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Ocena czynników ryzyka wystąpienia migotania przedsionków u pacjentów z ostrym zawałem mięśnia sercowego ze szczególnym uwzględnieniem chorych z pierwszym w życiu napadem arytmii

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Składam serdeczne podziękowania mojej Promotor
Pani Prof. dr hab. n. med. Ludmile Daniłowicz-Szymanowicz,
za inspirację, opiekę naukową, poświęcony czas, wsparcie
merytoryczne i nieocenioną pomoc w trakcie przygotowywania
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przy przygotowywaniu niniejszej rozprawy doktorskiej.

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które przyczyniły się do powstania tej rozprawy.

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a w sposób szczególny Piotrowi.

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1. Wprowadzenie

Rozprawa doktorska pt.: **„Ocena czynników ryzyka wystąpienia migotania przedsionków u pacjentów z ostrym zawałem mięśnia sercowego ze szczególnym uwzględnieniem chorych z pierwszym w życiu napadem arytmii”** powstała w oparciu o monotematyczny cykl trzech artykułów oryginalnych opublikowanych w czasopismach naukowych, indeksowanych w bazie PubMed.

1.1. Wykaz publikacji stanowiących rozprawę doktorską

Tytuł publikacji, autorzy, tytuł czasopisma	Punkty MNiSW	Impact Factor
Clinical and laboratory assessment of patients with new-onset atrial fibrillation in acute myocardial infarction **Raczkowska-Golanko Monika**, Daniłowicz-Szymanowicz Ludmiła, Nowak Radosław, Puchalski Wiesław, Gruchała Marcin, Kozłowski Dariusz, Raczak Grzegorz. Eur. J. Transl. Clin. Med. 2018: vol. 1, nr 1, s. 37-41; doi: 10.31373/ejtcm/95256	1	
Comprehensive use of routine clinical parameters to identify patients at risk of new-onset atrial fibrillation in acute myocardial infarction* **Raczkowska-Golanko Monika**, Raczak Grzegorz, Gruchała Marcin, Daniłowicz-Szymanowicz Ludmiła. J. Clin. Med. 2021: vol. 10, nr 16, s. 1-14; doi: 10.3390/jcm10163622	140	4,964
New-onset atrial fibrillation in acute myocardial infarction is a different phenomenon than other pre-existing types of that arrhythmia **Raczkowska-Golanko Monika**, Młodziński Krzysztof, Raczak Grzegorz, Gruchała Marcin, Daniłowicz-Szymanowicz Ludmiła. J. Clin. Med. 2022: vol. 11, nr 15, s. 1-15; doi: 10.3390/jcm11154410	140	4,964
Podsumowanie punktów	**281**	**9,928**

∗ Praca nagrodzona Nagrodą Specjalną Rektora Gdańskiego Uniwersytetu Medycznego

1.2. Wykaz doniesień zjazdowych

1. **Raczkowska-Golanko Monika**, Raczak Grzegorz, Puchalski Wiesław, Gruchała Marcin, Daniłowicz-Szymanowicz Ludmiła. Co wiemy o świeżo wykrytym migotaniu przedsionków w ostrym zawale mięśnia sercowego?" Sesja ustna na XXX Ogólnopolskiej Konferencji Sekcji Zaburzeń Rytmu Serca PTK „POLSTIM" w Toruniu (2019).

2. Daniłowicz-Szymanowicz Ludmiła, **Raczkowska-Golanko Monika**, Nowak Radosław, Puchalski Wiesław, Gruchała Marcin, Raczak Grzegorz. Świeżo wykryte migotanie przedsionków w ostrym zawale mięśnia sercowego: badanie jednoośrodkowe na podstawie danych z polskiego Uniwersyteckiego Centrum Klinicznego. Kardiol. Pol. Heart J. Cardiovasc. Imag. 2019 : t. 77, suppl. 1, s. 121. Sesja plakatowa podczas konferencji Polskiego Towarzystwa Kardiologicznego XXIII Międzynarodowy Kongres Polskiego Towarzystwa Kardiologicznego w Katowicach (2019).

3. **Raczkowska-Golanko Monika**, Raczak Grzegorz, Puchalski Wiesław, Gruchała Marcin, Daniłowicz-Szymanowicz Ludmiła. Świeżo wykryte migotanie przedsionków jest ważnym, wieloczynnikowym powikłaniem ostrego zawału mięśnia sercowego - dane z uniwersyteckiego centrum klinicznego. **Sesja najlepszych prac oryginalnych** podczas XXVII Konferencji Szkoleniowej Asocjacji Elektrokardiologii Nieinwazyjnej i Telemedycyny Polskiego Towarzystwa Kardiologicznego, Kasprowisko (2021).

4. **Raczkowska-Golanko Monika**, Raczak Grzegorz, Puchalski Wiesław, Gruchała Marcin, Daniłowicz-Szymanowicz Ludmiła. Podstawowe parametry echokardiograficzne mogą być pomocne w identyfikacji świeżo wykrytego napadu migotania przedsionków w ostrym zawale mięśnia sercowego. Sesja ustna na XXII Ogólnopolskiej Konferencji Sekcji Echokardiografii PTK „PolEcho" w Gdańsku (2021).

5. **Raczkowska-Golanko Monika**, Raczak Grzegorz, Gruchała Marcin, Daniłowicz-Szymanowicz Ludmiła. Simple clinical parameters could help to identify the patients with a high probability of new-onset atrial fibrillation in acute myocardial infarction. EP Europace 2021: vol. 23, suppl. 3, s. iii154. Sesja plakatowa podczas konferencji

Europejskiego Towarzystwa Kardiologicznego EHRA (on-line, 2021).

6. **Raczkowska-Golanko Monika**, Raczak Grzegorz, Gruchała Marcin, Daniłowicz-Szymanowicz Ludmiła. Simple echocardiographic parameters could be helpful in the identification of new-onset atrial fibrillation in acute myocardial infarction. Eur. Heart J. Cardiovasc. Imag. 2022: vol. 23, suppl. 1, s. i590. Sesja plakatowa podczas konferencji Europejskiego Towarzystwa Kardiologicznego EuroEcho (on-line, 2021).

2. Alfabetyczny wykaz używanych skrótów

AF – *atrial fibrillation* / migotanie przedsionków

ACS – *acute coronary syndrome* / ostry zespół wieńcowy

AMI – *acute myocardial infarction* / ostry zawał mięśnia sercowego

AUC – *area under curve* / pole pod krzywą

BNP – *brain natriuretic peptide* / mózgowy peptyd natriuretyczny

CK-MB – *creatine kinase muscle brain* / kinaza kreatynowa-izoenzym sercowy

CI – *confidence interval* / przedział ufności

CRP – *C-reactive protein* / białko C-reaktywne

hsTnI – *high sensitivity troponine I* / wysokoczuła troponina I

LA – *left atrium* / lewy przedsionek

LDL – *low-density lipoprotein* / lipoproteina o niskiej gęstości

LVEF – *left ventricular ejection fraction* / frakcja wyrzutowa lewej komory

NOAC – *new oral anticoagulants* / nowe doustne leki przeciwzakrzepowe

NOAF – *new-onset atrial fibrillation* / świeżo wykryte migotanie przedsionków

OR – *odds ratio* / iloraz szans

ROC – *receiver operating characteristic*

RVID – *right ventricular internal diameter* / wymiar wewnętrzny prawej komory

STEMI – *ST-elevation myocardial infarction* / zawał z uniesieniem odcinka ST

TAPSE – *tricuspid annular plane systolic excursion* / pomiar wychylenia skurczowego pierścienia trójdzielnego

3. Wstęp

Migotanie przedsionków (*atrial fibrillation*, AF) jest jedną z najczęstszych arytmii nadkomorowych populacji osób dorosłych występującą u około 3%. Znanymi czynnikami ryzyka wystąpienia AF są między innymi wiek, płeć żeńska, cukrzyca, palenie papierosów, spożycie alkoholu, nadciśnienie tętnicze, niewydolność serca, choroba wieńcowa i otyłość [1]. Wiadomo też, że AF jest najczęstszą arytmią będącą powikłaniem ostrego okresu zawału serca (*acute myocardial infarction*, AMI). Częstość występowania pierwszego w życiu tak zwanego świeżo wykrytego napadu AF (*new onset atrial fibrillation*, **NOAF**), u osób z AMI szacuje się na 6 - 21% [2]. Dokładna definicja NOAF określa go jako nowy napad AF, który wystąpił w trakcie pobytu w szpitalu u pacjentów z rytmem zatokowym podczas przyjęcia bądź u osób przyjętych do szpitala z napadem AF bez wcześniejszego wywiadu tej arytmii [3–5]. Wiadomo, że wystąpienie NOAF wiąże się z gorszym rokowaniem u pacjentów z AMI [6], w tym z większym ryzykiem udarów mózgu, innych incydentów zatorowo-zakrzepowych, niewydolności serca, zaburzeń funkcji lewej komory serca, jak również zgonu [7,8].

Związek pomiędzy występowaniem NOAF a zawałem serca jest złożony i nie do końca poznany. Podobnie jak w populacji ogólnej, wymienione wyżej czynniki ryzyka sprzyjają tej arytmii u pacjentów z AMI [1,2]. Wiadomo jednak, że istnieją dodatkowe, na chwilę obecną nie do końca sprecyzowane, czynniki ryzyka NOAF w większym lub mniejszym stopniu związane z samym zawałem serca, które predysponują do wystąpienia tej arytmii. Szczegółowe zbadanie chorych z NOAF w AMI, wydaje się dlatego niezwykle ważnym z klinicznego punktu widzenia zagadnieniem.

Dotychczasowe dane z piśmiennictwa oceniające czynniki ryzyka wystąpienia NOAF w AMI zwykle traktowały priorytetowo tylko jeden, wybrany parametr kliniczny, jak na przykład rolę poziomu troponiny [9,10], białka C-reaktywnego (*C-reactive protein*, CRP) [4,11], potasu w surowicy krwi [12–14], peptydu natriuretycznego (*brain natriuretic peptid*e, BNP) [5,15], hemoglobiny [16], a także innych pojedynczych parametrów klinicznych w przewidywaniu ryzyka AF [17–21]**,** albo uwzględniały tylko pacjentów z jednym typem zawału, głównie zawałem mięśnia sercowego z uniesieniem odcinka ST (*ST-elevation myocardial infarction*, STEMI) [22–26]. Część badań opierała się na rejestrach międzynarodowych [6,27–29], które poza oczywistymi zaletami, zawierały dane z ośrodków klinicznych pochodzących z różnych krajów, co mogło implikować różnorodne metody diagnostyczne i różne możliwości leczenia [19,30]**.** Co więcej,

w żadnej z publikacji dotyczącej poszczególnych istotnych parametrów laboratoryjnych, nie została oceniona dynamika zmian występująca w trakcie hospitalizacji. Dodatkowo, większość dostępnych w piśmiennictwie badań wykonana była we wcześniejszych latach, w oparciu o już nieaktualne wytyczne leczenia AMI.

4. Cele pracy

Celem niniejszej rozprawy doktorskiej była kompleksowa ocena czynników ryzyka wystąpienia i nawrotu AF u chorych z ostrym zawałem serca.

Szczegółowe cele:

1. Ocena czynników ryzyka NOAF u pacjentów z AMI hospitalizowanych i leczonych zgodnie z aktualnymi wytycznymi w dużym ośrodku klinicznym.
2. Porównanie przebiegu hospitalizacji i rokowania wewnątrzszpitalnego chorych w zależności od rodzaju AF w AMI, ze szczególnym uwzględnieniem NOAF.

Realizacja powyższych celów została opisana w trzech artykułach oryginalnych, na których bazuje niniejsza rozprawa: cel pierwszy badany był w pracy oryginalnej nr 1 (strony: 32–37) oraz nr 2 (strony: 38–52); cel trzeci w pracy oryginalnej nr 3 (strony: 53–68).

5. Metodyka

5.1. Populacja badana

Do badania retrospektywnie włączono kolejnych chorych z AMI będących pacjentami hospitalizowanymi w Uniwersyteckim Centrum Klinicznym w Gdańsku w latach 2017-2018. Dane zostały zebrane przy pomocy programu MedStream Designer, który jest w pełni zanonimizowany oraz zintegrowany z systemem informatycznym szpitala. Kryterium wyłączenia był wiek chorych poniżej 18 roku życia.

Termin NOAF był stosowany dla każdego nowo rozpoznanego AF (brak załamków P, aktywność przedsionków reprezentowana przez załamki migotania i nieregularne odstępy RR), które pojawiło się podczas hospitalizacji i trwało co najmniej 30 s lub było zarejestrowane w trakcie 12-odprowadzeniowego EKG. Szczegółowa procedura rozpoznania NOAF została opisana w pracy oryginalnej numer 2 (strony: 40), szczegółowe kryteria włączenia i wyłączenia podane są w każdej z publikacji (strony: 34, 40, 55). Protokół badań został zatwierdzony przez Niezależną Komisję Bioetyczną do Spraw Badań Naukowych przy Gdańskim Uniwersytecie Medycznym (NKBBN/290/2018).

5.2. Dane kliniczne

U wszystkich pacjentów oceniano parametry kliniczne (w tym dotychczasowy wywiad, choroby współistniejące, przyjmowane leki, nikotynizm, dokładny przebieg hospitalizacji z uwzględnieniem stanu naczyń wieńcowych i efektu koronarografii wykonanej w ostrej fazie zawału), parametry laboratoryjne (między innymi BNP, CRP, morfologia, kreatynina, glukoza, wysokoczuła troponina I (*high-sensitivity troponin I,* hsTnI), CK-MB (*creatine kinase muscle brain)*, lipidogram, z uwzględnieniem dynamiki wybranych parametrów w kolejnych dniach hospitalizacji), a także ocena parametrów echokardiograficznych (wielkość jam przedsionków i komór, parametru funkcji skurczowej i rozkurczowej lewej komory serca, parametry funkcji skurczowej prawej komory serca, obecność i stopień zaawansowania wad serca).

5.3. Analizy statystyczne

Analiza statystyczna została przeprowadzona z użyciem programów STATISTICA 9.0 (*StatSoft, Tulsa OK, USA*) oraz środowiska statystycznego R 2.15.2., R 3.1.2. i R 4.0.5. Wyczerpujący opis stosowanych metod statystycznych zawarty jest w artykułach wchodzących w skład dysertacji (strony: 34, 40-41, 55).

6. Wyniki

6.1. Wyniki szczegółowe pracy oryginalnej nr 1

Na podstawie danych z piśmiennictwa wiadomo, że pacjenci z NOAF w trakcie AMI obciążeni są zwiększonym ryzykiem powikłań sercowo-naczyniowych [6], dlatego identyfikacja czynników ryzyka tej arytmii wydaje się mieć szczególne znaczenie kliniczne. Pierwszy artykuł, na którym bazuje niniejsza rozprawa doktorska, koncentruje się na wstępnej, pilotażowej ocenie pacjentów z NOAF. Badaniem objęto 103 pacjentów z NOAF, wybranych na podstawie analizy danych 1155 hospitalizowanych z AMI chorych od stycznia 2016 do czerwca 2018 roku. Mediana wieku opisywanej grupy pacjentów wynosiła 72 (64 - 82) lata, 62% pacjentów stanowili mężczyźni, 36% tej grupy hospitalizowanych było z powodu STEMI.

Na podstawie analizy wyników badań laboratoryjnych z dnia przyjęcia i z dnia wystąpienia NOAF stwierdzono, że w dniu wystąpienia NOAF, w porównaniu do momentu przyjęcia chorego do szpitala, obserwowano istotny statystycznie wzrost CRP, wzrost hsTnI, z jednoczasowym istotnym spadkiem wartości hemoglobiny i stężenia potasu we krwi (Tabela 3, strona 35). W trakcie hospitalizacji doszło do zgonu wewnątrzszpitalnego 16 pacjentów (16%), z czego 11 pacjentów zmarło z przyczyn kardiologicznych, 2 z powodu sepsy, a jedna osoba z powodu udaru krwotocznego; u dwóch pozostałych chorych odnotowano inne przyczyny zgonu.

Na podstawie pilotażowych wyników pracy nr 1 w toku dalszej analizy znacząco poszerzono zakres badanych parametrów, a także zwiększono liczbę pacjentów.

6.2. Wyniki szczegółowe pracy oryginalnej nr 2

Drugi artykuł, na którym opiera się rozprawa doktorska, poświęcony został kompleksowej analizie parametrów klinicznych, rutynowo ocenianych podczas hospitalizacji, w celu identyfikacji czynników ryzyka NOAF w grupie hospitalizowanych z AMI, leczonych zgodnie z aktualnymi wytycznymi. Do badania włączono 954 pacjentów z AMI hospitalizowanych w Uniwersyteckim Centrum Klinicznym w latach 2017 – 2018, wśród których NOAF rozpoznano u 106 (11%) pacjentów.

Pacjenci z NOAF (Tabela 1, strona 40), w porównaniu do reszty pacjentów (określonych w pracy jako nie-NOAF), byli starsi, mieli niższy poziom wskaźnika masy ciała (*body mass index*, BMI). Obydwie grupy charakteryzował podobny odsetek dodatkowych obciążeń, takich jak wywiad choroby wieńcowej, przebytego zawału serca, nadciśnienia tętniczego, cukrzycy. Prawie 100% włączonych pacjentów miało wykonaną koronarografię w trakcie hospitalizacji, a 82% przeszło przezskórną interwencję wieńcową (*percutaneous coronary intervention*, PCI), jak przedstawiono w Tabeli 3 (strona 43). Pacjenci obydwu grup nie różnili się pod względem przyjmowanych przed hospitalizacją leków, jak aspiryna, inhibitory konwertazy angiotensyny/sartany, jak również statyny (Tabela 1, strona 41).

Pacjenci z NOAF w porównaniu do pozostałych zdecydowanie różnili się w ocenie parametrów laboratoryjnych i echokardiograficznych (Tabela 2, strona 42). Wykazano, że pacjenci z NOAF mieli przy przyjęciu wyższy poziom BNP, CRP, hsTnI, natomiast istotnie statystycznie niższy poziom sodu, potasu, hemoglobiny, cholesterolu LDL (*low-density lipoprotein cholesterol*, LDL-C), cholesterolu całkowitego. Jeśli chodzi o parametry echokardiograficzne, pacjenci z NOAF mieli istotnie niższą frakcję wyrzutową lewej komory (*left ventricular ejection fraction*, LVEF) i większy lewy przedsionek (*left atrium*, LA), a także gorsze parametry prawej komory, takie jak wewnętrzny wymiar prawej komory (*right ventricular internal diameter*, RVID) czy wskaźnik jej funkcji skurczowej (*tricuspid annular plane systoli excursion*, TAPSE).

Jednoczynnikowa analiza regresji logistycznej wykazała, że wiek, czas hospitalizacji, poziom BNP, hsTnI, CRP, potasu, hemoglobiny, leukocytów, stosunek neutrofili do limfocytów, poziom cholesterolu LDL, cholesterolu całkowitego, kreatyniny, a także wielkość LA i LVEF są istotnymi czynnikami determinującymi NOAF (Tabela 4, strona 43). Wiek chorych, BNP, CRP oraz LVEF okazały się również niezależnymi wskaźnikami NOAF w analizie wieloczynnikowej regresji logistycznej (Tabela 4, strona 43).

Wartości odcięcia dla tych parametrów, wyznaczone przy użyciu analizy ROC, wyniosły:

- wiek ≥ 66 lat,
- BNP ≥ 340 pg/ml,
- CRP ≥ 7,7 mg/l,
- LVEF ≤ 44%.

Parametrem o największej mocy diagnostycznej dla NOAF okazał się BNP (≥ 340 pg/ml): wartość AUC (*Area Under Curve*) wyniosła 70,5% [95% CI (*Confidence Interval*) 64,6 – 76,5%)], (Tabela 4, strona 43).

W odniesieniu do przebiegu hospitalizacji pacjenci z NOAF mieli dłuższy czas hospitalizacji, więcej zdarzeń niepożądanych i gorsze rokowanie (Tabela 6, strona 43). Ponadto stwierdzono, że **NOAF był istotnie związany ze śmiertelnością wewnątrzszpitalną** (OR (*Odds ratio*) 4,54 [95% CI 2,50 – 8,33], p < 0,001).

Jeżeli chodzi o farmakoterapię przy wypisie, główna różnica pomiędzy grupą NOAF, a pozostałymi chorymi dotyczyła leczenia przeciwkrzepliwego. W grupie NOAF istotnie wyższy odsetek stanowili pacjenci którym zalecono na nowe doustne leki przeciwzakrzepowe (*novel oral anticoagulants*, NOAC), a także w mniejszym stopniu zalecono przyjmowanie aspiryny i tikagreloru. Natomiast częstość przepisywania innych leków (beta-adrenolityki, inhibitory konwertazy angiotensyny/sartany, statyny) nie różniła się statystycznie między grupami (Tabela 7, strona 45).

Podsumowując wyniki pracy oryginalnej nr 2, należy zaznaczyć, że NOAF stanowi częstą komplikację nowoczesnej populacji chorych z AMI i jest związane z wyższą śmiertelnością wewnątrzszpitalną. Starszy wiek, obniżona LVEF, a także poziom prostych wskaźników laboratoryjnych (ze szczególną rolą podwyższonego ponad 340 pg/ml poziomu BNP), stanowią istotne wskaźniki ryzyka NOAF.

6.3. Wyniki szczegółowe pracy oryginalnej nr 3

Na podstawie dotychczasowych danych z literatury można domniemywać, że NOAF cechuje się innym obrazem klinicznym i rokowaniem w porównaniu do innych postaci AF u pacjentów w trakcie AMI [26,31–33]**.** Jednak dostępne prace dotyczące porównania pacjentów z różnymi postaciami AF zazwyczaj dotyczyły wybranej grupy chorych z AMI (na przykład wybrana grupa pacjentów ze STEMI, czy też tylko pacjenci leczeni inwazyjnie) [29,33–37]. Dlatego też nie odpowiedziano dotychczas jednoznacznie na pytanie, czy NOAF jest bardziej obciążającym rozpoznaniem u wszystkich pacjentów z AMI niż inne typy AF. Co więcej, ważnym aspektem wydaje się nie tylko ocena ryzyka wystąpienia AF *de novo*, ale także próba porównania wewnątrzszpitalnego przebiegu klinicznego i rokowania między pacjentami z NOAF, a pacjentami z wcześniej rozpoznanym AF, w tym chorymi, u których doszło do nawrotu AF w czasie hospitalizacji AMI. Praca nr 3 stanowi subanalizę bazy danych pracy nr 2. W celu wykonania odpowiednich porównań wszystkich pacjentów podzielono na 4 grupy:

- **NOAF** (grupa pacjentów z jakimkolwiek nowo rozpoznanym migotaniem przedsionków, które pojawiło się podczas hospitalizacji w AMI bez wcześniejszego rozpoznania AF, tak jak zostało to dokładnie opisane w pracy oryginalnej nr 2);
- **AF** (grupa pacjentów z wcześniej udokumentowanym rozpoznaniem AF, u których dodatkowo zanotowano nawrót tej arytmii podczas hospitalizacji z powodu AMI);
- **Prior-AF** (grupa pacjentów z wcześniej udokumentowaną diagnozą AF, u których nie odnotowano nawrotu AF podczas hospitalizacji z AMI);
- **Non-AF** (grupa pacjentów bez objawów migotania przedsionków podczas hospitalizacji z powodu AMI i bez uprzedniej diagnozy AF).

Grupa NOAF liczyła 106 pacjentów (11%), grupa AF obejmowała 95 pacjentów (10%), grupa Prior-AF - 60 pacjentów (6%), a pozostałych 693 (73%) stanowili pacjenci bez AF (Non-AF). U wszystkich pacjentów przeanalizowano oraz porównano szczegółowy wywiad i parametry kliniczne, a także oceniono przebieg leczenia szpitalnego. Dodatkowo poddano analizie dynamikę parametrów laboratoryjnych w ciągu pierwszych czterech kolejnych dni hospitalizacji z powodu AMI.

W odniesieniu do charakterystyki klinicznej, pacjenci z jakimkolwiek AF (grupa NOAF, AF, Prior-AF) byli starsi niż pacjenci Non-AF. Co ciekawe, chorzy NOAF,

podobnie do pacjentów bez AF, cechowali się mniej licznymi obciążeniami dodatkowymi niż pacjenci z wywiadem tej arytmii (czyli należący do grup AF i Prior-AF). U tych ostatnich (grupy AF i Prior-AF) częściej notowano w wywiadzie nadciśnienie tętnicze, cukrzycę, przewlekłą chorobę wieńcową, czy też udar (Tabela 1, strona 56). W analizie przedszpitalnego leczenia farmakologicznego łatwo było zauważyć mniejszą ilość pacjentów leczonych inhibitorami konwertazy angiotensyny/sartanami i statynami wśród pacjentów z NOAF, niż w obu grupach pacjentów z przebytym AF (AF i Prior-AF). Szczegółowe wyniki zostały przedstawione w Tabeli 1 (strona 56).

Co ciekawe, wśród wszystkich analizowanych grup chorych, pacjenci z NOAF cechowali się największym odsetkiem zawałów typu STEMI (40%), ponad dwukrotnie wyższym niż u innych pacjentów z AF (grupy AF i Prior-AF). Pacjenci z NOAF mieli najgorsze rokowanie wewnątrzszpitalne: najdłuższy czas hospitalizacji (10 dni, (7-17), $p < 0.001$), a także najwyższy odsetek zdarzeń niepożądanych takich jak: częstoskurcz komorowy (6%), migotanie komór (13%), blok przedsionkowo-komorowy III stopnia (6%) czy też udar (3%). Szczegółowe dane prezentuje Tabela 2 artykułu (strona 57). W grupie NOAF **śmiertelność wewnątrzszpitalna** była dwukrotnie większa niż w grupie AF i 4 - 6 razy większa niż w pozostałych grupach ($p < 0.001$) (Tabela 2, strona 57). Natomiast większość pacjentów z NOAF (85%), w przeciwieństwie do grupy AF (36%), miała przy wypisie rytm zatokowy.

Chorych z NOAF cechowała najniższa LVEF, podczas gdy wielkość LA, zgodnie z oczekiwaniami, była porównywalna wśród pacjentów z NOAF i Prior-AF, wyższa niż w grupie Non-AF, natomiast niższa niż w grupie AF. U pacjentów z jakimkolwiek AF w czasie hospitalizacji AMI (grupy NOAF i AF) RVID był największy (Tabela 3, strony 57-58).

Przechodząc do analizy wyników badań laboratoryjnych, obszernie opisanych w pracy oryginalnej nr 3, należy zwrócić uwagę, że grupa NOAF charakteryzowała się najwyższym poziomem hsTnI, BNP, CRP i glukozy przy jednocześnie najniższym stężeniu potasu w surowicy krwi. U tych chorych odnotowano najwyższy w trakcie hospitalizacji poziom hsTnI (co można powiązać z odpowiednio najwyższym odsetkiem zawałów STEMI w grupie NOAF). Dane parametrów laboratoryjnych szczegółowo przedstawia Tabela 3 (strony 57-58).

Dodatkowo przeprowadzono szczegółową ocenę dynamiki zmian parametrów laboratoryjnych w analizowanych grupach chorych w trakcie pierwszych czterech dni hospitalizacji. Pacjenci z NOAF, w odróżnieniu od innych grup, charakteryzowali

się istotnie wyrażonymi, dynamicznymi zmianami w zakresie poziomu CRP, leukocytów, hsTnI, a także potasu (Ryciny 1-3, 5, strony 59-61, 63). Pacjenci z grupy NOAF mieli największy wzrost hsTnI, z maksymalnym poziomem w trakcie drugiego dnia hospitalizacji (Rycina 1, strona 59). Co więcej, także poziom CRP był najwyższy wśród pacjentów z NOAF, ze stałym wzrostem w kolejnych dniach hospitalizacji (Rycina 2, strona 60). Jeżeli chodzi o leukocyty, pacjenci z NOAF mieli najwyższy poziom w trakcie drugiego dnia hospitalizacji, podczas gdy chorzy z grup AF i Prior-AF wykazywali stały spadek w trakcie czterech kolejnych dni (Rycina 3, strona 61). Co ciekawe, pacjentów z NOAF charakteryzował największy spadek hemoglobiny w trakcie czterech dni hospitalizacji (Rycina 5, strona 63). Jak już zostało wspomniane, pacjenci z NOAF mieli najwyższy wskaźnik występowania STEMI – 40% z równocześnie najwyższym poziomem hsTnI (Rycina 1, strona 59). W związku z tym wysunięto przypuszczenie, że NOAF może być zarówno konsekwencją ciężkiej martwicy mięśnia sercowego, jak i może stanowić bezpośrednie powikłanie rozległego zawału mięśnia sercowego.

Podsumowując, wyniki przeprowadzonych w pracy oryginalnej nr 3 analiz wskazują, że pacjentów z NOAF w AMI charakteryzuje najcięższy przebieg kliniczny i najgorsze rokowanie wewnątrzszpitalne w porównaniu do innych grup chorych. Przedstawione dane to pierwsza w literaturze kompleksowa ocena rutynowo mierzonych parametrów klinicznych i laboratoryjnych dotyczących różnych typów AF u nowocześnie leczonych pacjentów z AMI, ze szczególnym uwzględnieniem pacjentów z NOAF.

7. Ograniczenia

Niniejsza rozprawa doktorska posiada szereg ograniczeń. Pierwszym z nich jest jednoośrodkowy charakter. Po drugie, jest to badanie retrospektywne, ograniczone do dostępnych danych i parametrów w dokumentacji medycznej pacjentów. Z powodu braku precyzyjnego określenia pacjentów z niestabilną dławicą piersiową, do badania zostali włączeni jedynie pacjenci z AMI, a nie wszyscy pacjenci z ostrym zespołem wieńcowym (*acute coronary syndrome*, ACS). Kolejnym ograniczeniem jest brak obserwacji długoterminowej. Innym ograniczeniem jest prawdopodobne przeszacowanie NOAF, gdyż do tej grupy mogli być doliczeni chorzy z już występującym, ale wcześniej niewykrytym napadowym AF. Istnieje także ryzyko niedoszacowania właściwej częstotliwości AF (ze względu na ciche epizody AF). Podobne ograniczenie odnosi się do

precyzyjnego czasu wystąpienia częstoskurczu komorowego lub migotania komór lub bloku przedsionkowo-komorowego III stopnia w trakcie hospitalizacji; dlatego niektórzy pacjenci z tymi powikłaniami mogli mieć złośliwe zaburzenia rytmu w momencie przyjęcia, a nie tylko w czasie hospitalizacji.

8. Wnioski

NOAF jest istotną klinicznie arytmią będącą powikłaniem hospitalizacji, a także pogarszającą przebieg kliniczny i rokowanie chorych z AMI.

Wnioski szczegółowe:

1. Starszy wiek chorych, nieprawidłowe wartości szeroko dostępnych parametrów laboratoryjnych i klinicznych, takie jak podwyższona wartość BNP, wskaźniki zapalne (CRP), czy też obniżona wartość LVEF są istotnie związane z wystąpieniem NOAF w AMI.
2. NOAF w AMI wydaje się być innym zjawiskiem patofizjologicznym niż inne postacie AF. NOAF jest wskaźnikiem cięższego przebiegu i gorszego rokowania wewnątrzszpitalnego u chorych z AMI, pomimo wyjściowo mniejszego obciążenia dodatkowymi chorobami współistniejącymi.

9. Streszczenie pracy w języku angielskim

9.1. Background

Atrial fibrillation (AF) is one of the most common supraventricular arrhythmias in 3% of adults. Risk factors for AF occurrence include age, female gender, diabetes, smoking, alcohol consumption, hypertension, heart failure, coronary artery disease, and obesity [1]. It is also known that AF is the most common arrhythmia complicating acute myocardial infarction (AMI). The first-in-life so-called new-onset atrial fibrillation (NOAF) prevalence in people with AMI is estimated at 6 - 21% [2]. The exact definition of NOAF is a new attack of AF that occurred during a hospital stay in patients with sinus rhythm on admission or in those admitted to the hospital with an attack of AF without a previous history of this arrhythmia [3–5]. It is known that NOAF is associated with a worse prognosis in patients with AMI [6], including a higher risk of stroke, other thromboembolic events, heart failure, left ventricular dysfunction, and death [7,8].

The relationship between NOAF and myocardial infarction is complex and needs to be fully understood. As in the general population, the risk, as mentioned earlier, favours this arrhythmia in patients with AMI [1,2]. It is known that there are additional NOAF risk factors, to a greater or lesser extent, related to the infarction itself, which predispose to the occurrence of this arrhythmia, which is not fully specified at the moment. Therefore, a detailed examination of patients with NOAF in AMI is a critical issue from a clinical point of view.

Previous literature data assessing risk factors for NOAF in AMI usually prioritized only one selected clinical parameter, such as the role of troponin [9,10], C-reactive protein (CRP) [4,11], serum potassium [12–14], brain natriuretic peptide (BNP) [5,15], haemoglobin [16], as well as other single clinical parameters in predicting the risk of AF [17–21]**,** or they included only patients with one type of infarction, mainly ST-elevation myocardial infarction (STEMI) [22–26]**.** Some of the studies were based on international registries [6,27–29], which, apart from obvious advantages, contained data from various clinical centers, sometimes from different countries, which could imply different diagnostic methods and different treatment options [19,30]**.** Moreover, the dynamics of changes occurring during hospitalization were not assessed in any of the publications concerning the particular important laboratory parameters. In addition, most of the studies available in the literature were carried out in previous decades based

on the already outdated treatment guidelines for AMI.

9.2. The aims of the study

This doctoral dissertation aimed to comprehensively assess the risk factors for the occurrence and recurrence of AF in patients with acute myocardial infarction.

Detailed goals:

1. Assessment of NOAF risk factors in patients with AMI hospitalized and treated following current guidelines in a large clinical center.
2. Comparison of patients' clinical course and in-hospital prognosis depending on the type of AF in AMI, with particular emphasis on NOAF.

The above goals were established in three original articles on which this dissertation is based: the first goal was related to the original paper No. 1 (pages: 32 – 37) and No. 2 (pages: 38 – 52); the third goal to the original paper No. 3 (pages: 53 – 68).

9.3. Methods

9.3.1. Study population

The study included retrospective AMI patients hospitalized at the University Clinical Center in Gdańsk in 2017-2018. The data was collected using the MedStream Designer program, which is fully anonymized and integrated with the hospital's IT system. The exclusion criterion was the age of the patients under 18.

NOAF was used for any newly diagnosed AF (no P waves, atrial activity represented by fibrillation waves and irregular RR intervals) that occurred during hospitalization that lasted at least 30 seconds or was recorded during a 12-lead ECG. The detailed procedure for the diagnosis of NOAF was described in the original work number 2 (pages: 40), and detailed inclusion and exclusion criteria are given in each publication (pages: 34, 40, 55). The Independent Bioethical Committee approved the research protocol for Scientific Research at the Medical University of Gdańsk (NKBBN/290/2018).

9.3.2. Clinical data

Clinical parameters were assessed in all patients (including previous history, comorbidities, medications taken, smoking, and the exact course of hospitalization, taking into account the condition of the coronary vessels and the effect of coronary angiography performed in the acute phase of the infarction), laboratory parameters (including BNP, CRP, morphology, creatinine, glucose, high-sensitivity troponin I (hsTnI), CK-MB (creatine kinase muscle brain), lipidogram, taking into account the dynamics of selected parameters in consecutive days of hospitalization), as well as the assessment of echocardiographic parameters (size of atrial cavities and ventricles, left ventricular systolic and diastolic function parameters, parameters of right ventricular systolic function, presence and severity of heart defects).

9.3.3. Statistical analysis

Statistical analysis was performed using the STATISTICA 9.0 programs (*StatSoft, Tulsa, OK, USA*) and the statistical environment R 2.15.2., R 3.1.2. and R 4.0.5. A comprehensive description of the statistical methods used is contained in the articles included in the dissertation (pages: 34, 40-41, 55).

9.4. Results

9.4.1. Detailed results of the original study No. 1

Based on the data from the literature, it is known that patients with NOAF during AMI are at increased risk of cardiovascular complications [6]; therefore, identifying risk factors for this arrhythmia is of particular clinical importance. The first article on which this dissertation is based focuses on the initial pilot evaluation of patients with NOAF. One hundred three patients were included in the study from NOAF selected based on data analysis of 1,155 hospitalized AMI patients from January 2016 to June 2018. The median age of the described group of patients was 72 (64-82) years; 62% of patients were male, and 36% of this group were hospitalized for STEMI.

Based on the analysis of the results of laboratory tests on admission and the day of NOAF, it was found that on the day of NOAF, compared to the time of admission to the hospital, a statistically significant increase in CRP, an increase in hsTnI, with

a significant concurrent decrease in hemoglobin and blood potassium (Table 3, page 35). During hospitalization, 16 patients died in hospital (16%), of which 11 died of cardiological causes, two due to sepsis, and one due to hemorrhagic stroke; for another two patients, other causes of death were noted.

Based on the pilot results of work No. 1, in the course of further analysis, the scope of the parameters studied was significantly expanded, and the number of patients was increased.

9.4.2. Detailed results of the original study No. 2

The second article, on which the doctoral dissertation is based, was devoted to a comprehensive analysis of clinical parameters routinely assessed during hospitalization to identify NOAF risk factors in the group hospitalized with AMI, treated according to current guidelines. The study included 954 patients with AMI hospitalized at the University Clinical Center in 2017-2018, among whom NOAF was diagnosed in 106 (11%) patients.

Patients with NOAF (Table 1, page 41), compared to the rest of the patients (defined in this paper as non-NOAF), were older and had a lower body mass index (BMI). Both groups had a similar percentage of additional burdens, such as a history of coronary artery disease, myocardial infarction, hypertension, and diabetes. Nearly 100% of enrolled patients underwent coronary angiography during hospitalization, and 82% underwent percutaneous coronary intervention (PCI), as shown in Table 3 (page 43). The patients of both groups did not differ in terms of pre-hospitalization medications such as aspirin, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, and statins (Table 1, page 41).

Compared to the rest of the patients with NOAF, the assessment of laboratory and echocardiographic parameters was significantly different (Table 2, page 42). It was shown that patients with NOAF had higher levels of BNP, CRP, hsTnI on admission and statistically significantly lower levels of sodium, potassium, hemoglobin, LDL cholesterol (low-density lipoprotein cholesterol, LDL-C), and total cholesterol. Regarding echocardiographic parameters, patients with NOAF had significantly lower left ventricular ejection fraction (LVEF) and more enormous left atrium (LA), as well as poorer right ventricular parameters such as the right ventricular internal diameter (RVID) or its systolic function index (tricuspid annular plane systolic excursion, TAPSE).

Univariate logistic regression analyses showed age, length of hospitalization, BNP, hsTnI, CRP, potassium, hemoglobin, leucocytes, neutrophil to lymphocyte ratio, LDL-C, total cholesterol, creatinine, LA size, and LVEF are important determinants of NOAF (Table 4, page 43). Age, BNP, CRP, and LVEF also turned out to be independent predictors of NOAF in the multivariate logistic regression analysis (Table 4, page 43). The cut-off values for these parameters, determined using the ROC analysis, were:

- age $\geq$ 66 years,
- BNP $\geq$ 340 pg/ml,
- CRP $\geq$ 7,7 mg/l,
- LVEF $\leq$ 44%.

The parameter with the highest discriminatory power for NOAF was BNP ($\geq$340 pg/ml): AUC (Area Under Curve) was 70.5% [95% CI (Confidence Interval) 64.6-76.5%] (Table 4, page 43).

Regarding the course of hospitalization, patients with NOAF had more extended hospitalization, more adverse events, and worse prognosis (Table 6, page 44). In addition, NOAF was found to be significantly associated with in-hospital mortality (OR (Odds ratio) 4.54 [95% CI 2.50 - 8.33], p <0.001).

As for pharmacotherapy at discharge, the main difference between the NOAF group and the rest of the patients concerned anticoagulant treatment. In the NOAF group, a significantly higher proportion of patients were prescribed novel oral anticoagulants (NOAC) and, to a lesser extent, aspirin and ticagrelor. However, the frequency of prescribing other drugs (beta-blockers, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, statins) did not differ statistically between the groups (Table 7, page 45).

Summarizing the results of original work No. 2, it should be noted that NOAF is a frequent complication of the modern AMI population and is associated with higher in-hospital mortality. Older age, decreased LVEF, and the level of simple laboratory parameters (with a particular role of an elevated BNP level over 340 pg/ml) are essential predictors of NOAF.

9.4.3. Detailed results of the original study No. 3

Based on the existing literature data, it can be presumed that NOAF has a different clinical picture and prognosis than other AF forms in patients undergoing AMI [26,31–33]. However, the available studies comparing patients with various forms of AF usually concerned a selected group of patients with AMI (for example, a selected group of patients with STEMI, or only patients treated with invasive therapy) [29,33–37]. Therefore, the question of whether NOAF is a more aggravating diagnosis in all AMI patients than other types of AF has not been unequivocally answered so far. Moreover, an important aspect seems to be not only the risk assessment of de novo AF but also an attempt to compare the in-hospital clinical course and prognosis between patients with NOAF and patients with previously diagnosed AF, including patients with AF recurrence during hospitalization. AMI. Study No. 3 is a subanalysis of the database of study No. 2. In order to make appropriate comparisons, all patients were divided into four groups:

- **NOAF** (group of patients with any newly diagnosed AF that developed during AMI hospitalization without a prior diagnosis of AF, as described in detail in study No. 2);
- **AF** (group of patients with a previously documented diagnosis of AF who additionally had a recurrence of this arrhythmia during AMI hospitalization);
- **Prior-AF** (group of patients with a previously documented diagnosis of AF who had not developed AF during AMI hospitalization);
- **Non-AF** (group of patients without symptoms of AF during AMI hospitalization and without the prior AF diagnosis).

The NOAF group consisted of 106 patients (11%), the AF group included 95 patients (10%), the Prior-AF group had 60 patients (6%), and the remaining 693 (73%) patients were without AF (Non-AF). Detailed history and clinical parameters were analyzed and compared in all patients, and the course of hospital treatment was assessed. Additionally, the dynamics of laboratory parameters during the first four consecutive days of hospitalization due to AMI were analyzed.

Regarding the clinical characteristics, patients with any AF (NOAF, AF, Prior-AF group) were older than the Non-AF patients. Interestingly, NOAF patients, similarly to patients without AF, were less burdened with diseases than patients with a history of this arrhythmia (AF and Prior-AF groups). Hypertension, diabetes, chronic coronary artery

disease, or stroke were more frequently reported in the AF and Prior-AF groups (Table 1, page 56). In the analysis of pre-hospital pharmacological treatment, it was easy to notice fewer patients treated with angiotensin-converting enzyme inhibitors/angiotensin receptor blockers and statins among patients with NOAF than in both groups of patients with prior history of AF (AF and Prior-AF). Detailed results are presented in Table 1 (page 56).

Interestingly, among all analyzed groups of patients, patients with NOAF had the highest percentage of STEMI (40%), more than twice as high as in other patients with AF (AF and Prior-AF groups). Patients with NOAF had the worst in-hospital prognosis: the longest hospitalization time (10 days, (7-17), $p < 0.001$) as well as the highest rate of adverse events such as ventricular tachycardia (6%), ventricular fibrillation (13%), 3rd-degree atrioventricular block (6%) or stroke (3%). Detailed data are presented in Table 2 of the article (page 57). In the NOAF group, in-hospital mortality was twice as high as in the AF group and 4-6 times as high as in the other groups ($p < 0.001$) (Table 2, page 57). In contrast, most patients with NOAF (85%), as opposed to the AF group (36%), had a sinus rhythm at discharge.

Patients with NOAF had the lowest LVEF, while the LA size, as expected, was comparable among patients with NOAF and Prior-AF, higher than in the Non-AF group, but lower than in the AF group. In patients with any AF during hospitalization with AMI (NOAF and AF groups) had the highest RVID (Table 3, pages 57-58).

Moving on to the analysis of the results of laboratory tests, extensively described in the original work No. 3, the NOAF group was characterized by the highest levels of hsTnI, BNP, CRP, and glucose with the lowest concentration of potassium in the blood serum. Namely, these patients had the highest hsTnI level during hospitalization (which can be related to the highest percentage of STEMI in the NOAF group). The laboratory parameters data are presented in detail in Table 3 (pages 57-58).

Additionally, a detailed assessment of the dynamics of changes in laboratory parameters in the analyzed groups of patients during the first four days of hospitalization was performed. Patients with NOAF, unlike other groups, were characterized by significantly expressed, dynamic changes in the level of CRP, leukocytes, hsTnI, and potassium (Figures 1-3, 5, pages 59-61, 63). Patients in the NOAF group had the most significant increase in hsTnI, which peaked during the second day of hospitalization (Figure 1, page 59). Moreover, also CRP levels were highest among NOAF patients, with a steady increase over the following days of hospitalization (Figure 2, page 60). Regarding leukocytes, patients with NOAF had the highest levels on the second day of hospitalization. In contrast,

patients in the AF and Prior-AF groups showed a steady decline over four consecutive days (Figure 3, page 61).

Interestingly, patients with NOAF had the most significant decrease in hemoglobin over the four days of hospitalization (Figure 5, page 63). As already mentioned, NOAF patients had the highest rate of STEMI (40%) and the highest level of hsTnI (Figure 1, page 59). Therefore, NOAF may be both a consequence of severe myocardial necrosis and a direct complication of an extensive myocardial infarction.

Summarizing, the results of the analyzes carried out in the original study No. 3 indicate that patients with NOAF in AMI are characterized by the most severe clinical course and the worst in-hospital prognosis compared to other groups of patients. The presented data is the first comprehensive evaluation of routinely measured clinical and laboratory parameters in the literature for various types of AF in patients with modern AMI treatment, with particular emphasis on NOAF patients.

9.5. Limitations of the study

This doctoral dissertation has several limitations. The first is the single-center character. Second, it is a retrospective study, limited to the available data and parameters in patients' medical records. Due to the lack of precise identification of patients with unstable angina, only patients with AMI were enrolled on the study and not all patients with the acute coronary syndrome (ACS). The lack of long-term follow-up is another drawback. Another limitation is the probable overestimation of NOAF, as this group could include patients with pre-existing, but previously undetected, paroxysmal AF. There is also a risk of underestimating the proper AF frequency (due to asymptomatic AF episodes). A similar limitation applies to the precise onset of ventricular tachycardia, ventricular fibrillation, or 3rd-degree atrioventricular block during hospitalization; therefore, some patients with these complications may have had malignant arrhythmias on admission and not only at the time of hospitalization.

9.6. Conclusions

NOAF is a clinically significant arrhythmia that complicates hospitalization and worsens the clinical course and prognosis of patients with AMI.

Detailed conclusions:

1. Older age of patients, abnormal values of widely available laboratory and clinical parameters, such as elevated BNP, inflammatory markers (CRP), or decreased LVEF value, are significantly associated with the occurrence of NOAF in AMI.
2. NOAF in AMI appears to be a different pathophysiological phenomenon than other forms of AF. NOAF indicates a more severe course and a poorer in-hospital prognosis in patients with AMI, despite a lower burden of additional comorbidities at baseline.

10. Bibliografia

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RESEARCH ARTICLE

Clinical and laboratory assessment of patients with new-onset atrial fibrillation in acute myocardial infarction

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Abstract

Background: New-onset atrial fibrillation (NOAF) is one of the complications of acute myocardial infarction (AMI), and is associated with poor outcome. The aim of the study was clinical and laboratory assessment of patients with NOAF in AMI. **Material and methods:** This is a retrospective, single-centre study of AMI patients with NOAF, who were admitted to Clinical Centre of Cardiology of the University Clinical Centre in Gdansk, from January 2016 to June 2018. The medical history, echocardiography parameters, AMI localization and infarcted-related artery as well as laboratory parameters at the admission and at the moment of NOAF onset were taken into further analyses. **Results:** From 1155 consecutive AMI patients 103 (8.9%) with NOAF were enrolled into the study. A significant increase in C-reactive protein (CRP) and high-sensitive Troponine I (hsTnI) level, whereas significant decrease in potassium and hemoglobin level was observed at the moment of NOAF in comparison to admission. **Conclusions:** Our study suggests that markers of inflammation (CRP), myocardial necrosis (hsTnI), hemoglobin and serum potassium may be associated with NOAF in the setting on AMI. The aforementioned parameters are generally available and may be used as an inexpensive and rapid way to select patients who are at high risk of developing NOAF.

Keywords: atrial fibrillation • acute myocardial infarction • NOAF

Citation

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Introduction

Atrial fibrillation (AF) is the most common arrhythmia that is characterized by irregular and rapid activation in the atria without P waves in the electrocardiogram (ECG). In various countries around the world AF prevalence is estimated at 3% of adults aged 20 years or older [1]. The most significant risk factor for AF is age, although female sex, diabetes mellitus (DM), smoking, body mass index (BMI), alcohol consumption, hyperten-

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sion treatment, systolic blood pressure, heart failure, left ventricular hypertrophy and myocardial infarction also were identified [2]. The CHA_2DS_2-VASc score is used to estimate the risk of stroke in patients with AF and to guide prophylactic treatment. According to this score, patients with AF but without clinical risk factors for stroke do not need antithrombotic therapy, but oral anticoagulation is strongly recommended for patients with ≥1 risk factors [3] with a substantial increase in stroke and systemic thromboembolism. Strokes related to AF are associated with higher mortality, greater disability, longer hospital stays, and lower chance of being discharged home than strokes unrelated to AF.

According to the literature, AF coincides in 6-21% patients with acute myocardial infarction (AMI) [4]. It is well known that AF is connected with adverse outcomes in AMI [5]. Moreover, AF is independent risk factor of increased long-term mortality, regardless if AF is a primary or secondary diagnosis during hospitalization [6]. As in the general population, AF in AMI is associated with increased risks of cardiovascular and cerebrovascular complications [7]. Similiarly, in patients with AMI advanced age, heart failure, higher BMI, DM, and depression of left ventricular function are the risk factors of AF, but there are still some predictors which are not clearly defined in patients with AMI [2, 4]. Furthermore, there is no scoring system dedicated to assessing the risk of new-onset AF (NOAF) in patients who are having an AMI.

The knowledge about the pathogenesis of AF in the setting of AMI is still evolving. Due to the fact that AF is an independent predictor of mortality after AMI, the aim of our study was to conduct clinical and laboratory assessment of patients with NOAF in AMI and to define predictors of NOAF in the setting of AMI.

Material and methods

This single-centre retrospective study enrolled 103 consecutive patients with NOAF from 1155 patients hospitalized in 4 cardiology units between January 2016 and June 2018 due to AMI. 418 of those patients had ST segment elevation myocardial infarction (STEMI) and 737 had non-ST elevation myocardial infarction (NSTEMI). Data was collected through MedStream Designer (Transition Technologies, Poland) which was fully integrated with the hospital information system. The diagnosis of STEMI was made based on acute chest pain and ST-segment elevation. All of the patients had a 12-lead ECG acquired and interpreted as soon as possible. The diagnosis of NSTEMI was based on the serum markers of myocardial necrosis [8].

Diagnosis of AF, defined as irregular RR intervals and the absence of P waves lasting for ≥30 seconds, was based on physician interpretation of ECG. The term NOAF was applied to any newly diagnosed AF that appeared during the index hospitalization, irrespective of the duration of the arrhythmia. All the patients then had continuous ECG monitoring in the cardiac intensive care unit, afterwards they had 12-lead ECG performed daily during their hospital admission. The exclusion criteria were: <18 years of age and history of prior AF or atrial flutter.

The medical history (prior MI, revascularization, hypertension, diabetes, smoking), echocardiographic parameters (left ventricular ejection fraction [LVEF], left atrium size [LA], presence of mitral regurgitation [MR]), laboratory parameters (brain natriuretic peptide [BNP], C-Reactive Protein [CRP], high-sensitive Troponin I [hsTnI], creatine kinase muscle-brain, complete blood count, hemoglobin [Hgb], leucocytes, neutrophils, glucose, serum potassium) at the admission and at the moment of NOAF onset were taken into further analyses. The incidence of in-hospital mortality was also taken into consideration.

Coronary angiography and percutaneous coronary angioplasty (PCI) were performed according to standard practice in every patient. Coronary blood flow assessed during PCI was determined according to Thrombolysis in Myocardial Infarction (TIMI) classification. All angiograms were ranked as to the number of diseased major branches of coronary arteries. We classified a coronary artery as 'diseased' if there was any obstructive lesion ≥30% of that artery's diameter.

Patients were treated with anti-thrombotic agents, beta-blockers and angiotensin converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) and cholesterol-lowering agents according to contemporary guidelines [9-10].

The protocol of the study was approved by the local bioethics commmittee.

Statistical analysis

Continuous data are presented as median (25^{th}-75^{th} percentile), while categorical data are expressed in proportion. We performed the Shapiro-Wilk test to check whether our data were normally distributed. Majority of the analysed parameters did not have a normal distribution, even after logarithmic data transformation. Thus, we selected appropriate statistical analysis methods based on non-parametric tests: comparison of laboratory results upon admission and at the moment of NOAF onset was performed with Wilcoxon matched-pairs test. The statistical analysis was performed using STATISTICA 9.0 (StatSoft, Tulsa OK, USA) package and R 2.15.2 environment.

Results

Table 1. Demographic, clinical and laboratory data of the studied group

	NOAF patients n = 103
Age, years *	72 (64-82)
Male, n (%)	64 (62%)
Hypertension, n (%)	72 (70%)
Diabetes mellitus, n (%)	32 (31%)
Active smoker, n (%)	30 (30%)
Former smoker, n (%)	53 (51%)
BMI, kg/m^2	27 (24-30)
Previous MI/PCI/CABG, n (%)	39 (38%)
Previous ASA, n (%)	46 (45%)
Previous ACEI/ARB, n (%)	53 (51%)
Previous statins, n (%)	40 (39%)
In-hospital death, n (%)	16 (16%)
Hospitalization time, days *	10 (7-18)
Development of NOAF, day *	1 (1-3)
STEMI, n (%)	37 (36%)
NSTEMI, n (%)	66 (64%)
BNP, pg/ml *	371 (168-1064)
Creatinine, mg/ml *	0.96 (0.81-1.31)
Glucose, mg/dl *	153 (121-216)
Total cholesterol, mg/dl *	168 (131-193)
High density lipoprotein, mg/dl *	41 (33-52)
Low density lipoprotein, mg/dl *	94 (71-121)
Triglyceride, mg/dl *	108 (76-145)
C-reactive protein, mg/l *	12.3 (3.3-36.1)
hsTnI, ng/ml *	0.49 (0.07-4.08)
CK-MB, ng/ml *	4.8 (2.2-14.6)
Hemoglobin, g/dl *	13.3 (12.2 - 14.5)
Leukocytes, x10\^9/l *	10.6 (7.9-14.2)
Neutrophil/lymphocyte ratio *	3.8 (2.2-6.0)
K, mmol/l *	4.3 (3.9-4.6)

* data are presented as median (25th-75th percentile)
Abbreviations: MI– myocardial infarction; PCI – percutaneous coronary angioplasty; CABG – coronary artery bypass graft; ASA – acetylsalicylic acid; ACEI – angiotensin converting enzyme inhibitor; ARB – angiotensin receptor blocker, NOAF – new-onset atrial fibrillation; STEMI – ST-segment-elevation myocardial infarction; NSTEMI – non-ST-segment-elevation myocardial infarction; BNP – brain natriuretic peptide; CRP – C-Reactive Protein; hsTnI – high sensitive Troponine I; CK-MB – creatine kinase-muscle/brain; K – serum potassium

After applying the exclusion criteria, the final study cohort comprised a total of 103 patients with AMI, with no prior history of AF and who developed NOAF. From this group more than a half patients had NSTEMI. The overall incidence of NOAF was 8,9% (n=103) of the enrolled study population (n=1155), the mean age was 72 years, and more than a half of group were male. Most of the patients developed the NOAF in the first day of the admission (n=65), 28 patients developed the NOAF between second and fifth day of the index hospitalization, 10 patients developed after the fifth day.

A total of 16 patients died during the analyzed hospital stays: 69% (n=11) died due to cardiologic complications, 2 due to sepsis, 1 due to hemorrhagic stroke and 2 from other reasons. The demographic, clinical data and laboratory results (upon admission) of the studied group are summarized in Table 1.

Table 2. Angiographic and echocardiographic findings

NOAF patients n = 103	
Infarct-related artery in coronary angiography	
LM, n(%)	1 (1%)
LAD, n (%)	23 (22%)
RCA, n (%)	24 (24%)
LCX, n (%)	22 (21%)
Others, n (%)	10 (10%)
Multi-vessel coronary artery disease, n (%)	5 (5%)
TIMI 3	71 (70%)
Echocardiography	
LVEF, %*	42 (33-50)
LA diameter, mm*	41 (37-44)
Mitral regurgitation	
Mild, n (%)	70 (70%)
Moderate, n (%)	25 (24%)
Severe, n (%)	8 (8%)

* data are presented as median (25th-75th percentile)
Abbreviations: LM – left main artery; LAD – left anterior descending artery; RCA – right coronary artery; LCX – left circumflex artery; LVEF – left ventricular ejection fraction

Table 3. Laboratory parameters upon admission and at the moment of NOAF which are statistically significant or borderline

	On admission n = 103	NOAF onset n = 103	P
C-reactive protein, mg/l	12.3 (3.3-36.1)	30.4 (5.7-110.6)	< 0.0001
hsTnI, ng/ml	0.49 (0.07-4.08)	0.86 (0.08-8.29)	< 0.0001
CK-MB, ng/ml	4.8 (2.2-14.6)	25.9 (12.1-97.7)	0.083
Hemoglobin, g/dl	13.3 (12.2-14.5)	12.9 (11.4-14.0)	< 0.0001
Leukocytes, x10\^9/l	10.6 (7.9-14.2)	10.3 (8.1-14.6)	0.164
Neutrophil/lymphocyte ratio	3.8 (2.2-6.0)	7.2 (5.2-10.1)	0.110
K, mmol/l	4.3 (3.9-4.6)	4.1 (3.8-4.5)	< 0.013

* data are presented as median (25th-75th percentile)
Abbreviations: CRP – C-Reactive Protein; hsTnI – high sensitive Troponin I; CK-MB – creatine kinase-muscle/brain; K– serum potassium

The angiographic, echocardiographic characteristics of the studied group are presented in Table 2. All of the laboratory parameters withdrawn on admission and at the moment of NOAF, which are statistically significant (or borderline significant) are presented in Table 3.

Discussion

The major finding of this study is that markers of inflammation (CRP), myocardial necrosis (hsTnI), Hgb and serum potassium may be associated with NOAF in the setting of AMI. These simple, inexpensive parameters could be helpful in identification patients with higher risk of NOAF.

Our results confirm the role of the CRP-AF correlation which was demonstrated in prior studies [11-12]. However, there are still discussions about the role of CRP in the pathogenesis of myocardial infarction [13]. There is also a possibility that patients with AMI are more likely to develop inflammation, which may promote AF. Moreover, neutrophil/lymphocyte ratio, which is also a reflection of systemic inflammatory status, is also described as a predictive factor of NOAF [14]. Our results did not confirm that hypothesis, however our analysis was not restricted to just patients with STEMI as in the previously the aforementioned article.

Zhu et al recently established that hsTnI level is an independent predictor of AF incidents. Our results are similar, however we only claim the association between the increase of hsTnI and outcome of NOAF [15]. We found a similar increase in the level of CK-MB, but it was not statistically siginificant. In another study, Parashar et al denied the connection between another factor of myocardial necrosis – Troponin T [TnT] and the occurrence of NOAF [12]. However we analyzed the increase of hsTnI level between the hospital admission and day of NOAF, whereas Parashar et al measured the level of TnT only once.

Another predictive factor is the level of hemoglobin. Our study suggests that NOAF onset is associated with a decrease in hemoglobin level. The literature on this subject is inconsistent. For example, Distelmaier *et al.* demonstrated a statistically significant relationship between elevated levels of Hgb and occurrence of AF after AMI [16]. This might be due to the fact that they compared the level of Hgb between the NOAF after AMI patient group and matched controls [16]. In contrast, we analyzed the changes in Hgb level during the index hospitalization within the patient group only.

Several studies previously investigated the influence of potassium in the development of AF [17-19]. It is a well-known fact, that lower levels of serum potassium were associated with a higher risk of AF. We demonstrated that a decreasing level of serum potassium after AMI may be also the connected with NOAF.

There are a lot of echocardiographic parameters of AF, e.g. the parameters of systolic and diastolic LV function, as well as the LA parameters [20-23]. In our data, the LVEF value was below references range for healthy people. There were no data of LAVI, only LA diameter due to retrospective character of our study. Moreover, the Framingham Heart Study proved that every 5-mm increase in LA diameter increased the occurrence of AF by 39% while the Cardiovascular Health Study showed more than a double-fold increase in the developing NOAF when LA diameter >40 mm [22-23].

It should be noted that there are some limitations of the study. First of all, this was a single-centre retrospective study with a relatively small sample size. We did not analyze the entire hospitalized population with AMI to find the differences between those groups. Moreover, we do not have data on the duration of AF.

Conclusions

Our study suggests that markers of inflammation (CRP), myocardial necrosis (hsTnI), potassium and Hgb may be associated with NOAF in the setting on AMI. The aforementioned parameters are generally available and may be used as an inexpensive and rapid way to select patients who are at a high risk of developing NOAF. Further studies should be performed to design a dedicated scoring system for patients who are at risk of developing NOAF in the setting of AMI.

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Comprehensive Use of Routine Clinical Parameters to Identify Patients at Risk of New-Onset Atrial Fibrillation in Acute Myocardial Infarction

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Abstract: (1) Background: New-onset atrial fibrillation (NOAF) is a significant complication of acute myocardial infarction (AMI). Our study aimed to investigate whether routinely checked clinical parameters aid in NOAF identification in modernly treated AMI patients. (2) Patients and methods: Patients admitted consecutively within 2017 and 2018 to the University Clinical Centre in Gdańsk (Poland) with AMI diagnosis (necrosis evidence in a clinical setting consistent with acute myocardial ischemia) were enrolled. Medical history and clinical parameters were checked during NOAF prediction. (3) Results: NOAF was diagnosed in 106 (11%) of 954 patients and was significantly associated with in-hospital mortality (OR 4.54, 95% CI 2.50–8.33, $p < 0.001$). Age, B-type natriuretic peptide (BNP), C-reactive protein (CRP), high-sensitivity troponin I, total cholesterol, low-density lipoprotein cholesterol, potassium, hemoglobin, leucocytes, neutrophil/lymphocyte ratio, left atrium size, and left ventricular ejection fraction (LVEF) were associated with NOAF in the univariate logistic analysis, whereas age $\geq$ 66 yo, BNP $\geq$ 340 pg/mL, CRP $\geq$ 7.7 mg/L, and LVEF $\leq$ 44% were associated with NOAF in the multivariate analysis. (4) Conclusions: NOAF is a multifactorial, significant complication of AMI, leading to a worse prognosis. Simple, routinely checked clinical parameters could be helpful indices of this arrhythmia in current invasively treated patients with AMI.

Keywords: new-onset atrial fibrillation (NOAF); atrial fibrillation; acute myocardial infarction

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1. Introduction

Atrial fibrillation (AF) is the most common arrhythmia [1], present in approximately 0.4% of the general population and 2–4% of patients over 60 years old [2]. It often complicates acute myocardial infarction (AMI), with an incidence documented between 5 and 22% [3,4]. This arrhythmia is closely associated with prolonged hospitalization, higher in-hospital mortality, and worse outcomes [5,6]. The clinical significance and management of new-onset atrial fibrillation (NOAF) in patients with AMI is frequently debated and not fully understood; therefore, identifying risk factors related to NOAF in AMI is still of great clinical value. Most previous studies usually prioritized only one clinical parameter [7–15] or considered only patients with one type of AMI, mostly ST-Elevation Myocardial Infarction (STEMI) [9,16–20]. Some studies were based on international registers [21–24], which, beyond the obvious advantages, included data from different clinical centers, sometimes from different countries, which could implicate different diagnostic methods and different treatment possibilities [11,25]; most of them were performed in the earlier years, based upon the previous guidelines of AMI treatment. Our study aimed to check whether the comprehensive use of the routinely checked clinical parameters could help to identify

patients with a high probability of NOAF based on current, consecutive AMI patients hospitalized and treated according to the current guidelines in one large clinical center.

2. Materials and Methods

Our study retrospectively included all patients hospitalized with an AMI diagnosis in the University Clinical Centre in Gdańsk (Poland) from January 2017 to December 2018. The data were collected through MedStream Designer, which was fully integrated with the hospital information system. The exclusion criterion was age younger than 18 years. AMI was diagnosed based on the appropriate measures [26,27]. AMI was diagnosed if there was evidence of myocardial injury (defined as elevation of cardiac troponin values with at least one value above the 99th percentile upper reference limit) with necrosis in a clinical setting consistent with myocardial ischemia. Diagnosis of AF was based on the physician's interpretation of ECG according to the current guidelines [28]; all patients were 24 h monitored (with the possibility of the retrospective analysis of the ECG) during their hospital stay in the intensive cardiac care unit or monitoring room in the regular cardiac ward; afterward, they had 12-lead ECG performed daily during their hospital admission or when any new symptoms were noticed; any observations of rhythm changes were registered. The term NOAF was considered for any newly diagnosed AF (absence of P waves, atrial activity represented by fibrillatory waves, and irregular RR intervals) that appeared during the index hospitalization, which lasted at least 30 s or entire 12-lead ECG. Medical history (with particular attention to coronary artery disease, including myocardial infarction (MI) and revascularizations, and others), echocardiography, laboratory parameters at admission, and pharmacological and invasive treatment within the hospitalization were taken into consideration and compared between the patients with (NOAF group) and without (non-NOAF) this arrhythmia.

Coronary angiography and percutaneous coronary intervention (PCI) within hospitalization were performed according to the newest guidelines [26,27]; the results of angiograms were graded as to the number of diseased coronary arteries; a coronary artery was considered diseased if there was any obstructive lesion $\geq$ 50% in diameter in the left main stem, $\geq$70% in a major coronary vessel, or 30% to 70% stenosis with fractional flow reserve $\leq$ 0.8. Coronary blood flow assessed during PCI was determined according to Thrombolysis in Myocardial Infarction (TIMI) classification. Additionally, data regarding the length of hospitalization, in-hospital mortality, and post-discharge medical treatment were analyzed. The selection of antithrombotic therapy at discharge was at the discretion of the attending physician.

The Independent Bioethical Committee approved the study's protocol for Scientific Research of the Medical University of Gdansk (consent number NBBN/290/2018). This was a retrospective study of data routinely collected in clinical practice; therefore, the requirement for written and informed consent was waived.

Statistical Analysis

Continuous data are presented as median (25th–75th percentile) and categorical data as numbers (n) and percentages (%). We performed the Shapiro–Wilk test to determine whether our data were normally distributed; most of the analyzed parameters did not have a normal data distribution, even after logarithmic transformation; therefore, we selected appropriate statistical analysis methods based on non-parametric tests. Comparisons between groups were performed with the Mann–Whitney U-test for continuous variables and Pearson's chi-square test for categorical variables, as appropriate. The predictability of the established variables as potential predictors of NOAF was determined by the area (AUC) under the receiver operating characteristic (ROC) curve; adequate cut-off values were identified according to the best paring of sensitivity and specificity values. Logistic regression analyses were performed to detect which parameters (with pre-specified cut-off values) showed the most substantial relation to the NOAF (univariate analyses). Multivariate analysis was applied to continuous data (dichotomized according to the cut-off values

identified in ROC analyses) and categorical data significantly associated in the univariate analyses with NOAF (p-value of 0.05 or less); the set of variables accepted for the model was determined by the backward elimination method from the setting of all statistically significant predictors. Values of $p < 0.05$ were considered significant. The statistical analysis was conducted using the R 3.1.2 environment (R Core Team, Vienna, Austria).

3. Results

3.1. Baseline Clinical Characteristics

A total of 954 AMI patients were enrolled in the study. Of these patients, 106 (11%) were diagnosed with NOAF. Amongst 106 NOAF patients, the majority (66 patients—62%) had arrhythmia diagnosed within the first day of hospitalization, and 19 (18%) had NOAF at the time of admission. In addition, patients who developed NOAF were older and had a lower body mass index (BMI), without other baseline clinical differences (Table 1).

Table 1. Baseline clinical characteristics.

	All Patients ***n* = 954**	**NOAF** ***n* = 106**	**Non-NOAF** ***n* = 848**	***p***
Age (years old)	69 (61–78)	74 (66–84)	67 (60–76)	<0.001
Male sex, *n* (%)	637 (67%)	67 (63%)	571 (67%)	0.444
BMI (kg/m^2)	28 (25–31)	27 (24–30)	28 (25–31)	0.027
Prior MI, *n* (%)	276 (29%)	31 (29%)	245 (29%)	0.999
Prior revascularization (PCI/CABG), *n* (%)	270 (28%)	26 (25%)	244 (29%)	0.424
Hypertension, *n* (%)	719 (75%)	79 (75%)	640 (76%)	0.812
Diabetes mellitus, *n* (%)	314 (33%)	31 (29%)	283 (33%)	0.812
Previous stroke, *n* (%)	70 (7%)	10 (9%)	60 (7%)	0.427
Pacemaker, *n* (%)	29 (3%)	5 (5%)	24 (3%)	0.360
ICD, *n* (%)	35 (4%)	3 (3%)	32 (4%)	0.789
On-admission treatment				
Aspirin, *n* (%)	357 (38%)	43 (41%)	314 (37%)	0.524
Angiotensin converting enzyme inhibitors, angiotensin receptor blockers, *n* (%)	511 (54%)	53 (50%)	458 (54%)	0.470
Statins, *n* (%)	376 (40%)	41 (39%)	335 (40%)	0.916

BMI—body max index; CABG—coronary artery bypass grafting; ICD—implantable cardioverter-defibrillator; MI—myocardial infarction; PCI—percutaneous coronary intervention.

3.2. Laboratory and Echocardiographic Parameters

There were many significant differences in laboratory and echocardiography results between NOAF and non-NOAF patients (Table 2). At admission, patients with NOAF had a higher level of brain natriuretic peptide (BNP), C-reactive protein (CRP), leucocyte, and high-sensitivity troponin I (hsTnI). Although the free thyroxine (FT4) was within the normal range, the level was significantly higher in the NOAF patients. In addition, sodium, potassium, total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), and hemoglobin were significantly lower. Regarding echocardiography parameters, patients with NOAF had significantly lower left ventricular ejection fraction (LVEF) and left atrium (LA) size, as well as worse right ventricular (RV) parameters such as RV internal dimension (RVID) and tricuspid annular plane systolic excursion (TAPSE).

Table 2. Laboratory and echocardiographic parameters.

	All Patients (n = 954)	NOAF (n = 106)	Non-NOAF (n = 848)	p
Laboratory parameters				
BNP, pg/mL	512 (59–541)	791 (193–1087)	471 (54–429)	<0.001
hsTnI, ng/mL	4.89 (0.05–1.42)	6.41 (0.06–4.84)	4.70 (0.04–1.20)	0.020
CK-MB, ng/mL	19.2 (2.1–10.3)	18.42 (2.2–14)	19.30 (2.1–10)	0.167
CRP, mg/L	18.9 (1.6–14.2)	36.1 (3.3–36.2)	16.6 (1.5–11.3)	<0.001
Sodium, mmol/L	138 (136–140)	137 (135–140)	138 (136–140)	0.033
Potassium, mmol/L	4.3 (4–4.6)	4.2 (3.8–4.6)	4.35 (4–4.6)	0.008
Hemoglobin, g/dL	13.5 (12.4–15)	13.3 (12–14.9)	13.6 (12.4–15)	0.042
Leucocytes, 10^9/L	10.61 (7.82–12.48)	11.91 (8.07–13.91)	10.45 (7.80–12.34)	0.015
Neutrophil to lymphocyte ratio	5.3 (2.1–5.6)	6.0 (2.2–6.9)	5.3 (2.1–5.4)	0.051
Total cholesterol, mg/dL	180 (143–214)	165 (129–192)	182 (144–217)	0.005
LDL-C, mg/dL	110 (77–141)	98 (64–125)	112 (79–144)	0.011
Creatinine, ml/dL	1.17 (0.78–1.19)	1.14 (0.77–1.25)	1.17 (0.78–1.18)	0.225
TSH, uU/L	1.494 (0.577–1.721)	1.29 (0.66–1.86)	1.53 (0.52–1.70)	0.233
FT3, pmol/L	3.52 (2.63–3.70)	3.14 (2.74–3.41)	3.58 (2.60–3.70)	0.334
FT4, pmol/L	13.50 (11.68–14.84)	14.67 (13.26–16.20)	13.34 (11.55–14.74)	0.005
Glucose, mg/dL	159 (104–178)	184 (120–219)	156 (103–173)	<0.001
Echocardiographic parameters				
LA size, mm	40 (36–44)	43 (38–46)	40 (36–44)	<0.001
LVIDd, mm	50 (45–54)	51 (44–55)	50 (45–54)	0.208
LVIDs, mm	35 (30–39)	38 (31–44)	35 (29–39)	<0.001
LVEF, %	47 (40–56)	42 (32–51)	48 (40–57)	<0.001
RVID, mm	37 (32–41)	40 (34–44)	37 (32–40)	0.006
TAPSE, mm	20 (17–23)	18 (14–22)	20 (17–24)	0.003
RVSP, mmHg	41 (34–47)	42 (35–48)	40 (32–47)	0.277
Mitral regurgitation				
Moderate, n (%)	176 (25%)	29 (28%)	147 (24%)	0.082
Severe, n (%)	43 (6%)	7 (7%)	36 (6%)	

BNP—B-type natriuretic peptide; CK-MB—creatine kinase muscle-brain; CRP—C-reactive protein; FT3—free triiodothyronine; FT4—free thyroxine; hsTnI—high sensitivity troponin I; LA—left atrium; LDL-C—low-density lipoprotein cholesterol; left ventricular ejection fraction—LVEF; LVIDd—left ventricular internal diameter end diastole; LVIDs—left ventricular internal diameter end systole; LVEF—left ventricular ejection fraction; RVIDd—right ventricular internal dimension; RVSP—right ventricular systolic pressure; TAPSE—tricuspid annular plane systolic excursion; TSH—thyroid-stimulating hormone.

3.3. Percutaneous Coronary Interventions

The compared group did not differ in STEMI and non-STEMI types of AMI (Table 3). The majority of patients (97%) had coronary angiography during hospitalization, whereas 82% had a percutaneous coronary intervention. In addition, most of the patients had successful intervention (98% had TIMI flow 3), with no differences in angiographic results between the NOAF and non-NOAF groups.

Table 3. Types of myocardial infarction, results of coronary angiography, and effects of PCI.

	All Patients (n = 954)	NOAF (n = 106)	Non-NOAF (n = 848)	p
Types of myocardial infarction				
ST-elevation MI, n (%)	327 (34%)	42 (40%)	285 (34%)	0.233
Non-ST-elevation MI, n (%)	627 (66%)	64 (60%)	563 (66%)	0.233
Results of coronary angiography with the number of stenotic vessels				
In-hospital coronary angiography, n (%)	921 (97%)	99 (93%)	822 (97%)	0.083
Patients with PCI	779 (82%)	81 (76%)	698 (82%)	0.522
Results of coronary angiography—significant stenosis				
One vessel, n (%)	313 (34%)	33 (33%)	280 (35%)	0.317
Two vessels, n (%)	264 (29%)	25 (25%)	239 (29%)	
Multivessel disease, n (%)	286 (31%)	33 (33%)	253 (31%)	
None, n (%)	49 (5%)	9 (9%)	40 (5%)	
PCI effects				
TIMI flow 1	2 (0.3%)	0 (0%)	2 (0.2%)	0.522
TIMI flow 2	13 (1.7%)	0 (0%)	13 (1.8%)	
TIMI flow 3	764 (98%)	81 (100%)	683 (98%)	

MI—myocardial infarction; PCI—percutaneous coronary intervention; TIMI—Thrombolysis In Myocardial Infarction.

3.4. Predictors of NOAF

ROC analysis identified BNP with the cut-off value 340 pg/mL as the most accurate predictor of NOAF (AUC 70.5% [64.6–76.5%]). The rest of the parameters were characterized by lower discriminatory power (Table 4 presents parameters with AUC higher than 50% in ROC analysis).

Table 4. ROC analysis with cut-off values of the analyzed parameters as NOAF predictors.

	Cut-Off Values	AUC
Age	≥66 years old	65.4% (60.1–70.8%)
Length of hospitalization	≥6.5 days	67.8% (62.0–73.6%)
BNP	≥340 pg/mL	70.5% (64.6–76.5%)
hsTnI	≥1.85 ng/mL	57.0% (50.9–63.1%)
CRP	≥7.7 mg/L	66.1% (60.2–71.9%)
Potassium	≤4.2 mmol/L	57.9% (51.5–64.3%)
Hemoglobin	≤14 g/dL	55.2% (49.2–61.1%)
Leucocytes	≥10.2 × 10^9/L	57.3% (51.1–63.4%)
Neutrophil to lymphocyte ratio	≥4.6	57.9% (48.4–67.5%)
Total cholesterol	≤195 mg/dL	58.6% (52.7–64.6%)
LDL-C	≤128.5 mg/dL	56.8% (50.7–62.9%)
Creatinine	≥1.63 mL/dL	52.3% (46.3–58.2%)
LA size	≥41 mm	62.0% (56.0–68.0%)
LVEF	≤44 %	64.3% (58.6–70.1%)

AUC—area under the receiver-operating characteristic (ROC) curve; BNP—B-type natriuretic peptide; CRP—C-reactive protein; hsTnI—high sensitivity troponin I; LA—left atrium; LDL-C—low-density lipoprotein cholesterol; LVEF—left ventricular ejection fraction.

Univariate logistic regression analyses revealed age, length of hospitalization, BNP, hsTnI, CRP, potassium, hemoglobin, leucocytes, neutrophil to lymphocyte ratio, LDL-C, total cholesterol, creatinine, LA size, and LVEF with pre-specified cut-off values as significant predictors of NOAF (Figure 1).

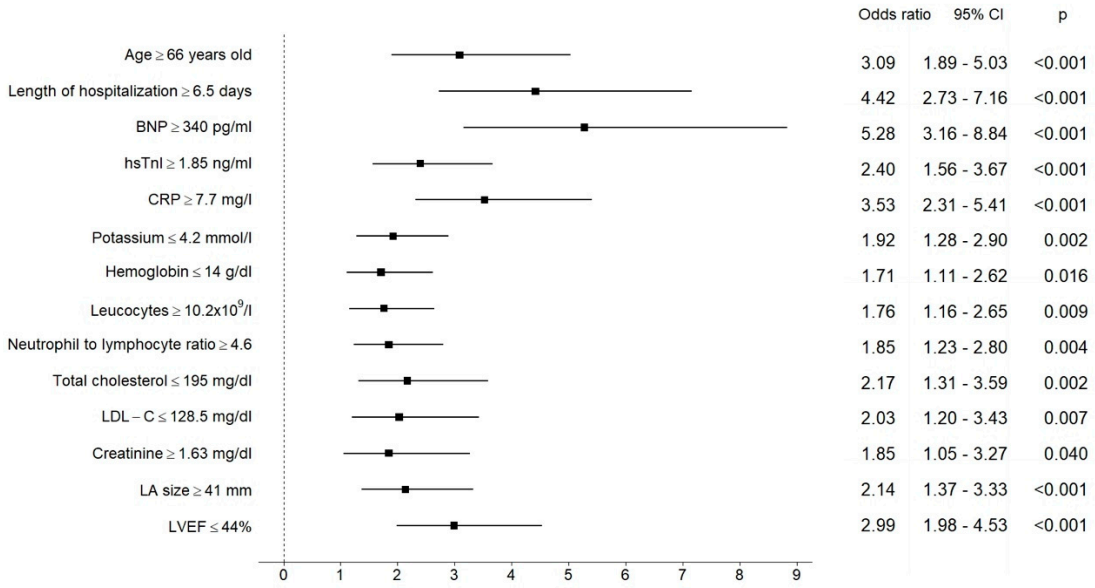

Figure 1. Results of univariate logistic regression analysis for the pre-specified cut-off values of analyzed parameters as predictors of NOAF. The central estimate and 95% confidence interval for odds ratio are shown.

Age ≥ 66 yo, BNP ≥ 340 pg/mL, CRP ≥ 7.7 mg/L, and LVEF ≤ 44% maintained their significance in NOAF prediction in multivariate analysis; BNP was found to be the parameter with the highest predictive power (Table 5).

Table 5. Significant predictors of NOAF in multivariate logistic regression analysis.

Cut-Off Value	OR (95% CI)	*p*
Age ≥ 66 years old	2.37 (1.23–4.58)	0.009
BNP ≥ 340 pg/mL	4.60 (2.27–9.32)	0.004
CRP ≥ 7.7 mg/L	2.02 (1.14–3.56)	0.010
LVEF ≤ 44%	1.93 (1.12–3.12)	0.020

BNP—B-type natriuretic peptide; CRP—C-reactive protein; LVEF—left ventricular ejection fraction. The multivariate model was determined by the backward elimination method from the setting of all parameters significantly predicted NOAF in univariate analysis (presented in Figure 1).

3.5. Outcomes

Patients with NOAF had more prolonged hospitalizations, more in-hospital adverse events, and worse in-hospital prognosis (Table 6). In addition, NOAF was found to be significantly associated with in-hospital mortality (OR 4.54 [95% CI 2.50–8.33], $p < 0.001$).

Only 74 of 87 surviving NOAF patients (85%) were discharged with sinus rhythm, which was a significantly lower rate than in the non-NOAF group (92%—745 of 809), $p < 0.001$.

Table 6. In-hospital prognosis.

	All Patients (*n* = 954)	NOAF (*n* = 106)	Non-NOAF (*n* = 848)	*p*
Length of hospitalization (days)	10 (5–11)	14 (7–17)	9 (5–9)	<0.001
VF during hospitalization, *n* (%)	65 (7%)	14 (13%)	51 (6%)	0.012
VT during hospitalization, *n* (%)	26 (3%)	6 (6%)	20 (2%)	0.059
AVB III during hospitalization, *n* (%)	15 (2%)	6 (6%)	9 (1%)	0.004
Stroke during hospitalization, *n* (%)	9 (1%)	3 (3%)	6 (1%)	0.068
In-hospital mortality, *n* (%)	58 (6%)	19 (18%)	39 (5%)	<0.001

AVB—atrioventricular block; SR—sinus rhythm; VF—ventricular fibrillation; VT—ventricular tachycardia.

3.6. Pharmacological Treatment at Discharge

Due to the retrospective nature of the study, information about pharmacological treatment for four patients was absent; therefore, further analyses were performed for 892 patients. The main difference between the groups that received antithrombotic therapy was a significantly higher rate of NOACs, but lower aspirin and ticagrelor were noticed in the NOAF group. The frequencies of other medications (beta-blockers, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, statins) were not statistically different between the groups (Table 7).

Table 7. Pharmacological treatment at discharge.

	All Patients (n = 892)	NOAF (n = 86)	Non-NOAF (n = 806)	p
Beta-blockers, n (%)	776 (87%)	76 (88%)	700 (87%)	0.866
ACE inhibitors/ARBs, n (%)	802 (90%)	73 (85%)	729 (91%)	0.127
Statins, n (%)	842 (94%)	81 (94%)	761 (94%)	0.809
Antithrombotic therapy				
Aspirin, n (%)	843 (94%)	76 (88%)	767 (95%)	0.020
Clopidogrel, n (%)	691 (77%)	72 (84%)	619 (77%)	0.174
Ticagrelor, n (%)	148 (17%)	3 (3%)	145 (18%)	<0.001
Vitamin K antagonists, n (%)	55 (6%)	8 (9%)	47 (6%)	0.233
NOACs, n (%)	141 (16%)	54 (63%)	87 (11%)	<0.001
Low-molecular-weight heparins, n (%)	42 (5%)	7 (8%)	35 (4%)	0.173
Triple antithrombotic therapy				
Aspirin + Clopidogrel + Vitamin K antagonists	46 (5.1%)	8 (9%)	38 (4.7%)	<0.001
Aspirin + Clopidogrel + NOACs	108 (12.1%)	40 (47%)	68 (8.4%)	
Aspirin + Clopidogrel + LMWH	3 (0.3%)	1 (1%)	2 (0.2%)	
Double antithrombotic therapy				
Aspirin + Clopidogrel	491 (55%)	14 (16%)	477 (59%)	<0.001
Aspirin + Ticagrelor	139 (16%)	2 (2%)	137 (17%)	

ACE—angiotensin-converting enzyme; ARBs—angiotensin receptor blockers; LMWH—low-molecular-weight heparin; NOACs—novel oral anticoagulants.

4. Discussion

Our study revealed that that in the modern revascularization era (when most of the patients with AMI are successfully treated invasively), routinely checked clinical parameters could help to identify those at risk of NOAF among consecutive patients, regardless of the type of infarction. To the best of our knowledge, this is the first study based on current patients with AMI, where a complex evaluation of the routinely checked clinical parameters based on the data from a high-volume tertiary care center was performed.

4.1. Clinical, Laboratory, and Echocardiographic Parameters

Data from the literature postulate that 5 to 22% of AMI patients have NOAF during their acute hospitalization [6,29,30]. In agreement with data from the literature, our patients with NOAF were older [6,13,23,31], and age was an independent predictor of this arrhythmia [22,32–34]. Among laboratory parameters, we revealed some statistical differences in NOAF compared to the non-NOAF group. Some of them are well-known predictors of AF, but there are some discrepancies in the literature regarding others. Moreover, some parameters are presented as NOAF risk factors for the first time in the literature.

One of the well-known parameters connected to AF development in the general population is low potassium level in serum [35–38]. In the Rotterdam Study [35], potassium below 3.50 mmol/L was associated with a higher risk of this arrhythmia. Campbell et al. [37] investigated the impact of maintaining serum potassium $\geq$ 3.6 mmol/L in comparison to $\geq$4.5 mmol/L on the incidence of NOAF after coronary artery bypass

grafting, but the authors did not publish the results. In another study [36], preoperative hypokalemia (<3.5 mmol/L) was associated with AF. None of the abovementioned data concerned patients with AMI. In our study, the median potassium value was within the normal range in both groups; however, for NOAF patients, it was significantly lower. In our study, the cut-off value for potassium calculated in the ROC analysis of 4.2 mmol/L was found to be crucial in revealing the NOAF probability, which is one of the novelties of our research.

Another predictor of NOAF in our results was hemoglobin. There is some discrepancy in the literature concerning this parameter. For instance, Distelmaier et al. [10] demonstrated that patients with AF in the setting of AMI displayed significantly higher levels of hemoglobin. However, other data [39,40] suggest that NOAF onset is associated with a lower hemoglobin level. Our results are in line with the latter findings. A potential explanation of the connection between AF and a lower hemoglobin level might be that anemia causes decreased oxygen-carrying capacity, increasing cardiac output to maintain tissue oxygen delivery [41]. Moreover, increased neurohormonal activity in anemia can cause arrhythmogenic remodeling susceptible to AF [40]. Our results postulate that not anemia but a hemoglobin level below 14 mg/dL in AMI patients could indicate a risk of NOAF development. This is another novelty of our study.

Troponin concentration as a marker of AMI intensity is another parameter that could influence AF. Data from the Framingham Heart Study [42] and the Atherosclerosis Risk in Communities (ARIC) study [43] revealed a prognostic role of troponins in AF prediction in a ten-year follow-up observation in the general population. Moreover, Parashar et al. [21] disproved the relationship between the level of troponins and the occurrence of NOAF, but his study did not concern AMI patients. Later data from the Busselton health study proved that elevated troponin levels could be an independent predictor of hospitalization due to AF [44]. For the first time in the literature, our study confirms the hsTnI level's significance in NOAF prediction in AMI, but only in the univariate logistic regression analysis.

Dyslipidemia is a significant factor in the development of coronary heart disease and atherosclerosis [45], whereas its role in the development of AF is less clear. Annoura et al. reported the "cholesterol paradox" in AF patients and found lower serum cholesterol levels and triglycerides in patients with paroxysmal AF [46]. Another study [25] showed that low serum levels of LDL-C and high-density lipoprotein cholesterol (HDL-C) were present in patients with AF, irrespective of the type of AF. Watanabe et al. [47] demonstrated that a low HDL-C level was strongly associated with an increased risk of developing AF, and the total cholesterol and LDL-C levels were contrarily associated with AF. In our study, total cholesterol and LDL-C were significantly lower in the NOAF group, which is in line with the previous literature.

Inflammation is a known process that can lead to atrial structural and electrical remodeling, predisposing patients to AF [12]. Extensive inflammation in patients with AMI can lead to the development of NOAF [11,46,48–50]. Moreover, inflammation has a fundamental role in atherosclerotic plaque rupture and seems to play an important role in the prothrombotic state associated with AF [51,52]. In our study, leucocytes, the neutrophil to lymphocyte ratio, and CRP as inflammation parameters were found to be significantly associated with NOAF in the univariate logistic regression analysis. Furthermore, CRP $\geq$ 7.7 mg/L, contrary to other inflammatory parameters and other abovementioned parameters connected to NOAF, displayed significance in the multivariate analysis.

A vital laboratory parameter that was found to be significant for revealing NOAF not only in the univariate but in the multivariate analysis in our study was BNP. BNP is a hormone secreted predominantly by the ventricles and increases markedly in patients with congestive heart failure in proportion to its severity [53]. According to data from the literature, an increased BNP level is reported in the first 24 h after AMI, revealing the compensatory role of ventricular dysfunction caused by AMI, reducing progressive ventricular enlargement and attenuating ventricular remodeling after AMI [54]. Moreover, data from the TRIUMPH registry showed that elevated BNP predicts NOAF in AMI patients [21].

Asanin et al. [9] demonstrated that BNP might be involved in the risk prediction of NOAF in the setting of STEMI treated by primary PCI, with BNP level ≥ 720 pg/mL as the most potent predictive factor. A lower cut-off value of BNP (263 pg/mL) was demonstrated in another study also for NOAF after STEMI [13]. We confirmed this observation in our research based on all AMI patients, not only those with STEMI. We proved that BNP with a cut-off value of ≥340 pg/mL is a significant, independent predictor of NOAF in the setting of AMI, which is consistent with previous findings [9,13].

It is well known that the probability of AF increases with the enlargement of LA and reduction in LVEF [6,55–57]. The Cardiovascular Health Study [58] proved more than a double-fold increase in the development of NOAF when the LA diameter is more than 40 mm. The GUSTO-I trial [30] demonstrated LVEF with a cut-off value of 42.7% as a predictor of NOAF in AMI patients. According to a meta-analysis conducted in 2017, including ten studies comprising a total of 708 NOAF patients and 6785 controls, both decreased LVEF and increased LA levels were associated with greater risk of NOAF following AMI [59]. Notably, the three most extensive studies revealed LVEF < 45% as an independent predictor of AF [8,49,60]. Our study is in line with these results: LA ≥ 41 mm and LVEF ≤ 44% were significant predictors of NOAF in the univariate logistic analysis in AMI patients; furthermore, LVEF remained significant in the multivariate analysis.

4.2. Prognosis of NOAF Patients

Many authors have intensively studied the influence of NOAF on prognosis [21,22,61,62]. An extensive meta-analysis from 2011, based on 43 studies involving 278,854 patients, showed that AF in AMI is associated with at least a 40% increase in mortality compared to patients with sinus rhythm [61]. Data from the literature have also demonstrated malignant ventricular arrhythmias (ventricular tachycardia and fibrillation) and complete atrioventricular blocks as more frequent complications in patients with NOAF [22,30,63]. Our data are in line with the previous results: we revealed that NOAF increased the risk of in-hospital mortality in AMI patients more than four-fold (OR 4.54 [95% CI 2.50–8.33], $p < 0.001$), and the frequency of life-threatening arrhythmias was higher in these patients.

4.3. Pharmacological Treatment

Antithrombotic therapy is the most important therapy in reducing the burden of stroke and death in patients with AF, including NOAF [61,64–66]. Our study shows a high rate of recommended anticoagulation at discharge: more than 70% of patients diagnosed with NOAF received oral anticoagulation at discharge, and most of them were on NOACs (63%). The worse compliance with recommendations in our population concerns triple antithrombotic treatment (oral anticoagulation and dual antiplatelet therapy), which, according to the most recent guidelines, should be used in every patient with AF undergoing a primary PCI for AMI [26,27]. As we show in Table 3, only 57% of NOAF patients were on triple antithrombotic therapy at discharge. Fortunately, this is a higher rate than described in the literature some years ago [22,64,67]. The disproportion between the guidelines and the real-life rate of triple antithrombotic treatment in NOAF patients could have several clinical explanations. On the one hand, the high risk of bleeding or bleeding-related complications could influence the physicians' decision to leave the patient on the double or even single antithrombotic therapy. On the other hand, there are no guidelines concerning precise information about the treatment of NOAF patients. Axelrod et al. [29] suggested that "early-paroxysmal AF" that resolved within 24 h of admission may not have a high stroke risk, questioning the indication for long-term anticoagulation contrary to "late-AF" beyond the first 24 h, which should be treated appropriately. These data need to be established in further research due to their potentially high clinical importance.

4.4. Novelties of the Study

The present study differs from similar previous ones in several features. Our study was based on a large group of current (treated in 2017 and 2018) European AMI patients,

including not only STEMI but NSTEMI patients as well. Our study was based on all consecutively admitted patients with a high rate of invasive treatment regardless of the type of infarction: 97% of patients had coronary angiography, and 82% of patients had PCI, in contrast to older studies [21,68]. Huge European registries were performed in earlier years based upon older guidelines [22–24]; some current registries include patients of various ethnicities [21].

In our recently treated group of patients, we focused on studying not only one, as in many other similar studies, but on many routinely checked clinical parameters in the prediction of NOAF. It is worth stressing that our analysis was based on all consecutive AMI patients, regardless of the type of infarction. We calculated cut-off values for these parameters. Age, length of hospitalization, BNP, hsTnI, CRP, potassium, hemoglobin, leucocytes, neutrophil to leucocyte ratio, TC, LDL-C, creatinine, LA size, and LVEF were found to be significant in the univariate logistic regression analysis, whereas age, BNP, CRP, and LVEF were independent indices of this arrhythmia in the multivariate analysis. The possibility of the prediction NOAF in current, recently treated AMI patients may have important clinical implications, allowing for more careful monitoring of such patients, longer ECG observation (more than 24 h), some laboratory parameters (mainly BNP and CRP), and precise measurement of LVEF within hospitalization and after discharge. This was not the subject of this study but requires further research, mainly since the guidelines covering ACS or AF describe a group of patients with NOAF to a minimal extent [28,69].

As we mentioned above, our group had a higher rate of triple antithrombotic treatment regarding NOAF patients than in previous studies [22,64,67]. However, this is still insufficient in order to maintain the guidelines. The main question of how to determine the optimal anticoagulation therapy in NOAF patients with AMI remains for future investigation. Our findings can improve the determination of patients that may develop NOAF in the setting of AMI and therefore need to be treated appropriately.

5. Limitations

Our study has several limitations. Firstly, this is a retrospective investigation, limited to available data and parameters in patients' medical records. Only patients with AMI (patients with evidence of myocardial injury with necrosis in a clinical setting consistent with myocardial ischemia) were included, and we could not include patients with unstable angina; therefore, our results could not be applied to all patients with acute coronary syndrome. Secondly, some patients with AF on admission may have had previous yet undiagnosed paroxysmal AF and new-onset arrhythmias, leading to an overestimated incidence. However, the 24 h monitoring in the intensive cardiac care unit and querying of symptoms during medical visits were achieved routinely during hospitalization; the actual incidence of NOAF may have been underestimated because of asymptomatic AF episodes. Since we do not have detailed data on the duration of AF, we cannot comment on cause and effect. There is a possibility that NOAF may lead to higher levels of biomarkers or higher levels of biomarkers in the setting of AMI may lead to NOAF. Moreover, we could not precisely define the time of VT/VF/AVB during hospitalization; therefore, some patients with these complications could have had malignant arrhythmias at the time of admission, not only during their hospitalization. Finally, our study was a single-center study, which is another limitation; however, some benefits associated with the single-center nature of the study could be identified (including laboratory and echocardiography data collected from the same laboratory, obtained mainly by the same experts, decreasing interobserver variability).

6. Conclusions

This study shows that in the era of modern revascularization, new-onset atrial fibrillation remains a frequent complication of acute myocardial infarction and is associated with higher in-hospital mortality. Older age and routinely checked parameters, such as

higher BNP and CRP levels, and lower LVEF could be helpful indices of this arrhythmia in current, mostly invasively treated patients with AMI.

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New-Onset Atrial Fibrillation in Acute Myocardial Infarction Is a Different Phenomenon than Other Pre-Existing Types of That Arrhythmia

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Abstract: (1) Background: Atrial fibrillation (AF) in acute myocardial infarction (AMI) could worsen the prognosis. Yet, there is no definitive answer to whether new-onset AF (NOAF) is a more aggravating diagnosis than other types of that arrhythmia. The purpose of our study was to compare in-hospital clinical course and outcomes of NOAF patients contrary to patients with other pre-existing types of AF. (2) Methods: AMI patients hospitalized in the high-volume cardiological center within 2017–2018 were included in the study. NOAF was noticed in 106 (11%) patients, 95 (10%) with an AF history and AF during AMI formed the AF group, 60 (6%) with an AF history but without AF during AMI constituted the Prior-AF group, and 693 (73%) patients were without an AF before and during AMI. Medical history, routinely monitored clinical parameters, and in-hospital outcomes were analyzed between the groups. (3) Results: NOAF patients, contrary to others, initially had the highest high-sensitivity troponin I (hsTnI), B-type natriuretic peptide (BNP), C-reactive protein (CRP), and glucose levels, and the lowest potassium concentration, with the worst profile of changes for that parameter within the first four days of hospitalization. NOAF patients had the highest rate of ST-elevated AMI (40%), the longest hospitalization ($p < 0.001$), and the highest in-hospital mortality ($p < 0.001$). Not NOAF, but other AF groups (AF and Prior-AF groups) were more burdened with the previous comorbidities. (4) Conclusions: NOAF could be a distinct phenomenon in AMI patients, identifying those with the worst clinical in-hospital course and outcomes as compared to other types of AF.

Keywords: atrial fibrillation; acute myocardial infarction; new-onset atrial fibrillation

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1. Introduction

Atrial fibrillation (AF) is the most common clinical arrhythmia, affecting 2–4% of the general population [1]. With an incidence of 5 to 23% [2–5] it is the most frequent arrhythmia connected with acute myocardial infarction (AMI). New-onset AF (NOAF), defined as newly diagnosed AF in AMI, constitutes a particular type of that arrhythmia. According to data from the literature [6–8] and the results of our previous study [9], NOAF is connected with worse clinical characteristics and poor outcomes in comparison to other patients with AMI [10]. However, there is no precise answer to whether NOAF is a more aggravating diagnosis in AMI patients than other types of AF. There were a few studies in the literature that tried to compare NOAF patients with other types of AF [10–15], however, they analyzed only selected groups of patients, preferably ST-elevation myocardial infarction (STEMI) [14,15], or only patients with AMI treated invasively [10], or only compared NOAF with one of other types of AF (i.e., chronic AF and NOAF [13], pre-existing AF and

NOAF AF [12]), or were performed earlier, before the widespread availability of thrombolytic and percutaneous treatment for AMI patients [11]. As a result, comparing these data is challenging, and they differ significantly. The purpose of our study was to compare in-hospital clinical course and prognosis between NOAF patients and other pre-existing types of AF. We tried to answer the question of whether the NOAF is the same disease as pre-existing arrhythmia in AMI patients.

2. Materials and Methods

This study is a sub-analysis of our previous retrospective research, where the recruitment process was precisely described [9]. The study population consisted of consecutive AMI patients hospitalized in the University Clinical Centre of Gdansk from January 2017 to December 2018. The data was collected through MedStream Designer, which is fully integrated with the hospital information system. The exclusion criterion was age younger than 18 years. AMI diagnosis was based on the appropriate measures [16,17].

All patients were divided into four groups:

- NOAF (group of patients with any newly diagnosed AF that appeared during AMI hospitalization without a prior diagnosis of AF as it was precisely described [9]);
- AF (group of patients with a previously documented diagnosis of AF who additionally had AF during AMI hospitalization);
- Prior-AF (group of patients with a previously documented diagnosis of AF who had not developed AF during AMI hospitalization); and
- Non-AF (group of patients with no evidence of AF during AMI hospitalization and without the prior AF diagnosis).

For all patients, detailed medical history and clinical parameters, as well as in-hospital treatment and outcomes, were analyzed. Additionally, the course for laboratory parameters within the first four consecutive days of AMI hospitalization was taken into consideration. The pharmacotherapy at discharge (that was under the discretion of the attending physician) was thoroughly collected. The Independent Bioethical Committee approved the study's protocol for Scientific Research of the Medical University of Gdansk (NBBN/290/2018). Due to the retrospective character of the study based on the routine clinical parameters, the necessity for written and informed consent was waived.

Statistical Analysis

Continuous data are presented as median (25th–75th percentile), and categorical as numbers (n) and percentages (%). We performed the Shapiro-Wilk test to determine whether our data were normally distributed; most of the analyzed parameters did not have a normal data distribution, even after logarithmic transformation; therefore, we selected appropriate statistical analysis methods based on non-parametric tests. Comparisons between all groups were performed by the Kruskal-Wallis test for continuous variables (with Dunn's post-hoc test for the multiple comparisons with Bonferroni adjusted) or by the chi-square test or Fisher test for categorical variables. The significance of differences for laboratory parameters analyzed within the first four consecutive days of AMI hospitalization was assessed using the Kruskal-Wallis tests for the group comparison and Friedman test and paired Wilcoxon test with Bonferroni adjusted. Linear mixed-effects models were used for data analysis with repeated measurements of the same variable for the four time points (from day 1 to day 4), to select the optimal set of predictors, the model was estimated using the backward stepwise method and Akaike Information Criterion. Values of $p < 0.05$ were considered significant. The statistical analysis was conducted with Statistics and R 4.0.5. environment (R Core Team, Vienna, Austria).

3. Results

3.1. Baseline Clinical Characteristics

As it was documented in our previous study [9], 954 patients with AMI were enrolled in the study. The NOAF group consisted of 106 patients (11%), whereas the AF group (a prehospital diagnosis of AF and AF during hospitalization) included 95 patients (10%), the Prior-AF group (patients with a previously documented diagnosis of AF who had not developed AF during hospitalization) - 60 patients (6%), and the remaining 693 (73%) were patients without AF (Non-AF group). Table 1 presents the baseline clinical characteristics of all studied patients. Patients with any AF (including the NOAF group) were older than Non-AF patients. Regarding comorbidities, AF and Prior-AF patients were more burdened with diseases; interestingly, the NOAF group was similar to Non-AF patients in this issue, with the only exception being in the rate of prior stroke. In the analysis of the prehospital pharmacological treatment, it was easy to notice the better treatment with angiotensin-converting enzyme (ACE) inhibitors/sartans and statins in both groups of patients with a previous history of AF contrary to NOAF and Non-AF patients.

Table 1. Baseline clinical characteristics.

	NOAF * ***n* = 106**	**AF §** ***n* = 95**	**Prior-AF ¶** ***n* = 60**	**Non-AF** ***n* = 693**	***p***
Age (years old)	73 (66–84)	74 (67–82)	72 (69–78)	65 (59–73), *,¶	0.001
Male sex, *n* (%)	67 (63%)	55 (58%)	42 (70%)	473 (68%)	0.172
Prior MI, *n* (%)	31 (29%), ¶	41 (43%)	32 (53%), *	172 (25%), §,¶	0.001
Prior revascularization (PCI/CABG), *n* (%)	26 (25%), §,¶	41 (43%), *	28 (47%), *	175 (25%), §,¶	0.001
Hypertension, *n* (%)	79 (75%), ¶	82 (86%)	55 (92%), *	502 (73%), §,¶	0.001
Diabetes mellitus, *n* (%)	31 (29%), §,¶	45 (47%), *	28 (47%), *	210 (30%), §,¶	0.001
Previous stroke, *n* (%)	10 (9.4%)	19 (20%)	5 (8%)	36 (5%), §	0.001
On-Admission Treatment					
Aspirin, *n* (%)	43 (41%)	32 (34%)	22 (37%)	259 (38%)	0.826
ACE inhibitors/sartans, *n* (%)	53 (50%), §,¶	67 (71%), *	44 (73%), *	346 (50%), §,¶	0.001
Statins, *n* (%)	41 (39%), ¶	48 (51%)	37 (62%), *	249 (36%), §,¶	0.001

Abbreviations: *p*-value: for differences among all groups with Kruskal–Wallis test for continuous variables or with chi-square test for categorical variables, $p < 0.05$ in post-hoc tests for differences with group NOAF (*), AF (§), or Prior-AF (¶). ACE—angiotensin-converting enzyme; BMI-body max index; CABG—coronary artery bypass grafting; ICD—implantable cardioverter-defibrillator; MI—myocardial infarction; PCI—percutaneous coronary intervention.

3.2. In-Hospital Characteristics and Outcomes

Among all analyzed groups, NOAF patients had the highest rate of STEMI-40%, more than two-fold higher than in other patients with AF (AF and Prior-AF groups). Almost 100% of enrolled patients had coronary angiography during the hospitalization, and 82% had a percutaneous coronary intervention (PCI), as is presented in Table 2. NOAF patients had the worst in-hospital prognosis, including the highest rate of adverse events (malignant arrhythmias or stroke) and in-hospital mortality: twice more than in the AF group and four to six times more than the remaining groups (Table 2). The majority of NOAF patients (85%), in contrast to the AF group (36%), had sinus rhythm at discharge.

Table 2. Types of AMI, results of coronary angiography, and in-hospital prognosis.

	NOAF * n = 106	AF § n = 95	Prior-AF ¶ n = 60	Non-AF n = 693	p
Types of Myocardial Infarction					
ST-elevation MI, *n* (%)	42 (40%), §,¶	16 (17%), *	9 (15%), *	260 (36%), §,¶	0.001
Non-ST-elevation MI, *n* (%)	64 (60%), §,¶	79 (83%), *	51 (85%), *	423 (62%), §,¶	0.001
In-hospital coronary angiography, *n* (%)	99 (93%)	90 (95%)	58 (97%)	674 (97%)	0.121
In-hospital PCI, *n* (%)	81 (76%)	69 (73%)	49 (82%)	580 (83%)	0.413
In-Hospital Prognosis					
Length of hospitalization (days)	10 (7–17), ¶	9 (6–14), ¶	7 (5–10), *, §	6 (5–8), *,§	0.001
VT during hospitalization, *n* (%)	6 (6%)	3 (3%)	2 (3%)	15 (2%)	0.166
VF during hospitalization, *n* (%)	14 (13%)	4 (4%)	1 (2%)	46 (7%)	0.023
AVB III during hospitalization, *n* (%)	6 (6%)	1 (1%)	1 (2%)	7 (1%), *	0.013
Stroke during hospitalization, *n* (%)	3 (3%)	2 (2%)	1 (2%)	3 (0.43%)	0.023
In-hospital mortality, *n* (%)	19 (18%), ¶	9 (9%)	2 (3%), *	28 (4%), *	0.001
Sinus rhythm at discharge, *n* (%)	74 (85%), §,¶	31 (36%), *,¶	52 (89%), *,§	661 (99%), *,§	0.001

Abbreviations: *p*-value: for differences among all groups with Kruskal–Wallis test for continuous variables or with chi-square test for categorical variables, $p < 0.05$ in post-hoc tests for differences with group NOAF (*), AF (§), or Prior-AF (¶). AVB—atrioventricular block; MI—myocardial infarction; PCI—Percutaneous coronary intervention; SR—sinus rhythm; VF—ventricular fibrillation; VT—ventricular tachycardia.

3.3. In-Hospital Laboratory and Echocardiographic Parameters

Table 3 presents the results of the laboratory parameters measured on the first day of hospitalization, and, additionally, the maximal level of high sensitivity troponin I (hsTnI) and echocardiographic measures. The four analyzed groups significantly differ regarding those parameters: most of which (B-type natriuretic peptide (BNP), troponin, C-reactive protein (CRP), glucose, and hemoglobin) were worse in the patients with any AF (NOAF, Prior-AF, AF groups) in comparison to the Non-AF group. The NOAF group was characterized by the highest level of hsTnI, BNP, CRP, and glucose, and the lowest potassium concentration. Total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C) were significantly higher in the Non-AF group in comparison to all AF patients. Patients with AF (NOAF, AF, and Prior-AF groups) had significantly worse left ventricular ejection fraction (LVEF), with the lowest level for the NOAF group. Patients without AF, as expected, had the smallest left atrium (LA) size. In patients with AF in AMI (NOAF and AF groups), the right ventricular size was the largest (Table 3).

Table 3. Laboratory and echocardiographic parameters of the studied groups.

	NOAF * n = 106	AF § n = 95	Prior-AF ¶ n = 60	Non-AF n = 693	p
BNP, pg/mL	491 (193–1087), ¶	270 (158–895)	248 (78–622), *	114 (43–362), *, §	0.001
hsTnI, ng/mL	0.64 (0.06–4.84), §,¶	0.148 (0.04–0.78), *	0.127 (0.03–0.55), *	0.215 (0.05–1.40)	0.026
hsTnI max, ng/mL	10.59 (2.98–36.62), §,¶	3.11 (0.91–13.48), *	2.37 (0.78–6.64), *	6.51 (1.35–28.11), *,§,¶	0.001
CK-MB, ng/mL	4.75 (2.2–14)	4 (2.0–7.5)	3.35 (1.5–6.2)	4.05 (2.1–11.2)	0.136

Table 3. *Cont.*

	NOAF * n = 106	AF § n = 95	Prior-AF ¶ n = 60	Non-AF n = 693	p
CRP, mg/L	11.2 (3.55–34.5), ¶	6.5 (2.8–16.6), *	3.56 (1.8–12.4), *	3.4 (1.4–9.9), *,§	0.001
Sodium, mmol/L	138 (135–140)	138 (135–140)	138 (136–140)	138 (136–140)	0.167
Potassium, mmol/L	4.1 (3.8–4.5), §	4.4 (4.1–4.8), *	4.3 (3.9–4.7)	4.3 (4.0–4.6), *	0.007
Hemoglobin, g/dL	13.5 (12.1–14.8)	13.3 (11.7–14.5)	13.0 (12.1–14.3)	14 (12.6–15.1), §,¶	0.001
Leucocytes, $\times 10^9$/L	10.87 (8.18–13.91)	10.23 (7.84–13.3)	9.08 (7.13–12.69)	9.77 (7.86–12.12), *	0.065
Neutrophil to lymphocyte ratio	3.81 (2.2–6.8)	3.82 (2.5–8.0)	3.8 (2.5–6.5)	3.08 (2.0–5.1), §	0.002
Total cholesterol, mg/dL	169 (129–191)	148 (128–189)	159 (136–196)	181 (148–218), *,§,¶	0.001
LDL-C, mg/dL	98 (64–124)	87 (72–107)	94 (78–130)	109 (80–145), *,§	0.001
Creatinine, ml/dL	0.96 (0.78–1.24), §	1.14 (0.94–1.48), *	0.95 (0.8–1.33)	0.92 (0.78–1.13), §	0.004
TSH, uU/L	1.16 (0.66–1.85)	1.13 (0.60–2.22)	1.24 (0.82–2.59)	1.06 (0.48–1.67)	0.147
FT3, pmol/L	2.97 (2.75–3.30)	3.41 (2.54–3.78)	2.94 (2.54–3.42)	3.12 (2.67–3.7)	0.696
FT4, pmol/L	14.74 (13.40–16.10)	14.07 (12.36–15.27)	13.44 (12.49–14.54)	12.71 (11.31–14.51), *	0.009
Glucose, mg/dL	155 (120–219), §,¶	132 (101–186), *	118 (106–163), *	126 (103–172), *	0.001
Echocardiographic Parameters					
LVEF, %	40 (33–50)	44 (32–55)	49 (40–55)	50 (41–58), *,§	0.001
LA size, mm	42 (38–46), §	45 (41–50), *,¶	42 (38–45), §	39 (35–42), *,§,¶	0.001
LVIDd, mm	50 (44–55)	50 (46–56)	49 (45–56)	49 (45–53)	0.204
RVID, mm	42 (34–44)	42 (35–49)	36 (32–43)	35 (32–39), *,§	0.001
TAPSE, mm	19 (15–22)	17 (15–20)	19 (17–22)	21 (18–24), *,§	0.001
RVSP, mmHg	43 (35–47)	45 (35–46)	40 (31–47)	40 (30–46)	0.410

Abbreviations: *p*-value: for differences among all groups with Kruskal–Wallis test for continuous variables or with chi-square test for categorical variables, $p < 0.05$ in post-hoc tests for differences with group NOAF (*), AF (§), or Prior-AF (¶). BNP—B-type natriuretic peptide; CK-MB—creatine kinase muscle-brain; CRP—C-reactive protein; FT3-free triiodothyronine; FT4—free thyroxine; hsTnI—high sensitivity troponin I; LA—left atrium; LDL—C-low-density lipoprotein cholesterol; LVIDd—left ventricular internal diameter end diastole; LVEF-left ventricular ejection fraction; RVIDd—right ventricular internal dimension; RVSP-right ventricular systolic pressure; TAPSE—tricuspid annular plane systolic excursion; TSH—thyroid-stimulating hormone.

3.4. In-Hospital Laboratory Parameters Dynamic

Figures 1–5 present the dynamic changes in some of the laboratory parameters within the first four consecutive days of hospitalization. As is easy to note, the NOAF patients are characterized by the most prominent changes in CRP, leucocytes, and hsTnI, as well as the lowest potassium level. NOAF patients had the most significant increase in hsTnI level, with the maximum level being on the second day of hospitalization (Figure 1). Similarly, the NOAF patients had the highest CRP level, which steadily increased during the four days and was two to three times higher than in the Non-AF group (Figure 2). NOAF patients had the maximal values of leucocytes on the first day of hospitalization, with a peak on the second day, whereas the remaining AF patients (AF and Prior-AF groups) experienced a slight decrease of this parameter during the consecutive four days. (Figure 3). The potassium level was the lowest in the NOAF group throughout the whole four-day period of measurements (Figure 4). NOAF patients were characterized by the biggest reduction in hemoglobin level during the consequent four days of our observation (Figure 5).

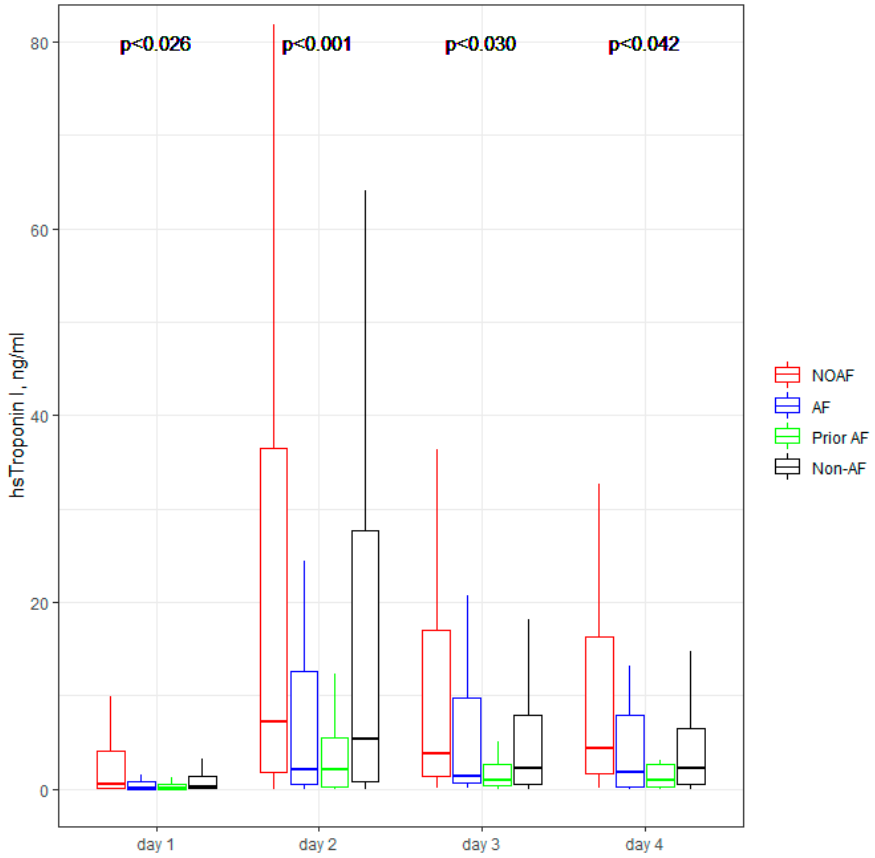

Figure 1. hsTnI concentration within the first four days of hospitalization. The center represents the median value. The upper and lower quartiles values are displayed with whiskers. *p*-values on the figure represent the group changes (the Kruskal–Wallis test). The time changes were calculated by the Friedman test and paired samples Wilcoxon test with Bonferroni adjusted ($p < 0.001$). hsTnI—high sensitivity troponin I; NOAF—group of patients with any newly diagnosed AF that appeared during AMI hospitalization; AF—group of patients with a previously documented diagnosis of AF who additionally had AF during AMI hospitalization; Prior AF—group of patients with a previously documented diagnosis of AF who had not developed AF during AMI hospitalization; Non-AF—group of patients with no evidence of AF during AMI hospitalization and without the prior AF diagnosis.

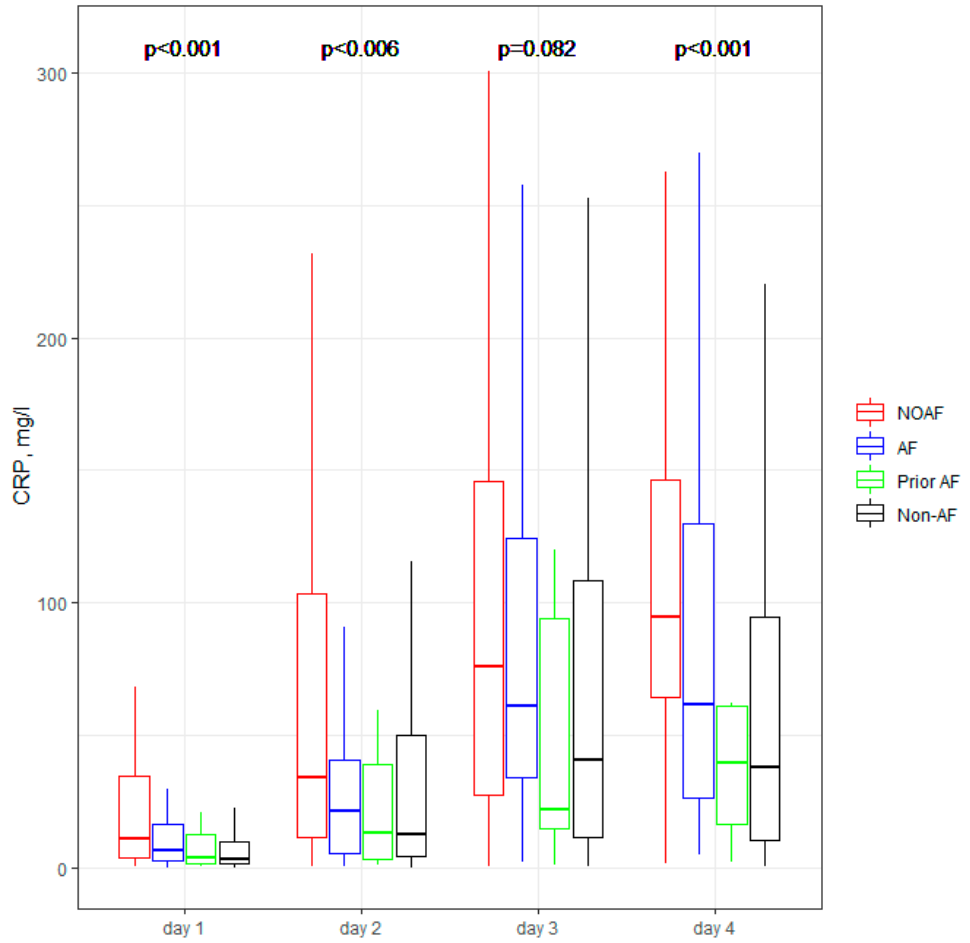

Figure 2. CRP concentration within the first four days of hospitalization. The center represents the median value. The upper and lower quartiles values are displayed with whiskers. *p*-values on the figure represent the group changes (the Kruskal–Wallis test). The time changes were calculated by the Friedman test and paired samples Wilcoxon test with Bonferroni adjusted ($p < 0.001$). CRP—C-reactive protein; NOAF—group of patients with any newly diagnosed AF that appeared during AMI hospitalization; AF—group of patients with a previously documented diagnosis of AF who additionally had AF during AMI hospitalization; Prior AF—group of patients with a previously documented diagnosis of AF who had not developed AF during AMI hospitalization; Non-AF—group of patients with no evidence of AF during AMI hospitalization and without the prior AF diagnosis.

In the linear mixed model analysis, the impact of some clinical characteristics was determined: age ($p < 0.001$), male sex ($p = 0.008$), and history of diabetes mellitus ($p = 0.009$) on CRP level, hypertension history ($p = 0.017$) on leucocytes level, male sex ($p = 0.019$), and prior MI ($p = 0.008$) on potassium level, age ($p < 0.001$), myocardial infarction history ($p = 0.009$), diabetes mellitus ($p = 0.004$), and history of stroke ($p = 0.021$) on hemoglobin level. However, no interactions with the assessment of the group effect and time effect were noticed.

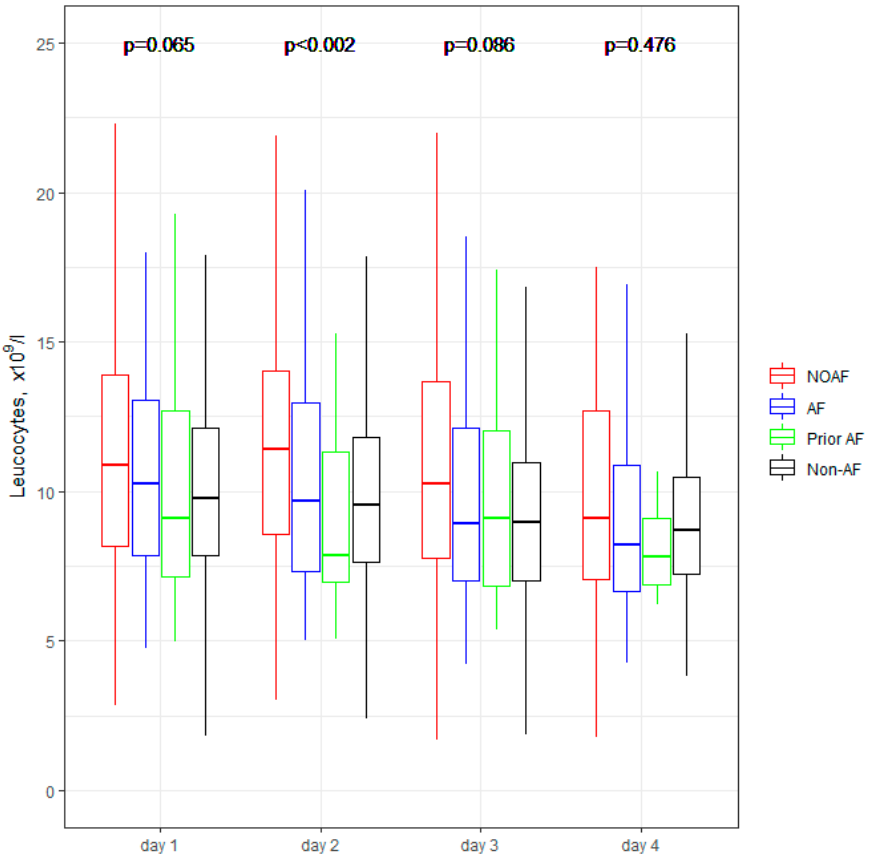

Figure 3. Leucocytes within the first four days of hospitalization. The center represents the median value. The upper and lower quartiles values are displayed with whiskers. *p*-values on the figure represent the group changes (the Kruskal–Wallis test). The time changes were calculated by the Friedman test and paired samples Wilcoxon test with Bonferroni adjusted ($p < 0.001$). NOAF—group of patients with any newly diagnosed AF that appeared during AMI hospitalization; AF—group of patients with a previously documented diagnosis of AF who additionally had AF during AMI hospitalization; Prior AF—group of patients with a previously documented diagnosis of AF who had not developed AF during AMI hospitalization; Non-AF—group of patients with no evidence of AF during AMI hospitalization and without the prior AF diagnosis.

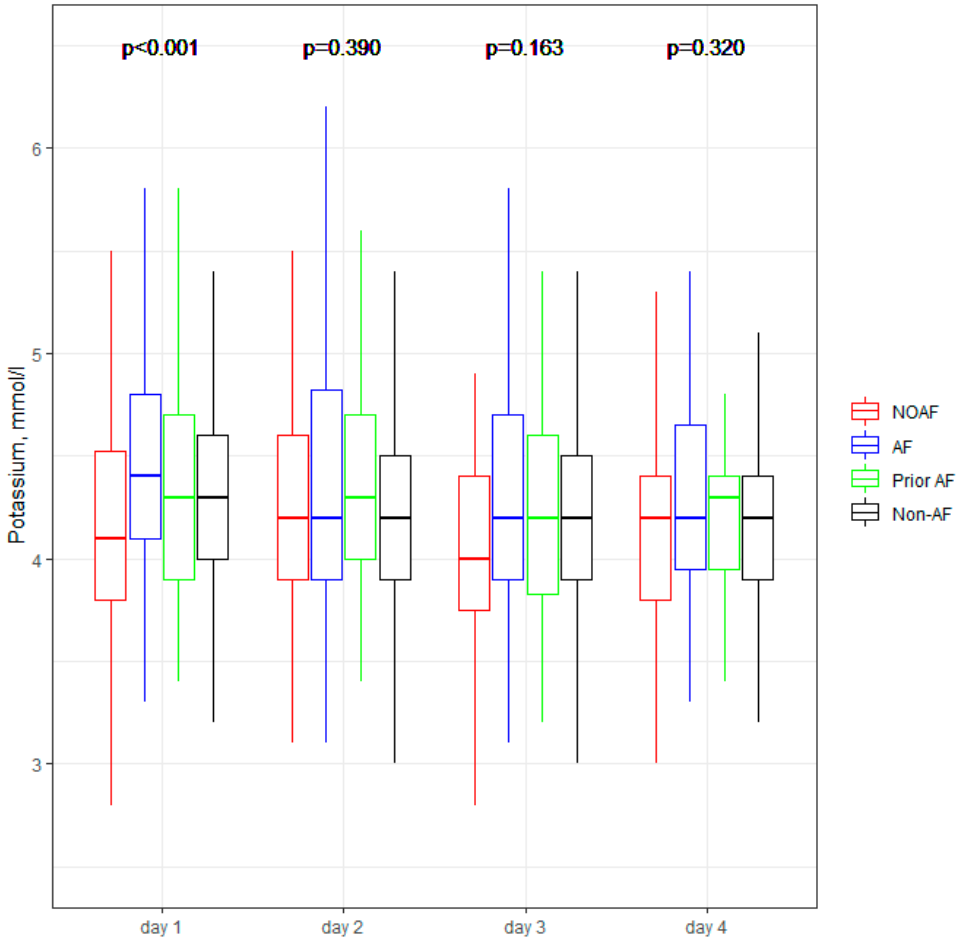

Figure 4. Potassium concentration within the first four days of hospitalization. The center represents the median value. The upper and lower quartiles values are displayed with whiskers. *p*-values on the figure represent the group changes (the Kruskal–Wallis test). The time changes were calculated by the Friedman test and paired samples Wilcoxon test with Bonferroni adjusted ($p < 0.004$). NOAF—group of patients with any newly diagnosed AF that appeared during AMI hospitalization; AF—group of patients with a previously documented diagnosis of AF who additionally had AF during AMI hospitalization; Prior AF—group of patients with a previously documented diagnosis of AF who had not developed AF during AMI hospitalization; Non-AF—group of patients with no evidence of AF during AMI hospitalization and without the prior AF diagnosis.

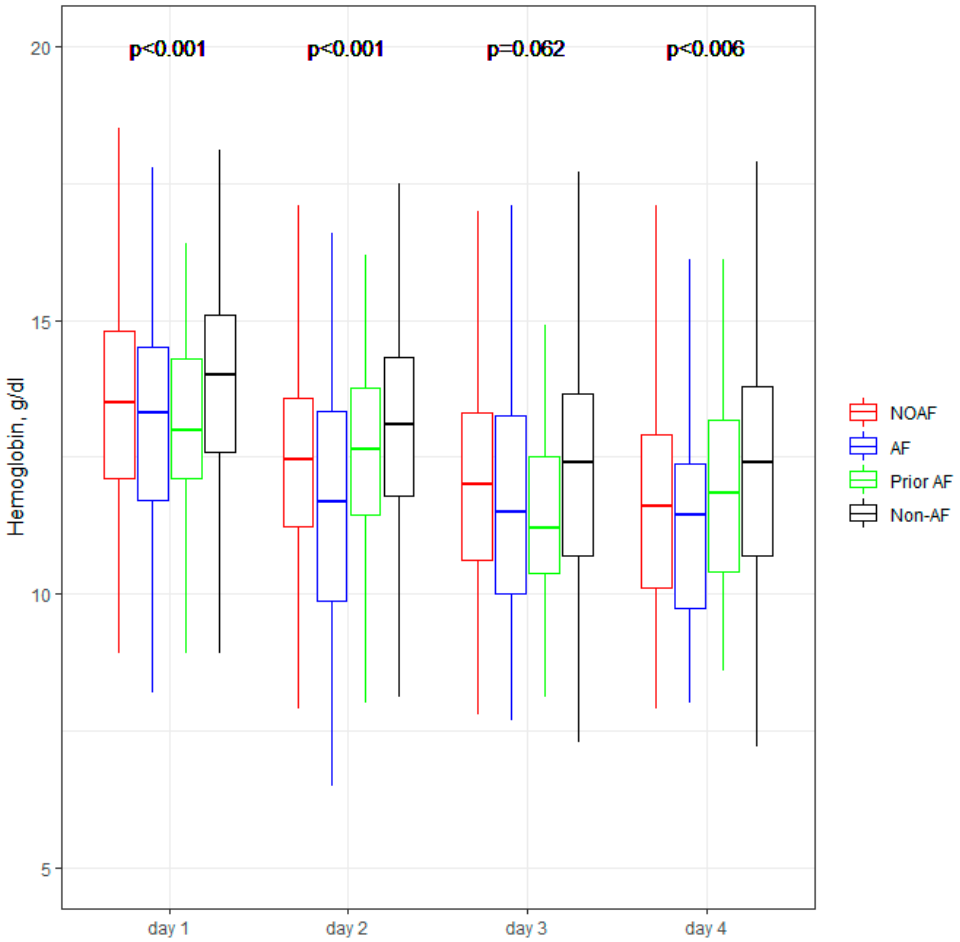

Figure 5. Hemoglobin within the first four days of hospitalization. The center represents the median value. The upper and lower quartiles values are displayed with whiskers. *p*-values on the figure represent the group changes (the Kruskal–Wallis test). The time changes were calculated by the Friedman test and paired samples Wilcoxon test with Bonferroni adjusted ($p < 0.001$). NOAF—group of patients with any newly diagnosed AF that appeared during AMI hospitalization; AF—group of patients with a previously documented diagnosis of AF who additionally had AF during AMI hospitalization; Prior AF—group of patients with a previously documented diagnosis of AF who had not developed AF during AMI hospitalization; Non-AF—group of patients with no evidence of AF during AMI hospitalization and without the prior AF diagnosis.

3.5. Pharmacological Treatment at Discharge

The studied groups significantly differed in pharmacological treatment at discharge (Table 4). Patients with arrhythmia within AMI hospitalization (NOAF and AF groups) had prescribed NOACs and triple antithrombotic therapy more often than patients without AF onset during hospitalization (Prior-AF and Non-AF groups). Moreover, triple therapy was prescribed more often for AF group patients (70%) than for NOAF (57%).

Table 4. Pharmacological treatment at discharge.

	NOAF *n*= 86	AF *n* = 85	Prior-AF *n* = 58	Non-AF *n* = 662	*p*
Beta-blockers, *n* (%)	76 (88%)	76 (89%)	48 (83%)	575 (87%)	0.677
ACE inhibitors/sartans, *n* (%)	73 (85%)	73 (86%)	47 (81%)	608 (92%)	0.006
Statins, *n* (%)	81 (94%)	74 (87%)	53 (91%)	633 (96%)	0.011
Antithrombotic Therapy					
Aspirin, *n* (%)	76 (88%)	74 (87%)	53 (91%)	639 (97%)	0.001
Clopidogrel, *n* (%)	72 (84%)	72 (85%)	51 (88%)	495 (75%)	0.012
Ticagrelor, *n* (%)	3 (3%)	0 (0%)	0 (0%)	145 (22%)	0.001
Vitamin K antagonists, *n* (%)	8 (9%)	24 (28%)	10 (17%)	13 (2%)	0.001
NOACs, *n* (%)	54 (63%)	51 (60%)	23 (40%)	12 (2%)	0.001
Low-molecular-weight heparins, *n* (%)	7 (8%)	8 (10%)	9 (16%)	18 (3%)	0.001
Triple Antithrombotic Therapy					
Aspirin + Clopidogrel + Vitamin K antagonists	8 (9%)	19 (22%)	10 (17%)	9 (1%)	0.001
Aspirin + Clopidogrel + NOACs	40 (47%)	40 (47%)	16 (28%)	12 (2%)	0.001
Aspirin + Clopidogrel + LMWH	1 (1%)	1 (1%)	0 (0%)	1 (1%)	0.001
Double Antithrombotic Therapy					
Aspirin + Clopidogrel	14 (16%)	3 (4%)	16 (28%)	457 (69%)	0.001
Aspirin + Ticagrelor	2 (2%)	0 (0%)	0 (0%)	137 (21%)	0.001

ACE—angiotensin-converting enzyme; ARBs—angiotensin receptor blockers; LMWH—low-molecular-weight heparin; NOACs—novel oral anticoagulants.

4. Discussion

The main finding of our study is that NOAF is a distinct phenomenon in comparison to other pre-existing AF types in patients with AMI. The appearance of NOAF seems to be the indicator of poor AMI course and worse in-hospital prognosis contrary to patients with a previous history of AF, who are, however, more burdened with comorbidities before AMI, but had better prognosis within hospitalization. To the best of our knowledge, this is the first study in which the complex evaluation of routinely measured clinical and laboratory parameters regarding different types of AF in the modernly treated AMI patients, with special attention to NOAF patients, was performed.

Data from the literature confirms that AF is common in patients with AMI [2,10–14,18,19]. Our results are in line with that: every fifth enrolled patient (21%) had AF with the highest frequency for NOAF (11%). All patients with a history of AF (AF and Prior-AF groups) accounted for 16% (10% and 6% respectively). According to data from the literature, the clinical profile of patients with AF during AMI differs significantly from other patients: they are older, have an increased burden of cardiovascular risk factors like coronary artery disease, history of hypertension, diabetes mellitus, and stroke [12,20]. In our study, that characteristic was related only to patients with a prior history of AF, but not to NOAF. Contrary to possible predictions, patients with NOAF had a better medical history but were characterized by worse in-hospital clinical course and prognosis.

Our previous study proved that age, BNP, CRP, and LVEF were associated with NOAF [9]. One of the results of current research is that NOAF patients were characterized by the highest troponin level (Figure 1). Troponin concentration is a well-known measure of AMI intensity, with a high level in STEMI rather than NSTEMI [21], and according to some data, a prognostic factor of poor prognosis [22]. Our results confirm that information: NOAF patients had the highest rate of STEMI (40%), contrary to only 17% in AF and 15% in Prior-AF groups. Interestingly, Non-AF patients had a similar rate of STEMI (36%),

however, their troponin level was slightly lower than in NOAF, but higher than in AF and Prior-AF groups (Table 3). We could suppose that NOAF presentation could be a consequence of severe myocardial necrosis and occur especially in sick patients with a large myocardial infarction. As NOAF patients have a more significant occurrence of STEMI, that can explain their worse outcomes [23]. In our study, NOAF patients had the highest in-hospital mortality (19%) in comparison to other sub-groups: twice that of AF patients (9%) and four to six times that of the other groups.

Regarding laboratory parameters, we noticed some important differences between the studied sub-groups in our study. Patients with AF (NOAF, AF and Prior-AF groups) had higher than Non-AF patients BNP level (Table 3). According to the literature, BNP could be elevated in patients with AF, and this elevation returns to normal value after sinus rhythm restoration, suggesting that BNP may play a role in predicting AF recurrence [24,25]. That could explain the above-mentioned differences. However, in our results, NOAF patients had the highest BNP level, which could suggest that NOAF is connected with the most prominent hemodynamic changes, in contrast with other AF during AMI. Our previous study demonstrated that BNP with a cut-off value of $\geq$340 pg/mL is a robust and independent predictor of NOAF [9]; that could suppose that the occurrence of AF itself is associated with higher BNP level. Inflammation, which can cause structural and electrical changes in the atrium, predisposing patients to AF, could be connected with the changes in the laboratory parameters such as CRP and white blood cells (WBC) [26,27]. For instance, CRP has been reported as a risk factor for AF episodes, including AF recurrences after successful cardioversion [28]. Similarly, WBC is one of the predictors of AF after cardiac surgery [29,30]. According to Yoshizaki et al., CRP and WBC were linked to NOAF in the early stages of STEMI, and an increase of both of those parameters was observed during the next days of hospitalization for AF patients [31]. Our results are in line with the above-mentioned information, and we revealed that patients with any AF in AMI (NOAF and AF groups) had two to three folds higher CRP levels compared with patients without AF (Table 3 and Figure 2). NOAF and AF groups had the highest WBC on admission, and the NOAF group had a peak WBC during the second day of in-hospital treatment (Table 3, Figure 3). Low serum potassium level is the next well-known characteristic linked to the development of AF in the general population [23,32–34]. In our previous study, potassium levels below 4.2 mmol/L were found to be crucial in revealing the NOAF probability [9]. The present study shows similar results, indicating the main difference between the compared groups on the first day of hospitalization: the lowest level was found in the NOAF group; AF and Prior-AF patients had higher potassium levels than NOAF, and the highest level was observed in the Non-AF group (Figure 4). Beginning from the second day of hospitalization, there were more differences: Prior-AF patients had higher potassium level than other groups, and NOAF patients always had the worst levels. That could be explained by the fact that in usual clinical practice, the patients with a documented history of AF usually receive more potassium supplements to prevent AF onset. Decreased hemoglobin level has been linked to poor outcomes in patients with AF in AMI [35]. In the presented study, NOAF patients had the most profound reduction in hemoglobin levels during the first four days of hospitalization (Figure 5). The highest level of hemoglobin was found in Non-AF patients.

Regarding echocardiographic parameters, the probability of AF increases with the enlargement of LA and reduction in LVEF [36,37]. Our latest study proved that LA diameter $\geq$ 41 mm and LVEF $\leq$ 44% were significant predictors of NOAF in the univariate analysis, with maintained significance for LVEF in the multivariate calculations [9], which is also in line with the latest research considering NOAF patients [38]. The present study shows that NOAF patients had the lowest LVEF (Table 3); however, the largest LA was not connected with the NOAF patients, but with patients from AF groups (patients with a previous history of AF and AF during AMI hospitalization). That result could confirm our supposition that NOAF is not a typical burden, but a consequence of severe AMI course.

When describing the pharmacological treatment of the studied patients, it should be mentioned that physicians make difficult therapeutic decisions when managing AF during the AMI, especially if AF onset is only during the acute phase of AMI, balancing embolic and hemorrhagic risks. These decisions are frequently based on expert consensus [38] and current guidelines [16,17,39]. Our study shows, however, high rate of recommended triple antithrombotic treatment (oral anticoagulation and dual antiplatelet therapy), but possibly not efficient: 70% for AF patients, 57% for NOAF and 45% for Prior-AF group (Table 4). Importantly, this is still a rate that is much higher than previously reported in other research [12,14], showing the growing awareness of the present recommendations.

5. Limitations

Our study presents some limitations. This single-center, retrospective study limits some of the data and parameters available in patients' medical records. Due to the general nature of data encoding, only patients with AMI were accurately coded; therefore, we were unable to use the term acute coronary syndrome (we do not have any data about patients with unstable angina). Due to the retrospective nature of our research and the use of an anonymous medical database (MedStream Designer), we could not perform the adequate long-term follow-up. Another limitation is possibly overestimating the NOAF (qualifying here patients with previously undetected paroxysmal AF). On the other hand, we could have underestimated the proper frequency of AF (due to silent AF episodes). Moreover, patients with permanent AF and a history of AF and an episode of AF in AMI are in one group, which is a rather inhomogeneous group, but it was impossible to separate them correctly in a retrospective evaluation.

6. Conclusions

New-onset atrial fibrillation in acute myocardial infarction is a different phenomenon than other pre-existing types of that arrhythmia. Its appearance seems to be the indicator of poor AMI course and worse in-hospital prognosis contrary to patients with a previous history of AF, who are, however, more burdened with comorbidities before AMI, but had better prognosis within hospitalization.

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Institutional Review Board Statement: The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Institutional Review Board (or Ethics Committee) of the Independent Bioethical Committee for Scientific Research of the Medical University of Gdansk (consent number NBBN/290/2018).

Informed Consent Statement: Patient consent was waived due to the retrospective nature of the study.

Data Availability Statement: Data are available on request due to privacy and ethical restrictions.

Conflicts of Interest: The authors declare no conflict of interest.

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