF persistent	765 (23%)	168 (28%)	**<0.01**
AF permanent	971 (29%)	172 (29%)	1.00
AF history			
Prior AF history	3138 (92%)	559 (93%)	**0.87**
Prior DC cardioversion for AF	821 (24%)	99 (16%)	**<0.01**
Prior AF-ablation	226 (6.7%)	38 (6.3%)	0.79
EHRA I	1306 (54%) *n=2411*	49 (13%) *n=369*	**<0.01**
EHRA II	720 (30%) *n=2411*	247 (67%) *n=369*	**<0.01**
- EHRA IIa	348 (14%) *n=2409*	46 (12%) *n=369*	0.34
- EHRA IIb	289 (13%) *n=2409*	47 (13%) *n=369*	0.67
EHRA III	313 (14%) *n=2411*	64 (17%) *n=369*	**0.03**
EHRA IV	72 (3.0%) *n=2411*	9 (2.4%) *n=369*	0.74
HF			
HF	2480 (73%)	342 (57%)	**<0.01**
Previous HF diagnosis	2291 (67%)	330 (55%)	**<0.01**
HF de novo	189 (5.6%)	12 (2.0%)	**<0.01**
Comorbidities			
Hypertension	2853 (84%)	491 (81%)	0.12
Vascular disease	1996 (59%)	249 (41%)	**<0.01**
Previous stroke	424 (12%)	76 (13%)	0.95
Thromboembolic events	548 (16%)	111 (18%)	0.17
Hemorrhagic events	222 (6.5%)	29 (4.8%)	0.12
Diabetes mellitus	1153 (34%)	213 (35%)	0.51
Chronic kidney disease	866 (26%)	163 (27%)	0.45
Smoking (current/former)	855 (27%) *n=3218*	196 (35%) *n=557*	**<0.01**
Alcohol overconsumption (≥8 drinks/week)	128 (4.0%) *n=3206*	22 (3.7%) *n=602*	0.82
Liver disease	241 (7.1%)	20 (3.3%)	**<0.01**
Thyroid disease	608 (18%)	119 (20%)	0.28
COPD/asthma	372 (11%)	76 (13%)	0.23
Device therapy*	794 (23%)	85 (14%)	**<0.01**
CHA_2DS_2-VASc score	5 [3-6]	4 [3-5]	**<0.01**

	4.4+1.8	4.3±1.8	
HAS-BLED score	2 [2-3] 2.1±1.0	2 [1-2] 2.1±1.0	**<0.01**
Medications at hospital admission			
No OAC	573 (17%) *n=3374*	89 (15%) *n=601*	0.21
No OAC despite class I recommendations	509 (16%) *n=3098*	74 (13%) *n=553*	0.08
VKA	667 (20%) *n=3374*	48 (8.0%) *n=601*	**<0.01**
Dabigatran	623 (18%) *n=3374*	142 (24%) *n=601*	**<0.01**
Rivaroxaban	990 (29%) *n=3374*	165 (27%) *n=601*	0.35
Apixaban	521 (15%) *n=3374*	157 (26%) *n=601*	**<0.01**
Antiplatelet drugs	565 (17%) *n=3371*	27 (4.5%) *n=601*	**<0.01**
Medications at hospital discharge			
No OAC	300 (8.9%) *n=3354*	45 (7.5%) *n=602*	0.27
No OAC despite class I recommendations	269 (8.7%) *n=3079*	41 (7.4%) *n=554*	0.32
VKA	603 (18%) *n=3354*	37 (6.1%) *n=602*	**<0.01**
Dabigatran	661 (20%) *n=3354*	158 (26%) *n=602*	**<0.01**
Rivaroxaban	1028 (31%) *n=3354*	171 (28%) *n=602*	0.29
Apixaban	762 (23%) *n=3354*	191 (32%) *n=602*	**<0.01**
Antiplatelet drugs	511 (15%) *n=3370*	19 (3.2%) *n=601*	**<0.01**
Beta-blockers	2906 (87%)	492 (82%)	**<0.01**
Digoxin	261 (7.8%) *n=3351*	56 (9.3%) *n=602*	0.22
NdhpCCB	24 (0.7%) *n=3351*	3 (0.5%) *n=602*	1.00
Amidarone	554 (17%) *n=3351*	197 (33%) *n=602*	**<0.01**
AAD I class	359 (11%) *n=3350*	24 (4.0%) *n=602*	**<0.01**
AAD I class in patients with HFpEF	195 (16%) *n=1219*	7 (5.3%) *n=131*	**<0.01**
RAS inhibitors	2672 (79%)	430 (71%)	**<0.01**
DhpCCB	1044 (31%) *n=3351*	220 (37%) *n=602*	**0.01**
MRA	1338 (40%) *n=3351*	262 (44%) *n=602*	0.10
Diuretics	2125 (63%) *n=3351*	441 (73%) *n=602*	**<0.01**

Abbreviations: AAD, antiarrhythmic drug; AF, atrial fibrillation; BMI, body mass index; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; DC, direct current; dhpCCB, dihydropyridine calcium channel blockers; EHRA, European Heart Rhythm Association; HF, heart failure; HFmEF, heart failure with mild-range ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; MRA, mineralocorticoid receptor antagonist; ndhpCCB, non-dihydropyridine calcium channel blockers; NYHA, New York Heart Association; OAC, oral anticoagulation; PAD, peripheral artery disease; RAS, renin-angiotensin system; VKA, vitamin K antagonist

Figure S1. Heart rhythm at hospital admission and its changes during hospitalization.

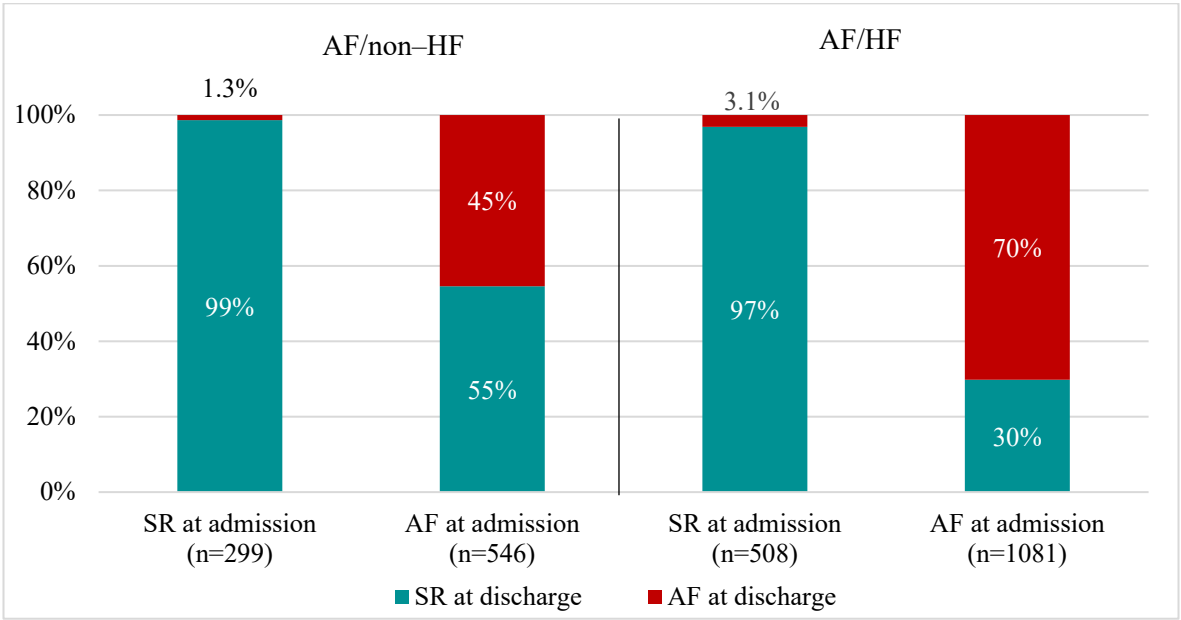
a) Proportion of patients in atrial fibrillation and those in sinus rhythm at hospital admission with regard to presence or absence of heart failure



Differences between AF/non–HF vs AF/HF group were statistically significant.

Presented data included only patients with information on heart rhythm on hospital admission.

b) Proportion of patients who converted from atrial fibrillation to sinus rhythm during hospitalization and those who remained in sinus rhythm throughout hospitalization with regard to presence or absence of heart failure

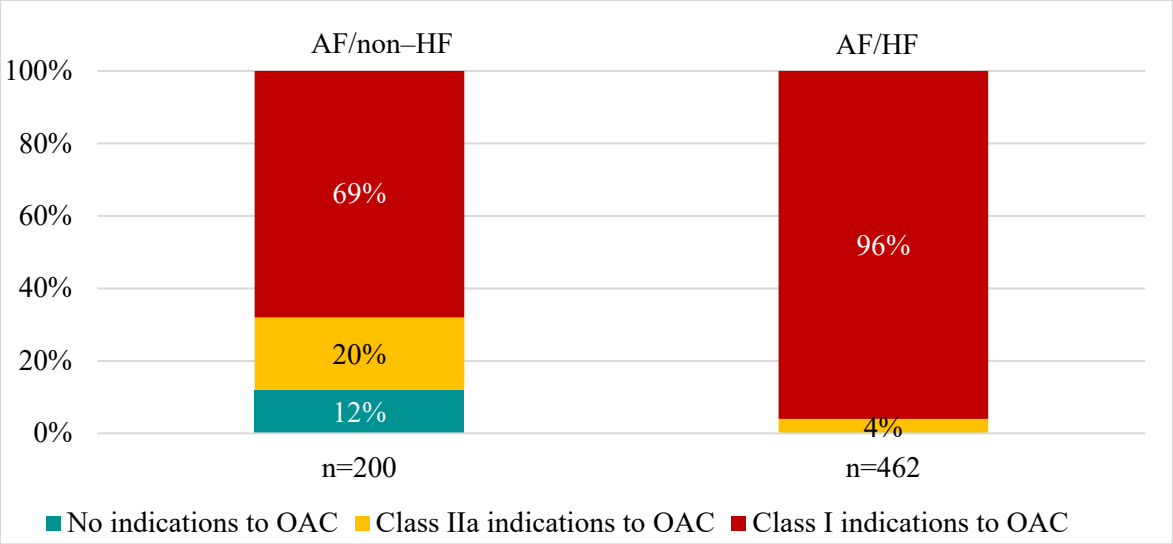


Differences between AF/non–HF vs AF/HF group were statistically significant.

Presented data included only patients with simultaneous information on heart rhythm both on admission and at discharge.

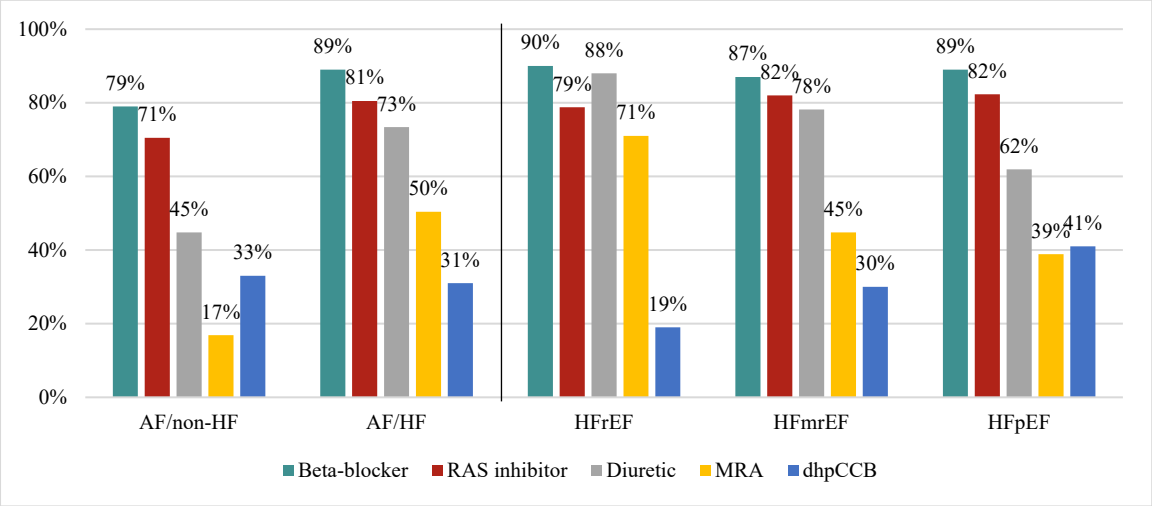
Abbreviations: See **Table 1**; SR, sinus rhythm

Figure S2. Proportion of patients not receiving oral anticoagulation at hospital admission in relation to presence or absence of heart failure and indications to oral anticoagulation. (2)



Abbreviations: See **Figure 4**

Figure S3. Prescription rate of heart failure medications in patients with and without heart failure (medication at discharge)**.**



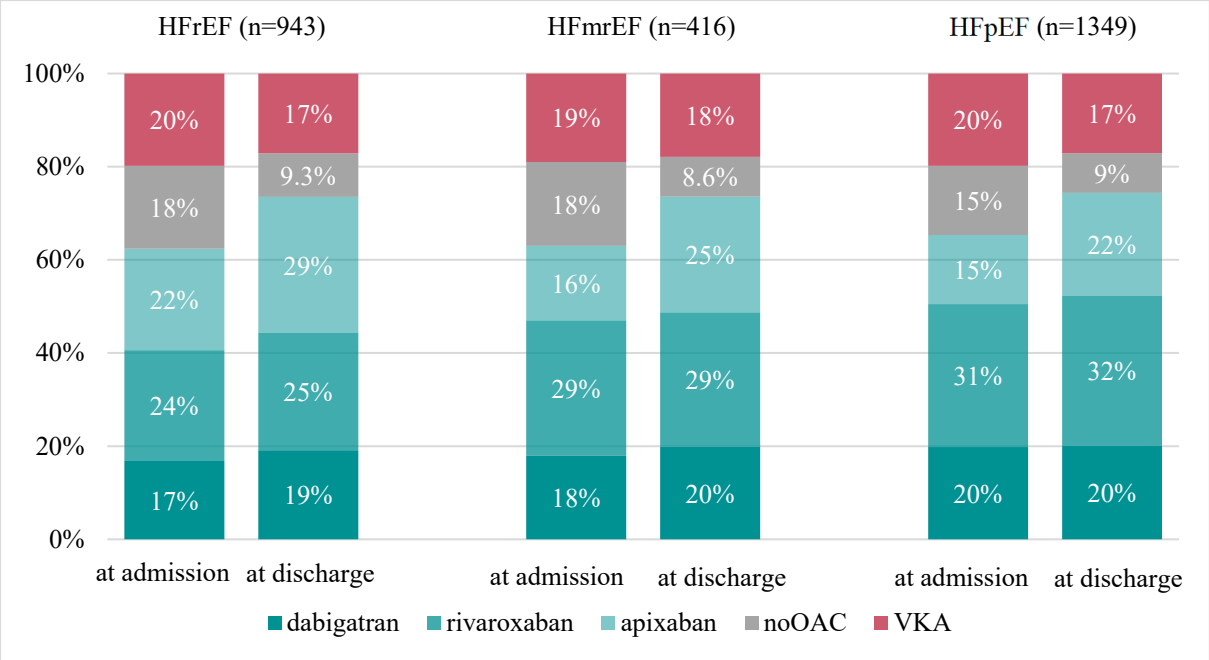
Differences in pharmacotherapy between AF/nonHF vs AF/HF group were statistically significant ($p<0.05$), expect dihydropyridine calcium channel blocker treatment ($p=0.27$).

Differences in pharmacotherapy between HFrEF, HFmrEF and HFrEF groups were statistically significant ($p<0.05$), except expect RAS inhibitor ($p=0.11$) and beta-blocker ($p=0.26$) treatment.

Abbreviations: See **Table 1**; nhpCCB, dihydropyridine calcium channel blocker; MRA, mineralocorticoid receptor antagonist; RAS, renin-angiotensin system

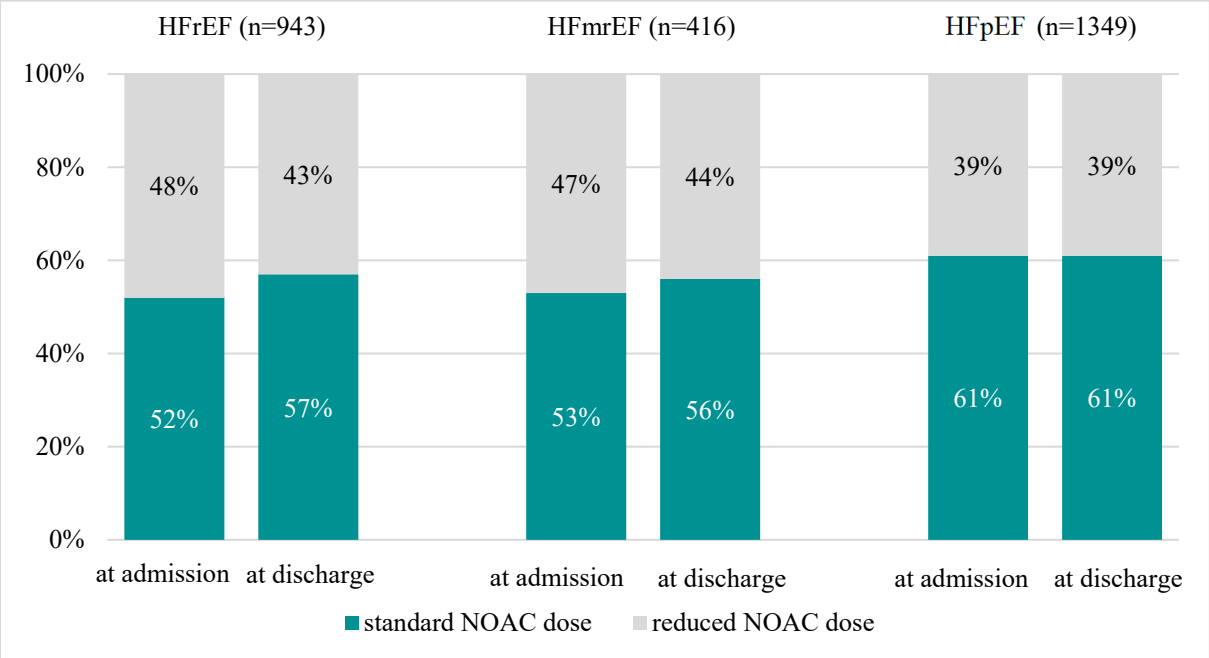
Figure S4. Pharmacotherapy of hospitalized atrial fibrillation patients depending on presence or absence of heart failure and its subtypes.

a) Anticoagulation



There were statistically significant differences ($p<0.05$) between HFrEF, HFmrEF and HFpEF groups with regard to treatment with rivaroxaban and apixaban (both at baseline and at discharge).

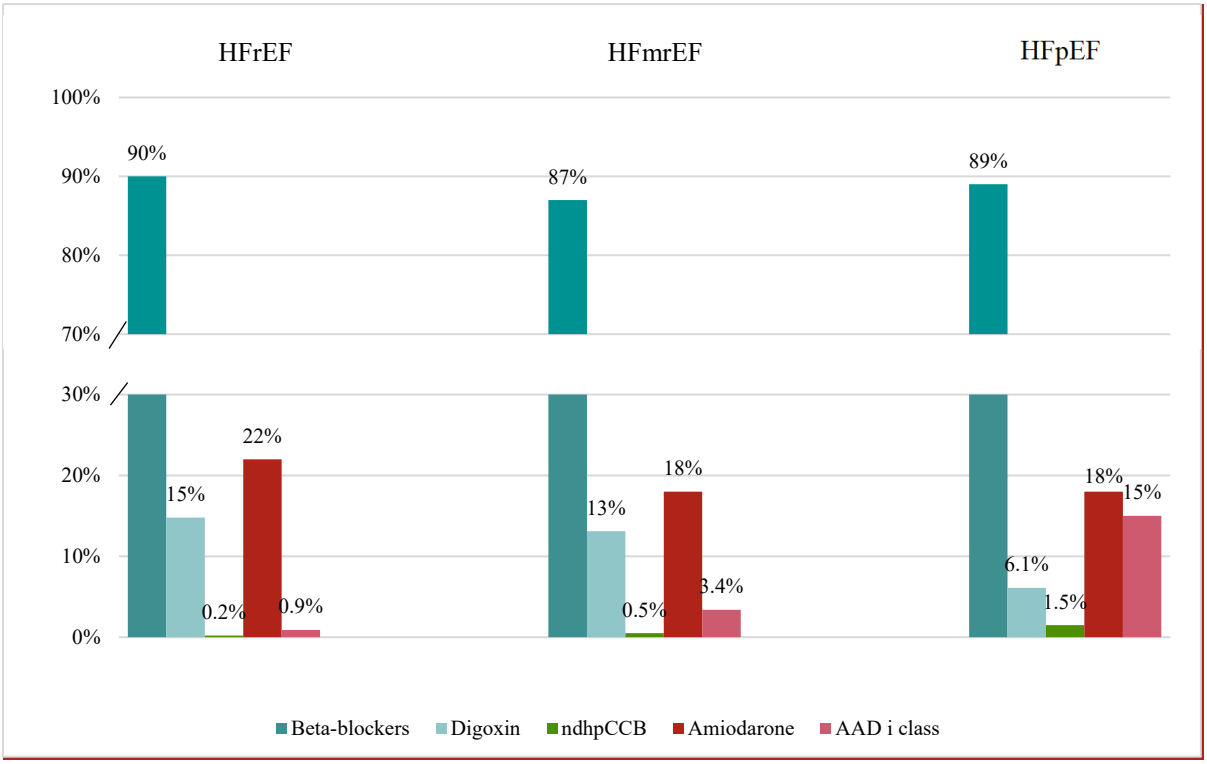
b) NOAC standard and reduced doses



Differences between HFrEF, HFmrEF and HFpEF groups with regard to reduction in NOAC doses at baseline were statistically significant ($p<0.05$).

Abbreviations: See **Table 1**; NOAC, non-vitamin K antagonist oral anticoagulant

c) rate and rhythm controlling drugs at discharge



Dronedarone was not prescribed in any of the groups.

Differences in pharmacotherapy between HFrEF, HFmrEF and HFpEF groups were statistically significant ($p<0.05$), except beta-blockers treatment ($p=0.26$). **Abbreviations:** See **Table 1**; AAD, antiarrhythmic drug; ndhpCCB, non-dihydropyridine calcium channel blockers

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Decreased left atrial appendage emptying velocity as a link between atrial fibrillation type, heart failure and older age and the risk of left atrial thrombus in atrial fibrillation

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Abstract

Introduction: Decreased left atrial appendage emptying velocity (LAAV) is a known predictor of LAA thrombus in atrial fibrillation (AF). The aim of our study was to identify which of the clinical risk factors for LAA thrombus are associated with decreased LAAV.

Methods: The study included 1476 consecutive AF patients who underwent transesophageal echocardiography (TEE) before AF direct current cardioversion or ablation in two high-reference cardiology departments. Patients were divided into two groups: 71 (4.8%) patients with LAAV < 20 cm/s and 1405 patients (95%) with LAAV ≥ 20 cm/s.

Results: Compared with patients with LAAV ≥ 20 cm/s, those with decreased LAAV were older, more often had non-paroxysmal AF, were burdened with more concomitant diseases (including hypertension, diabetes, vascular disease, and heart failure [HF]) with higher median CHA_2DS_2-VASc score (3 [2-4] vs 2 [1-3], $P < .0001$), and had lower glomerular filtration rate (GFR). Prevalence of LAA thrombus was higher in patients with decreased LAAV compared with those with LAAV ≥ 20cm/s (20% vs 4.6%, $P < .0001$). In patients with decreased LAAV, there was no difference in the frequency of LAA thrombus between those treated with VKA and those receiving NOAC, while in patients with LAAV ≥ 20 cm/s a trend was observed towards a benefit with NOAC. In multivariate logistic regression, non-paroxysmal AF, HF and age ≥ 65 years predicted both LAAV < 20 cm/s and LAA thrombus, while GFR < 60 mL/min/1.73 m^2 predicted only the presence of LAA thrombus.

Conclusion: One in five AF patients with decreased LAAV had LAA thrombus, regardless of the type of OAC. Non-paroxysmal AF, HF and age ≥ 65 years might increase LAA thrombus risk via reduced LAAV.

1 | INTRODUCTION

The risk of thromboembolism in atrial fibrillation (AF) is closely related to the presence of well-defined clinical risk factors, encompassed by the CHA2DS2-VASc score. Left atrial appendage (LAA) is the most common source of cardioembolic stroke in AF, representing the site of thrombus formation in more than 90% of cases.[1] Recently, non-paroxysmal AF and renal dysfunction have been proposed as additional predictors of LAA thrombus in AF.[2,3] Decreased LAA emptying velocity (LAAV), defined as less than 20 cm/s, is a known predictor of LAA thrombus[4,5] and, as an element of the Virchow's triad, constitutes a pathomechanism linking some of clinical risk factors with LAA thrombus formation. The aim of our study was to identify which of the known clinical risk factors for LAA thrombus are associated with decreased LAAV, defined as <20 cm/s. In addition, we investigated, whether there was any difference in the efficacy of vitamin K antagonists (VKA) vs non-VKA oral anticoagulants (NOAC) depending on LAAV.

What's known?

The risk of thromboembolism in atrial fibrillation (AF) is closely related to the presence of well-defined clinical risk factors, encompassed by the CHA2DS2-VASc score. Left atrial appendage (LAA) is the most common source of cardioembolic stroke in AF, representing the site of thrombus formation in more than 90% of cases. Recently, non-paroxysmal AF and renal dysfunction have been proposed as additional predictors of LAA thrombus in AF. Decreased LAA emptying velocity (LAAV), defined as less than 20 cm/s, is a known predictor of LAA thrombus and, as an element of the Virchow's triad, constitutes a pathomechanism linking some of clinical risk factors with LAA thrombus formation.

What's new?

In AF patients with LAAV below 20 cm/s, one in five had LAA thrombus, regardless of the type of OAC. In patients with non-paroxysmal AF, HF or age >65 years one of the mechanisms leading to increased thrombotic risk may involve decreased LAA mechanical function. In the studied group of AF patients scheduled for cardioversion or ablation, renal dysfunction seemed to increase thrombotic risk via mechanisms other than LA dysfunction.

2 | METHODS

Data reported herein are based on retrospectively analysed medical records of consecutive AF patients who underwent transoesophageal echocardiography (TEE) before AF direct current cardioversion or ablation in two high-reference cardiology departments (in an academic and a military hospital) in years 2014-2018.

In the academic department, all patients have TEE performed routinely before direct current cardioversion of AF or catheter ablation for AF (pulmonary vein isolation) excluding those admitted for cardioversion for emergency indications, as described previously.[2,6] In the military hospital, preprocedural TEE was performed in case of any doubt regarding the efficacy of oral anticoagulation (OAC) or patient's compliance.[7,8] In both departments, TEE was conducted within 48 hours prior to the scheduled procedure (usually directly or a few hours before the procedure). All TEE studies were performed by certified echocardiographers (certified with accreditation of the Section of Echocardiography of the Polish Cardiac Society), using EPIQ 7 Ultrasound Machine® (Philips Medical Systems, Andover, Massachusetts, United States), iE33 Ultrasound Machine® (Philips Medical Systems), General Electric Vivid 7 (GE Healthcare, Milwaukee, Wisconsin, United States) or E95 Ultrasound Machine® (GE Healthcare). In case of LAA thrombus suspicion, the study was evaluated by at least two echocardiographers to establish the most reliable and unanimous diagnosis and enable safe referral for cardioversion or ablation. For the assessment of LAAV, pulsed-wave Doppler outflow velocity signals during diastole were measured 1 cm below the orifice of the LAA. The optimal cut-off of LAAV (ie, 20 cm/s) was established based on Youden index and literature.[4,9,10] Written informed consent for TEE was obtained from all patients.

Patients were divided into two groups based on LAAV (<20 and ≥20 cm/s) and included in the analyses irrespectively of the presence or type of anticoagulation (OAC) prior to TEE.

The presence of LAA thrombus on TEE was deemed the primary endpoint of the study.

Research protocol and retrospective review of medical records was approved by the Ethics Committee, that also waived the requirement to obtain informed consent from the patients.

2.1 | Statistical analysis

Data were presented as a median and interquartile range (IQR) or number (percentage) of patients where appropriate. Statistical significance of differences in medians was analysed using Kruskal-Wallis test. Frequencies of parameters or events were compared using chi-squared test or Fisher's exact test, as appropriate. For all tests, a $P < .05$ was considered statistically significant. To determine predictors of LAA thrombus in both LAAV groups, univariate and multivariate logistic regression analyses were performed. Table S1 presents variables included in univariate logistic regression analyses. Only variables which were available for more than 99% of patients were included in the logistic regression analysis. Multivariate logistic regression model included all variables found to be predictors of LAA thrombus in univariate analyses. Statistical analysis was performed with StatsModels: Statistic in Python—v0.10.1 documentation.

3 | RESULTS

A total of 1476 AF patients with available LAAV measurements were included in the study. Patients were divided into two groups: 71

TABLE 1 Clinical characteristics of patients with left atrial appendage emptying velocity (LAAV) of less than 20 cm/s compared with those with LAAV of 20 cm/s and more

Variable	LAAV < 20 cm/s (n = 71)	LAAV > 20 cm/s (n = 1405)	*P*
Age [y]	66 [61-71]	62 [55-68]	**<.0001**
Female [n (%)]	28 (39%)	514 (37%)	.63
BMI [kg/m^2]	29 [26-31] n = 70	29 [26-32] n = 1332	.92
Type of atrial fibrillation (AF) [n (%)]			
Paroxysmal AF	20 (28%)	825 (59%)	**<.0001**
Non-paroxysmal AF	51 (72%)	580 (41%)	**<.0001**
Persistent AF	47 (66%)	522 (37%)	**<.0001**
Long-standing persistent AF	4 (5.6%)	58 (4.1%)	.38
Type of procedure planned [n (%)]			
Cardioversion	34 (48%)	327 (23%)	**<.0001**
Ablation	37 (52%)	1078 (77%)	**<.0001**
Concomitant diseases [n (%)]			
Hypertension	57 (80%)	949 (68%)	**.03**
Diabetes	20 (28%)	243 (17%)	**.02**
Vascular disease (CAD and/or PAD)	25 (35%)	235 (17%)	**<.0001**
Heart failure	34 (48%)	222 (16%)	**<.0001**
Previous stroke/TIA/peripheral embolism	6 (8.5%)	86 (6.1%)	.43
Chronic respiratory disease	3 (12%) n = 25	49 (5.0%) n = 989	.12
Chronic kidney disease	18 (25%)	147 (11%)	**<.0001**
Hyperthyroidism	3 (4.2%)	122 (8.7%)	.19
Hypothyroidism	11 (16%)	138 (9,8%)	.12
Previous bleeding	4 (5.6%)	28 (2.0%)	**.04**
Smoking	13 (52%) n = 25	347 (35%) n = 989	.08
Thromboembolic risk			
CHA_2DS_2-VASc score	3 [2-4]	2 [1-3]	**<.0001**
CHA_2DS_2-VASc score [n (%)]			
0	1 (1.4%)	199 (14%)	**.002**
1	9 (13%)	373 (27%)	**.009**
>2	61 (86%)	833 (59%)	**<.0001**
Bleeding risk			
HAS-BLED score	2 [1-2]	1 [1-2]	**<.0001**
HAS-BLED score [n (%)]			
0	5 (7.0%)	300 (21%)	**.004**
1	22 (31%)	594 (42%)	.06
2	27 (38%)	393 (28%)	.07
≥3	17 (24%)	118 (8.4%)	**<.0001**

Note: AF, atrial fibrillation; BMI, body mass index; CABG, coronary artery bypass graft; CAD, coronary artery disease; LAAV, left atrial appendage emptying velocity; PAD, peripheral artery disease; PCI, percutaneous coronary intervention; TIA, transient ischemic attack.
Bold values mean those statistically significant ($P < .05$).

(4.8%) patients with LAAV < 20 cm/s and 1405 patients (95%) with LAAV ≥ 20 cm/s. Compared with patients with LAAV ≥ 20 cm/s, those with decreased LAAV were older, more often had non-paroxysmal AF, and were burdened with more concomitant diseases (including hypertension, diabetes, vascular disease, chronic kidney disease and heart failure [HF]). Noteworthy, patients with reduced LAAV had higher thromboembolic and bleeding risk based on CHA2DS2-VASc and HAS-BLED risk scores, respectively, and had larger left atrium size, lower

TABLE 2 Laboratory and echocardiographic characteristics of patients with left atrial appendage emptying velocity (LAAV) of less than 20 cm/s compared with those with LAAV of 20 cm/s and more

Variable	LAAV < 20 cm/s (n = 71)	LAAV > 20 cm/s (n = 1405)	P
Laboratory parameters			
Hemoglobin [g/dL]	15 [13-15] n = 71	14 [13-15] n = *1399*	.07
Hematocrit [%]	43 [40-46] n = 71	43 [40-45] n = *1403*	.44
WBC [K/μL]	7.6 [6.6-9.1] n = 71	7.4 [6.3-8.7] n = *1401*	.11
Platelet count [K/μL]	213 [172-243] n = 71	219 [183-254] n = *1401*	.12
GFR [mL/min/1.73 m^2]	68 [54-90] n = 71	79 [62-90] n = 1397	**.03**
AST	27 [20-32] n = 24	24 [20-30] n = *947*	.24
ALT	35 [28-44] n = 24	32 [24-42] n = *952*	.21
INR (for those on VKA)	2.7 [2.0-3.0]	2.3 [1.8-2.9]	**.01**
APTT [s]	35 [31-42] n = 64	35 [30-42] n = 1326	.25
Transthoracic echocardiography[a]			
Ejection fraction [%]	55 [40-59] n = *51*	60 [50-60] n = *496*	**<.0001**
Left atrial diameter [cm]	47 [44-49] n = *36*	44 [40-48] n = *582*	**.01**
Transesophageal echocardiography[a]			
Thrombus [n (%)]	14 (20%)	64 (4.6%)	**<.0001**
LAAV [cm/s]	17 [15-18]	50 [33-72]	**<.0001**
SEC [n (%)]	61 (86%)	250 (18%)	**<.0001**

Abbreviations: ALT, alanine transaminase; APTT, Activated Partial Thromboplastin Time; AST, aspartate transaminase; GFR, glomerular filtration rate; INR, international normalized ratio; LAAV, left atrial appendage emptying velocity; SEC, spontaneous echo contrast; WBC, white blood cells; VKA, vitamin K antagonists.

Bold values mean those statistically significant ($P < .05$).

[a]Performed during index hospitalization.

ejection fraction and more often were presented with spontaneous echo contrast as compared with patients with normal LAAV. Detailed clinical characteristics of both groups is shown in Tables 1 and 2.

OAC was prescribed in 99% of patients with LAAV < 20 cm/s compared with 92% of those with LAAV ≥ 20 cm/s ($P = .04$). Among patients treated with OAC, there were no differences in the frequency of VKA vs NOAC between the two LAAV groups ($P = .35$, with VKA prescribed in 41% of patients with LAAV < 20 cm/s and 43% with LAAV ≥ 20 cm/s, and NOAC prescribed in 59% and 57%, respectively). In patients receiving NOAC, patients with decreased LAAV were more often prescribed reduced doses of NOAC compared with those with LAAV ≥ 20 cm/s (20% vs 7.2%, $P = .002$). No significant differences in relation to antiplatelet therapy were seen between the two groups. Details on antithrombotic treatment in both groups are presented in Table S2 and Figure 1.

On TEE, LAA thrombi were detected in 78 (5.3%) patients. The frequency of LAA thrombus was higher in patients with decreased LAAV compared with those with LAAV ≥ 20 cm/s (20% vs 4.6%, $P < .0001$; as shown in Table 2). There was no difference in the frequency of LAA thrombus between patients treated with VKA and NOAC in patients with decreased LAAV, while in those with LAAV ≥ 20 cm/s a trend was observed in favor of NOAC (5.7% for VKA, 3.6% for NOAC, $P = .06$), despite higher prevalence of non-paroxysmal AF and lower LAAV in the NOAC subgroup (Table 3 and Figure 2). Within patients with reduced LAAV, there was no statistically significant difference in left atrial thrombus and/or spontaneous echo contrast (SEC) prevalence between patients on reduced or standard doses of NOACs (25% vs 19%, $P = .69$). However, patients treated with reduced doses of NOAC with reduced LAAV had higher incidence of LAA thrombus (25% vs 3.8%, $P < .05$) and SEC (88% vs 17%, $P < .05$) than those with normal LAAV (Table S3).

In multivariate logistic regression, common predictors of LAA thrombus and decreased LAAV were non-paroxysmal AF, HF and age ≥65 years, as shown in Tables 4 and 5. Glomerular filtration rate (GFR) below 60 mL/min/1.73 m^2 predicted LAA thrombus, but not decreased LAAV (Table 4).

4 | DISCUSSION

The major finding of the present study is that non-paroxysmal AF, HF and older age predict both LAA thrombus and decreased LAAV. In our cohort (median age of 62 [58-66] years), lower GFR predicted LAA thrombus but not decreased LAAV. This suggests that non-paroxysmal AF, HF and older age promote LAA thrombus formation inter alia through impaired LAA mechanical function leading to blood stasis, whereas lower GFR might lead to LAA thrombus development mainly via other elements of the Virchow's triad, such as hypercoagulability.

AF associated thrombotic material arises most frequently in LAA.[1] Thrombus formation begins with the Virchow's triad of stasis, endothelial dysfunction, and hypercoagulable state. LAAV is one of the most used parameters for evaluating atrial mechanical dysfunction associated with blood stasis.[5,11,12] In healthy individuals, LAAV ranges from 50 ± 6 cm/s to 83 ± 25 cm/s.[5,11,12] Velocities of less than 40 cm/s are associated with a higher risk of stroke, and velocities of less than 20 cm/s—with LAA thrombus and a higher incidence of thromboembolic events.[5,13,14] In a study by Bernhardt et al, 42% of AF patients with cerebral embolism had LAAV lower than 20 cm/s, whereas only 6% of AF patients without cerebral embolism had decreased LAAV ($P < .0001$).[15] Moreover in the study by the same authors, patients in whom LAA thrombi persisted after treatment had

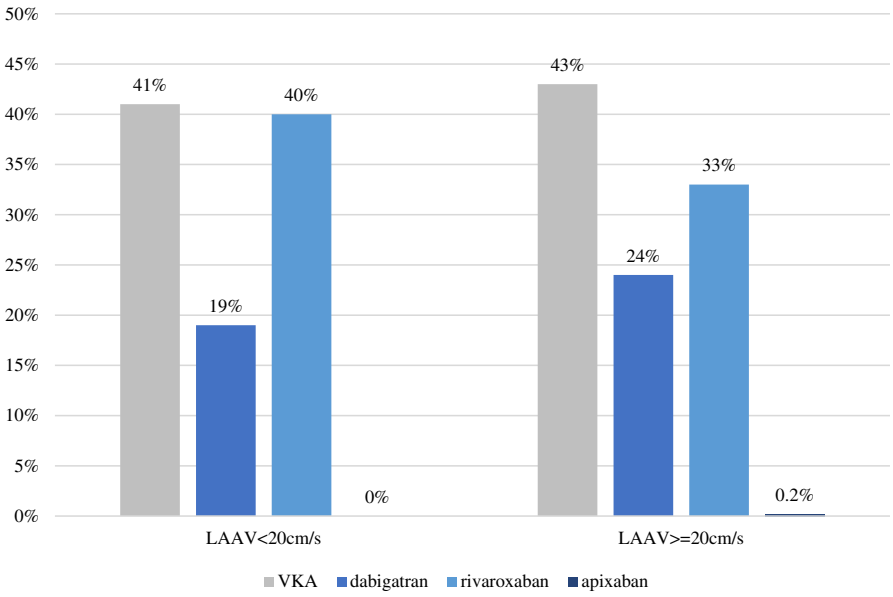

FIGURE 1 Type of anticoagulation in analysed groups (in patients receiving oral anticoagulation). LAAV, left atrial appendage emptying velocity, VKA, vitamin K antagonist

lower, although not significantly, LAAV values than those with LAA thrombus resolution.[16]

Heart failure, irrespectively of type, is a prothrombotic condition.[17] It predisposes to thrombi formation through endothelial damage, increased levels of prothrombotic molecules (fibrinogen and von Willebrand factors) and mechanical dysfunction, involving all three elements of the Virchow's triad.[18] Active emptying LA function is depressed in advanced stages of diastolic dysfunction. LAAV < 30 cm/s predicted left ventricular end-diastolic pressure > 25 mm Hg.[19] In a study by Bytyçi et al impaired LA emptying function, irrespective of restrictive filling, was the best predictor of exercise capacity in HF patients.[20] Presence of HF and persistent AF ($P = .04$) is independently associated with presence of LAA thrombus.[21] In study by Watanabe et al, receiver operating characteristic (ROC) curve analysis indicated that lower LAA flow velocity (area under curve, 0.92) and left ventricular ejection fraction (0.91) predicted OAC resistant LA thrombus.[22] Thus, HF is a well-proven risk factor for LAA thrombus formation and thromboembolic events in AF and is included in the CHA2DS2-VASc score.

Impaired renal function is a pro-thrombotic state, associated with endothelial dysfunction, subclinical inflammation, abnormal activity of coagulation factors, volume overload, activation of the renin-angiotensin-aldosterone and autonomic nervous systems, leading to atrial remodelling. All these mechanisms (endothelial dysfunction, hypercoagulability and impaired mechanical function) increase the risk of thromboembolic evets.[23] Addition of renal function to the $CHADS_2$ or CHA_2DS_2-VASc score improved stratification of thromboembolic risk.[2,24] The results of our study suggest that even mild impairment of kidney function might lead to increased thromboembolic risk through endothelial injury or hypercoagulability, rather than by worsening mechanical LAA function.

Recent studies also confirmed that patients with decreased LAAV or LA thrombus on TEE are more likely to have persistent or permanent AF.[25,26] The risk of stroke or systemic embolism is doubled in patients with AF burden of 5.5 or more hours on any of the 30 prior days.[26] The study by Khurram et al demonstrated a stiffer LA, associated with increased risk of thromboembolic events, in patients with persistent compared with those with paroxysmal AF.[27] The close relationship between HF, kidney disease and non-paroxysmal AF, and their effect on LA remodelling explains why those factors increased both the risk of LAA thrombus and decreased LAAV in our study. Our results are in line with those by Alyeshmerni et al demonstrating that reduced LAAV ($P < .001$), HF ($P = .04$), and chronic kidney disease ($P = .05$) were predictors of thrombogenic milieu development in LA.[28]

Older age is a well-known risk factor for stroke in AF. In the Framingham Study, the percentage of stroke attributable to AF increased steeply from 1.5% at the age of 50-59 years, to 23.5% at the age of 80-89 years.[29] Data from the ENGAGE-TIMI 48 trial indicated a 2-fold elevation of thromboembolic events when comparing patients aged ≥75 years to those <65 years.[30] Those findings expand observations from the PREvention oF Thromboembolic Events-European Registry in Atrial Fibrillation, showing that regardless of antithrombotic therapies in patients aged ≥85 years, the overall risk of thromboembolic events is 2.6- and 1.6-fold higher compared with patients aged <75 years and those aged 75-84 years, respectively.[31] In our study, older age might increase the risk of LAA thrombus via lower LAAV, what is in line with exists evidence that LAAV decreases with age.[32] In study by Ilercil et al, older patients with AF had more significantly impaired LAA function than younger patients despite comparable LA sizes, higher left ventricular ejection fraction and size; and based on multivariate analysis older age was the only significant independent predictor of reduced LAAV.[32]

Our study has several limitations. Firstly, data on heart rhythm during TEE were not available for patients scheduled for ablation. As "cardioversion" patients (who were known to be in AF during TEE) constituted less than one quarter of all patients, limiting our

TABLE 3 Comparison of patients on different anticoagulant regimens in relation to left atrial appendage emptying velocity

	Patients with LAAV < 20 cm/s			Patients with LAAV > 20 cm/s		
Variable	**VKA (n = 29)**	**NOAC (n = 41)**	***P***	**VKA (n = 560)**	**NOAC (n = 732)**	***P***
Age [y]	66 [58-71]	66 [62-71]	0.54	62 [56-67]	62 [55-68]	.18
Female [n (%)]	10 (34%)	18 (44%)	0.43	196 (35%)	285 (39%)	.15
Paroxysmal AF [n (%)]	11 (38%)	8 (20%)	0.09	339 (61%)	392 (54%)	**.01**
Non-paroxysmal AF [n (%)]	18 (62%)	33 (80%)	0.09	221 (39%)	340 (46%)	**.01**
Previous ischemic stroke/ TIA/peripheral embolism [n (%)]	3 (10%)	3 (7.3%)	0.66	38 (6.8%)	44 (6.0%)	.57
Previous bleeding [n (%)]	2 (6.9%)	2 (4.9%)	0.72	9 (1.6%)	11 (1.5%)	.88
Thromboembolic and bleeding risk						
CHA_2DS_2-VASc score	4 [2- 5]	3 [2-4]	0.19	2 [1-3]	2 [1-3]	.96
CHA2DS2-VASc score [n (%)]						
0	1 (3.4%)	0 (0%)	0.23	64 (11%)	93 (13%)	.49
1	2 (6.9%)	7 (17%)	0.21	146 (26%)	192 (26%)	.95
>2	36 (90%)	34 (83%)	0.43	350 (63%)	447 (61%)	.60
HAS-BLED score	2 [1-3]	2 [1-2]	0.58	1 [1-2]	1 [1-2]	.97
HAS-BLED score [n (%)]						
0	1 (3.4%)	4 (9.8%)	0.32	101 (18%)	151 (21%)	.24
1	10 (35%)	12 (29%)	0.65	256 (46%)	302 (41%)	.11
2	10 (35%)	17 (42%)	0.56	157 (28%)	214 (29%)	.64
> 3	8 (28%)	8 (20%)	0.43	46 (8.2%)	65 (8.9%)	.67
Transesophageal echocardiography[a]						
Thrombus [n (%)]	6 (21%)	8 (20%)	0.90	32 (5.7%)	26 (3.6%)	.06
LAA emptying velocity [cm/s]	15 [15-18]	17 [15-18]	0.16	52 [35-74]	47 [30-68]	**.004**
SEC [n (%)]	24 (83%) n = *387*	36 (88%) n = *525*	0.56	102 (18%) n = *235*	141 (19%) n = *386*	.63

Abbreviations: AF, atrial fibrillation; LAA, left atrial appendage; NOAC, non-vitamin K antagonist oral anticoagulants; SEC, spontaneous echo contrast; TIA, transient ischemic attack;, VKA, vitamin K antagonists.

Bold values mean those statistically significant ($P < .05$).

[a]Performed during index hospitalization.

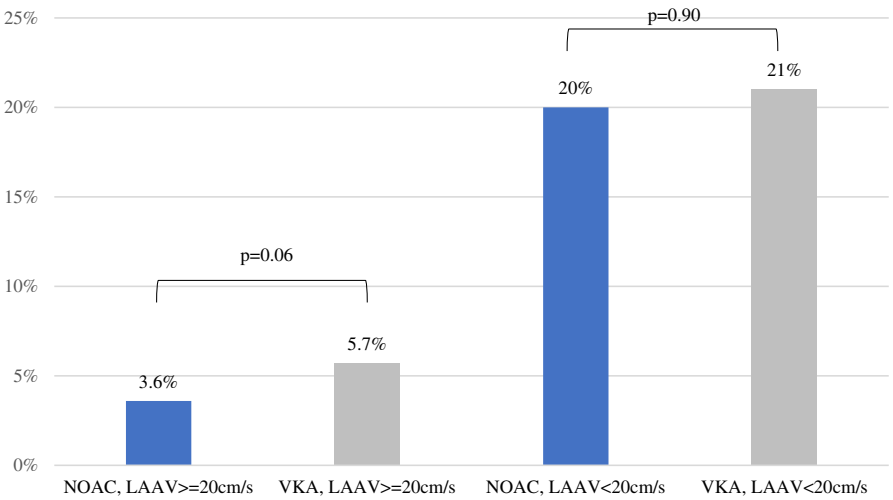

FIGURE 2 Prevalence of left atrial appendage (LAA) thrombus according to reduced and normal LAA emptying velocity levels and concomitant treatment with vitamin K antagonists (VKA) and non-VKA oral anticoagulants (NOAC). NOAC, non-vitamin K antagonist oral anticoagulants, VKA, vitamin K antagonists

TABLE 4 Logistic regression analyses of predictors of left atrial appendage thrombus

Variable	Univariate analysis	Multivariate analysis		
		OR	95% CI	*P*
Age >65 y	**<0.0001**	1.68	1.01-2.78	**.04**
AF non-paroxysmal (vs paroxysmal AF)	**<0.0001**	4.92	2.71-8.92	**<.0001**
Heart failure	**<0.0001**	1.98	1.17-3.32	**.01**
Diabetes	**0.007**	1.04	0.58-1.83	.90
GFR < 60 mL/min/1.73 m^2	**<0.0001**	2.12	1.29-3.48	**.003**
WBC (per 1 000/μL)	**0.02**	1.04	0.92-1.18	.52

Abbreviations: AF, atrial fibrillation; CI, coincidence interval; GFR, glomerular filtration rate; OR, odds ratio; WBC, white blood cells.

Bold values mean those statistically significant ($P < .05$).

TABLE 5 Logistic regression analyses of predictors of left atrial appendage emptying velocity of less than 20 cm/s

Variable	Univariate analysis	Multivariate analysis		
		OR	95% CI	*P*
Age >65 y	**<0.0001**	1.84	1.08-3.15	**.03**
Non-paroxysmal AF (vs paroxysmal AF)	**<0.0001**	2.46	1.41-4.29	**.002**
Hypertension	**0.03**	1.43	0.77-2.66	.25
Diabetes	**0.02**	0.84	0.46-1.53	.58
Vascular disease	**<0.0001**	1.51	0.86-2.65	.16
Heart failure	**<0.0001**	2.93	1.68-5.10	**.0001**
GFR < 60 mL/min/1.73 m^2	**0.001**	1.56	0.93-2.63	.09

Abbreviations: AF, atrial fibrillation; CI, coincidence interval; GFR-glomerular filtration rate; OR, odds ratio.

Bold values mean those statistically significant ($P < .05$).

analysis to those patients would significantly decrease statistical power of our analysis. Thus, we decided to include "ablation" patients, despite their unknown heart rhythm status. Comparison of "cardioversion" and "ablation" patients is presented in Table S4. It is well known that AF onset causes a decrease in LAAV.[33] In a study by Handke et al, LAAV differed significantly among patients with sinus rhythm (71 ± 16 cm/s), paroxysmal AF and in sinus rhythm during TEE (46 ± 13 cm/s), paroxysmal AF and AF during TEE (32 ± 12 cm/s), and persistent AF (27 ± 9 cm/s, $P < .001$). However, independent of the basic rhythm, the risk of LA thrombus/SEC increased significantly at LAAV of less than 55 cm/s.[33] Moreover, Kusa et al concluded that long-term maintenance of sinus rhythm after catheter ablation for persistent AF does not guarantee LAAV recovery.[34] A study by Warraich et al showed that 25% of patients with paroxysmal AF demonstrate a prothrombotic AF LAA pulse-wave Doppler phenotype despite concurrent sinus-rhythm ECG, and that LAAV was decreasing in this AF population, compared with that in a similarly aged cohort without a history of AF.[35] Based on aforementioned studies AF patients remained to have comparatively decreased values of LAAV despite sinus or atrial fibrillation rhythm assed during TEE study.

Secondly, inclusion of AF patients routinely referred for TEE enabled assessment of the presence of LAA thrombus and LAAV but limited the study group to patients scheduled for cardioversion or ablation who are younger and at lower thromboembolic risk than the AF population in general. Finally, this was not a randomized controlled study comparing NOAC with VKA, and thus, no ultimate conclusion on the relative efficacy of either OAC regimen can be drawn from our analysis.

5 | CONCLUSIONS

In AF patients with LAAV below 20 cm/s, one in five had LAA thrombus, regardless of the type of OAC. In patients with non-paroxysmal AF, HF or age ≥65 years one of the mechanisms leading to increased thrombotic risk may involve decreased LAA mechanical function. In the studied group of AF patients scheduled for cardioversion or ablation, renal dysfunction seemed to increase thrombotic risk via mechanisms other than LA dysfunction.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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Supplementary material

Table S1. A list of candidate predictor variables for univariate logistic regression analyses.

Clinical characteristics	Laboratory parameters	Antithrombotic treatment
Age ≥ 65 years Female gender Non-paroxysmal AF (vs paroxysmal AF) Hypertension Diabetes Vascular disease Heart failure Prior stroke/TIA/peripheral embolism Hyperthyroidism Hypothyroidism Previous bleeding	Hematocrit WBC Platelet count GFR <60 mL/min/1.73m^2	OAC (*vs* no OAC) VKA (*vs* NOAC)

Only variables that were available for more than 99% of patients were included in the logistic regression analysis.

AF - atrial fibrillation, GFR - glomerular filtration rate, NOAC - non-vitamin K antagonist oral anticoagulants, OAC - oral anticoagulants, TIA - transient ischemic attack, WBC - white blood cells, VKA - vitamin-K antagonists

Table S2. Antithrombotic treatment in analyzed groups.

Variable	LAAV <20 cm/s (n=71)	LAAV ≥20 cm/s (n=1405)	p
Antithrombotic treatment in the whole population of AF patients undergoing TEE [n (%)]			
No OAC	1 (1.4%)	113 (8.0%)	**0.04**
OAC	70 (99%)	1292 (92%)	**0.04**
Antiplatelets	2 (8.0%) *n=25*	66 (6.7%) *n=989*	0.79
Combination of OAC and antiplatelet treatment	2 (8.0%) *n=25*	42 (4.2%) *n=989*	0.36
Type of treatment in patients receiving OAC [n (%)]			
VKA	29 (41%)	560 (43%)	0.35
NOAC	41 (59%)	732 (57%)	0.35
- dabigatran - rivaroxaban - apixaban	13 (19%) 28 (40%) 0 (0%)	307 (24%) 423 (33%) 2 (0.2%)	0.48 0.10 0.75
Reduced dose of NOAC	8 (20%)	53 (7.2%)	**0.002**

OAC - oral anticoagulants, NOAC - non-vitamin K antagonist oral anticoagulants, VKA - vitamin K antagonists

Table S3. Comparison of patients with reduced and normal left atrial appendage velocity according to reduced or standard dose of non-vitamin K antagonist oral anticoagulants.

Variable	LAAV<20		p value	LAAV≥20		p value
	Reduced dose of NOAC (n=8)	Standard dose of NOAC (n=63)		Reduced dose of NOAC (n=53)	Standard dose of NOAC (n=1352)	
LAA thrombus	**2 (25%)[1, 4]**	**12 (19%)[2, 3]**	0.69	**2 (3.8%)[1, 3]**	**62 (4.6%)[2, 4]**	0.78
SEC	**7 (88%)[1, 4]**	**54 (86%)[2, 3]**	0.89	**9 (17%)[1, 3]**	**241 (18%)[2, 4]**	0.88
eGFR [mL/min/1.73 m2]	72 [52-90]	**68 [56-90] [2]**	0.79	58 [47-90]	**79 [61-90] [2]**	**<0.01**
Age [years]	**71 [67-76][4]**	**66 [60-71] [2, 3]**	0.08	**75 [65-82] [3]**	**61 [55-67] [2, 4]**	**<0.01**

statistically significant difference ($p<0.05$) between groups:

[1] LAAV<20cm/s and reduced dose of NOAC vs LAAV≥20cm/s and reduced dose of NOAC;

[2] LAAV<20cm/s and standard dose of NOAC vs LAAV≥20cm/s and reduced dose of NOAC;

[3] LAAV<20cm/s and standard dose of NOAC vs LAAV≥20cm/s and reduced dose of NOAC;

[4] LAAV<20cm/s and reduced dose of NOAC vs LAAV≥20cm/s and standard dose of NOAC

eGFR, estimated glomerular filtration rate; LAAV, left atrial appendage velocity; NOAC, non-vitamin K antagonist oral anticoagulant; SEC, spontaneous echo contrast

Table S4. Clinical, laboratory and echocardiographic characteristics of patients with atrial fibrillation (AF) regarding AF-related procedure (cardioversion vs ablation).

Variable	Cardioversion (n=361)	Ablation (n=1115)	p
Age [years]	66 [61-73]	61 [54-66]	**<0.0001**
Female [n (%)]	128 (36%)	414 (37%)	0.57
BMI [kg/m^2]	30 [26-34] *n=329*	29 [26-32] *n=1073*	**0.002**
Type of atrial fibrillation (AF) [n (%)]			
Paroxysmal AF	55 (15%)	790 (71%)	**<0.0001**
Non-paroxysmal AF	306 (85%)	325 (29%)	**<0.0001**
- persistent AF	282 (78%)	287 (26%)	**<0.0001**
- long-standing persistent AF	24 (6.6%)	38 (3.4%)	**0.008**
Concomitant diseases [n (%)]			
Hypertension	277 (78%)	729 (65%)	**<0.0001**
Diabetes	91 (25%)	172 (15%)	**<0.0001**
Vascular disease (CAD and/or PAD)	87 (24%) *n=361*	173 (16%) *n=1116*	**<0.0001**
Heart failure	116 (32%)	140 (13%)	**<0.0001**
Previous stroke/TIA/ peripheral embolism	6 (8.5%)	86 (6.1%)	0.43
Chronic respiratory disease	19 (9.7%) *n=25*	33 (4.0%) *n=989*	**0.001**
Chronic kidney disease	62 (17%)	103 (9.2%)	**<0.0001**

Hyperthyroidism	16 (4.4%)	109 (9.8%)	**0.002**
Hypothyroidism	34 (9.4%)	115 (10.3%)	0.62
Previous bleeding	5 (1.4%)	27 (2.4%)	0.24
Smoking	82 (42%) *n=194*	278 (34%) *n=820*	**0.03**
Thromboembolic risk			
CHA_2DS_2-VASc score	3 [2-4]	2 [1-3]	**<0.0001**
CHA_2DS_2-VASc score [n (%)]			
= 0	1 (1.4%)	199 (14%)	**0.002**
= 1	9 (13%)	373 (27%)	**0.009**
≥ 2	61 (86%)	833 (59%)	**<0.0001**
Bleeding risk			
HAS-BLED score	2 [1-2]	1 [1-2]	**<0.0001**
HAS-BLED score [n (%)]			
= 0	5 (7.0%)	300 (21%)	**0.004**
= 1	22 (31%)	594 (42%)	0.06
= 2	27 (38%)	393 (28%)	0.07
≥ 3	17 (24%)	118 (8.4%)	**<0.0001**
Laboratory parameters			
Hemoglobin [g/dL]	14.2 [13.2-15.3] n=359	14 [14-15] *n=1111*	0.29
Hematocrit [%]	43 [40-46] n=360	43 [40-45] *n=1114*	0.81
WBC [K/µL]	7.5 [6.4-8.8] n=359	7.3 [6.2-8.7] *n=1113*	0.13
Platelet count [K/µL]	214 [179-255] n=359	220 [185-252] *n=1113*	0.33

GFR [mL/min/1.73 m^2]	81 [59-90] n=358	75 [62-90] n=1110	0.89
AST	25 [20-33] n=182	24 [20-29] *n=789*	**0.04**
ALT	34 [25-48] n=183	31 [24-41] *n=793*	**0.048**
INR (for those on VKA)	2.5 [2.0-2.9]	2.3 [1.8-2.8]	**0.01**
APTT [s]	37 [32-43] n=323	34 [29-42] n=1067	**<0.0001**
Transthoracic echocardiography*			
Ejection fraction [%]	55 [46-60] *n=226*	60 [54-62] *n=321*	**<0.0001**
Left atrial diameter [cm]	46 [42-49] *n=174*	44 [40-48] *n=444*	**<0.0001**
Transesophageal echocardiography*			
Thrombus [n (%)]	18 (5.0%)	60 (5.4%)	0.77
LAAV [cm/s]	37 [25-59]	50 [34-75]	**<0.0001**
SEC [n (%)]	112 (31%)	199 (18%)	**<0.0001**

* performed during index hospitalization

AF - atrial fibrillation, ALT – alanine transaminase, APTT - Activated Partial Thromboplastin Time, AST - aspartate transaminase, BMI - body mass index, CABG – coronary artery bypass graft, CAD - coronary artery disease, GFR - glomerular filtration rate, INR - international normalized ratio, LAAV - left atrial appendage emptying velocity, PAD - peripheral artery disease, PCI – percutaneous coronary intervention, SEC - spontaneous echo contrast, TIA - transient ischemic attack, WBC - white blood cells, VKA – vitamin K antagonists

8. Podsumowanie i wnioski

8.1. Podsumowanie

W ramach prospektywnego, międzynarodowego rejestru EORP-AF General Long-Term Registry włączono 701 polskich pacjentów z AF. VD stwierdzono u 44% polskich pacjentów z AF (CAD u 37% oraz PAD u 13%). W porównaniu z naszymi wynikami, w całej populacji rejestru EORP-AF Long-Term General Registry, częstość występowania CAD i PAD była niższa i wynosiła odpowiednio 29% i 8,1% (40). Skala rozpowszechnienia tych jednostek chorobowych na postawie dostępnych danych jest szeroka, wynosząc w przypadku PAD i CAD odpowiednio 4-17% (41), 17-47% (42), co może wynikać ze zróżnicowanego charakteru przeprowadzonych badań, od randomizowanych badań klinicznych, przez badania kohortowe do badań opartych na narodowych bazach danych i Międzynarodowej Klasyfikacji Chorób (ICD). Występowanie VD było niezależnie związane ze starszym wiekiem, cukrzycą, hipercholesterolemią i HF. Wśród pacjentów z AF i VD, 96% było leczonych przeciwzakrzepowo (wśród nich potrójną terapię przeciwzakrzepową otrzymywało 11% chorych, podwójną terapię przeciwzakrzepową – 14%, OAC – 63%, a leczenie przeciwpłytkowe – 8.6%) a 4.1% nie otrzymywało żadnej formy leczenia przeciwzakrzepowego. Jednoczesne stosowanie potrójnej terapii przeciwzakrzepowej było związane ze zwiększonym ryzykiem poważnych zdarzeń niepożądanych, w tym zgonu z jakiejkolwiek przyczyny, w porównaniu z pacjentami stosującymi tylko OAC lub OAC i jeden lek przeciwpłytkowy. Na podstawie dostępnej literatury, połączenie terapii przeciwpłytkowej i OAC zwiększa ryzyko wystąpienia powikłań krwotocznych (od 2% przypadku podwójnej terapii przeciwpłytkowej do 14% po dołączeniu OAC) (43). Dlatego wybór optymalnej strategii leczenia przeciwzakrzepowego dla pacjenta z AF i VD jest niezwykle trudny i wymaga równowagi między ryzykiem zatorowo-zakrzepowym a krwawienia. Jednocześnie pacjenci, którzy wymagają skojarzonej terapii przeciwpłytkowej i przeciwkrzepliwej powinni zostać poddani szczególnie uważnej kontroli w trakcie trwania takiego leczenia.

Do prospektywnego, wieloośrodkowego rejestru POL-AF włączono 3999 pacjentów z AF hospitalizowanych w 10 polskich ośrodkach kardiologicznych. Ponad 70% pacjentów miało rozpoznanie HF, z czego połowa – HF z zachowaną frakcją wyrzutową. Częstość występowania HF w populacji POL-AF była wyższa niż we wcześniejszych badaniach (18-34%) (44-53). Można to wytłumaczyć faktem, że rejestr POL-AF rekrutował pacjentów hospitalizowanych w ośrodkach kardiologicznych o wysokim stopniu referencyjności (a zatem potencjalnie chorych bardziej obciążonych), a także tym, że wcześniejsze badania

odnosiły się głównie do HF z umiarkowanie lub znacznie obniżoną frakcją wyrzutową, podczas gdy w rejestrze POL-AF uwzględniono także pacjentów z HF z zachowaną frakcją wyrzutową – stanowili połowę wszystkich przypadków HF. To odzwierciedla ścisły związek między HF z zachowaną frakcją wyrzutową a AF. W ESC-HF Long-Term Registry, częstość występowania AF u pacjentów z HF z zachowaną frakcją wyrzutową wynosiła 18% (54), natomiast w naszym badaniu ten odsetek był znacznie wyższy (48%), co dodatkowo potwierdza silny związek AF z HF z zachowaną frakcją wyrzutową (54). Pacjenci ze współistniejącą HF byli starsi, obciążeni większą liczbą chorób współistniejących i dwukrotnie częściej mieli utrwalone AF (34%) niż pacjenci bez HF (15%). Niemal jedna piąta pacjentów z AF i współistniejącą HF miała wywiad przebytego zdarzenia zakrzepowo-zatorowego. Aż 15% pacjentów z rozpoznaną HF z zachowaną frakcją wyrzutową otrzymało przy wypisie leki antyarytmiczne klasy I, pomimo rozpoznania choroby strukturalnej serca. Mimo wskazań klasy I do OAC u 98% pacjentów z AF i współistniejącą HF, aż 16% z nich nie było leczonych przeciwkrzepliwie przed przyjęciem do szpitala. Odsetek ten był porównywalny do pacjentów z AF bez towarzyszącej HF (17%), którzy charakteryzowali się niższym ryzykiem zakrzepowo-zatorowym (wynik w skali CHA_2DS_2-VASc 3 [2-4] vs 5 [4-6], $p<0.01$). Warto zauważyć, że 85% pacjentów rejestrze POL-AF było zrekrutowanych w ośrodkach akademickich. Oznacza to, że odsetek pacjentów nieotrzymujących OAC pomimo wskazań lub otrzymujących leki antyarytmiczne klasy I pomimo przeciwwskazań może być jeszcze wyższy w szpitalach pozaakademickich, biorąc pod uwagę różnice w charakterystyce i leczeniu pacjentów hospitalizowanych w szpitalach akademickich i pozaakademickich. Otrzymane wyniki są zbliżone do tych otrzymanych z naszego poprzedniego badania, w którym 17% pacjentów przyjętych w celu kardiowersji elektrycznej lub ablacji podłoża AF nie było leczonych przeciwkrzepliwie. Warto jednak zauważyć, że obydwie populacje pacjentów różniły się między sobą (55). Powyższe wyniki świadczą o niedostatecznym przestrzeganiu zaleceń ESC dotyczących leczenia przeciwkrzepliwego u pacjentów z AF. Do predyktorów nieprzyjmowania OAC przed przyjęciem do szpitala u pacjentów z AF i HF należały wiek powyżej ≥75 lat, przebyte zdarzenia krwotoczne, niedokrwistość i terapia przeciwpłytkowa. Zgodnie z wytycznymi ESC dostępne skale ryzyka krwawienia u pacjentów z AF służą identyfikacji modyfikowalnych czynników ryzyka krwawienia (celem ich kontroli), ale nie dyskwalifikacji pacjenta z leczenia przeciwkrzepliwego. U części pacjentów z wysokim ryzykiem krwawień, zwłaszcza w przypadku przebytego zagrażającego życiu krwawienia bez odwracalnej przyczyny, można rozważyć zamknięcie uszka lewego przedsionka. Spośród pacjentów z AF i HF nieleczonych przeciwkrzepliwie przed przyjęciem

do szpitala, 63% otrzymało OAC (najczęściej apiksaban) przy wypisie. Można to wyjaśnić danymi sugerującymi większe bezpieczeństwo stosowania apiksabanu w porównaniu do innych NOAC. W porównaniu z VKA, wszystkie NOAC są związane z niższym ryzykiem krwawienia wewnątrzczaszkowego, a u pacjentów z AF i HF – także z mniejszą liczbą zdarzeń sercowo-naczyniowych, w tym zawału mięśnia sercowego i udaru mózgu (56). W badaniu Amina i wsp. wykazano, że pacjenci z AF i HF, którym przepisano NOAC, mieli o 36% mniejsze ryzyko udaru mózgu i zatorowości obwodowej, o 34% mniejsze prawdopodobieństwo poważnego krwawienia i 27% mniejsze prawdopodobieństwo wystąpienia poważnych niepożądanych zdarzeń sercowo-naczyniowych w porównaniu z VKA (56). Ponadto, pacjenci przyjmujący apiksaban mieli o 45% mniejsze ryzyko krwawienia i o 14% mniejsze ryzyko poważnych niepożądanych zdarzeń sercowo-naczyniowych w porównaniu do pacjentów stosujących riwaroksaban, a zmniejszenie ryzyka w porównaniu z dabigatranem wynosiło odpowiednio 29% i 20% (56). Aczkolwiek, dane dotyczące wyższości jednego leku z grupy NOAC nad innymi, szczególnie w populacji pacjentów starszych (>85 lat) (57) lub przyjmujących liczne leki ingerujące w farmakokinetykę NOAC (58) są niejednoznaczne i wymagają dalszych badań.

W ramach dwuośrodkowego rejestru włączono 1476 pacjentów z AF poddanych TEE przed kardiowersją elektryczną AF lub ablacją podłoża AF. W trakcie TEE oceniano obecność skrzepliny w lewym przedsionku oraz czynność mechaniczną uszka lewego przedsionka przy pomocy pomiaru LAAV. Pacjenci zostali podzieleni na dwie grupy: z LAAV obniżoną <20 cm/s oraz z LAAV ≥20 cm/s. Częstość występowania skrzepliny w uszku lewego przedsionka była ponad czterokrotnie większa u pacjentów z obniżoną LAAV w porównaniu do pacjentów z LAAV ≥20 cm/s (20% vs 4.6%). W wieloczynnikowej analizie regresji logistycznej, nie-napadowe AF, HF i wiek ≥65 lat były predyktorami zarówno wystąpienia skrzepliny w uszku lewego przedsionka, jak i obniżonej LAAV, natomiast dysfunkcja nerek była predyktorem skrzepliny w lewym przedsionku, ale nie obniżonej LAAV. Niewydolność serca, niezależnie od fenotypu, jest stanem prozakrzepowym, predysponując do tworzenia się skrzeplin z udziałem wszystkie trzech elementów triady Virchowa (59), LAAV jest obniżone w zaawansowanych stadiach dysfunkcji rozkurczowej. W badaniu Bytyçi i wsp. zmniejszona LAAV była najlepszym predyktorem wydolności wysiłkowej u pacjentów z HF (60). Z kolei w badaniu Watanabe i wsp., zmniejszona LAAV i frakcja wyrzutowa lewej komory wykazywały najwyższą wartość predykcyjną powstania skrzepliny wewnątrzsercowej opornej na leczenie OAC (61). Ostatnie badania pokazały, że pacjenci ze zmniejszoną LAAV lub skrzepliną w lewym przedsionku

częściej mają nie-napadowe AF (62, 63). Badanie Khurram i wsp. wykazało, że zmniejszenie podatności ścian lewego przedsionka, związane ze zwiększonym ryzykiem zdarzeń zakrzepowo-zatorowych, jest znacznie częstsze w przypadku nie-napadowego (vs napadowego) AF (64). Starszy wiek jest dobrze znanym czynnikiem ryzyka udaru mózgu w AF. Z kolei LAAV zmniejsza się wraz z wiekiem (65). W badaniu Ilercil i wsp., starsi pacjenci z AF mieli niższą LAAV niż osoby młodsze pomimo porównywalnych rozmiarów lewego przedsionka i wyższej frakcji wyrzutowej. W analizie wieloczynnikowej jedynie starszy wiek był istotnym, niezależnym predyktorem obniżonego LAAV. (65) Upośledzona czynność nerek jest stanem prozakrzepowym, związanym z dysfunkcją śródbłonka, nieprawidłową aktywnością czynników krzepnięcia, przeciążeniem objętościowym, aktywacją układu renina-angiotensyna-aldosteron i autonomicznego układu nerwowego, prowadząc do przebudowy przedsionków (66). Wyniki naszego badania sugerują, że nawet łagodne upośledzenie czynności nerek może prowadzić do zaburzeń hemostazy, zwiększając ryzyko zakrzepowe raczej w mechanizmie uszkodzenia śródbłonka lub nadkrzepliwości niż przez pogorszenie funkcji mechanicznej lewego przedsionka.

W pracy wykorzystane zostały dane z dużych rejestrów wieloośrodkowych, obejmujących polskich pacjentów z AF. Zgromadzone dane pozwalają na wiarygodną ocenę rzeczywistego obrazu klinicznego współczesnych polskich pacjentów z AF. Uzyskane wyniki pokazują znaczenie chorób współistniejących, takich jak VD i HF, u pacjentów z AF, a jednocześnie pewną rozbieżność między codzienną praktyką kliniczną a obowiązującymi wytycznymi.

8.2. Implikacje kliniczne

W badaniu wykorzystane zostały dane z dużych rejestrów wieloośrodkowych, obejmujących polskich pacjentów z AF. W niewyselekcjonowanej populacji pacjentów z AF, częstość występowania VD i HF jest wysoka, co ma istotne znaczenie dla leczenia tych pacjentów. Duża część pacjentów z VD przyjmuje terapię skojarzoną przeciwpłytkową i przeciwkrzepliwą, w tym terapię potrójną, która, na podstawie naszych badań, wiąże się z większym ryzykiem poważnych zdarzeń niepożądanych. Stąd, tacy pacjenci powinni być poddawani częstszym wizytom kontrolnym i/lub modyfikacji terapii (np. przeciwkrzepliwej). Terapia zarówno przeciwzakrzepowa jak i antyarytmiczna u części pacjentów z AF i HF odbiega od obowiązujących zaleceń ESC, co wskazuje na konieczność bardziej ścisłego ich przestrzegania w Polsce

8.3. Ograniczenia badania

Rejestr EORP-AF Long-Term General Registry był prowadzony w dużych ośrodkach kardiologicznych, często o najwyższym stopniu referencyjności, co mogło wiązać się z rekrutacją pacjentów bardziej obciążonych i doprowadzić do przeszacowania częstości występowania VD.

Ograniczenia rejestru POL-AF dotyczą braku niektórych parametrów, w tym stężeń peptydów natriuretycznych i echokardiograficznych wskaźników dysfunkcji rozkurczowej lewej komory oraz danych odnośnie etiologii HF (dane te nie były zbierane w ramach rejestru POL-AF). W związku z tym, ostateczna weryfikacja trafności rozpoznania HF z zachowaną frakcją wyrzutową na etapie analizy danych nie była możliwa, co mogło prowadzić do pewnego przeszacowania częstości HF w tej populacji. Jednak należy podkreślić, że rejestr był prowadzony w ośrodkach akademickich i pozaakademickich z dużym doświadczeniem w prowadzeniu badań klinicznych i rejestrowych, a rozpoznanie HF było weryfikowane przez badaczy na podstawie dostępnych badań i dokumentacji medycznej w oparciu o obowiązujące wytyczne (67, 68). Stężenia peptydów natriuretycznych i echokardiograficzne wykładniki funkcji rozkurczowej lewej komory, nawet jeśli nieuwzględnione w bazie rejestru POL-AF, były zapewne oznaczone przynajmniej u części pacjentów włączonych do badania, co umożliwiło postawienie rozpoznania HF przez lekarzy prowadzących. Odrębnym problemem jest kwestia ograniczeń tych parametrów dla rozpoznania HF z zachowaną frakcją wyrzutową u pacjentów z AF (69). Pacjenci hospitalizowani w celu ablacji podłoża AF zostali wyłączeni z rejestru POL-AF, ponieważ biorąc pod uwagę dużą liczbę ośrodków z pracownią elektrofizjologiczną biorących udział w rejestrze, liczba młodszych pacjentów przyjmowanych do ablacji podłoża AF byłaby wysoka, a włączenie takich pacjentów do rejestru prowadziłoby do zaniżenia wieku badanej populacji i zmniejszenia liczby chorób współistniejących, prowadząc do tzw. *selection bias*. Nie odzwierciedlałoby to rzeczywistej charakterystyki klinicznej hospitalizowanych pacjentów z AF. Ponadto pacjenci kierowani do ablacji podłoża AF są zwykle kierowani do szpitala z pracownią elektrofizjologiczną z całego regionu, podczas gdy pacjenci przyjmowani w przypadku innych zabiegów planowych (takich jak kardiowersja elektryczna AF) lub ze wskazań nagłych są często kierowani do najbliższego szpitala.

Analiza danych z rejestru dwuośrodkowego także miała pewne ograniczenia. Po pierwsze, dane zbierane były retrospektywnie. Po drugie, informacje na temat rytmu serca podczas TEE nie były dostępne dla pacjentów kierowanych do ablacji podłoża AF. Epizod AF powoduje zmniejszenie LAAV w porównaniu do rytmu zatokowego. Jednak ograniczenie

badania wyłącznie do pacjentów z epizodem AF, u których TEE było wykonywane przed kardiowersją elektryczną, znacznie zmniejszyłoby wielkość grupy badanej. Dlatego zdecydowaliśmy się na włączenie do rejestru także pacjentów kierowanych na TEE przed ablacją podłoża AF, pomimo braku danych na temat rytmu serca u tych chorych i porównaliśmy pacjentów poddawanych zabiegom kardiowersji i ablacji. Pacjenci poddawani zabiegom kardiowersji elektrycznej byli starsi, obciążeni wyższym ryzykiem zatorowo-zakrzepowym (wynik w skali CHA_2DS_2-VASc 3 [2-4] vs 2 [1-3], $p<0.01$) i krwotocznym (wynik w skali HAS-BLED 2[1-2] vs 1 [1-2], $p<0.01$) względem pacjentów przyjętych celem wykonania ablacji podłoża AF. Włączenie do rejestru pacjentów kierowanych na TEE ograniczyło grupę badaną do pacjentów kierowanych do kardiowersji elektrycznej AF lub ablacji podłoża AF, którzy są młodsi i mają mniejsze ryzyko zakrzepowo-zatorowe niż ogólna populacja chorych z AF.

8.4. Wnioski

W ramach niniejszej rozprawy wykazano, że wśród polskich pacjentów z AF częstość występowania VD oraz HF jest wysoka i wynosi odpowiednio 44% i 71%. Profil kliniczny pacjentów z AF znacząco różni się w zależności od obecności bądź nieobecności tych chorób współistniejących. Leczenie polskich pacjentów z AF i współistniejącą HF nie zawsze jest zgodne z obowiązującymi wytycznymi. U chorych z AF, HF zwiększa ryzyko powstania skrzepliny w uszku lewego przedsionka na drodze upośledzenia jego czynności mechanicznej.

Ponadto to odniesieniu do szczegółowych celów rozprawy wykazano:

- Wśród chorych z AF, główną manifestacją kliniczną VD jest CAD.
- Aż jedna czwarta pacjentów z AF i współistniejącą VD przyjmowała skojarzoną terapię przeciwkrzepliwą i przeciwpłytkową, z czego niemal połowa chorych – terapię potrójną. Potrójna terapia przeciwzakrzepowa wiązała się z większym ryzykiem poważnych zdarzeń niepożądanych w tej grupie chorych.
- Wśród pacjentów z AF, głównym fenotypem HF jest HF z zachowaną frakcją wyrzutową.
- Pomimo bezwzględnych wskazań do OAC u większości pacjentów z AF i HF, istotny odsetek tych chorych nie jest leczony przeciwkrzepliwie.

- Leki antyarytmiczne klasy I są stosowane u pacjentów z AF i współistniejącą HF z zachowaną frakcją wyrzutową, pomimo przeciwwskazań do ich stosowania u pacjentów z chorobą strukturalną serca.
- U pacjentów z AF, zarówno HF jak i przewlekła choroba nerek zwiększają ryzyko powstania skrzepliny w lewym przedsionku, jednak w różnych mechanizmach.

Podsumowując, wyniki pracy mogą stanowić podstawę do poprawy w zakresie leczenia pacjentów z AF i współistniejącą VD lub HF.

9. Opinia Komisji Bioetycznej

Prospektywny, wieloośrodkowy rejestr EORP-AF General Long-Term Registry. Badanie uzyskało zgodę komisji bioetycznej niezależnie w każdym z uczestniczących krajów.

Prospektywny, wieloośrodkowy rejestr POL-AF. Rejestr został zatwierdzony przez Komisję Bioetyczną przy Świętokrzyskiej Izbie Lekarskiej (AKBE/104/2018). Komisja Bioetyczna uchyliła wymóg uzyskania świadomej zgody od pacjentów włączanych do rejestru.

Retrospektywny rejestr dwuośrodkowy. Rejestr został zatwierdzony przez Komisję Bioetyczną przy Warszawskim Uniwersytecie Medycznym (AKBE/29/2019). Komisja Bioetyczna uchyliła wymóg uzyskania świadomej zgody na włączenie do rejestru od pacjentów.

Komisja Bioetyczna
przy Warszawskim Uniwersytecie Medycznym

Tel.: 022/ 57 - 20 -303
Fax: 022/ 57 - 20 -165

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e-mail: komisja.bioetyczna@wum.edu.pl
www.komisja-bioetyczna.wum.edu.pl

Warszawa, dnia 14 stycznia 2019 r

AKBE/ 29 / 2019

Dr hab. n. med. Agnieszka Kapłon- Cieślicka
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OŚWIADCZENIE

Niniejszym oświadczam, że Komisja Bioetyczna przy Warszawskim Uniwersytecie Medycznym w dniu 14 stycznia 2019r. przyjęła do wiadomości informację na temat badania pt.: „Ocena częstości występowania oraz czynników predykcyjnych skrzeplin w uszku lewego przedsionka u pacjentów z migotaniem przedsionków". Przedstawione badanie nie stanowi eksperymentu medycznego w rozumieniu art. 21 ust. 1 ustawy z dnia 5 grudnia 1996 r. o zawodach lekarza i lekarza dentysty (Dz.U. z 2018 r. poz. 617) i nie wymaga uzyskania opinii Komisji Bioetycznej przy Warszawskim Uniwersytecie Medycznym, o której mowa w art. 29 ust. 1 ww. ustawy.

Przewodnicząca Komisji Bioetycznej

Prof. dr hab. n. med. Magdalena Kuźma –Kozakiewicz

KOMISJA BIOETYCZNA
PRZY ŚWIĘTOKRZYSKIEJ IZBIE LEKARSKIEJ
25-389 Kielce, ul. Wojska Polskiego 52
tel.: 41 362 15 40 faks: 41 362 15 00

Uchwała Nr 104/2018 - VII

Kielce, 29 listopada 2018 r.

Na podstawie art. 29 ust. 6 ustawy z dnia 05 grudnia 1996 r. o zawodach lekarza i lekarza dentysty (t.j. Dz. U. z 2011 r. nr 277 poz. 1634 ze zm.) oraz Rozporządzenia Ministra Zdrowia i Opieki Społecznej z dnia 11 maja 1999 r. w sprawie szczegółowych zasad powoływania i finansowania oraz trybu działania komisji bioetycznych (Dz. U. z 1999 r. Nr 47 poz. 480) oraz działając zgodnie z zasadami GCP (Good Clinical Practice):

Komisja Bioetyczna przy Świętokrzyskiej Izbie Lekarskiej w Kielcach na posiedzeniu w dniu 29 listopada 2018 r. zapoznała się z przedstawionymi dokumentami projektu badania pod tytułem:

„Ogólnopolski rejestr pacjentów z migotaniem przedsionków – POL-AF".

Projekt przedstawiony przez:

Dr n. med. Iwona Gorczyca

I Klinika Kardiologii i Elektroterapii Świętokrzyskiego Centrum Kardiologii
Wojewódzki Szpital Zespolony w Kielcach
Grunwaldzka 45
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Opiekun naukowy:
Prof. dr hab.n. med. Beata Wożakowska-Kapłon
I Klinika Kardiologii i Elektroterapii, Świętokrzyskiego Centrum Kardiologii

Badacze:
Lek. Olga Jelonek
I Klinika Kardiologii i Elektroterapii, Świętokrzyskiego Centrum Kardiologii

Studentka Anna Michalska
Studenckie Koło Naukowe, Uniwersytet Jana Kochanowskiego w Kielcach

Do Komisji wpłynęły następujące dokumenty:

1. Wniosek do Komisji Bioetycznej z dnia 26 listopada 2018 r.
2. Opis projektu.
3. Wykaz publikacji opiekuna oraz badacza.

4. Życiorys badacza.
5. Ubezpieczenie badacza.

Komisja Bioetyczna przy Świętokrzyskiej Izbie Lekarskiej zapoznała się z całością dokumentacji do badania i po przeprowadzeniu dyskusji oraz głosowaniu **pozytywnie zaopiniowała zgłoszony projekt badania.**

Wydana opinia dotyczy tylko rozpatrywanego wnioski z uwzględnieniem przedstawionego projektu; każda zmiana i modyfikacja wymaga uzyskania odrębnej opinii. Wnioskodawca zobowiązany jest do informowania o wszelkich poprawkach, które mogłyby mieć wpływ na opinię Komisji, o ciężkich lub niespodziewanych zdarzeniach niepożądanych i nieprzewidzianych okolicznościach, o zakończeniu badania, o jego wynikach i istotnych decyzjach innych komisji bioetycznych.

Od niniejszej uchwały, podmiot zamierzający przeprowadzić eksperyment medyczny, kierownik zakładu opieki zdrowotnej, w którym eksperyment medyczny ma być przeprowadzony oraz komisja bioetyczna właściwą dla ośrodka, który ma uczestniczyć w wieloośrodkowym eksperymencie medycznym, mogą wnieść odwołanie do Odwoławczej Komisji Bioetycznej przy Ministrze Zdrowia, za pośrednictwem Komisji Bioetycznej przy Świętokrzyskiej Izbie Lekarskiej w Kielcach, w terminie 14 dni od daty otrzymania niniejszej uchwały.

Przewodniczący Komisji Bioetycznej
Świętokrzyskiej Izby Lekarskiej
dr n. med. Krzysztof Bartosz

Kielce, 29 listopada 2018 r.

10. Oświadczenia Współautorów publikacji

Warszawa, 09.04.2021

Lek. Monika Maria Gawałko
I Katedra i Klinika Kardiologii
Warszawski Uniwersytet Medyczny
ul. Banacha 1A, 02-097 Warszawa

OŚWIADCZENIE WSPÓŁAUTORA

Oświadczam, że w przygotowaniu artykułu pt. **„Vascular disease in patients with atrial fibrillation. A report from Polish participants in the EORP-AF General Long-Term Registry”,** autorstwa Gawałko M, Lodziński P, Budnik M, Tymińska A, Wancerz A, Ozierański K, Kapłon-Cieślicka A, Grabowski M, Opolski G, Lenarczyk R, Kalarus Z, Lip GYH, Balsam P, opublikowanego we wrześniu 2020 w Interantional Journal of Clinical Practice, mój udział polegał na opracowaniu założeń badania oraz analiz, postawieniu hipotez badawczych, zbieraniu i ujednolicaniu danych, przeprowadzeniu całości analiz statystycznych, interpretacji wyników, przygotowaniu wszystkich tabel i rycin, analiz piśmiennictwa, napisania całości manuskryptu. Mój udział procentowy w powstaniu pracy wynosił 80%.

Monika Gawałko

…….

Podpis

Warszawa, 09.04.2021

Dr n.med. Piotr Lodziński
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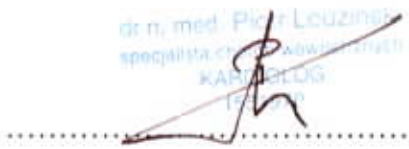

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Podpis

Warszawa, 09.04.2021

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Podpis

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Warszawa, 07.04.2021

Dr n.med. Agata Tymińska
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OŚWIADCZENIE WSPÓŁAUTORA

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A Tymińska

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Podpis

Warszawa, 07.04.2021

Lek. Anna Wancerz
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AWancerz

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Podpis

Warszawa, 09.04.2021

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Podpis

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Podpis

dr n. med. Monika Budnik
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Olga Jelonek
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ul. Szaserów 128, 04-141 Warszawa

OŚWIADCZENIE WSPÓŁAUTORA

Oświadczam, że w przygotowaniu artykułu pt. **„Characteristics and Treatment of Atrial Fibrillation with Respect to the Presence or Absence of Heart Failure. Insights from the Multicenter Polish Atrial Fibrillation (POL-AF) Registry”,** autorstwa Gawałko M, Budnik M, Gorczyca I, Jelonek O, Uziębło-Życzkowska B, Maciorowska M, Wójcik M, Błaszczyk R, Tokarek T, Rajtar-Salwa R, Bil J, Wojewódzki M, Szpotowicz A, Krzciuk M, Bednarski J, Bakuła-Ostalska E, Tomaszuk-Kazberuk A, Szyszkowska A, Wełnicki M, Mamcarz A, Kapłon-Cieślicka A, opublikowanego w marcu 2021 w Journal of Clinical Medicine, mój udział polegał na zbieraniu danych i redagowaniu manuskryptu. Mój udział procentowy w powstaniu pracy wynosił 5%.

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Podpis

Warszawa, 09.04.2021

Lek. Monika Maria Gawałko
I Katedra i Klinika Kardiologii
Warszawski Uniwersytet Medyczny
ul. Banacha 1A, 02-097 Warszawa

OŚWIADCZENIE WSPÓŁAUTORA

Oświadczam, że w przygotowaniu artykułu pt. **„ Decreased left atrial appendage emptying velocity as a link between atrial fibrillation type, heart failure and older age and the risk of left atrial thrombus in atrial fibrillation”,** autorstwa Gawałko M, Budnik M, Uziębło-Życzkowska B, Krzesiński P, Scisło P, Kochanowski J, Jurek A, Kiliszek M, Gielerak G, Filipiak KJ, Opolski G, Kapłon-Cieślicka A, opublikowanego w czerwcu 2020 w International Journal of Clinical Practice, mój udział polegał na opracowaniu założeń badania oraz analiz, postawieniu hipotez badawczych, zbieraniu i ujednolicaniu danych, przeprowadzeniu całości analiz statystycznych, interpretacji wyników, przygotowaniu wszystkich tabel i rycin, analiz piśmiennictwa, napisania całości manuskryptu. Mój udział procentowy w powstaniu pracy wynosił 80%.

…….

Podpis

Warszawa, 09.04.2021

Dr n.med. Monika Budnik
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ul. Banacha 1A, 02-097 Warszawa

OŚWIADCZENIE WSPÓŁAUTORA

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Podpis

dr n. med. [illegible] Budnik
SPECJALISTA [illegible]OLOG
[illegible]

Warszawa, 07.04.2021

Dr n.med. Beata Uziębło-Życzkowska
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OŚWIADCZENIE WSPÓŁAUTORA

Oświadczam, że w przygotowaniu artykułu pt. **„ Decreased left atrial appendage emptying velocity as a link between atrial fibrillation type, heart failure and older age and the risk of left atrial thrombus in atrial fibrillation”,** autorstwa Gawałko M, Budnik M, Uziębło-Życzkowska B, Krzesiński P, Scisło P, Kochanowski J, Jurek A, Kiliszek M, Gielerak G, Filipiak KJ, Opolski G, Kapłon-Cieślicka A, opublikowanego w czerwcu 2020 w Interantional Journal of Clinical Practice, mój udział polegał na zbieraniu danych i redagowaniu manuskryptu. Mój udział procentowy w powstaniu pracy wynosił 5%.

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Podpis

Warszawa, 08.04.2021

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Wojskowy Instytut Medyczny
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OŚWIADCZENIE WSPÓŁAUTORA

Oświadczam, że w przygotowaniu artykułu pt. **„ Decreased left atrial appendage emptying velocity as a link between atrial fibrillation type, heart failure and older age and the risk of left atrial thrombus in atrial fibrillation”,** autorstwa Gawałko M, Budnik M, Uziębło-Życzkowska B, Krzesiński P, Scisło P, Kochanowski J, Jurek A, Kiliszek M, Gielerak G, Filipiak KJ, Opolski G, Kapłon-Cieślicka A, opublikowanego w czerwcu 2020 w Interantional Journal of Clinical Practice, mój udział polegał na zbieraniu danych i redagowaniu manuskryptu. Mój udział procentowy w powstaniu pracy wynosił 5%.

dr hab. n. med. Paweł Krzesiński
specjalista chorób wewnętrznych
KARDIOLOG
1316559

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Podpis

Warszawa, 07.04.2021

Dr n.med. Piotr Scisło
I Katedra i Klinika Kardiologii
Warszawski Uniwersytet Medyczny
ul. Banacha 1A, 02-097 Warszawa

OŚWIADCZENIE WSPÓŁAUTORA

Oświadczam, że w przygotowaniu artykułu pt. **„ Decreased left atrial appendage emptying velocity as a link between atrial fibrillation type, heart failure and older age and the risk of left atrial thrombus in atrial fibrillation”,** autorstwa Gawałko M, Budnik M, Uziębło-Życzkowska B, Krzesiński P, Scisło P, Kochanowski J, Jurek A, Kiliszek M, Gielerak G, Filipiak KJ, Opolski G, Kapłon-Cieślicka A, opublikowanego w czerwcu 2020 w Interantional Journal of Clinical Practice, mój udział polegał na zbieraniu danych i redagowaniu manuskryptu. Mój udział procentowy w powstaniu pracy wynosił 5%.

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Podpis

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12. Dorobek publikacyjny

BIBG/Punktacja/ 484 /21/SL

Warszawa, 8 kwietnia 2021 r.

ANALIZA BIBLIOMETRYCZNA CAŁOKSZTAŁTU DOROBKU PUBLIKACYJNEGO

PANI MONIKI GAWAŁKO

W POSTĘPOWANIU O NADANIE STOPNIA NAUKOWEGO DOKTORA

Lp.	Opis bibliograficzny	Impact Factor	MEiN (dawniej MNiSW)
I. Artykuły opublikowane w czasopismach naukowych lub w recenzowanych materiałach z konferencji międzynarodowych ujętych w aktualnym wykazie MEiN[1]			
1.	Grabowski Marcin Dominik, **Gawałko Monika**, Michalak Marcin, Cacko Andrzej, Opolski Grzegorz. Ventricular tachycardia successfully treated with wearable cardioverter-defibrillator. Kardiologia Polska. 2017; 75(12): 1355-1355. (Rodzaj publikacji: praca kazuistyczna)	1,215	15
2.	Lodziński Piotr Ryszard, Balsam Paweł, Peller Michał, **Gawałko Monika**, Opolski Grzegorz, Grabowski Marcin Dominik. Three-dimensional print facilitated ventricular tachycardia ablation in patient with corrected congenital heart disease. Cardiology Journal (d. Folia Cardiologica). 2017; 24(5): 584-585. (Rodzaj publikacji: praca kazuistyczna, list do redakcji)	1,339	20
3.	**Gawałko Monika**, Kapłon-Cieślicka Agnieszka, Budnik Monika, Babiarz Aldona, Bodys Aleksandra, Uliński Robert, Żochowski Maciej, Peller Michał, Scisło Piotr Rafał, Kochanowski Janusz Ireneusz, Filipiak Krzysztof Jerzy, Opolski Grzegorz. Comparison of different oral anticoagulant regimens in patients with atrial fibrillation undergoing ablation or cardioversion. Polskie Archiwum Medycyny Wewnętrznej. 2017; 127(12): 823-831. (Rodzaj publikacji: praca oryginalna)	2,658	30
4.	Grabowski Marcin Dominik, Filipiak Krzysztof Jerzy, Opolski Grzegorz, Główczyńska Renata Elwira, **Gawałko Monika**, Balsam Paweł, Cacko Andrzej, Huczek Zenon, Karpiński Grzegorz, Kowalik Robert, Majstrak Franciszek, Kochman Janusz. Risk factors for adverse outcomes of patients with acute coronary syndrome: single-centre experience with long-term follow-up of treated patients. Kardiologia Polska. 2018; 76(5): 881-888. (Rodzaj publikacji: praca oryginalna)	1,674	15
5.	Czub Paweł, Cacko Andrzej, **Gawałko Monika**, Tataj Emanuel, Poliński Jakub, Pawlik Kacper, Cichoń Romuald, Hendzel Piotr. Perioperative risk assessment with Euroscore and Euroscore II in patients with coronary artery or valvular disease. Medicine. 2018; 97(50): 1-6. (Rodzaj publikacji: praca oryginalna)	1,870	40

[1] Wykaz sporządzony zgodnie z przepisami wydanymi na podstawie art. 267 ust. 2 pkt 2 lit. b Ustawy z dnia 20 lipca 2018 r. - Prawo o szkolnictwie wyższym i nauce (Dz. U. z 2018 r., poz. 1668 ze zm.). Wykaz stanowi załącznik do komunikatu MEiN z dnia 18 lutego 2021r. o zmianie i sprostowaniu komunikatu w sprawie wykazu czasopism naukowych i recenzowanych materiałów z konferencji międzynarodowych.

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6.	Cacko Andrzej, Kondracka Agnieszka Iwona, **Gawałko Monika**, Główczyńska Renata Elwira, Filipiak Krzysztof Jerzy, Bartoszewicz Zbigniew Piotr, Opolski Grzegorz, Grabowski Marcin Dominik. Novel biochemical predictors of unfavorable prognosis for stable coronary disease. Medicine. 2018; 97(37): 1-7. (Rodzaj publikacji: praca oryginalna)	1,870	40
7.	Grabowski Marcin Dominik, Filipiak Krzysztof Jerzy, Opolski Grzegorz, Główczyńska Renata Elwira, **Gawałko Monika**, Balsam Paweł, Cacko Andrzej, Huczek Zenon, Karpiński Grzegorz, Majstrak Franciszek, Kochman Janusz. Long-term prognosis following acute coronary syndromes: a prospective observational study of an unselected group treated in the 24/7 cardiac catheterisation laboratory at a university hospital. Kardiologia Polska. 2018; 76(4): 755-763. (Rodzaj publikacji: praca oryginalna)	1,674	15
8.	Pietrzak Radosław, Lodziński Piotr Ryszard, Książczyk Tomasz, Balsam Paweł, **Gawałko Monika**, Opolski Grzegorz, Werner Bożena Barbara. Initial experience of catheter ablation for cardiac arrhythmias in children and adolescents at a newly built ablation centre. Kardiologia Polska. 2018; 76(1): 130-135. (Rodzaj publikacji: praca oryginalna)	1,674	15
9.	Balsam Paweł, **Gawałko Monika**, Peller Michał, Tymińska Agata, Ozierański Krzysztof, Zaleska Martyna, Żukowska Katarzyna, Szepietowska Katarzyna, Maciejewski Kacper, Grabowski Marcin Dominik, Borkowski Mariusz, Kołtowski Łukasz, Praska-Ogińska Anna, Zaboyska Inna, Opolski Grzegorz, Bednarski Janusz. Clinical characteristics and thromboembolic risk of atrial fibrillation patients with and without congestive heart failure. Results from the CRATF study. Medicine. 2018; 97(45): 1-7. (Rodzaj publikacji: praca oryginalna)	1,870	40
10.	Michalik Joanna Irena, Cacko Andrzej, Poliński Jakub, Pawlik Kacper, Tataj Emanuel, **Gawałko Monika**, Opolski Grzegorz, Grabowski Marcin Dominik. An interactive assistant for patients with cardiac implantable electronic devices: A study protocol of the LUCY trial. Medicine. 2018; 97(39): 1-4. (Rodzaj publikacji: praca oryginalna)	1,870	40
11.	Cacko Andrzej, Kozyra-Pydyś Eliza, **Gawałko Monika**, Opolski Grzegorz, Grabowski Marcin Dominik. The role of hemostatic markers as venous stenosis or occlusion predictors following first transvenous cardiac device implantation. Cardiology Journal (d. Folia Cardiologica). 2019; :1-7. (Rodzaj publikacji: praca oryginalna)	1,669	100
12.	Kapłon-Cieślicka Agnieszka, Budnik Monika, **Gawałko Monika**, Wójcik M., Błaszczyk R., Uziębło-Życzkowska B., Krzesiński P, Starzyk K, Gorczyca I, Szymańska A, Dłużniewski M, Daniłowicz-Szymanowicz L., Kaufmann D., Mizia-Szubryt M, Wybraniec M. T., Haberka M, Kucio M, Tomaszuk-Kazberuk A., Wilk K., Burchardt P., Gościnska-Bis K, Hiczkiewicz J, Łojewska K, Koziński M, Michalski B., Tomaszewski A., Scisło Piotr Rafał, Kochanowski Janusz Ireneusz, Filipiak Krzysztof Jerzy, Opolski Grzegorz. The rationale and design of the LATTEE registry - the first multicenter project on the Scientific Platform of the "Club 30" of the Polish Cardiac Society. Kardiologia Polska. 2019; 77(11): 1078-1080. (Rodzaj publikacji: praca oryginalna)	1,874	70
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14.	Zbroński Karol, Huczek Zenon, **Gawałko Monika**, Ćwiek A., Rymuza Bartosz, Grodecki K, Scisło Piotr Rafał, Wilimski Radosław Mikołaj, Kochman Janusz, Filipiak Krzysztof Jerzy, Opolski Grzegorz. Paradoxical low-flow aortic stenosis - baseline characteristics, impact on mortality. Postępy w Kardiologii Interwencyjnej. 2019; 15(1): 13-19. (Rodzaj publikacji: praca oryginalna)	1,347	40

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16.	Grabowski Marcin Dominik, **Gawałko Monika**, Michalak Marcin, Cacko Andrzej, Kowara Michał, Kołodzińska Agnieszka, Januszkiewicz Łukasz, Balsam Paweł, Vitali-Serdoz Laura, Winter Joachim, Opolski Grzegorz. Initial experience with the subcutaneous implantable cardioverter-defibrillator with the real costs of hospitalization analysis in a single Polish center. Cardiology Journal (d. Folia Cardiologica). 2019; 26(4): 360-367. (Rodzaj publikacji: praca oryginalna)	1,669	100
17.	Michalak Marcin, Januszkiewicz Łukasz, Majstrak Franciszek, **Gawałko Monika**, Opolski Grzegorz, Grabowski Marcin Dominik. Endovascular extraction of entrapped long-term central feeding catheter: Case series. Journal of Vascular Access. 2019; 20(3): 329-332. (Rodzaj publikacji: praca kazuistyczna)	1,223	70
18.	Balsam Paweł, Ozierański Krzysztof, Marchel Michał, **Gawałko Monika**, Niedziela Łukasz, Tymińska Agata, Sieradzki Bartosz, Sieradzki Maciej, Fojt Anna, Bakuła Elwira, Główczyńska Renata Elwira, Peller Michał, Markulis Maciej, Bednarski Janusz, Kowalik Robert, Cacko Andrzej, Niewiński Grzegorz, Filipiak Krzysztof Jerzy, Opolski Grzegorz, Grabowski Marcin Dominik. Comparative effectiveness of torasemide versus furosemide in symptomatic therapy in heart failure patients: Preliminary results from the randomized TORNADO trial. Cardiology Journal (d. Folia Cardiologica). 2019; 26(6): 661-668. (Rodzaj publikacji: praca oryginalna)	1,669	100
19.	Kapłon-Cieślicka Agnieszka, Budnik Monika, **Gawałko Monika**, Peller Michał, Gorczyca I, Michalska A, Babiarz A., Bodys A., Uliński R., Żochowski M., Scisło Piotr Rafał, Kochanowski Janusz Ireneusz, Filipiak Krzysztof Jerzy, Opolski Grzegorz. Atrial fibrillation type and renal dysfunction as important predictors of left atrial thrombus. Heart. 2019; 105(17): 1310-1315. (Rodzaj publikacji: praca oryginalna)	5,213	140
20.	Gorczyca Iwona, Jelonek Olga, Uziębła-Życzkowska Beata, Chrapek Magdalena, Maciorowska Małgorzata, Wójcik Maciej, Błaszczyk Robert, Kapłon-Cieślicka Agnieszka, **Gawałko Monika**, Budnik Monika, Tokarek Tomasz, Rajtar-Salwa Renata, Bil Jacek, Wojewódzki Michał, Szpotowicz Anna, Bednarski Janusz, Bakuła-Ostalska Elwira, Tomaszuk-Kazberuk Anna, Szyszkowska Anna, Wełnicki Marcin, Mamcarz Artur Jacek, Wożakowska-Kapłon Beata. Trends in the Prescription of Non-Vitamin K Antagonist Oral Anticoagulants for Atrial Fibrillation: Results of the Polish Atrial Fibrillation (POL-AF) Registry. Journal of Clinical Medicine. 2020; 9(11): 1-14. (Rodzaj publikacji: praca oryginalna)	3,303	140
21.	Lodziński Piotr Ryszard, **Gawałko Monika**, Budnik Monika, Tymińska Agata, Ozierański Krzysztof, Grabowski Marcin Dominik, Janion-Sadowska A., Opolski Grzegorz, Lenarczyk R, Kalarus Z., Lip GYH, Balsam Paweł. Trends in Antithrombotic Management of Patients With Atrial Fibrillation. A Report From the Polish Part of the EURObservational Research Programme - Atrial Fibrillation General Long-Term Registry. Polskie Archiwum Medycyny Wewnętrznej. 2020; 130(3): 196-205. (Rodzaj publikacji: praca oryginalna)	3,007	100

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23.	Pietrzak Radosław, Franke Magda, **Gawałko Monika**, Lodziński Piotr Ryszard, Balsam Paweł, Grabowski Marcin Dominik, Werner Bożena Barbara. Success rate and safety of catheter ablation in preexcitation syndrome: A comparison between adult and pediatric patients. Cardiology Journal (d. Folia Cardiologica). 2020; :1-5. (Rodzaj publikacji: praca oryginalna)	1,669	100
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28.	Uziębło-Życzkowska Beata, Krzesiński Paweł, Jurek Agnieszka, Kapłon-Cieślicka Agnieszka, Gorczyca Iwona, Budnik Monika, Gielerak Grzegorz, Kiliszek Marek, **Gawałko Monika**, Scisło Piotr Rafał, Kochanowski Janusz Ireneusz, Jelonek Olga, Michalska Anna, Starzyk Katarzyna, Filipiak Krzysztof Jerzy, Wożakowska-Kapłon Beata, Opolski Grzegorz. Left Ventricular Ejection Fraction Is Associated with the Risk of Thrombus in the Left Atrial Appendage in Patients with Atrial Fibrillation. Cardiovascular Therapeutics. 2020; 2020:1-7. (Rodzaj publikacji: praca oryginalna)	2,538	100

29.	Gorczyca Iwona, Chrapek Magdalena, Jelonek Olga, Michalska Anna, Kapłon-Cieślicka Agnieszka, Uziębło-Życzkowska Beata, Budnik Monika, **Gawałko Monika**, Krzesiński Paweł, Jurek Agnieszka, Scisło Piotr Rafał, Kochanowski Janusz Ireneusz, Kiliszek Marek, Gielerak Grzegorz, Filipiak Krzysztof Jerzy, Opolski Grzegorz, Wożakowska-Kapłon Beata. Left Atrial Appendage Thrombus Formation Despite Continuous Non-Vitamin K Antagonist Oral Anticoagulant Therapy in Atrial Fibrillation Patients Undergoing Electrical Cardioversion or Catheter Ablation: A Comparison of Dabigatran and Rivaroxaban. Cardiology Research and Practice. 2020; :1-10. (Rodzaj publikacji: praca oryginalna)	1,292	100
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31.	Grabowski Marcin Dominik, Michalak Marcin, **Gawałko Monika**, Gajda Sylwia, Cacko Andrzej, Januszkiewicz Łukasz, Kołodzińska Agnieszka, Mitkowski Przemysław M., Duray Gabor Z., Opolski Grzegorz. Implantation of the Micra transcatheter pacing system: Single Polish center experience with the real costs of hospitalization analysis. Cardiology Journal (d. Folia Cardiologica). 2020; 27(1): 47-53. (Rodzaj publikacji: praca oryginalna)	1,669	100
32.	Krzowski Bartosz, Balsam Paweł, Peller Michał, Lodziński Piotr Ryszard, Grabowski Marcin Dominik, Drozd-Sokołowska Joanna Ewa, Basak Grzegorz Władysław, **Gawałko Monika**, Opolski Grzegorz, Kosiuk J. Electrophysiological Procedures in Patients With Coagulation Disorders - A Systemic Review. Circulation Journal. 2020; 84(6): 875-882. (Rodzaj publikacji: przegląd systematyczny)	2,540	100
33.	Michalska A, Gorczyca I, Chrapek M., Kapłon-Cieślicka Agnieszka, Uziębło-Życzkowska B., Starzyk K, Jelonek O, Budnik Monika, **Gawałko Monika**, Krzesiński P, Jurek A., Scisło Piotr Rafał, Kochanowski Janusz Ireneusz, Kiliszek M, Gielerak G, Filipiak Krzysztof Jerzy, Opolski Grzegorz, Wożakowska-Kapłon B.. Does the CHA2DS2-VASc scale sufficiently predict the risk of left atrial appendage thrombus in patients with diagnosed atrial fibrillation treated with non-vitamin K oral anticoagulants?. Medicine. 2020; 99(25): 1-8. (Rodzaj publikacji: praca oryginalna)	1,552	70
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36.	van der Velden Rachel MJ, Hermans Astrid NL, Pluymaekers Nikki AHA, **Gawałko Monika**, Vorstermans Bianca, Martens Herm, Buskes Saskia, Crijns Harry JGM, Linz Dominik, Hendriks Jeroen M. Coordination of a remote mHealth infrastructure for atrial fibrillation management during COVID-19 and beyond: TeleCheck-AF. International Journal of Care Coordination. 2020; 23(2-3): 65-70. (Rodzaj publikacji: praca poglądowa)	-	70

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38.	**Gawałko Monika**, Budnik Monika, Uziębło-Życzkowska Beata, Gorczyca Iwona, Krzesiński Paweł, Scisło Piotr Rafał, Kochanowski Janusz Ireneusz, Michalska Anna, Jelonek Olga, Starzyk Katarzyna, Jurek Agnieszka, Kiliszek Marek, Wożakowska-Kapłon Beata, Gielerak Grzegorz, Filipiak Krzysztof Jerzy, Opolski Grzegorz, Kapłon-Cieślicka Agnieszka. Risk of left atrial appendage thrombus in older patients with atrial fibrillation. Archives of Medical Science. 2020;5:1-10. (Rodzaj publikacji: praca oryginalna)	2,807	70
39.	**Gawałko Monika**, Jespersen Thomas, Dobrev Dobromir, Linz Dominik. The gut microbial-derived metabolite trimethylamine N-oxide: A missing link between lifestyle-components and atrial fibrillation?. International Journal of Cardiology. Heart & Vasculature. 2020; 29:1-3. (Rodzaj publikacji: komentarz)	-	-
40.	Linz Dominik, van der Velden Rachel MJ, **Gawałko Monika**, Hermans Astrid NL, Pluymaekers Nikki AHA, Hendriks Jeroen M. Remote management and education in patients with cardiovascular conditions during COVID-19 and beyond. International Journal of Cardiology. Heart & Vasculature. 2020; 30:1-3. (Rodzaj publikacji: komentarz)	-	-
41.	**Gawałko Monika**, Elliott Adrian, Kadhim Kadhim, Sanders Prashanthan, Linz Dominik. A call for a more objective and longitudinal reporting of lifestyle components in cardiovascular research. International Journal of Cardiology. Heart & Vasculature. 2020; 27:1-3. (Rodzaj publikacji: komentarz)	-	-
42.	**Gawałko Monika**, Lodziński Piotr Ryszard, Budnik Monika, Tymińska Agata, Wancerz Anna, Ozierański Krzysztof, Kapłon-Cieślicka Agnieszka, Grabowski Marcin Dominik, Opolski Grzegorz, Lenarczyk Radosław, Kalarus Zbigniew, Lip Gregory Y H, Balsam Paweł. Vascular disease in patients with atrial fibrillation. A report from Polish participants in the EORP-AF General Long-Term Registry. International Journal of Clinical Practice. 2021; 75:e13701-e13701. (Rodzaj publikacji: praca oryginalna)	2,444	70
43.	Kiliszek Marek, Uziębło-Życzkowska Beata, Gorczyca Iwona, Maciorowska Małgorzata, Jelonek Olga, Wożakowska-Kapłon Beata, Wójcik Maciej, Błaszczyk Robert, **Gawałko Monika**, Kapłon-Cieślicka Agnieszka, Tokarek Tomasz, Rajtar-Salwa Renata, Bil Jacek, Wojewódzki Michał, Szpotowicz Anna, Krzciuk Małgorzata, Bednarski Janusz, Bakuła-Ostalska Elwira, Tomaszuk-Kazberuk Anna, Szyszkowska Anna, Wełnicki Marcin, Mamcarz Artur Jacek, Krzesiński Paweł. Symptomatic and Asymptomatic Patients in the Polish Atrial Fibrillation (POL-AF) Registry. Journal of Clinical Medicine. 2021; 10(5): 1-9. (Rodzaj publikacji: praca oryginalna)	3,303	140
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45.	Pluymaekers Nikki AHA, van der Velden Rachel MJ, Hermans Astrid NL, **Gawałko Monika**, Buskes Saskia, Keijenberg Joyce JHMW, Vorstermans Bianca, Crijns Harry JGM, Hendriks Jeroen M, Linz Dominik. On-Demand Mobile Health Infrastructure for Remote Rhythm Monitoring within a Wait-and-See Strategy for Recent-Onset Atrial Fibrillation: TeleWAS-AF. Cardiology. 2021; :1-5. (Rodzaj publikacji: praca oryginalna)	1,791	40

46.	Hermans Astrid NL, **Gawałko Monika**, Pluymaekers Nikki AHA, Dinh Trang, Weijs Bob, van Mourik Manouk JW, Vorstermans Bianca, den Uijl Dennis W, Opsteyn Ludo, Snippe Hilco, Vernooy Kevin, Crijns Harry JGM, Linz Dominik, Luermans Justin GLM. Long-term intermittent versus short continuous heart rhythm monitoring for the detection of atrial fibrillation recurrences after catheter ablation. International Journal of Cardiology. 2021; :1-27. (Rodzaj publikacji: praca oryginalna)	3,229	100
47.	Pluymaekers Nikki AHA, Hermans Astrid NL, van der Velden Rachel MJ, **Gawałko Monika**, den Uijil Dennis W, Buskes Saskia, Vernooy Kevin, Crijns Harry JGM, Hendriks Jeroen M, Linz Dominik. Implementation of an on-demand app-based heart rate and rhythm monitoring infrastructure for the management of atrial fibrillation through teleconsultation: TeleCheck-AF. Europace. 2021; 23(3): 345-352. (Rodzaj publikacji: praca poglądowa)	4,045	140
48.	**Gawałko Monika**, Budnik Monika, Gorczyca Iwona, Jelonek Olga, Uziębło-Życzkowska Beata, Maciorowska Małgorzata, Wójcik Maciej, Błaszczyk Robert, Tokarek Tomasz, Rajtar-Salwa Renata, Bil Jacek, Wojewódzki Michał, Szpotowicz Anna, Krzciuk Małgorzata, Bednarski Janusz, Bakuła-Ostalska Elwira, Tomaszuk-Kazberuk Anna, Szyszkowska Anna, Wełnicki Marcin, Mamcarz Artur Jacek, Kapłon-Cieślicka Agnieszka. Characteristics and Treatment of Atrial Fibrillation with Respect to the Presence or Absence of Heart Failure. Insights from the Multicenter Polish Atrial Fibrillation (POL-AF) Registry. Journal of Clinical Medicine. 2021; 10(7): 1-17. (Rodzaj publikacji: praca oryginalna)	3,303	140
49.	Uziębło-Życzkowska Beata, Krzesiński Paweł, Maciorowska Małgorzata, Gorczyca Iwona, Jelonek Olga, Wójcik Maciej, Błaszczyk Robert, Kapłon-Cieślicka Agnieszka, **Gawałko Monika**, Tokarek Tomasz, Rajtar-Salwa Renata, Bil Jacek, Wojewódzki Michał, Szpotowicz Anna, Krzciuk Małgorzata, Bednarski Janusz, Bakuła-Ostalska Elwira, Tomaszuk-Kazberuk Anna, Szyszkowska Anna, Wełnicki Marcin, Mamcarz Artur Jacek, Wożakowska-Kapłon Beata. Antithrombotic therapy in patients with atrial fibrillation undergoing percutaneous coronary intervention, including compliance with current guidelines—data from the POLish Atrial Fibrillation (POL-AF) Registry. Cardiovascular Diagnosis and Therapy. 2021; 11(1): 14-27. (Rodzaj publikacji: praca oryginalna)	2,615	100
50.	**Gawałko Monika**, Dobrev D. Surgery-related cardiac stress: A susceptibility test of late atrial fibrillation recurrence? International Journal of Cardiology. Heart & Vasculature. 2021;32(100693):1-2. (Rodzaj publikacji: komentarz)	-	-
51.	**Gawałko Monika**, Dobrev D. Pericardial adipose tissue: An emerging biomarker of atrial fibrillation?. International Journal of Cardiology. 2021;331:122-123. (Rodzaj publikacji: komentarz)	-	-
Liczba punktów:		95,642	3590
II. Artykuły opublikowane przed 1.01.2019 r. w czasopismach ujętych w wykazie czasopism MNiSW z dnia 25.01.2017 r., o ile czasopismo uzyskało co najmniej 10 pkt.			
52.	-	-	-
Liczba punktów:			
III. Pozostałe artykuły			
53.	**Gawałko Monika**, Kołodzińska Agnieszka, Grabowski Marcin Dominik, Kutarski Andrzej, Opolski Grzegorz. Transvenous lead removal with a fragment of a papillary muscle - a silent complication. Heart Beat Journal. 2016; 1:41-42. (Rodzaj publikacji: praca kazuistyczna)	-	-

54.	Balsam Paweł, **Gawałko Monika**, Lodziński Piotr Ryszard, Grabowski Marcin Dominik, Kołtowski Łukasz, Peller Michał, Opolski Grzegorz. Atrioventricular block registration with smart phone associated ECG device. Heart Beat Journal. 2016; (1): 54-55. (Rodzaj publikacji: praca kazuistyczna)	-	-
55.	Zaczek Rajmund, Balsam Paweł, Peller Michał, **Gawałko Monika**, Łyżwiński Łukasz, Kiliszek Marek, Baranowski Rafał, Opolski Grzegorz. Wpływ rehabilitacji kardiologicznej po zawale serca na mikrowoltowy alternans załamka T oraz czynniki ryzyka wyniku nieujemnego. Kardiologia Inwazyjna. 2017; 12(1): 48-55. (Rodzaj publikacji: praca oryginalna)	-	-
56.	**Gawałko Monika**, Balsam Paweł. Połączenie ramiprylu i indapamidu w leczeniu nadciśnienia tętniczego samoistnego. Świat Medycyny i Farmacji. 2018; (6): 52-55. (Rodzaj publikacji: praca poglądowa)	-	-
57.	**Gawałko Monika**, Balsam Paweł. Podwójne leczenie przeciwpłytkowe w chorobie wieńcowej - nowe wytyczne ESC 2017. Medycyna po Dyplomie. 2018; 27(2): 18-21. (Rodzaj publikacji: praca poglądowa)	-	5
Liczba punktów:		-	5
Punktacja łączna (cz. I- III):		**95,642**	**3595**
IV. Monografie naukowe/rozdziały w monografiach wydane przez wydawnictwa ujęte w wykazie MNiSW[2] lub jednostki organizacyjne podmiotów, których wydawnictwa są ujęte w tym wykazie			
58.	-		
V. Pozostałe monografie lub rozdziały w monografiach			
-			
VI. Patenty			
-			

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mgr Anna Ajdukiewicz-Tarkowska

[2] Wykaz sporządzony zgodnie z przepisami wydanymi na podstawie art. 267 ust. 2 pkt 2 lit. a Ustawy z dnia 20 lipca 2018 r. - Prawo o szkolnictwie wyższym i nauce (Dz. U. z 2018 r., poz. 1668 ze zm.). Wykaz ogłoszony komunikatem MNiSW z dnia 29 września 2020 r. w sprawie wykazu wydawnictw publikujących recenzowane monografie naukowe.