Uniwersytet Jagielloński
Collegium Medicum
Wydział Lekarski

Magdalena Jędrychowska

Ocena wybranych czynników ryzyka i rokowania u chorych z zawałem mięśnia sercowego bez istotnych zmian miażdżycowych w tętnicach wieńcowych oraz porównanie z innymi zespołami chorobowymi o podobnym przebiegu klinicznym

Assessment of selected risk factors and prognosis in patients with myocardial infarction with non-obstructive coronary artieries and comparison with other syndromes with a similar clinical course

Praca doktorska

Promotor: Dr hab. n. med. Rafał Januszek

Pracę wykonano w Oddziale Kardiologii oraz Interwencji Sercowo-Naczyniowych, Uniwersytet Jagielloński Collegium Medicum

Kierownik jednostki: Prof. dr hab. med. Andrzej Surdacki

Mojemu Promotorowi,

Dr hab. n. med. Rafałowi Januszkowi

dziękuję za wszelką pomoc jaką mi udzielił, życzliwość oraz bezcenne rady

Gorące podziękowania składam Prof. dr hab. med. Stanisławowi Bartusiowi za umożliwienie realizacji mojej pracy doktorskiej

Spis treści

1. Wprowadzenie

Niniejsza rozprawa doktorska pt. „Ocena wybranych czynników ryzyka i rokowania u chorych z zawałem mięśnia sercowego bez istotnych zmian miażdżycowych w tętnicach wieńcowych oraz porównanie z innymi zespołami chorobowymi o podobnym przebiegu klinicznym", powstała w oparciu o monotematyczny cykl trzech artykułów opublikowanych w międzynarodowych czasopismach naukowych indeksowanych w bazie PubMed o łącznym impact factor równym 7.622.

Na pracę doktorską składają się następujące artykuły:

1. Jędrychowska M, Januszek R, Plens K, Surdacki A, Bartuś S, Dudek D. "Impact of sex on the follow-up course and predictors of clinical outcomes in patients hospitalised due to myocardial infarction with non-obstructive coronary arteries: a single-centre experience". Kardiol Pol. 2019; 77: 198-206. (IF-1.874, MNiSW-100)

2. Jędrychowska M, Januszek R, Wańha W, Malinowski KP, Kunik P, Trznadel A, Bartuś J, Staszczak B, Januszek SM, Kameczura T, Wojakowski W, Surdacki A, Bartuś S. „Long-Term Prognostic Significance of High-Sensitive Troponin I Increase during Hospital Stay in Patients with Acute Myocardial Infarction and Non-Obstructive Coronary Arteries". Medicina (Kaunas). 2020; 56: 432. (IF-2.430, MNiSW-40)

3. Jędrychowska M, Januszek R, Wańha W, Malinowski KP, Wojakowski W, Bartuś K, Surdacki A, Dudek D, Bartuś S. „Long-term prognosis in patients suffering from myocardial infarction with non-obstructive coronary arteries, ST-segment elevation myocardial infarction, infective myocarditis and tako-tsubo cardiomyopathy – all-cause mortality comparison. Archives of Medical Science. 2021. (IF-3.318, MNiSW-100)

Łączna wartość "Impact factor" według Thomson Reuters Journal Citation Reports 2021 dla wymienionego cyklu wynosi 7.622 oraz 240 punktów według wykazu czasopism naukowych Ministerstwa Nauki i Szkolnictwa Wyższego na 2021 rok (lista A)

2. Podsumowanie pracy doktorskiej w języku polskim

WSTĘP

Choroba wieńcowa jest w głównej mierze związana z tworzeniem się blaszek miażdżycowych w tętnicach wieńcowych. Pęknięcie blaszki miażdżycowej powodujące powstanie zakrzepu w świetle naczynia oraz jego skurczu jest najczęstszą przyczyną prowadzącą do zawału mięśnia sercowego [1]. Mimo to u ok. 3-10% pacjentów, zawał serca występuję bez istotnych zwężeń w naczyniach wieńcowych [2-4]. Pierwsze prace badawcze opisujące pacjentów z zawałem mięśnia sercowego bez istotnych zwężeń w naczyniach wieńcowych pojawiły się już ponad 80 lat temu i rozpowszechniały się coraz bardziej wraz z rozwojem techniki angiografii naczyń wieńcowych [5]. Mimo to, termin MINOCA (*myocardial infarction with non-obstructive coronary arteries*, zawał serca bez istotnych zwężeń w naczyniach wieńcowych) pojawił się w literaturze naukowej dopiero w ostatniej dekadzie [6]. Z uwagi na liczbę chorych z zawałem mięśnia sercowego, u których nie znaleziono istotnych zwężeń podczas koronarografii [7,8] oraz niekorzystne rokowanie odległe [9] temat ten stał się bardzo popularny w ostatnich latach w światowej, a także polskiej kardiologii.

Zawał mięśnia sercowego bez istotnych zwężeń w tętnicach wieńcowych możemy rozpoznać pod warunkiem spełnienia kryteriów czwartej definicji zawału mięśnia sercowego według aktualnego stanowiska Europejskiego Towarzystwa Kardiologicznego (ESC, *European Society of Cardiology*) oraz braku zwężeń w naczyniach wieńcowych $\geq$ 50% w wykonanej angiografii tętnic wieńcowych [10]. W ostatnich latach pojawiło się stanowisko ekspertów dotyczące zalecanych metod rozpoznawania, identyfikacji potencjalnej etiologii oraz prowadzenia diagnostyki u osób z tej grupy chorych [11]. Różnorodność przyczyn w grupie pacjentów z rozpoznaniem MINOCA stawia przed kardiologami duże wyzwanie diagnostyczne. Prawidłowa identyfikacja przyczyny prowadzącej do zawału mięśnia sercowego ma istotne znaczenie w prowadzeniu optymalnej terapii oraz prewencji wtórnej w tej grupie chorych.

Wśród przyczyn MINOCA możemy rozróżnić stany związane z chorobą naczyń wieńcowych, mięśnia sercowego lub pozasercowe. Do przyczyn pozasercowych zaliczamy te związane m.in. z zawałem typu 2 w sytuacji nierównowagi między podażą tlenu a jego zapotrzebowaniem np. w przebiegu uszkodzenia nerek, sepsy, zespołu ostrej niewydolności oddechowej (ARDS, *acute respiratory distress syndrome*) czy też zatorowości płucnej. Wśród

przyczyn związanych z patologią naczyń wieńcowych wyróżniamy: skurcz naczyń wieńcowych, pękniętą blaszkę miażdżycową, dyssekcje tętnicy wieńcowej, dysfunkcję mikrokrążenia wieńcowego, jak również embolizację dystalną. Do przyczyn związanych z uszkodzeniem mięśnia sercowego należą: kardiomiopatia Takotsubo TTC (*Taktsubo cardiomyopathy*), zapalenie mięśnia sercowego (IM, *infective myocarditis*) oraz inne kardiopatie [11]. Biorąc pod uwagę często heterogenną etiologię, rozpoznanie robocze MINOCA może zostać postawione do czasu poszerzenia diagnostyki. Przykładowo, IM jest diagnozowane nawet u ok. 33% pacjentów i jest zdecydowanie najczęstszą przyczyną odpowiedzialną za zawał typu MINOCA [7]. Pęknięcie blaszki miażdżycowej z przejściową zakrzepicą i spontaniczną fibrynolizą należy do najczęstszych przyczyn związanych z patologią naczyń wieńcowych [12]. W praktyce klinicznej pacjenci w stanie ciężkim, prezentują zawał serca typu 2 częściej aniżeli chorzy w lepszym stanie klinicznym. W takiej sytuacji, priorytetem terapeutycznym jest odwrócenie stanu nierównowagi leżącego u podstaw dysproporcji pomiędzy podażą tlenu, a jego zapotrzebowaniem. Do najczęstszych stanów odpowiedzialnych za zawał serca typu 2 należą: niedokrwistość, tachy- i brady-arytmie, niewydolność oddechowa, niedociśnienie tętnicze, wstrząs, ciężkie nadciśnienie tętnicze z lub bez przerostu lewej komory serca, ciężka wada zastawki aortalnej, niewydolność serca oraz szkodliwe skutki toksyn (np. posocznica lub zatrucie tlenkiem węgla).

Biorąc pod uwagę dotychczas dostępne wyniki badań, odsetek MINOCA wśród kobiet w porównaniu do zawału serca z istotnymi zwężeniami w naczyniach wieńcowych (MI-CAD, *myocardial infarction with obstructive coronary disease*) jest większy w porównaniu do mężczyzn. Pacjenci z grupy MINOCA są młodsi, a ich średnia wieku w różnych badaniach wacha się od 55 do 63 lat [13,14].

Należy także zwrócić uwagę na fakt, że MINOCA jest rozpoznaniem roboczym i zobowiązuje nas do poszerzenia diagnostyki i poszukiwania bezpośredniej przyczyny zawału serca. Najbardziej dostępnym i najszybszym do wykonania już na etapie przyjęcia chorego jest badanie echokardiograficzne serca. Echokardiografia przezklatkowa jest jednym z pierwszych badań zalecanych w ścieżce diagnostycznej u pacjentów z rozpoznaniem MINOCA. Dzięki niemu możemy ocenić kurczliwość lewej komory serca, w tym odcinkowe zaburzenia kurczliwości, grubość ścian i wielkość lewej komory serca, obecność płynu w worku osierdziowym, obecność wegetacji na zastawkach serca, ocenę obecności i istotności wad zastawkowych, zwapnień czy skrzeplin w jamach serca. Badanie echokardiograficzne może pomóc w identyfikacji powikłań zatorowo – zakrzepowych, zapalenia mięśnia sercowego lub

TTC jako przyczyny MINOCA [11,15,16]. Innym nieinwazyjnym badaniem pozwalającym na bardzo dokładną ocenę patologii w zakresie naczyń wieńcowych jest tomografia komputerowa. Badanie to umożliwia wykluczenie istotnych zwężeń w zakresie tętnic wieńcowych, obecności zwapnień, dysekcji oraz ocenę anomalii w zakresie ich anatomii [17]. Tomografia komputerowa jest złotym standardem w diagnostyce zatorowości płucnej oraz rozwarstwienia aorty. Do bardzo ważnych metod poszerzenia diagnostyki MINOCA należy obrazowanie wewnątrznaczyniowe. Wewnątrznaczyniowa ultrasonografia (IVUS, *intravascular ultrasound*) i optyczna tomografia koherentna (OCT, *optical coherence tomography*) pozwalają na szczegółową ocenę ściany naczynia, w tym zobrazowanie pękniętych blaszek miażdżycowych, dyssekcji, skrzeplin czy krwiaków. Niektóre badania podają, że pęknięta blaszka miażdżycowa może być przyczyną nawet do 40% zawałów mięśnia sercowego bez istotnych zwężeń w naczyniach wieńcowych [18,19]. OCT lub IVUS są jedną z metod zalecanych w diagnostyce pacjentów przyjętych do pracowni hemodynamiki z rozpoznaniem zawału mięśnia sercowego, u których standardowy angiogram tętnic wieńcowych nie wykazał istotnych zmian [11]. Do innych zagadnień należy ocena funkcji mikrokrążenia. Dostępne techniki pozwalają na ocenę rezerwy przepływu wieńcowego (CFR, *coronary flow reserve*), a także wskaźnika oporu mikrokrążenia (IMR, *index of microcirculatory resistance*), co umożliwia rozpoznanie dysfunkcji mikrokrążenia wieńcowego. Dysfunkcja mikrokrążenia wieńcowego jest uważana za ważny mechanizm niedokrwienia mięśnia sercowego, występuje u dużego odsetka pacjentów zarówno z chorobą wieńcową lub bez niej i wiąże się zarówno z przewlekłymi jak i ostrymi zespołami wieńcowymi [15]. Z uwagi na zwiększającą się liczbę pacjentów bez istotnych zwężeń w tętnicach wieńcowych wieńcowych i utrzymującymi się objawami niedokrwienia mięśnia sercowego, coraz większą wagę przykłada się do prawidłowego rozpoznania dławicy naczynioskurczowej. Testy z dowieńcowym podaniem ergonowiny lub acetylocholiny są bezpieczne i mogą pomóc w postawieniu odpowiedniej diagnozy. Z reguły, najczęściej podawanym lekiem dowieńcowym w przypadku podejrzenia dławicy naczynioskurczowej jest nitrogliceryna.

Kluczowym narzędziem diagnostycznym u pacjentów z rozpoznaniem MINOCA jest rezonans magnetyczny serca (CMR, *cardiac magnetic resonance*). Obecność późnego wzmocnienia pokontrastowego (LGE, *late gadolinum enhancement*) w CMR pozwala nam na lokalizację uszkodzenia mięśnia sercowego oraz wgląd w mechanizm uszkodzenia. Obszar późnego wzmocnienia pokontrastowego w warstwie podwsierdziowej sugeruje niedokrwienną przyczynę uszkodzenia, jakkolwiek nie wskazuje bezpośrednio na mechanizm niedokrwienia

(pęknięta blaszka miażdżycowa, skurcz czy rozwarstwienie naczynia). Z kolei lokalizacja podnasierdziowa przemawia za kardiomiopatią. Brak niedokrwiennego LGE może również przemawiać za rozpoznaniem zapalenia mięśnia sercowego lub choroby naciekowej. CMR może być również pomocny w uwidocznieniu obrzęku mięśnia sercowego i ocenie funkcji skurczowej [20,21]. Wykonanie CMR pozwala na rozpoznanie potencjalnej przyczyny zawału mięśnia sercowego u ok. 74.2-89.7% pacjentów [22,23]. Na podstawie wyników dotychczas opublikowanych badań wykazano, że w większości przypadków CMR pozwoliło na rozpoznanie zapalenia mięśnia sercowego jako najczęstszej przyczyny MINOCA. W drugiej kolejności do najczęstszych przyczyn MINOCA należała TTC. Etiologia niedokrwienna okazała się przyczyną MINOCA w kilku do kilkunastu procentach [22,23]. Oprócz rozbudowanych metod diagnostyki obrazowej, w diagnostyce MINOCA znaczenie ma wykonanie pełnego panelu badań laboratoryjnych, które mogą pozwolić na rozpoznanie zawału typu 2. U młodych osób hospitalizowanych z powodu MINOCA, należy wykonać badania w kierunku zaburzeń krzepnięcia krwi [11], które mogą okazać się przyczyną ostrego niedokrwienia mięśnia sercowego nawet w 24% przypadków [24].

Dokładna diagnostyka i ustalenie jednoznacznej przyczyny MINOCA jest niezbędne do prowadzenia prawidłowej terapii. Wciąż brak jednoznacznych wytycznych dotyczących prowadzenia leczenia farmakologicznego u pacjentów z rozpoznaniem MINOCA. Terapia powinna być dopasowana do każdego pacjenta, w zależności od najbardziej prawdopodobnej przyczyny prowadzącej do zawału mięśnia sercowego. Przykładowo, w zapaleniu mięśnia sercowego pacjenci zazwyczaj nie wymagają standardowego leczenia przeciw niedokrwiennego. W przypadku zapalenia mięśnia sercowego z upośledzoną funkcją skurczową lewej komory najkorzystniejsze wyniki przynosi stosowanie beta-blokerów i inhibitorów enzymu konwertującego angiotensynę (ACEI, *angiotensine converting enzyme inhibitors*). W kardiomiopatii stresowej zaleca się leki stosowane typowo w terapii niewydolności serca, w tym diuretyki pętlowe oraz unikanie leków z grupy sympatykomimetyków. Leczenie bywa zróżnicowane w zależności od przebiegu fazy ostrej. Przykładowo, w przypadku wstrząsu kardiogennego, należy rozważyć zastosowanie urządzeń do wspomagania pracy lewej komory serca (LVAD, *left ventricle assist device*), np. kontrpulsację wewnątrzaortalną (IABP, *intra-aortic balloon counterpulsation*) [25]. Kolejnym przykładem jest rodzaj leczenia w przypadku, gdy najbardziej prawdopodobną przyczyną zawału mięśnia sercowego jest skurcz naczyń wieńcowych. Wówczas, właściwym postępowaniem będzie włączenie blokerów kanału wapniowego [26,27]. Nadal nie ma

ewidencji na konieczność stosowania podwójnej terapii przeciwpłytkowej (DAPT, *dual antiplatelet therapy*), u pacjentów, u których przyczyna zawału mięśnia sercowego nie została jednoznacznie zidentyfikowana. Bezwzględnie, w wyborze leczenia należy uwzględnić ryzyko powikłań zatorowo-zakrzepowych i krwotocznych. Terapia i jej długość powinna być dopasowana do chorego. Wydaje się, że korzyści z DAPT mogą odnieść chorzy po wcześniejszych interwencjach w zakresie naczyń wieńcowych. Nie ulega wątpliwości, farmakoterapia DAPT powinna być stosowana przez rok u pacjentów, u których istnieje silne podejrzenie lub potwierdzono obecność pękniętej blaszki miażdżycowej [27-29].

Pacjenci z grupy MINOCA mają stosunkowo lepsze rokowanie od chorych z zawałem mięśnia sercowego MI-CAD. Roczna śmiertelność całkowita w grupie chorych MINOCA wynosi wg. różnych doniesień ok. 2.4 – 4.7 % [30,31]. Jakkolwiek, niektóre z dostępnych badań wykazały większą śmiertelność chorych z grupy MINOCA, jednakże było to głównie związane z większą śmiertelnością poza sercową [32]. Wykazano że w grupie chorych MI-CAD częściej obserwuje się re-hospitalizację oraz konieczność rewaskularyzacji naczyń wieńcowych [32]. Szacuje się, że niepożądane zdarzenia sercowo-naczyniowe występują w grupie MINOCA z częstością ok. 10.7- 18.7% w obserwacji rocznej [33,34].

CELE PRACY

1. Charakterystyka pacjentów przyjętych z ostrym zawałem mięśnia sercowego typu MINOCA.

2. Ocena najczęstszych przyczyn i mechanizmów oraz analiza czynników ryzyka wpływających na rokowanie długoterminowe.

3. Porównanie rokowania pacjentów z grupy MINOCA z wybranymi ostrymi jednostkami chorobowymi przebiegającymi z martwicą mięśnia sercowego.

HIPOTEZY BADAWCZE

1. Płeć męska nie jest mniej dominującym czynnikiem rokowniczym w grupie pacjentów z zawałem serca typu MINOCA aniżeli w grupie chorych z zawałem serca z istotnymi zwężeniami w tętnicach wieńcowych.

2. Zależność między stężeniem wysokoczułej troponiny, a częstością występowania niepożądanych zdarzeń sercowo-naczyniowych i śmiertelność w grupie pacjentów z

rozpoznaniem roboczym MINOCA nie jest tak silna jak w grupie chorych z zawałem serca z istotnymi zwężeniami w tętnicach wieńcowych.

3. Pacjenci z zawałem serca typu MINOCA mają korzystniejsze rokowanie, w porównaniu do pacjentów z zawałem serca z uniesieniem odcinka ST ściany przedniej z istotnymi zwężeniami tętnic wieńcowych, chorzy z TTC oraz pacjenci z IM.

MATERIAŁ i METODY

Badaniem objęto pacjentów, którzy zostali przyjęci do Pracowni Hemodynamiki Szpitala Uniwersyteckiego w Krakowie oraz Pracowni Hemodynamiki Oddziału Kardiologii Górnośląskiego Centrum Medycznego w Ochojcu w latach 2015-2019 z podejrzeniem zawału mięśnia sercowego i w wykonanej angiografii tętnic wieńcowych nie uwidoczniono zwężeń ≥50% w tętnicach wieńcowych oraz z roboczym rozpoznaniem MINOCA. Dodatkowo celem przeprowadzenia analizy porównawczej do badania włączono grupę pacjentów przyjętych z rozpoznaniem ostrego zawału mięśnia sercowego ściany przedniej z uniesieniem odcinka ST (STEMI, *ST-segment elevation myocardial infarction*). Dane antropometryczne, demograficzne, kliniczne oraz dane dotyczące aktualnego leczenia farmakologicznym były zbierane przy przyjęciu do szpitala na podstawie szczegółowo zebranego wywiad z pacjentem oraz na dostarczonej dokumentacji medycznej. Leczenie farmakologiczne i interwencyjne prowadzono zgodnie z zaleceniami aktualnie obowiązujących wytycznych Europejskiego Towarzystwa Kardiologicznego [35,36]. Obserwacja długoterminowa była prowadzona w trakcie wizyt kontrolnych w poradni kardiologicznej przyklinicznej lub telefonicznie.

Definicje

Robocza diagnoza poszczególnych typów OZW (zawał serca z uniesieniem odcinka ST i zawał serca bez uniesienia odcinka ST) to pojęcie stosowane w niniejszym badaniu dla

pacjentów przyjętych do oddziału i zakwalifikowanych do koronarografii. U wszystkich pacjentów ostateczne rozpoznanie zawału serca zostało postawione zgodnie z czwartą uniwersalną definicją zawału mięśnia sercowego i stanowiskiem grupy roboczej dotyczącej MINOCA opublikowanego przez Europejskie Towarzystwo Kardiologiczne [10,11]. Robocza diagnoza MINOCA została postawiona natychmiast po koronarografii, gdy nie stwierdzono istotnego zwężenia tętnic wieńcowych i nie było wskazań do dalszej rewaskularyzacji. W kolejnych dniach hospitalizacji u części pacjentów w oparciu o całokształt obrazu klinicznego, wyniki badań obrazowych i wyniki badań biochemicznych krwi zmieniono rozpoznanie. Przedstawiona etiologia została ustalona do końca hospitalizacji i nie została uznana za ostateczną ale za najbardziej prawdopodobną etiologię, ze względu na fakt, że niektóre badania, np. rezonans magnetyczny serca, badania krwi (pakiet badań w kierunku trombofilii) lub badania w kierunku choroby nowotworowej (pozytonowa tomografia emisyjna) wykonano po wypisie ze szpitala i z różnych powodów nie zostały uwzględnione w końcowej etiologii. Końcowa diagnoza była diagnozą postawioną na karcie wypisu pacjenta z oddziału kardiologii, która została oparta na całym obrazie klinicznym i wynikach badań zebranych do czasu wypisu chorego ze szpitala.

Celem ujednolicenia wyników oznaczeń troponin sercowych, opracowano na użytek przeprowadzonych analiz tzw. indeks troponinowy, za który przyjęto iloraz jej stężenia maksymalnego oraz górnej granicy normy. Zakres odniesiono dla konkretnego testu. Jak wspomniano wcześniej rozpoznanie ostrego zawału mięśnia sercowego zostało postawione zgodnie z czwartą uniwersalną definicją zawału mięśnia opublikowaną przez Europejskie Towarzystwo Kardiologiczne [10,11]. Również zawał serca typu 2 i jego indywidualną etiologię określono zgodnie z aktualnym wytycznymi i zalecanym konsensusem [10,11].

Zwężenie nieistotne zostało zdefiniowane jako zwężenie w angiografii tętnic wieńcowych poniżej 50%, co zostało potwierdzone w co najmniej dwóch projekcjach. Blaszkę miażdżycową

zdefiniowano jako ekscentryczną, gdy blaszka miażdżycowa nie obejmowała obwodu całej tętnicy wieńcowej. Choroby autoimmunologiczne i onkologiczne uwzględniano w oparciu o dostarczoną przez pacjenta dokumentację medyczną. TTC była diagnozowana zgodnie z ogólnie przyjętymi zaleceniami, po wykonaniu badania echokardiograficznego [37]. Skurcz tętnicy wieńcowej zdefiniowano jako zmniejszenie średnicy światła naczynia o >50% ocenionej za pomocą koronarografii z towarzyszącymi objawami i/lub niedokrwiennymi zmianami w badaniu elektrokardiograficznym. Współczynnik filtracji kłębuszkowej (GFR) oszacowano według formuły Cockroft-Gault. Na potrzeby obecnie prowadzonego badania, za niewydolność nerek uznano poziom GFR mniejszy od 60 mL/min. Prędkość przepływu krwi przez tętnice wieńcowe była oceniana angiograficznie z zastosowaniem międzynarodowej czterostopniowej skali TIMI (*Thrombolysis In Myocardial Infarction*) [38]. Zwolniony przepływ w tętnicach wieńcowych (TIMI 2) przyjęto za pośredni wskaźnik dysfunkcji mikrokrążenia. Kryterium wykluczenia była kwalifikacja do rewaskularyzacji wieńcowej, pomostowania aortalno - wieńcowego lub brak wzrostu markerów uszkodzenia mięśnia sercowego, u chorych przyjętych bezpośrednio do hemodynamiki z podejrzeniem AMI.

Punkty końcowe

Punktami końcowymi badania były śmiertelność z jakiejkolwiek przyczyny oraz poważne niepożądane incydenty sercowe (MACE, *major adverse cardiac events*) oraz poważne niepożądane incydenty sercowe i naczyniowo-mózgowe (MACCE, *major adverse cardiac and cerebrovascular events)*. Protokół badania został zatwierdzony przez Komisje Bioetyczną CMUJ, a badanie zostało przeprowadzone zgodnie z zaleceniami Deklaracji Helsińskiej i jej późniejszych modyfikacji. Wszyscy uczestnicy wyrazili pisemną zgodę na przezskórną angiografię wieńcową i/lub przezskórną interwencję wieńcową (PCI, *percutaneous coronary intervention*).

Analiza statystyczna

Zmienne kategorialne prezentowane są w postaci liczb i procentów. Zmienne ciągłe przedstawiono jako średnie oraz odchylenie standardowe lub medianę oraz zakres międzykwartylowy, w zależności od normalności rozkładu. Normalność oceniano testem Shapiro-Wilka. Równość wariancji oceniano za pomocą testu Levene'a. Test U Manna-Whitneya używano dla porównania nienormalnie rozproszonych zmiennych ciągłych. Zmienne kategoryczne porównano z testem Chi2 Pearsona lub dokładnym test Fishera, w przypadku kiedy 20% komórek miało oczekiwany wynik w liczbie mniejszej niż 5 (symulacja Monte Carlo do testu Fishera zastosowano tabele o wyższym wymiarze niż 2 x 2). Wielokrotne porównania grupowe zostały przeprowadzone przy użyciu analizy wariancji lub testu Kruskala-Wallisa. Przedstawiono krzywe przeżycia za pomocą estymatora Kaplana-Meiera i porównano za pomocą testu log-rank. Użyto modeli jednozmiennych i wielozmiennych proporcjonalnego hazardu Coxa do identyfikacji predyktorów MACCE i śmierci. Wszystko analizy statystyczne przeprowadzono przy użyciu programu JMP®, wersja 14.2.0 (SAS Institute INC., Cary, NC, USA). Wszystkie testy statystyczne były dwustronne (poziom $p<0.05$ uznano za istotne statystycznie).

PODSUMOWANIE WYNIKÓW:

Artykuł (1)

W pierwszym artykule dokonano oceny wpływu płci na rokowanie u pacjentów z zawałem serca typu MINOCA oraz identyfikacji czynników wpływających na częstość występowania poważnych niepożądanych zdarzeń sercowo – naczyniowych w tej grupie chorych.

Do badania włączono 134 pacjentów, w tym 78 kobiet hospitalizowanych w Klinice Kardiologii w okresie styczeń 2015 - czerwiec 2018. Wszyscy chorzy spełniali kryteria rozpoznania zawału mięśnia sercowego. W wykonanym badaniu koronarograficznym nie stwierdzono zwężeń ≥ 50% w tętnicach wieńcowych. Średni czas obserwacji wyniósł 609.5 ± 412.2 dnia. Do pierwszorzędowych punktów końcowych należały MACCE oraz zgon z jakiejkolwiek przyczyny. Drugorzędowymi punktami końcowymi były nawracające bóle w klatce piersiowej podczas obserwacji i ponowna hospitalizacja z powodów innych niż MACCE.

Pacjenci z rozpoznaniem MINOCA stanowili 6.75% wśród wszystkich pacjentów przyjętych do pracowni hemodynamiki z rozpoznaniem zawału mięśnia sercowego. MINOCA częściej rozpoznawano u kobiet niż u mężczyzn (11.3% vs 4.7%, p<0,001).

Średni wiek mężczyzn przyjętych z powodu zawału mięśnia sercowego typu MINOCA był znacząco mniejszy niż kobiet (56 ± 41.8 vs 66.6 ± 13.7, p<0.001). Kobiety miały mniejszy wskaźnik masy ciała od mężczyzn (26.4 ± 5.8 kg/m2 vs. 28.1 ± 4.4 kg/m2) ale co ciekawe częściej chorowały z powodu nadciśnienia tętniczego (p=0.04), hiperlipidemii (p=0.03), i niewydolności nerek (p=0.007). Zatrzymanie krążenia w przebiegu zawału mięśnia sercowego typu MINOCA przy przyjęciu było odnotowane tylko u mężczyzn (6 przypadków, p=0.002).

Najczęstszą zdiagnozowaną przyczyną zawału serca typu MINOCA była TTC - 20 chorych (14.9%). U 11 (8.2%) chorych rozpoznano IM, odpowiednio u 16 (11.9 %) i 5 (3.7%) pacjentów wystąpiło niedokrwienie mięśnia sercowego w przebiegu tachyarytmii oraz kryzy

nadciśnieniowej. Zawał typu 2 rozpoznano u 9 (6.7%). U 9 (6.7%) chorych zaobserwowano zwolniony przepływ kontrastu w naczyniach wieńcowych. Odnotowano też pojedyncze przypadki kardiomiopatii przerostowej, powikłań zatorowo-zakrzepowych w przebiegu choroby nowotworowej (3 chorych [2.2%]) oraz choroby zakrzepowo-zatorowej tętnic, zaburzeń przewodnictwa przedsionkowo-komorowego, rozwarstwienia aorty, stenozy aortalnej, zespołu antyfosfolipidowego, dystrofii mięśniowej, udaru mózgu oraz kardiomiopatii alkoholowej (0.7%). W dużej część przypadków nie znaleziono przyczyny prowadzącej bezpośrednio do zawału mięśnia sercowego 50 (37.3%).

Nie znaleziono istotnych różnic w badaniu elektrokardiograficznym względem płci z wyjątkiem ujemnych załamków T, które częściej występowały w zapisie EKG u kobiet niż u mężczyzn (p=0.02). W badaniu echokardiograficznym znacznie częściej obserwowano obniżoną frakcje wyrzutową lewej komory serca < 40% w grupie kobiet (p=0.18). Przerost lewej komory odnotowano częściej w grupie mężczyzn (p=0.12).

Średni czas obserwacji był prawie równy dla mężczyźni i kobiety (609.5 ± 434.7 dnia vs. 609.5 ± 398.1 dnia). Nie stwierdzono istotnych statystycznie różnic między częstością MACCE i zgonów w obydwu grupach chorych, jakkolwiek częstość występowania MACCE i śmiertelność ogólna była większa w grupie kobiet (22.5 % vs 19.2%) oraz (18.6% vs 11.5%). Re-hospitalizacje i nawracające dolegliwości bólowe w klatce piersiowej były zbliżone w obydwu grupach pacjentów (15.9% vs 19.6%) oraz (18.8% vs 19.6%).

Analiza wieloczynnikowa wykazała liczbę leukocytów (współczynnik ryzyka [RR] 1,23; 95% CI 1,08–1,4, p = 0,002), liczbę płytek krwi (RR 0,99; 95% CI 0,98–0,99, p = 0,02), wskaźnik troponiny (RR 1,001; 95% CI 1,0001–1,002, p = 0,029), stężenie hemoglobiny we krwi (RR 0,74; 95% CI 0,55–0,98, p = 0,03), hiperlipidemię (RR 0,06; 95% CI 0,01–0,27, p <0,0001) oraz obniżenie odcinka ST w zapisie EKG przy przyjęciu do szpitala (RR 2,96; 95% CI 1,05–8,88, p = 0,04) jako niezależne czynniki predykcyjne zgonu z przyczyn ogólnych.

Analiza wieloczynnikowa wykazała jako istotne czynniki predykcyjne dla MACCE: indeks troponiny (RR 1,002; 95% CI 1 0005–1,0026, p = 0,004), wiek (RR 1,04; 95% CI 1,008–1,065, p = 0,01), stężenie kreatyniny w surowicy (RR 1,01; 95% CI 1,001–1,01, p = 0,02), hiperlipidemię (RR 0,26; 95% CI 0,07–0,75, p = 0,01) i obecność przebytej choroby zakrzepowo-zatorowej w wywiadzie (RR 8,28; 95% CI 1,15–38, p = 0,04).

Podsumowując, nie stwierdzono istotnego związku płci z rokowaniem i wynikami klinicznymi w okresie obserwacji u pacjentów z rozpoznaniem MINOCA zarówno dla śmiertelności ogólnej jak również dla MACCE i drugorzędowych punktów końcowych.

Artykuł (2)

Celem drugiego artykułu była ocena związku między stężeniem uwolnionej troponiny w trakcie hospitalizacji, a występowaniem niepożądanych zdarzeń sercowo-naczyniowych i śmiertelnością w grupie pacjentów z rozpoznaniem roboczym MINOCA.

W pracy tej badaniem objęto 337 kolejnych pacjentów przyjętych do szpitala z zawałem mięśnia sercowego, u których wykonano koronarografię i nie stwierdzono zwężeń ≥50% w naczyniach wieńcowych w związku z czym postawiono robocze rozpoznanie MINOCA zostało przydzielonych do trzech grup ze względu na stopień wzrostu uwolnionej wysokoczułej troponiny I w trakcie hospitalizacji (wzrost ≤5-krotny w stosunku do górnej granicy normy, wzrost > 5 i ≤20-krotny oraz> 20-krotny). Do punktów końcowych badania należały MACCE oraz zgon z jakiejkolwiek przyczyny. Ze względu na to, że stężenia troponiny we krwi oszacowano za pomocą różnych testów i metod, do porównania wyników wykorzystaliśmy stworzony na użytek tej pracy index troponiny.

Zgodnie z głównym założeniem wszystkich pacjentów podzielono na trzy grupy ze względu na stopień zwiększenia hs-TnI we krwi. Pierwszą grupę stanowiło 87 (25.8%) pacjentów z

łagodnym wzrostem hs-TnI. Do drugiej grupy włączono 77 (22.8%) pacjentów z umiarkowanym wzrostem hs-TnI. Trzecia grupa obejmowała 173 pacjentów (51.3%) z największym zwiększeniem się hs-TnI. Biorąc pod uwagę trzy wybrane grupy pacjentów objętych badaniem, zakres troponiny był odwrotnie skorelowany z wiekiem chorych. Pacjenci z pierwszej grupy byli starsi w porównaniu z pozostałymi dwiema grupami ($p = 0,008$). Jak również byli częściej obciążeni czynnikami ryzyka sercowo-naczyniowego, tj: hiperlipidemia, nadciśnienie tętnicze i cukrzyca.

Odsetek pacjentów przyjętych z rozpoznaniem zawału serca typu STEMI był istotnie większy w trzeciej grupie w porównaniu z pozostałymi dwiema grupami (9.3% vs 11.5% vs 21.4%; $p <0.001$). Pacjenci w pierwszej grupie mieli niższą frakcję wyrzutową lewej komory w porównaniu z grupą drugą i trzecią (43.6±15.8% vs 52.1±11.8% vs 47.8±14.3%; $p<0.001$).

Nie obserwowaliśmy istotnych różnic w obrazie koronarografii z wyjątkiem zjawiska „slow flow phenomenon", które występowało istotnie częściej w trzeciej grupie aniżeli w pozostałych dwóch (2.3% vs 2% vs 11%; $p=0.02$).

U dużej części pacjentów nie udało się jednoznacznie ustalić przyczyny wystąpienia zawału serca, jakkolwiek najwięcej chorych o nieznanej etiologii było w grupie trzeciej (16.1% vs. 23.4% vs. 33.4%; $p<0.001$). Odsetek pacjentów z zawałem mięśnia sercowego typu 2, zaostrzeniem niewydolności serca oraz przełomem nadciśnieniowym był istotnie większy w grupie pierwszej w porównaniu do dwóch pozostałych grup. (43.7% vs 29.8% vs 10.4%, $p<0.001$), (31% vs 3,9% vs 11,5%; $p <0,001$), (8,1% vs. 6,5% vs. 2,3%; $p=0.01$). TTC stwierdzano istotniej częściej w grupie trzeciej w porównaniu z pozostałymi dwoma (0% wobec 5.2% wobec 15.5%; $p<0.001$).

Średni czas trwania obserwacji wynosił 516,1 ± 299,9 dnia i nie różnił się istotnie między grupami (482 ± 173 dni vs. 461 ± 245 dni vs. 566 ± 382 dni). Częstość MACCE we wszystkich trzech grupach wyniosła łącznie 12.1%. Śmiertelność ogólna wynosiła 7.5%, ponowny zawał

mięśnia sercowego wystąpił u 9.5% chorych, 1.1% pacjentów wymagało ponownej przezskórnej angioplastyki wieńcowej. U niewielkiego odsetka chorych wystąpił udar lub przejściowe niedokrwienie mózgu (1.1%). Ogólna częstość występowania MACCE w poszczególnych grupach była istotnie większa w grupie z największym wzrostem troponiny w porównaniu z pozostałymi dwoma (4.6% vs 9.4% vs 18.4%; p=0.005). Śmiertelność była również istotnie większa w trzeciej grupie w porównaniu z pierwszą i drugą (1.1% wobec 4% wobec 13.1%; p=0.001).

Analiza wieloczynnikowa pozwoliła zidentyfikować następujące czynniki predykcyjne zwiększonej śmiertelności: zatrzymanie krążenia przy przyjęciu, wysięk osierdziowy i wiek. Wśród istotnych predyktorów mniejszej śmiertelność potwierdziliśmy: ból w klatce piersiowej przy przyjęciu, nadciśnienie tętnicze i większą liczbę płytek krwi.

Natomiast wśród czynników predykcyjnych związanych ze zwiększonym ryzykiem MACCE potwierdziliśmy: wyższe stężenie kreatyniny w surowicy, zwiększoną liczbę leukocytów we krwi i nadużywanie alkoholu. Wśród istotnych czynników mniejszego ryzyka wystąpienia MACCE wyodrębniono: hiperlipidemie i zwiększone stężenie hemoglobiny we krwi.

Podsumowując, pacjenci z zawałem serca typu MINOCA oraz z największym wzrostem hs-TnI w trakcie hospitalizacji cechują się najwyższym odsetkiem śmiertelności. Podobny związek odnotowano dla występowania MACCE w grupie chorych z największym wzrostem hs-TnI, jednak bez istotności statystycznej. Mimo że hipercholesterolemia i zwiększone stężenie cholesterolu LDL w surowicy jest znanym czynnikiem ryzyka zawału serca typu MI-CAD oraz występowania MACCE, to w przypadku pacjentów z MINOCA jest on związany z mniejszą śmiertelnością ogólną i mniejszym ryzykiem wystąpienia MACCE w obserwacji długoterminowej. Zjawisko to było już opisywane i zostało nazwane „paradoksem hipercholesterolemii". Choć nie znamy jeszcze jednoznacznie etiologii tego paradoksu, to wydaje się, że w tej grupie chorych zwiększone stężenie cholesterolu w surowicy krwi ma

korzystny wpływ na rokowanie odległe w tej grupie chorych. Mimo, że istnieje związek między maksymalnym stężeniem uwolnionej troponiny, śmiertelnością i częstością MACCE w grupie pacjentów MINOCA, należy pamiętać, że wyodrębniliśmy szereg innych czynników mających związek z rokowaniem m.in. te związane z etologią zawału serca.

Artykuł (3)

Celem trzeciej publikacji było porównanie cech klinicznych, rokowania oraz identyfikacja czynników prognostycznych dla występowania MACCE i śmiertelności w grupie pacjentów leczonych z powodu MINOCA, zawału typu STEMI ściany przedniej, TTC oraz zapalenia mięśnia sercowego (IM).

Badanie zostało przeprowadzono na grupie 596 pacjentów przyjętych do szpitala z powodu: zawału mięśnia sercowego typu MINOCA oraz zawału serca ściany przedniej typu STEMI. Następnie z grupy pacjentów z roboczym rozpoznaniem MINOCA zostali wyłonieni chorzy z IM oraz TTC.

Pierwszorzędowe punkty końcowe zostały określone jako śmiertelność ogólna z jakichkolwiek przyczyn oraz MACCE. Śmiertelność oraz MACCE zostały ocenione po 30 dniach, 12 miesiącach oraz 36 miesiącach od wyjściowego incydentu sercowego.

Spośród 596 pacjentów objętych analizą, 318 pacjentów było z rozpoznaniem MINOCA, 31 z TTC, 22 z IM i 225 z zawałem STEMI ściany przedniej. Średni wiek pacjentów wynosił 63.3±13.8 lat. Najmłodsi pacjenci znajdowali się w grupie IM 43.7±16.2, najstarsi w grupie TTC 70.7 ±13, natomiast średni wiek pacjentów w grupie MINOCA i grupie STEMI: był bardzo zbliżony i wynosił odpowiednio 65.1±13.4 i 61.6±12.2 ($p<0.001$). Najwyższe wartości troponiny odnotowano w grupie pacjentów z zawałem STEMI ściany przedniej, natomiast najniższe w grupie pacjentów MINOCA. Pacjenci z zawałem STEMI ściany przedniej częściej chorowali z powodu hipercholesterolemii oraz cukrzycy w porównaniu do pozostałych. Chorzy

z grupy MINOCA częściej byli leczeni z powodu nadciśnienia tętniczego. Pacjenci z grupy TTC i STEMI ściany przedniej mieli istotnie niższą frakcję wyrzutową lewej komory serca w porównaniu z pacjentami z grupy MINOCA i IM ($p<0.001$). Najczęstszym dostępem naczyniowym w grupie pacjentów ze STEMI był dostęp udowy, natomiast w pozostałych grupach pacjentów przeważał dostęp promieniowy.

Śmiertelność z jakiekolwiek przyczyny nie różniła się istotnie statystycznie pomiędzy badanymi grupami w kolejnych punktach czasowych. Analizując częstość MACCE w poszczególnych grupach, największa częstość występowania MACCE po 30 dniach została zaobserwowana w grupie TCC (7.4%) oraz STEMI (6.7%), jakkolwiek bez znamienności statystycznej. Po roku oraz po trzech latach obserwacji częstość występowania MACCE zwiększyła się i była znamiennie statystycznie największa w grupie pacjentów ze STEMI ściany przedniej.

Podsumowując, podczas 3-letniego okresu obserwacji pacjenci ze STEMI ściany przedniej mieli znacznie gorszą prognozę pod względem częstości występowania MACCE w porównaniu do grup TTC, IM i MINOCA. Analiza pozwoliła na porównanie wyników leczenia pomiędzy wybranymi grupami pacjentów ograniczonych do dwóch ośrodków akademickich i konfrontacji ich z wynikami innych badań,\. Badanie pomogło także na identyfikację podgrupy pacjentów z najgorszym rokowaniem oraz predyktorów(czynników wpływających na wyniki?) wyników leczenia w wybranych grupach chorych. Dane lokalne często znacznie różnią się od danych uzyskanych w badaniach wieloośrodkowych , co pozwala dostosować opiekę nad pacjentami w wybranych grupach chorych a tym samym poprawiając efekty leczenia w dedykowanych centrach.

BIBLIOGRAFIA:

1. Falk E, Nakano M, Bentzon JF, et al. Update on acute coronary syn-dromes: the pathologists' view. Eur Heart J. 2013; 34: 719–728.

2. Larsen AI, Galbraith PD, William A Ghali et al. Characteristics and outcomes of patients with acute myocardial infarction and angiographically normal coronary arteries. Am J Cardiol. 2005; 95: 261-263.

3. Planer D, Mehran R, Ohman EM et al. Prognosis of patients with non-ST-segment-elevation myocardial infarction and nonobstructive coronary artery disease: propensity-matched analysis from the Acute Catheterization and Urgent Intervention Triage Strategy trial. Circ Cardiovasc Interv. 2014; 7: 285-293.

4. Gehrie ER1, Reynolds HR, Chen AY et al. Characterization and outcomes of women and men with non-ST-segment elevation myocardial infarction and nonobstructive coronary artery disease: results from the Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes with Early Implementation of the ACC/AHA Guidelines (CRUSADE) quality improvement initiative. Am Heart J. 2009; 158: 688-694.

5. Gross H, William H. Sternberg, M.D. Myocardial infarction without significant lesions of coronary arteries. Arch Intern Med (Chic). 1939; 64: 249-267.

6. Beltrame JF. Assessing patients with myocardial infarction and non-obstructed coronary arteries (MINOCA). J Intern Med. 2013; 273: 182–185.

7. Pasupathy S, Air T, Dreyer RP, Tavella R, Beltrame JF. Systematic review of patients presenting with suspected myocardial infarction and nonobstructive coronary arteries. Circulation. 2015; 131: 861-870.

8. Dreyer RP, Tavella R, Curtis JP et al. Myocardial infarction with non-obstructive coronary arteries as compared with myocardial infarction and obstructive coronary disease: outcomes in a Medicare population. Eur Heart J. 2020; 41: 870-878.

9. Nordenskjöld AM, Baron T, Eggers KM, et al. Predictors of adverse outcome in patients with myocardial infarction with non-obstructive coronary artery (MINOCA) disease. Int J Cardiol. 2018; 261: 18–23.

10. Thygesen K, Alpert JS, Jaffe AS, et al; Executive Group on behalf of the Joint European Society of Cardiology (ESC)/American College of Cardiology (ACC)/American Heart Association (AHA)/World Heart Federation (WHF) Task Force for the Universal Definition of Myocardial Infarction. Fourth Universal Definition of Myocardial Infarction (2018). Circulation. 2018; 138: e618-e651.

11. Agewall S, Beltrame JF, Reynolds HR et al. ESC working group position paper on myocardial infarction with non-obstructive coronary arteries. Eur Heart J. 2017; 38: 143-153.

12. Safdar B, Spatz ES, Dreyer RP et al. Presentation, Clinical Profile, and Prognosis of Young Patients With Myocardial Infarction With Nonobstructive Coronary Arteries (MINOCA): Results From the VIRGO Study. J Am Heart Assoc. 2018; 7: e009174.

13. Ballesteros-Ortega D, Martínez-González O, Gómez-Casero RB et al. Characteristics of patients with myocardial infarction with nonobstructive coronary arteries (MINOCA) from the ARIAM-SEMICYUC registry: development of a score for predicting MINOCA. Vasc Health Risk Manag. 2019; 15: 57-67.

14. Rakowski T, De Luca G, Siudak Z et al. Characteristics of patients presenting with myocardial infarction with non-obstructive coronary arteries (MINOCA) in Poland: data from the ORPKI national registry. J Thromb Thrombolysis. 2019; 47: 462-466.

15. Pustjens TFS, Appelman Y, Damman P et al. Guidelines for the management of myocardial infarction/injury with non-obstructive coronary arteries (MINOCA): a position paper from the Dutch ACS working group. Neth Heart J. 2020; 28: 116–130.

16. Montone RA, Niccoli G, Russo M et al. Clinical, angiographic and echocardiographic correlates of epicardial and microvascular spasm in patients with myocardial ischaemia and non-obstructive coronary arteries. Clin Res Cardiol. 2020; 109: 435-443.

17. Munusamy V, Sriram V, Elumalai DV. Coronary computed tomography angiography in patients with myocardial infarction and non-obstructed coronary arteries. International Archives of Integrated Medicine. 2019; 6, 8.

18. Ouldzein H, Elbaz M, Roncalli J et al. Plaque rupture and morphological characteristics of the culprit lesion in acute coronary syndromes without significant angiographic lesion: analysis by intravascular ultrasound. Ann Cardiol Angeiol (Paris). 2012; 61: 20–26

19. Reynolds HR, Srichai MB, Iqbal SN et al. Mechanisms of myocardial infarction in women without angiographically obstructive coronary artery disease. Circulation. 2011; 124: 1414–1425.

20. Alasnag M, Jelani Q, Johnson TW et al. The Role of Imaging for MINOCA (Myocardial Infarction with No Obstructive Coronary Artery Disease): a Review of Literature and Current Perspectives. Current Cardiovascular Imaging Reports. 2020; 13, 21.

21. Gatti M, Carisio A, D'Angelo T et al. Cardiovascular magnetic resonance in myocardial infarction with non-obstructive coronary arteries patients: A review. World J Cardiol. 2020; 12: 248–261.

22. Reynolds HR, Maehara A, Kwong RY, et al. Coronary Optical Coherence Tomography and Cardiac Magnetic Resonance Imaging to Determine Underlying Causes of Myocardial Infarction With Nonobstructive Coronary Arteries in Women. Circulation. 2021; 143: 624-640.

23. Leurent G, Langella B, Fougerou C, et al. Diagnostic contributions of cardiac magnetic resonance imaging in patients presenting with elevated troponin, acute chest pain syndrome and unobstructed coronary arteries. Arch Cardiovasc Dis. 2011; 104: 161-170.

24. Stepien K, Nowak K, Wypasek E et al. High prevalence of inherited thrombophilia and antiphospholipid syndrome in myocardial infarction with non-obstructive coronary arteries: Comparison with cryptogenic stroke. Int J Cardiol. 2019; 290: 1-6.

25. Ponikowski P, Voors AA, Anker SD et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur J Heart Fail. 2016; 18:891-975.

26. Scalone G, Niccoli G, Crea F et al. Editor's Choice- Pathophysiology, diagnosis and management of MINOCA: an update. Eur Heart J Acute Cardiovasc Care. 2019; 8: 54-62.

27. Sá FM, Carvalho R, Santos L et al. Dual antiplatelet therapy in myocardial infarction with non-obstructive coronary artery disease - insights from a nationwide registry. Rev Port Cardiol. 2020; 39: 679-684.

28. Bossard M, Gao P, Boden W et al. Antiplatelet therapy in patients with myocardial infarction without obstructive coronary artery disease. Heart. 2021; heartjnl-2020-318045.

29. Ciliberti G, Verdoia M, Merlo M et al. Pharmacological therapy for the prevention of cardiovascular events in patients with myocardial infarction with non-obstructed coronary arteries (MINOCA): Insights from a multicentre national registry. Int J Cardiol. 2020; S0167-5273(20)34163-2.

30. Pelliccia F, Pasceri V, Niccoli G et al. Predictors of Mortality in Myocardial Infarction and Nonobstructed Coronary Arteries: A Systematic Review and Meta-Regression. Am J Med. 2020; 133: 73-83.e4.

31. Pizzi C, Xhyheri B, Costa GM et al. Nonobstructive Versus Obstructive Coronary Artery Disease in Acute Coronary Syndrome: A Meta-Analysis. J Am Heart Assoc. 2016; 5: e004185.

32. Planer D, Mehran R, Ohman EM et al. Prognosis of patients with non-ST-segment-elevation myocardial infarction and nonobstructive coronary artery disease: propensity-matched analysis from the Acute Catheterization and Urgent Intervention Triage Strategy trial. Circ Cardiovasc Interv. 2014; 7: 285-293.

33. Lopez-Pais J, Izquierdo Coronel B, Galán Gil D et al. Clinical characteristics and prognosis of myocardial infarction with non-obstructive coronary arteries (MINOCA): A prospective single-center study. Cardiol J. 2020.

34. Dreyer RP, Tavella R, Curtis JP et al. Myocardial infarction with non-obstructive coronary arteries as compared with myocardial infarction and obstructive coronary disease: outcomes in a Medicare population. Eur Heart J. 2020; 41: 870-878.

35. Ibanez B, James S, Agewall S, et al. ESC Scientific Document Group. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: the task force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). Eur Heart J 2018; 39: 119-77.

36. Roffi M, Patrono C, Collet JP, et al. ESC Scientific Document Group. 2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: task force for the management of acute coronary syndromes in patients presenting without persistent ST-Segment elevation of the European Society of Cardiology (ESC). Eur Heart J 2016; 37: 267-315.

37. Tsuchihashi, K. Angina pectoris-myocardial infarction investigations in Japan. Transient left ventricular apical ballooning without coronary arterystenosis: A novel heart syndrome mimicking acute myocardial infarction. Angina pectoris-myocardial infarction investigations in Japan. J Am Coll Cardiol 2001; 38: 11-18.

38. Gibson CM, Cannon CP, Daley WL, et al. TIMI frame count: a quantitative method of assessing coronary artery flow. Circulation 1996; 93: 879-888.

3. Podsumowanie pracy doktorskiej w języku angielskim

INTRODUCTION

Coronary artery disease is mainly related to the formation of atherosclerotic plaques in the coronary arteries. The rupture of atherosclerotic plaques, causing thrombosis in the vessel lumen as well as its spasm. This is the most common cause of myocardial infarction [1]. In approximately 3-10% of patients, myocardial infarction occurs without significant narrowing of the coronary arteries [2-4]. The first research papers in which cases of patients with myocardial infarction with non-obstructive coronary arteries were reported appeared more than 80 years ago and started to spread more and more along with the development of the coronary angiography diagnostic technique [5]. Nevertheless, the term MINOCA (myocardial infarction with non-obstructive coronary arteries) appeared in the scientific literature in the last decade [6]. Due to the number of patients with myocardial infarction in whom no significant stenosis was found during coronary angiography [7,8] and poor long-term prognosis [9], this topic has become very popular in recent years in both world and Polish cardiology.

We can diagnose myocardial infarction without significant stenosis in the coronary arteries using the criteria of the fourth definition of myocardial infarction, which is established according to the current position of the European Society of Cardiology (ESC) and the absence of stenosis in the coronary artery $\geq$ 50% in the performed angiography of the coronary arteries [10]. In recent years, an expert opinion has appeared on the recommended methods of diagnosis, identification of potential etiology and conducting diagnostics in patients from this group [11]. The variety of causes in the group of patients diagnosed with MINOCA poses a major diagnostic challenge for cardiologists, which is gaining importance in light of the possibilities for improving the poor prognosis of patients from this group at baseline. Among the causes of MINOCA, we can distinguish conditions associated with diseases of the coronary arteries, myocardium or non-cardiac. Among non-cardiac causes, we may further distinguish those

related with type 2 myocardial infarction as an effect of an imbalance between the supply of oxygen and its demand, e.g. in the course of kidney damage, sepsis, acute respiratory distress syndrome (ARDS) or pulmonary embolism. The causes related to the pathology of the coronary vessels include: coronary spasm, ruptured plaque, coronary artery dissection, coronary microcirculation dysfunction as well as distal embolisation. The causes of heart muscle damage include: Taktsubo cardiomyopathy (TTC), infective myocarditis (IM) and other cardiomyopathies [11]. Given the often heterogenous etiology, a working diagnosis of MINOCA can be made until the diagnostics is extended. For example, IM is diagnosed in up to 33% of patients and is by far the most common cause responsible for MINOCA infarction [7]. Rupture of atherosclerotic plaque with transient thrombosis and spontaneous fibrinolysis is one of the most common causes of coronary artery pathology [12]. In clinical practice, patients with type 2 myocardial infarction are more often in a severe clinical condition. In such situation, the therapeutic priority is to reverse the state of imbalance underlying the disproportion between the supply of oxygen and its demand. The most common conditions responsible for type 2 myocardial infarction include: anemia, tachy- and brady-arrhythmias, respiratory failure, hypotension, shock, severe hypertension with or without left ventricular hypertrophy, severe aortic valve disease, heart failure and harmful the effects of toxins (e.g. sepsis or carbon monoxide poisoning).

Taking the research results available into account so far, the percentage of MINOCA in women compared to myocardial infarction with obstructive coronary disease (MI-CAD) is higher than in men. Patients in the MINOCA group are younger, and their mean age in various studies ranges from 55 to 63 years [13, 14].

It should also be noted that MINOCA is a working diagnosis and obliges us to extend the diagnosis and look for the cause of acute myocardial ischemia. Echocardiographic examination of the heart is the most accessible and the fastest to perform, already at the stage

of admission. Transthoracic echocardiography is one of the first tests recommended in the diagnostic pathway among patients diagnosed with MINOCA. Thanks to it, we can assess the contractility of the left ventricle, including segmental contractility disorders, the thickness of the walls and the size of the left ventricle, the presence of fluid in the pericardial sac, the presence of vegetation on the heart valves, and the assessment of the presence and significance of valvular defects, calcifications or thrombi in the heart cavities. Echocardiography can help identify thromboembolic complications, myocarditis or TTC as the cause of MINOCA [11, 15, 16]. Another non-invasive examination that allows for a very accurate assessment of coronary pathology is computed tomography. This examination makes it possible to exclude significant stenosis of the coronary arteries, the presence of calcifications, dissection and the assessment of anatomy anomalies [17]. Computed tomography is the gold standard in the diagnosis of pulmonary embolism and aortic dissection. Intravascular imaging is one of the most important methods of extending MINOCA diagnostics. Intravascular ultrasound (IVUS) and optical coherence tomography (OCT) allow for a detailed assessment of the vessel wall, including imaging of ruptured atherosclerotic plaques, dissections, thrombi and hematomas. Some studies indicate that atherosclerotic plaque ruptured may be the cause of up to 40% of myocardial infarctions without significant narrowing of the coronary vessels [18, 19]. OCT or IVUS are one of the methods recommended in the diagnosis of patients admitted to the hemodynamics catheterisation laboratory (CathLab) with the diagnosis of myocardial infarction, in whom the standard angiogram of the coronary arteries showed no significant changes [11]. Other problems include the assessment of the microcirculation function. The available techniques allow the assessment of the coronary flow reserve (CFR) as well as the index of microcirculatory resistance (IMR), which allows the diagnosis of coronary microcirculation dysfunction. Coronary microcirculation dysfunction is considered an important mechanism of myocardial ischemia, it occurs in a large percentage of patients with or without coronary

disease, and is associated with both chronic and acute coronary syndromes [15]. Due to the increasing number of patients without significant stenosis of the coronary arteries and persistent symptoms of myocardial ischemia, more and more attention is paid to the correct diagnosis of vasospastic angina. Tests with coronary ergonovine or acetylcholine administration are safe and can help to make an appropriate diagnosis. As a rule, nitroglycerin is the most frequently administered coronary drug when vasospastic angina is suspected. Cardiac magnetic resonance (CMR) is a key diagnostic tool in patients with MINOCA. The presence of late gadolinium enhancement (LGE) in CMR allows us to locate myocardial damage and to provide insight into the damage mechanism. The area of late post-contrast enhancement in the subendocardium suggests an ischemic cause of damage, although it does not directly indicate the mechanism of ischemia (ruptured plaque, spasm or dissection of the vessel). On the other hand, the subepicardial localization suggests cardiomyopathy. The absence of ischemic LGE may also support the diagnosis of myocarditis or infiltrative disease. CMR may also be helpful in visualizing myocardial edema and assessing systolic function [20,21]. CMR enables the diagnosis of a potential cause of myocardial infarction in approximately 74.2-89.7% of patients [22, 23]. Based on the results of studies published so far, it has been shown that in most cases CMR allowed the diagnosis of myocarditis as the most common cause of MINOCA. TTC was the second most common cause of MINOCA. Ischemic aetiology turned out to be the cause of MINOCA in several to several percent [22,23]. In addition to extensive imaging diagnostic methods, in the diagnosis of MINOCA, it is important to perform a full panel of laboratory blood tests that may allow the diagnosis of type 2 infarction. In young people hospitalized for MINOCA, tests for blood coagulation disorders should be performed [11]. It may turn out to be the cause of acute myocardial ischemia in up to 24% of cases [24].

Accurate diagnosis and establishing an unequivocal cause of MINOCA is essential for proper therapy. There are still no standardized guidelines regarding pharmacological treatment

in patients diagnosed with MINOCA. Therapy should be adjust to each patient depending on the most likely cause leading to myocardial infarction. For example, in myocarditis, patients do not require standard anti-ischemic therapy. In the case of myocarditis with impaired systolic function of the left ventricle, the most favorable results are obtained with the use of beta-blockers and angiotensin converting enzyme inhibitors (ACEI). Medications typically used in stress cardiomyopathy are similar to these used in the treatment of heart failure, including loop diuretics, beta-blockers and the avoidance of drugs from the sympathomimetic group. Treatment choice depending on the course of the acute phase. For example, in the event of cardiogenic shock, consider the use of left ventricle assist devices (LVAD), such as intra-aortic balloon counterpulsation (IABP) [25]. Another example is the type of treatment when coronary spasm is the most likely cause of a myocardial infarction. Then, the appropriate management are calcium channel blockers [26, 27]. There is still no hard evidence of the benefits of using dual antiplatelet therapy (DAPT) in patients with unidentified cause of myocardial infarction. In any event, the choice of treatment should take into account the risk of thromboembolic and haemorrhagic complications. The therapy and its length should be adjust to the patient. It seems that DAPT therapy may be beneficial in patients with previous coronary interventions. Undoubtedly, pharmacotherapy with DAPT is obligatory for one year in patients with strong suspicion or confirmed presence of ruptured plaque [27-29]. Patients in the MINOCA group have a relatively better prognosis than patients with MI-CAD. The annual total mortality in the group of MINOCA patients is according to various reports approx. 2.4 - 4.7% [30,31]. Some of the available studies showed higher mortality in the MINOCA group, however it was mainly associated with higher non-cardiac mortality [32]. It has been shown that in the group of MI-CAD patients, re-hospitalization and the need for coronary revascularization are more frequent [32]. Adverse cardiovascular events occur in the MINOCA group with the frequency of approximately 10.7-18.7% in one-year follow-up [33, 34].

OBJECTIVES

1. Characteristics of patients admitted with acute myocardial infarction with non-obstructive coronary arteries.

2. Assessment of the most common causes and mechanisms of MINOCA and analysis of long-term risk factors

3. Comparison of the prognosis of the patients with MINOCA to the patients with other selected syndromes with acute myocardial injury and necrosis.

HYPOTHESES

1. Male gender is not a less dominant prognostic factor in the group of patients with MINOCA myocardial infarction than in the group of patients presenting myocardial infarction with significant stenosis in the coronary arteries.

2. The influence of high-sensitive troponin blood concentration on the incidence of adverse cardiovascular events and mortality in the group of patients with a working diagnosis of MINOCA is not as strong as in the group of patients demonstrating myocardial infarction with significant stenosis in the coronary arteries.

3. Patients with MINOCA myocardial infarction have a better prognosis compared to patients with myocardial infarction presenting ST segment elevation, significant stenosis of the coronary arteries, and patients with TTC or IM.

Material and methods

The study included patients who were admitted to the CathLab of the University Hospital in Kraków and the CathLab of the Cardiology Department of the Upper Silesian Medical Centre in Ochojec in 2015-2019 with suspected myocardial infarction and no stenosis ≥50% in the coronary arteries, as well as a working diagnosis of MINOCA. Additionally, in order to conduct

a comparative analysis, the group of patients admitted with the diagnosis of acute myocardial infarction presenting ST-segment elevation (STEMI, ST-segment elevation myocardial infarction) was taken into account. Anthropometric, demographic, clinical and current pharmacological treatment data were collected on admission to the hospital, based on a detailed interview with the patient and on the provided medical documentation. Pharmacological and interventional treatment was carried out in accordance with the recommendations of the current guidelines of the European Society of Cardiology [35, 36]. Long-term follow-up was conducted during follow-up visits at the clinical cardiology clinic or by telephone.

Definitions

A working diagnosis of individual types of ACS (myocardial infarction with ST segment elevation and non-ST segment elevation myocardial infarction) is the concept used in this study for patients admitted to the department and qualified for coronary angiography. In all patients, the final diagnosis of myocardial infarction was made according to the fourth universal definition of myocardial infarction and the position of the MINOCA working group published by the European Society of Cardiology [10,11]. A working diagnosis of MINOCA was made immediately after coronary angiography, when there was no significant stenosis of the coronary arteries and there were no indications for further revascularization. In the following days of hospitalization, the diagnosis was changed in some patients based on the overall clinical picture, the results of imaging tests and the results of blood chemistry. The presented etiology was established by the end of hospitalization and was not considered definitive, but the most probable, due to the fact that some tests, e.g. cardiac magnetic resonance imaging, blood tests (thrombophilia test package) or cancer tests (positron emission tomography) were performed after discharge from hospital and were not included in the final etiology for various reasons. The final diagnosis was made on the patient's discharge card from the cardiology department,

which was based on the entire clinical picture and the results of the tests collected up to the time of the patient's discharge from the hospital.

In order to standardize the results of cardiac troponin determinations, the so-called troponin index, which was assumed to be the quotient of its maximum concentration and the upper limit of normal. The range was referenced for a specific test. As mentioned earlier, the diagnosis of acute myocardial infarction was made in accordance with the fourth universal definition of myocardial infarction published by the European Society of Cardiology [10,11]. Also, type 2 myocardial infarction and its individual etiology were determined according to current guidelines and the recommended consensus [10, 11].

Non-significant stenosis was defined as a coronary angiography stenosis of less than 50% and was confirmed in at least two projections. Atherosclerotic plaque was defined as eccentric when the atherosclerotic plaque did not extend to the circumference of the entire coronary artery. Autoimmune and oncological diseases were considered based on the medical documentation provided by the patient. TTC was diagnosed according to generally accepted recommendations after echocardiography [37]. Coronary artery spasm was defined as a reduction in vessel lumen diameter of> 50% as assessed by coronary angiography accompanied by symptoms and / or ischemic electrocardiographic changes. The glomerular filtration rate (GFR) was estimated according to the Cockroft-Gault formula. For the purposes of the current study, renal failure was considered a GFR level lower than 60 mL / min. The velocity of blood flow through the coronary arteries was assessed angiographically using the international four-level TIMI scale (Thrombolysis In Myocardial Infarction) [38]. The slow flow in the coronary arteries (TIMI 2) was taken as an indirect indicator of microcirculation dysfunction. The exclusion criterion was qualification for coronary revascularization, aorto-coronary bypass surgery, or no increase in markers of myocardial damage in patients admitted directly to hemodynamics with suspected AMI.

Study endpoints

Study endpoints were all-cause mortality and major adverse cardiac events (MACE), as well as major adverse cardiac and cerebrovascular events (MACCEs). The study protocol was approved by the local Bioethics Committee, and the study was conducted in accordance with the recommendations of the Declaration of Helsinki and its subsequent modifications. All participants provided their written consent to undergo the percutaneous coronary intervention (PCI) and/or the percutaneous coronary intervention.

Statistical analysis

Categorical variables are presented as numbers and percentages. Continuous variables are presented as mean and standard deviation or median and interquartile range, depending on the normality of the distribution. Normality was assessed using the Shapiro-Wilk test. Equality of variance was assessed via Levene's test. The Mann-Whitney U test was applied to compare abnormal distributed continuous variables. Categorical variables were compared with Pearson's Chi2 test or Fisher's exact test when 20% of the cells had an expected result of less than 5 (Monte Carlo simulation for Fisher's test tables larger than 2x2 were used). Multiple group comparisons were performed using analysis of variance or the Kruskal-Wallis test. Survival curves are presented using the Kaplan-Meier estimator and compared implementing the log-rank test. Univariate and multivariate Cox proportional hazards models were applied to identify MACCE and death predictors. All statistical analyses were performed using JMP®, version 14.2.0 (SAS Institute INC., Cary, NC, USA). All statistical tests were two-sided ($p<0.05$ was considered statistically significant).

SUMMARY OF RESULTS:

Article (1)

In the first article, the influence of gender on the prognosis of patients with MINOCA myocardial infarction was assessed, and identification of factors influencing the incidence of serious adverse cardiovascular events in this group of patients was performed.

The study comprised 134 patients, including 78 women hospitalised at the Department of Cardiology in the period from January 2015 to June 2018. All patients met the criteria for MI diagnosis. In the performed coronary angiography, no stenosis of ≥ 50% was found in the coronary arteries. The mean follow-up time was 609.5 ± 412.2 days. The primary endpoints included MACCE and all-cause death. Secondary endpoints were recurrent chest pain during follow-up and rehospitalisation for reasons other than MACCE.

Patients diagnosed with MINOCA constituted 6.75% of all patients admitted to the CathLab with a diagnosis of MI. MINOCA was diagnosed more often in women than in men (11.3% vs. 4.7%, $p<0.001$).

The mean age of the men admitted for MINOCA was significantly lower than that of women (56 ± 41.8 vs. 66.6 ± 13.7, $p<0.001$). Women had a lower body mass index than men (26.4 ± 5.8 kg/m^2 vs. 28.1 ± 4.4 kg/m^2), but interestingly, they more often they suffered from arterial hypertension ($p=0.04$), hyperlipidaemia ($p=0.03$) and renal failure ($p=0.007$). Cardiac arrest in the course of MINOCA at admission was reported only in men (6 cases, $p=0.002$).

The most commonly diagnosed cause of MINOCA was TTC - 20 patients (14.9%). In 11 (8.2%) patients IM was diagnosed; 16 (11.9%) and 5 (3.7%) patients, respectively, developed myocardial ischemia in the course of tachyarrhythmia and hypertensive crisis. Type 2 infarction was diagnosed in 9 (6.7%). In 9 (6.7%) patients, the slow-flow phenomenon was observed. There were also isolated cases of hypertrophic cardiomyopathy, thromboembolic complications in the course of neoplastic disease (3 patients [2.2%]) and arterial thromboembolism, atrioventricular conduction disorders, aortic dissection, aortic stenosis, antiphospholipid syndrome, muscular dystrophy, stroke and alcoholic cardiomyopathy (0.7%).

In most cases, no causes leading directly to myocardial infarction were found 50 (37.3%). No significant gender-related differences were noted in electrocardiography, except for negative T waves, which were more common on the ECG in women than in men (p=0.02). Echocardiography showed a significantly more frequent reduction in left ventricular ejection fraction of <40% in the female group (p=0.18). Left ventricular hypertrophy was reported more frequently in the male group (p=0.12).

The mean follow-up period was almost equal for males and females (609.5 ± 434.7 days vs. 609.5 ± 398.1 days). There were no statistically significant differences between the MACCE frequency and deaths in either group of patients, although the MACCE frequency and all-cause mortality were higher in the group comprising women (22.5% vs. 19.2% and 18.6% vs. 11.5%, respectively). Re-hospitalisations and recurrent chest pain were similar in both patient groups (15.9% vs. 19.6% and 18.8% vs. 19.6%).

Multivariate analysis showed leukocyte counts (hazard ratio [RR] 1.23; 95% CI 1.08–1.4, p=0.002), platelet count (RR 0.99; 95% CI 0.98–0.99, p=0.02), troponin index (RR 1.001; 95% CI 1.0001–1.002, p=0.029), blood haemoglobin concentration (RR 0.74; 95% CI 0.55–0.98, p=0.03), ECG depression at admission to hospital (RR 2.96; 95% CI 1.05–8.88, p=0.04) and hyperlipidaemia (RR 0.06; 95% CI 0.01–0.27, p<0.0001) as independent all-cause predictors of death.

Multivariate analysis also demonstrated the following significant predictors for MACCE: troponin index (RR 1.002; 95% CI 1,0005–1.0026, p=0.004), age (RR 1.04; 95% CI 1.008–1.065, p=0.01), serum creatinine concentration (RR 1.01; 95% CI 1.001–1.01, p=0.02), hyperlipidaemia (RR 0.26; 95% CI 0.07–0.75, p=0.01) and a history of thromboembolism (RR 8.28; 95% CI 1.15–38, p=0.04).

In conclusion, there were no significant relationships between gender and prognosis expressed as clinical outcomes during the follow-up period in patients diagnosed with MINOCA for both overall mortality as well as for MACCE and secondary endpoints.

Article (2)

The aim of the second article was to assess the relationship between the concentration of released troponin during hospitalisation and the occurrence of major adverse cardiovascular events (MACCE) and overall mortality in a group of patients with a working diagnosis of MINOCA.

The study included 337 consecutive patients admitted to hospital with MI, who had undergone coronary angiography and no stenosis of ≥ 50% in the coronary vessels, therefore, a working diagnosis was made, MINOCA was assigned to 3 groups due to the degree of increase in the released highly-sensitive troponin I levels during hospitalisation (increase of ≤ 5 times the upper limit of the norm, > 5 and ≤ 20 times, and> 20 times). Study endpoints included MACCE and all-cause death. Due to the fact that troponin levels were estimated using various tests and methods, we used the Troponin index created for this work to compare the results.

In line with the main assumption, all patients were divided into 3 groups according to the degree of increase in hs-TnI in the blood. The first group consisted of 87 (25.8%) patients with a mild increase in hs-TnI. The second group included 77 (22.8%) patients with moderate increases in hs-TnI. The third group comprised 173 patients (51.3%) with the greatest increase in hs-TnI. Taking the 3 selected groups of patients included in the study into account, the level of troponin was inversely correlated with the age of the patients. The patients in the first group were older compared to the other 2 groups (p=0.008). They were also more frequently burdened with cardiovascular risk factors such as hyperlipideamia, hypertension and diabetes.

The percentage of patients admitted with a STEMI MI diagnosis was significantly higher in the third group compared to the other 2 groups (9.3% vs. 11.5% vs. 21.4%, $p<0.001$). Patients in the first group had lower left ventricular ejection fraction compared to the second and third groups (43.6 ± 15.8% vs. 52.1 ± 11.8% vs. 47.8 ± 14.3%, $p<0.001$).

We did not observe any significant differences in the coronary angiography image, with the exception of the "slow flow phenomenon", which occurred significantly more often in the third group than in the other 2 (2.3% vs. 2% vs. 11%, $p=0.02$).

In a large proportion of patients, the cause of MI could not be clearly established, although the largest number of patients with unknown etiology was in the third group (16.1% vs. 23.4% vs. 33.4%, $p<0.001$). The percentage of patients with type 2 MI, exacerbation of heart failure and hypertensive crisis was significantly higher in the first group compared to the remaining 2 groups (43.7% vs. 29.8% vs. 10.4%, $p<0.001$; 31% vs. 3.9% vs. 11.5%, $p<0.001$; 8.1% vs. 6.5% vs. 2.3 %, $p=0.01$). TTC was found more often in the third group compared to the other 2 (0% vs. 5.2% vs. 15.5%, $p<0.001$).

The mean duration of the follow-up was 516.1 ± 299.9 days and did not differ significantly between the groups (482 ± 173 days vs. 461 ± 245 days vs. 566 ± 382 days). MACCE frequency was 12.1% in the whole group of patients. All-cause mortality was 7.5%, recurrent MI occurred in 9.5% of patients, and 1.1% of patients required re-percutaneous coronary angioplasty. A small percentage of patients experienced stroke or transient ischaemia (1.1%). The overall incidence of MACCE in each of the groups was significantly greater in the one with the highest troponin increase compared to the other 2 (4.6% vs. 9.4% vs. 18.4%, $p=0.005$). Mortality was also significantly higher in the third group compared to the first and second groups (1.1% vs. 4% vs. 13.1%, $p=0.001$).

Multivariate analysis allowed to identify the following predictors of increased mortality: cardiac arrest at admission, pericardial effusion and age. Among the significant predictors of

lower mortality, we confirmed: chest pain on admission, arterial hypertension, and higher platelet count.

However, among the predictors associated with increased MACCE risk, we confirmed: higher serum creatinine, increased blood leukocyte count and alcohol abuse. Among the significant factors concerning a lower risk of MACCE occurrence, the following were distinguished: hyperlipidaemia and increased haemoglobin concentration in the blood.

In conclusion, patients with MINOCA and with the greatest increase in hs-TnI during hospitalisation had the highest mortality rate. A similar relationship was found for the occurrence of MACCE in the group of patients with the highest increase in hs-TnI, but this was without statistical significance. Although hypercholesterolaemia and elevated serum LDL cholesterol levels are known risk factors for MI-CAD and MACCE, MINOCA patients are associated with lower overall mortality and a lower risk of long-term MACCE. This phenomenon has already been described as the "hypercholesterolaemia paradox". Although we do not yet know the etiology of this paradox, it seems that in this group of patients, the increased concentration of serum cholesterol has beneficial effects on the long-term prognosis in this group of patients. Although there is a relationship between the maximum concentration of released troponin, mortality and the frequency of MACCE in the group of MINOCA patients, it should be borne in mind that we have identified a number of other factors associated with prognosis, including those related to the etiology of myocardial infarction.

Article (3)

The aim of the third publication was to compare the clinical features, prognosis and identify the prognostic factors for MACCE and mortality in a group of patients treated for MINOCA, anterior wall STEMI, TTC and infective myocarditis (IM).

The study was conducted on a group of 596 patients admitted to hospital due to: MINOCA and anterior wall STEMI. Then, from the group of patients with a working diagnosis of MINOCA, patients with IM and TTC were selected.

The primary endpoints were defined as all-cause mortality and MACCE. Mortality and MACCEs were assessed at 30 days, 12 months and 36 months from the baseline cardiac event.

Of the 596 patients included in the analysis, 318 patients were diagnosed with MINOCA, 31 with TTC, 22 with IM and 225 with anterior wall STEMI. The mean age of the patients was 63.3 ± 13.8 years. The youngest patients were in the IM group (43.7 ± 16.2), the oldest in the TTC group (70.7 ± 13), while the mean age of patients in the MINOCA group was 65.1 ± 13.4, and in the STEMI group, 61.6 ± 12.2 (p<0.001), these values were very similar. The highest troponin values were recorded in the group of patients with anterior wall STEMI, while the lowest in the group of MINOCA patients. Patients with anterior wall STEMI more often suffered from hypercholesterolaemia and diabetes compared to other patients. Patients in the MINOCA group were more frequently treated for arterial hypertension. Patients in the TTC and anterior wall STEMI groups had significantly lower left ventricular ejection fraction compared to subjects from the MINOCA and IM groups (p<0.001). The most common vascular access in the group of patients with STEMI was the femoral, while in the remaining groups of patients, the radial approach was the most conventional.

All-cause mortality did not differ statistically significantly between the study groups at subsequent time points. When analysing the frequency of MACCE in individual groups, its highest frequency after 30 days was observed in the TCC (7.4%) and STEMI (6.7%) groups, although this was without statistical significance. After 1 and 3 years of follow-up, the incidence of MACCE increased and was statistically significantly highest in the group of patients with anterior wall STEMI.

In conclusion, during the 3-year follow-up period, patients with STEMI of the anterior wall had a significantly worse prognosis in terms of MACCE incidence compared to the TTC, IM and MINOCA groups. The analysis allowed for the comparison of treatment results between selected groups of patients limited to 2 academic centres and their confrontation with the results of other studies, as well as the identification of a sub-group of patients with the worst prognosis and treatment outcome predictors in selected groups of patients. Local data often differ significantly from the data obtained in multicentre studies, which allows to adjust patient care in selected groups of patients and thus, improve the effects of treatment at dedicated centres.

REFERENCES:

1. Falk E, Nakano M, Bentzon JF, et al. Update on acute coronary syndromes: the pathologists' view. Eur Heart J. 2013; 34: 719–728.

2. Larsen AI, Galbraith PD, William A Ghali et al. Characteristics and outcomes of patients with acute myocardial infarction and angiographically normal coronary arteries. Am J Cardiol. 2005; 95: 261-263.

3. Planer D, Mehran R, Ohman EM et al. Prognosis of patients with non-ST-segment-elevation myocardial infarction and nonobstructive coronary artery disease: propensity-matched analysis from the Acute Catheterization and Urgent Intervention Triage Strategy trial. Circ Cardiovasc Interv. 2014; 7: 285-293.

4. Gehrie ER1, Reynolds HR, Chen AY et al. Characterization and outcomes of women and men with non-ST-segment elevation myocardial infarction and nonobstructive coronary artery disease: results from the Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes with Early Implementation of the ACC/AHA Guidelines (CRUSADE) quality improvement initiative. Am Heart J. 2009; 158: 688-694.

5. Gross H, William H. Sternberg, M.D. Myocardial infarction without significant lesions of coronary arteries. Arch Intern Med (Chic). 1939; 64: 249-267.

6. Beltrame JF. Assessing patients with myocardial infarction and non-obstructed coronary arteries (MINOCA). J Intern Med. 2013; 273: 182–185.

7. Pasupathy S, Air T, Dreyer RP, Tavella R, Beltrame JF. Systematic review of patients presenting with suspected myocardial infarction and nonobstructive coronary arteries. Circulation. 2015; 131: 861-870.

8. Dreyer RP, Tavella R, Curtis JP et al. Myocardial infarction with non-obstructive coronary arteries as compared with myocardial infarction and obstructive coronary disease: outcomes in a Medicare population. Eur Heart J. 2020; 41: 870-878.

9. Nordenskjöld AM, Baron T, Eggers KM, et al. Predictors of adverse outcome in patients with myocardial infarction with non-obstructive coronary artery (MINOCA) disease. Int J Cardiol. 2018; 261: 18–23.

10. Thygesen K, Alpert JS, Jaffe AS, et al; Executive Group on behalf of the Joint European Society of Cardiology (ESC)/American College of Cardiology (ACC)/American Heart Association (AHA)/World Heart Federation (WHF) Task Force for the Universal Definition of Myocardial Infarction. Fourth Universal Definition of Myocardial Infarction (2018). Circulation. 2018; 138: e618-e651.

11. Agewall S, Beltrame JF, Reynolds HR et al. ESC working group position paper on myocardial infarction with non-obstructive coronary arteries. Eur Heart J. 2017; 38: 143-153.

12. Safdar B, Spatz ES, Dreyer RP et al. Presentation, Clinical Profile, and Prognosis of Young Patients With Myocardial Infarction With Nonobstructive Coronary Arteries (MINOCA): Results From the VIRGO Study. J Am Heart Assoc. 2018; 7: e009174.

13. Ballesteros-Ortega D, Martínez-González O, Gómez-Casero RB et al. Characteristics of patients with myocardial infarction with nonobstructive coronary arteries (MINOCA) from the

ARIAM-SEMICYUC registry: development of a score for predicting MINOCA. Vasc Health Risk Manag. 2019; 15: 57-67.

14. Rakowski T, De Luca G, Siudak Z et al. Characteristics of patients presenting with myocardial infarction with non-obstructive coronary arteries (MINOCA) in Poland: data from the ORPKI national registry. J Thromb Thrombolysis. 2019; 47: 462-466.

15. Pustjens TFS, Appelman Y, Damman P et al. Guidelines for the management of myocardial infarction/injury with non-obstructive coronary arteries (MINOCA): a position paper from the Dutch ACS working group. Neth Heart J. 2020; 28: 116–130.

16. Montone RA, Niccoli G, Russo M et al. Clinical, angiographic and echocardiographic correlates of epicardial and microvascular spasm in patients with myocardial ischaemia and non-obstructive coronary arteries. Clin Res Cardiol. 2020; 109: 435-443.

17. Munusamy V, Sriram V, Elumalai DV. Coronary computed tomography angiography in patients with myocardial infarction and non-obstructed coronary arteries. International Archives of Integrated Medicine. 2019; 6, 8.

18. Ouldzein H, Elbaz M, Roncalli J et al. Plaque rupture and morphological characteristics of the culprit lesion in acute coronary syndromes without significant angiographic lesion: analysis by intravascular ultrasound. Ann Cardiol Angeiol (Paris). 2012; 61: 20–26

19. Reynolds HR, Srichai MB, Iqbal SN et al. Mechanisms of myocardial infarction in women without angiographically obstructive coronary artery disease. Circulation. 2011; 124: 1414–1425.

20. Alasnag M, Jelani Q, Johnson TW et al. The Role of Imaging for MINOCA (Myocardial Infarction with No Obstructive Coronary Artery Disease): a Review of Literature and Current Perspectives. Current Cardiovascular Imaging Reports. 2020; 13, 21.

21. Gatti M, Carisio A, D'Angelo T et al. Cardiovascular magnetic resonance in myocardial infarction with non-obstructive coronary arteries patients: A review. World J Cardiol. 2020; 12: 248–261.

22. Reynolds HR, Maehara A, Kwong RY, et al. Coronary Optical Coherence Tomography and Cardiac Magnetic Resonance Imaging to Determine Underlying Causes of Myocardial Infarction With Nonobstructive Coronary Arteries in Women. Circulation. 2021; 143: 624-640.

23. Leurent G, Langella B, Fougerou C, et al. Diagnostic contributions of cardiac magnetic resonance imaging in patients presenting with elevated troponin, acute chest pain syndrome and unobstructed coronary arteries. Arch Cardiovasc Dis. 2011; 104: 161-170.

24. Stepien K, Nowak K, Wypasek E et al. High prevalence of inherited thrombophilia and antiphospholipid syndrome in myocardial infarction with non-obstructive coronary arteries: Comparison with cryptogenic stroke. Int J Cardiol. 2019; 290: 1-6.

25. Ponikowski P, Voors AA, Anker SD et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur J Heart Fail. 2016; 18:891-975.

26. Scalone G, Niccoli G, Crea F et al. Editor's Choice- Pathophysiology, diagnosis and management of MINOCA: an update. Eur Heart J Acute Cardiovasc Care. 2019; 8: 54-62.

27. Sá FM, Carvalho R, Santos L et al. Dual antiplatelet therapy in myocardial infarction with non-obstructive coronary artery disease - insights from a nationwide registry. Rev Port Cardiol. 2020; 39: 679-684.

28. Bossard M, Gao P, Boden W et al. Antiplatelet therapy in patients with myocardial infarction without obstructive coronary artery disease. Heart. 2021; heartjnl-2020-318045.

29. Ciliberti G, Verdoia M, Merlo M et al. Pharmacological therapy for the prevention of cardiovascular events in patients with myocardial infarction with non-obstructed coronary arteries (MINOCA): Insights from a multicentre national registry. Int J Cardiol. 2020; S0167-5273(20)34163-2.

30. Pelliccia F, Pasceri V, Niccoli G et al. Predictors of Mortality in Myocardial Infarction and Nonobstructed Coronary Arteries: A Systematic Review and Meta-Regression. Am J Med. 2020; 133: 73-83.e4.

31. Pizzi C, Xhyheri B, Costa GM et al. Nonobstructive Versus Obstructive Coronary Artery Disease in Acute Coronary Syndrome: A Meta-Analysis. J Am Heart Assoc. 2016; 5: e004185.

32. Planer D, Mehran R, Ohman EM et al. Prognosis of patients with non-ST-segment-elevation myocardial infarction and nonobstructive coronary artery disease: propensity-matched analysis from the Acute Catheterization and Urgent Intervention Triage Strategy trial. Circ Cardiovasc Interv. 2014; 7: 285-293.

33. Lopez-Pais J, Izquierdo Coronel B, Galán Gil D et al. Clinical characteristics and prognosis of myocardial infarction with non-obstructive coronary arteries (MINOCA): A prospective single-center study. Cardiol J. 2020.

34. Dreyer RP, Tavella R, Curtis JP et al. Myocardial infarction with non-obstructive coronary arteries as compared with myocardial infarction and obstructive coronary disease: outcomes in a Medicare population. Eur Heart J. 2020; 41: 870-878.

35. Ibanez B, James S, Agewall S, et al. ESC Scientific Document Group. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: the task force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). Eur Heart J 2018; 39: 119-77.

36. Roffi M, Patrono C, Collet JP, et al. ESC Scientific Document Group. 2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: task force for the management of acute coronary syndromes in patients presenting without persistent ST-Segment elevation of the European Society of Cardiology (ESC). Eur Heart J 2016; 37: 267-315.

37. Tsuchihashi, K. Angina pectoris-myocardial infarction investigations in Japan. Transient left ventricular apical ballooning without coronary artery stenosis: A novel heart syndrome mimicking acute myocardial infarction. Angina pectoris-myocardial infarction investigations in Japan. J Am Coll Cardiol 2001; 38: 11-18.

38. Gibson CM, Cannon CP, Daley WL, et al. TIMI frame count: a quantitative method of assessing coronary artery flow. Circulation 1996; 93: 879-888.

4. Artykuł nr 1

Jędrychowska M, Januszek R, Plens K, Surdacki A, Bartuś S, Dudek D.

Impact of sex on the follow-up course and predictors of clinical outcomes in patients hospitalised due to myocardial infarction with non-obstructive coronary arteries: a single-centre experience

Kardiologia Polska, 2019

Kardiologia Polska 2019, 77, 2: 198–206, DOI: 10.5603/KP.a2018.0245

ORIGINAL ARTICLE

Impact of sex on the follow-up course and predictors of clinical outcomes in patients hospitalised due to myocardial infarction with non-obstructive coronary arteries: a single-centre experience

Magdalena Jędrychowska[1], Rafał Januszek[2], Krzysztof Plens[3], Andrzej Surdacki[4], Stanisław Bartuś[1, 4], Dariusz Dudek[1, 4, 5]

[1]2nd Department of Cardiology and Cardiovascular Interventions, University Hospital, Krakow, Poland
[2]Department of Clinical Rehabilitation, University of Physical Education, Krakow, Poland
[3]Krakow Cardiovascular Research Institute (KCRI), Krakow, Poland
[4]2nd Department of Cardiology, Jagiellonian University Medical College, Krakow, Poland
[5]Department of Interventional Cardiology, Jagiellonian University Medical College, Krakow, Poland

Abstract

Background: Myocardial infarction with non-obstructive coronary arteries (MINOCA) occurs more often in women.

Aim: We sought to assess the relationship between sex and clinical outcomes during follow-up in patients after MINOCA and to identify predictors of major adverse cardiac and cerebrovascular events (MACCE).

Methods: The study comprised 134 patients (78 women) at the mean age of 61.6 years, who were diagnosed with MINOCA at the Department of Cardiology between January 2015 and June 2018. The mean follow-up duration was 609.5 ± 412.2 days. Primary study endpoints were MACCE, which included all-cause death, myocardial infarction, reintervention, and cerebral stroke. Secondary endpoints were recurrent chest pain during follow-up and rehospitalisation for reasons other than MACCE.

Results: Kaplan-Meier survival curve analysis did not reveal any significant differences in the frequency of MACCE (p = 0.63) or mortality rate (p = 0.29) between men and women. There was no significant impact of sex on secondary study endpoints either. Sex was not identified as a predictor of primary or secondary study endpoints in univariate or multivariate analysis. Troponin index (risk ratio [RR] 1.002; 95% confidence interval [CI] 1.0005–1.0026, p = 0.004), age (RR 1.04; 95% CI 1.008–1.065, p = 0.01), serum creatinine level (RR 1.01; 95% CI 1.001–1.01, p = 0.02), hyperlipidaemia (RR 0.26; 95% CI 0.07–0.75, p = 0.01), and prior venous thromboembolic disease (RR 8.28; 95% CI 1.15–38, p = 0.04) were found to be predictors of MACCE in multivariate analysis.

Conclusions: Sex was not found to be significantly associated with clinical outcomes during the follow-up period in patients with MINOCA.

Key words: clinical outcomes, follow-up, myocardial infarction with non-obstructive coronary arteries, predictors, sex

Kardiol Pol 2019; 77, 2: 198–206

INTRODUCTION

Symptomatic coronary artery disease (CAD) presenting as chest pain does not always coexist with obstructive CAD. In some patients various forms of the disease (stable CAD or acute coronary syndrome) coincide with non-obstructive CAD [1, 2]. Several mechanisms have been found to be responsible for different clinical presentation of CAD in those patients. In patients with myocardial infarction with non-obstructive coronary arteries (MINOCA), the aetiology of the disease is very heterogeneous, and atherosclerosis is

Address for correspondence:
Rafał Januszek, MD, PhD, 2nd Department of Cardiology and Cardiovascular Interventions, University Hospital in Krakow, ul. Kopernika 17, 31–501 Kraków, Poland, tel: +48 12 424 71 70, fax: +48 12 424 71 80, e-mail: jaanraf@interia.pl
Received: 9.10.2018 **Accepted:** 28.12.2018 **Available as AoP:** 28.12.2018

not the most prevalent cause, in contrast to patients with typical risk factors for atherosclerosis or those with myocardial infarction (MI) with obstructive CAD. In a large proportion (up to 25%) of patients with MINOCA, the aetiology is linked to hypercoagulable states. This especially concerns women who, in many of the published studies, make up the vast majority the population and in whom blood clotting disorders may be due to menopause, pregnancy, or childbirth [2, 3]. Recently published studies performed in patients with ST-segment elevation myocardial infarction (STEMI) and MINOCA diagnosed with intravascular ultrasound increased the significance of coronary atherosclerotic lesions, which are often assessed as mild via regular coronary angiography [4]. It was also shown that plaque burden was the most powerful predictor of future acute coronary events [5]. Large registry studies revealed that the incidence of MINOCA is higher in women compared to men and that MINOCA patients more often present with non-ST-segment elevation myocardial infarction (NSTEMI) than STEMI [6].

The aim of the current study was to assess the relationship between sex and clinical outcomes during follow-up in patients after MINOCA and to identify predictors of major adverse cardiac and cerebrovascular events (MACCE) in this group.

METHODS

We retrospectively analysed 1984 consecutive patients admitted to our catheterisation laboratory and to our Department of Cardiology due to MI from January 2015 until June 2018. From this group we extracted 134 (6.75%) patients with MINOCA (56 [41.8%] men). Both MI and MINOCA were diagnosed according to the previous definition of MI [2, 3]. Due to the fact that the troponin level was estimated using different assays, we calculated the troponin index from the maximal troponin value measured during hospitalisation in order to unify the results. The troponin index was calculated by dividing the troponin concentration by the upper limit of the reference range for the particular assay. Glomerular filtration rate (GFR) was estimated according to the Cockroft-Gault formula. Kidney failure was diagnosed when the GFR level was lower than 60 mL/min. Coronary slow-flow phenomenon was diagnosed on the basis of grade 2 on the Thrombolysis in Myocardial Infarction (TIMI) scale [7]. Slow flow was assumed as an indirect indicator of microcirculatory dysfunction.

This study complies with the Declaration of Helsinki. All subjects gave informed consent to participate before the investigation began.

Study endpoints

This was an observational follow-up study. Primary endpoints were main MACCE, which included cerebral stroke, MI, death, percutaneous coronary reintervention, and coronary artery bypass grafting. Secondary study endpoints were recurrent chest pain as well as rehospitalisation for reasons other than MACCE, such as anaemia, gastrointestinal bleedings, infections (e.g. pneumonia), and any other conditions that could possibly lead to the onset of type 2 MI. Data regarding primary and secondary endpoints were obtained on the basis of medical records gathered during follow-up visits at the outpatient clinic or by telephone.

Statistical analysis

Continuous variables are expressed as means and standard deviations or median and interquartile range, and categorical variables are shown as numbers and percentages. The investigated groups were analysed using the Shapiro-Wilk test to assess continuous data distribution. We compared men and women with the Mann-Whitney U-test, Student t test, Welch's t test, Person's χ^2 test, Fisher's exact test, and the Cochrane-Armitage test for trends when appropriate. Kaplan-Meier analysis was used for primary endpoint assessment. Mantel-Cox analysis was used for comparison between Kaplan-Meier survival curves for death and MACCE. In order to identify factors influencing the primary study endpoints, univariate and multivariate Cox regression proportional hazard models were constructed. Univariate Cox regression analysis was also adjusted for sex. To identify factors influencing secondary study endpoints, logistic regression analysis was performed along with adjustment for sex. Statistical significance was accepted at a p-value of 0.05. The statistical analyses were performed using the Statistica 10.0 software (Dell Software, Inc., Round Rock, TX, USA) and the SPSS STATISTICS 24 (IBM, SPSS Inc., Chicago, IL, USA).

RESULTS

Epidemiology, frequency, and aetiology of MINOCA

The overall frequency of MINOCA among all the patients admitted to our department was estimated at 6.75% and it was higher in women than in men (11.3% vs. 4.7%, $p < 0.001$) (Fig. 1). On admission, 104 (77.6%) patients with MINOCA were diagnosed with NSTEMI, whereas 30 (22.4%) patients had STEMI. Upon discharge from hospital, 68 (50.7%) patients were diagnosed with NSTEMI, 11 (8.2%) had myocarditis, 17 (12.7%) had takotsubo cardiomyopathy, five (3.7%) had tachyarrhythmia, 12 (8.9%) had STEMI, there were six (4.5%) cases of heart failure, nine (6.7%) patients had type 2 MI, two (1.5%) had hypertrophic cardiomyopathy, and there were single cases of thromboembolic disease, arterial hypertension, myocardial bridge, and cerebral stroke (0.7% of patients each). The following aetiologies of MINOCA were revealed: unknown aetiology in 50 (37.3%) patients, takotsubo cardiomyopathy in 20 (14.9%) patients, tachyarrhythmia in 16 (11.9%) patients, myocarditis in 11 (6.7%) patients, slow-flow phenomenon in nine (6.7%) patients, arterial hypertension in five (3.7%) patients, myocardial bridge in four (3%) patients, arterial spasm, hypertrophic cardiomyopathies, and tumour embolisations in three

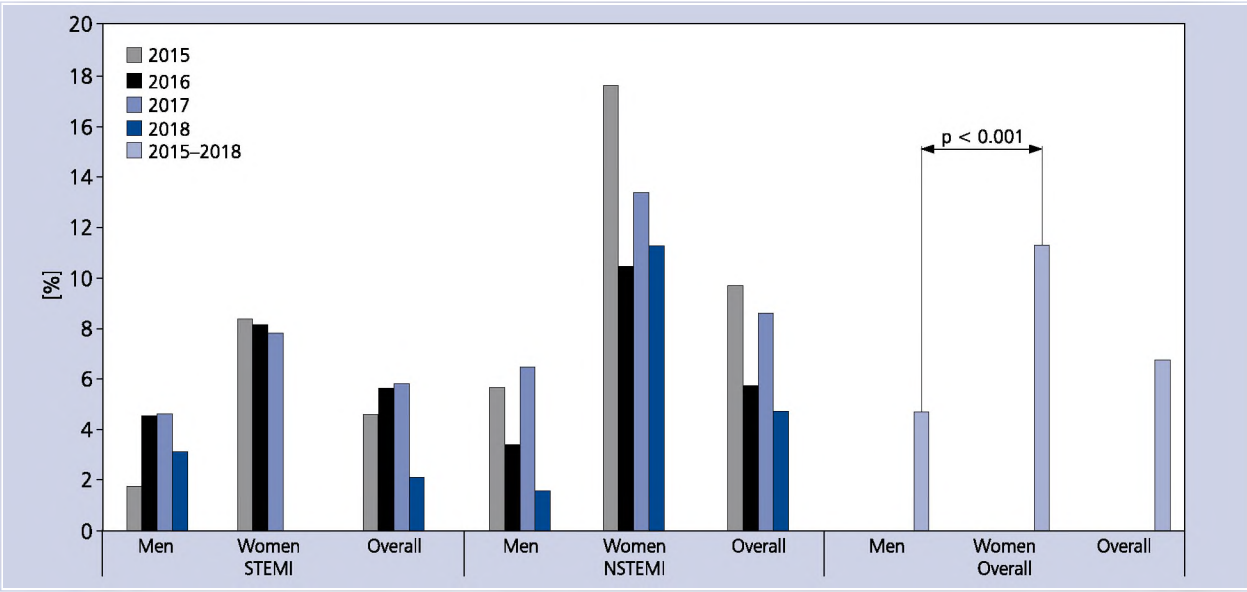


Figure 1. The rate of myocardial infarction with non-obstructive coronary arteries diagnosed at the Cardiology Department of the University Hospital in Krakow in the years 2015–2018, according to sex and the type of myocardial infarction; STEMI — ST-segment elevation myocardial infarction; NSTEMI — non-ST-segment elevation myocardial infarction

(2.2%) patients each, anaemia in two (1.5%) patients, as well as atrioventricular block, aortic dissection, muscular dystrophy, cerebral stroke, alcohol-induced cardiomyopathy, aortic valve stenosis, and antiphospholipid syndrome in one (0.7%) patient each.

General characteristics

In the group of patients included in the study, women were significantly older than men (66.6 ± 13.7 years vs. 56 ± 41.8 years, $p < 0.001$). The mean body mass index (BMI) was significantly lower in women compared to men (26.4 ± 5.8 kg/m^2 vs. 28.1 ± 4.4 kg/m^2, $p = 0.02$). Cardiac arrest on admission occurred only in men (six cases, $p = 0.002$), whereas women, in comparison to men, more often suffered from hyperlipidaemia (24.5% vs. 42.3%, $p = 0.03$), hypertension (59.2% vs. 75.6%, $p = 0.04$), and chronic kidney failure (11.8% vs. 32.8%, $p = 0.007$) (Table 1).

Pharmacotherapy

Women with MINOCA were numerically more often treated with acetylsalicylic acid before admission to hospital, but without statistical significance (16% vs. 29.8%, $p = 0.08$). However, statins were significantly more often used in women compared to men (16% vs. 32.8%, $p = 0.03$) (Table 2).

Biochemical indices

With regard to biochemical indices, there was a significantly greater mean value of troponin index in men compared to women (243.3 ± 302 vs. 167 ± 265.1, $p = 0.03$), whereas the mean N-terminal pro–B-type natriuretic peptide (NT-proBNP) concentration was significantly higher in women (2671.0 [692.5–5102.0] pg/mL) than in men (485.6 [156.0–1393.3] pg/mL); $p = 0.02$. The mean haemoglobin concentration was significantly lower in women compared to men (12.5 ± 1.5 g/dL vs. 13.5 ± 2.2 g/dL, $p < 0.001$). The mean high-density lipoprotein cholesterol concentration was higher in women compared to men (1.4 ± 0.4 mmol/L vs. 1.1 ± 0.3 mmol/L, $p < 0.001$), and the mean serum creatinine concentration was significantly greater in men (86.2 ± 37.4 μmol/L vs. 76 ± 42.8 μmol/L, $p < 0.001$). The mean GFR was significantly lower in women compared to men (83 ± 41 mL/min vs. 120 ± 52.3 mL/min, $p < 0.001$; Table 3).

Electrocardiography, cardiac echocardiography, and coronary angiography

There were no significant differences in electrocardiographic signs of myocardial ischaemia, except for the T-wave inversion, which occurred significantly more often in women compared to men (24.3% vs. 8.9%, $p = 0.02$). Also, echocardiographic parameters did not differ significantly between these two groups, despite the fact that there were numerically more female than male patients with impaired left ventricular ejection fraction (LVEF) below 40% (28.2% vs. 18.2%, $p = 0.18$), left ventricular akinesis (33.3% vs. 24.4%, $p = 0.08$), and pericardial effusion (11.7% vs. 5.9%, $p = 0.26$). Conversely, left ventricular hypertrophy tended to be observed more often in men compared to women (29.4% vs. 17.9%, $p = 0.12$).

In terms of coronary angiography findings, there were numerically more cases of muscular bridges (12.5% vs. 5.1%, $p = 0.12$), arterial spasms (5.3% vs. 1.3%, $p = 0.17$), contrast slow-flows (19.6% vs. 14.1%, $p = 0.39$), and atherosclerotic

Table 1. Clinical characteristics of MINOCA patients

	Men (n = 56)	Women (n = 78)	p	Overall (n = 134)
Age [years]	54.5 ± 17.4	66.6 ± 13.7	< 0.001	61.6 ± 16.4
BMI [kg/m^2]	28.1 ± 4.4	26.4 ± 5.8	0.02	27.1 ± 5.3
Hospitalisation time [days]	6 ± 3.1	7.1 ± 3.5	0.055	6.7 ± 3.4
Second episode of MINOCA	5 (8.9)	7 (9.1)	0.97	12 (9)
Chest pain on admission	23 (44.2)	27 (34.6)	0.26	50 (38.5)
Cardiac arrest during MI	6 (11)	0 (0)	0.002	6 (4.5)
NSTEMI on admission	42 (75)	62 (79.5)	0.53	104 (77.6)
Diabetes	11 (20.4)	18 (23.1)	0.71	29 (22)
Hyperlipidaemia	13 (24.5)	33 (42.3)	0.03	46 (35.1)
Hypertension	32 (59.2)	59 (75.6)	0.04	91 (68.9)
Smoking	19 (35.2)	17 (22.1)	0.09	36 (27.5)
COPD/Bronchial asthma	3 (5.5)	7 (9)	0.46	10 (7.6)
Chronic kidney failure	6 (11.8)	22 (32.8)	0.007	28 (23.7)
Venous thromboembolic disease	1 (1.8)	0 (0)	0.23	1 (0.8)
Prior MI	7 (12.7)	13 (16.7)	0.53	20 (15)
Prior PCI	7 (12.7)	7 (9)	0.48	14 (10.5)
Prior TIA/cerebral stroke	1 (1.9)	7 (9)	0.08	8 (6)
Pacemaker/ICD/CRT	1 (1.9)	4 (5.2)	0.31	5 (3.8)
Autoimmune diseases	2 (3.8)	2 (2.6)	0.71	4 (3.1)
Cancer	1 (1.9)	2 (2.7)	0.77	3 (2.3)
Alcohol abuse	2 (3.8)	1 (1.4)	0.38	3 (2.4)

Data are presented as arithmetic mean ± standard deviation or number (percentage). BMI — body mass index; COPD — chronic obstructive pulmonary disease; CRT — cardiac resynchronisation therapy; ICD — implantable cardioverter-defibrillator; MI — myocardial infarction; MINOCA — myocardial infarction with non-obstructive coronary artery; NSTEMI — non-ST-segment elevation myocardial infarction; PCI — percutaneous coronary intervention; TIA — transient ischaemic attack

Table 2. Pharmacotherapy before admission to hospital

	Men	Women	P	Overall
Acetylsalicylic acid	8 (16)	20 (29.8)	0.08	28 (23.9)
Anticoagulant	6 (12.2)	8 (11.9)	0.96	14 (12.1)
Statin	8 (16)	22 (32.8)	0.03	30 (25.6)
DAPT	3 (6)	3 (4.4)	0.69	6 (5.1)
β-blocker	11 (22)	23 (34.3)	0.14	34 (29)
Glucocorticosteroids	1 (2)	4 (5.9)	0.3	5 (4.2)
Hormonal contraception	0 (0)	1 (1.4)	0.38	1 (0.8)
HRT	0 (0)	1 (1.4)	0.38	1 (0.8)
Amphetamine	2 (3.6)	0 (0)	0.09	2 (1.5)

Data are presented as numbers (percentages). DAPT — dual antiplatelet therapy; HRT — hormone replacement therapy

plaques (85% vs. 71.8%, p = 0.11) in men compared to women, but without statistical significance (Table 4).

Primary and secondary study endpoints

The mean duration of the follow-up period was almost equal in men and women (609.5 ± 434.7 days vs. 609.5 ± 398.1 days, p = 0.99). The percentage of completed follow-ups (92.8% vs. 91%, p = 0.7) and MACCE rate (19.2% vs. 22.5%, p = 0.65) also did not differ significantly between these two groups. With regard to primary and secondary study endpoints, mortality was similar between the two groups (18.6% vs. 11.5%, p = 0.3) (Table 5).

Table 3. Biochemical parameters

	Men	Women	P	Overall
Maximum troponin index	243.3 ± 302	167 ± 265.1	0.03	198.8 ± 282.5
CK-MB on admission [IU/L]	50.2 ± 100.4	34.6 ± 36.4	0.12	41 ± 70.1
Maximum CK-MB [IU/L]	78.9 ± 253.3	39.4 ± 39.9	0.1	56.1 ± 167.5
Elevated C-reactive protein (> ULN)	27 (75)	35 (85.3)	0.25	60 (77)
C-reactive protein [mg/L]	33.6 ± 51.5	36.6 ± 41.1	0.99	35.3 ± 45.5
NT-proBNP [pg/mL]	485.6 [156.0–1393.3]	2671.0 [692.5–5102.0]	0.02	4170 ± 6779
D-dimer [mg/L]	3.73 ± 6.4	1.74 ± 5.64	0.6	2.49 ± 6
Leucocytes [$\times 10^3/\mu$L]	8.7 ± 2.6	9.6 ± 3.6	0.24	9.23 ± 3.3
Haemoglobin [g/dL]	13.5 ± 2.2	12.5 ± 1.5	< 0.001	12.9 ± 1.9
Platelet count [$\times 10^3/\mu$L]	205.3 ± 54.1	217.1 ± 73.4	0.37	221.3 ± 66.1
Total cholesterol [mmol/L]	4.5 ± 1	4.9 ± 1.2	0.08	4.74 ± 1.1
HDL-C [mmol/L]	1.1 ± 0.3	1.4 ± 0.4	< 0.001	1.3 ± 0.4
LDL-C [mmol/L]	2.7 ± 1	2.8 ± 1.1	0.62	2.8 ± 1.1
Triglycerides [mmol/L]	1.5 ± 0.8	1.4 ± 0.6	0.65	1.5 ± 0.7
Creatinine [μmol/L]	86.2 ± 37.4	76 ± 42.8	< 0.001	80.2 ± 40.8
GFR [mL/min]	120 ± 52.3	83 ± 41	< 0.001	99.4 ± 49.7

Data are presented as arithmetic mean ± standard deviation or median [interquartile range], or number (percentage); CK-MB — creatine kinase-MB; GFR — glomerular filtration rate; HDL-C— high-density lipoprotein cholesterol; LDL-C — low-density lipoprotein cholesterol; NT-proBNP — N-terminal pro–B-type natriuretic peptide; ULN — upper limit of normal

Table 4. Electrocardiography, cardiac echocardiography, and coronary angiography

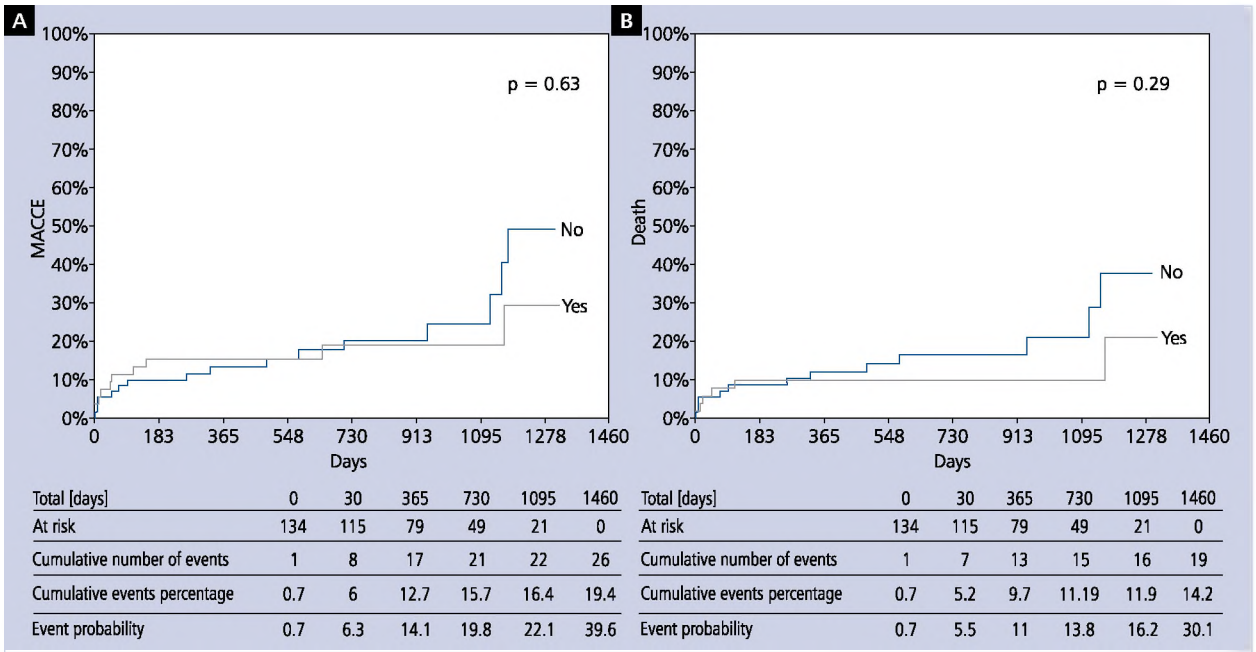
	Men	Women	P	Overall
Electrocardiography on admission:				
ST-segment elevation	14 (25)	15 (19.2)	0.42	29 (21.6)
ST-segment depression	8 (14.3)	15 (19.2)	0.45	23 (17.2)
T-wave changes	5 (8.9)	19 (24.3)	0.02	24 (17.9)
Other*	29 (51.8)	29 (37.2)	0.09	58 (43.3)
Echocardiography on admission:				
LVEF [%]	51.7 ± 15.7	50.3 ± 14.1	0.38	50.9 ± 14.7
LVEF < 40%	10 (18.2)	22 (28.2)	0.18	32 (24.1)
Wall motion disorders on admission:	34 (66.7)	60 (76.9)	0.2	94 (72.9)
Hypokinesis	24 (58.5)	34 (43.6)	0.69	58 (45)
Akinesis	10 (24.4)	26 (33.3)	0.08	36 (27.9)
Pericardial effusion	3 (5.9)	9 (11.7)	0.26	12 (9.4)
Left ventricular hypertrophy	15 (29.4)	14 (17.9)	0.12	29 (22.5)
Coronary angiography				
Plaques (> 0% stenosis < 50%)	34 (85)	56 (71.8)	0.11	90 (76.3)
Bridges	7 (12.5)	4 (5.1)	0.12	11 (8.2)
Arterial spasm	3 (5.3)	1 (1.3)	0.17	4 (3)
Contrast slow-flow	11 (19.6)	11 (14.1)	0.39	22 (16.4)

Data are presented as arithmetic mean ± standard deviation or number (percentage). LVEF — left ventricular ejection fraction; *e.g. tachyarrhytmias/bradyarrhytmias, atrial fibrillation/flagellation, repolarisation disorders, conduction disorders

Table 5. Primary and secondary study endpoints according to sex

	Men	Women	P	Overall
Follow-up time [days]	609.5 ± 434.7	609.5 ± 398.1	0.99	609.5 ± 412.2
Completed follow-up	52 (92.8)	71 (91)	0.7	123 (91.8)
MACCE	10 (19.2)	16 (22.5)	0.65	26 (21.1)
Myocardial infarction	2 (3.8)	1 (1.4)	0.38	3 (2.4)
Cerebral stroke	1 (1.9)	0 (0)	0.24	1 (0.8)
CABG	0 (0)	0 (0)	-	0 (0)
Death	6 (11.5)	13 (18.6)	0.3	19 (15.4)
Reintervention	1 (1.9)	2 (2.8)	0.75	3 (2.4)
Recurrent chest pain	10 (19.6)	13 (18.8)	0.91	23 (19.2)
Rehospitalisation not related to MACCE	10 (19.6)	11 (15.9)	0.6	21 (17.5)

Data are presented as arithmetic mean ± standard deviation or number (percentage). CABG — coronary artery bypass grafting; MACCE — major adverse cardiac and cerebrovascular events



Total [days]	0	30	365	730	1095	1460
At risk	134	115	79	49	21	0
Cumulative number of events	1	8	17	21	22	26
Cumulative events percentage	0.7	6	12.7	15.7	16.4	19.4
Event probability	0.7	6.3	14.1	19.8	22.1	39.6

Total [days]	0	30	365	730	1095	1460
At risk	134	115	79	49	21	0
Cumulative number of events	1	7	13	15	16	19
Cumulative events percentage	0.7	5.2	9.7	11.19	11.9	14.2
Event probability	0.7	5.5	11	13.8	16.2	30.1

Figure 2. **A.** Kaplan-Meier survival curves according to sex — days to major adverse cardiac and cerebrovascular events (MACCE) for male grouping variable. The log rank test p-value = 0.63; **B.** Kaplan-Meier survival curves according to sex — days to death for male grouping variable. The log rank test p-value = 0.29

Kaplan-Meier survival curves according to sex

Due to the low number of particular components of MACCE, except for death, which was the leading component, we limited the analysis to MACCE and death. The analysis of MACCE survival curves during the follow-up period revealed no significant differences between men and women (p = 0.63). However, the occurrence of MACCE tended to be higher in women compared to men (Fig. 2A, Table 5). The analysis of death survival curves during the follow-up period also did not demonstrate any significant difference between the sexes (p = 0.29). The frequency of deaths tended to be higher in women (Fig. 2B, Table 5).

Predictors of MACCE and death

Again, due to the low number of particular MACCE components, except for death, only the predictors of MACCE and death were analysed.

Univariate Cox regression analysis identified the following variables as predictors of death during the follow-up: chest pain on admission to hospital (hazard ratio [HR] 0.21; 95% confidence interval [CI] 0.03–0.7, p = 0.01), treatment with glucocorticosteroids (GCSs) (HR 14.2; 95% CI 4.29–43.05, p = 0.0001), smoking (HR 0.13; 95% CI 0.008–0.677, p = 0.009), pericardial effusion (HR 4.13; 95% CI 1.15–11.8, p = 0.03), serum C-reactive protein (CRP) level below upper

limit of normal (HR 0.000; 95% CI 0.00–0.63, p = 0.01), age (HR 1.8; 95% CI 1.26–2.7, p = 0.0007), BMI (HR 0.88; 95% CI 0.79–0.98, p = 0.02), serum creatinine level (HR 1.008; 95% CI 1.001–1.012, p = 0.02), GFR (HR 0.97; 95% CI 0.95–0.98, p < 0.001), LVEF (HR 0.96; 95% CI 0.94–0.99, p = 0.03), troponin index (HR 1.002; 95% CI 1.001–1.003, p = 0.004), creatine kinase-MB (CK-MB) on admission to hospital (HR 1.006; 95% CI 1.003–1.008, p = 0.002), maximal serum CK-MB (HR 1.002; 95% CI 1.001–1.003, p = 0.008), blood haemoglobin concentration (HR 0.665; 95% CI 0.53–0.82, p < 0.001), white blood cell count (HR 1.19; 95% CI 1.06–1.33, p = 0.003), total cholesterol level (HR 0.49; 95% CI 0.25–0.97, p = 0.04), and low-density lipoprotein cholesterol (LDL-C) level (HR 0.44; 95% CI 0.18–0.97, p = 0.04).

After adjustment for male sex, the following predictors remained significant: chest pain on admission, cardiac arrest on admission, treatment with GCSs, smoking, pleural effusion, CRP level on admission below upper limit of normal, age, serum creatinine concentration, GFR level, LVEF value, troponin index, CK-MB on admission, maximal CK-MB, haemoglobin concentration, and leucocyte count. Proportional hazard multivariate analysis confirmed that leucocyte count (risk ratio [RR] 1.23; 95% CI 1.08–1.4, p = 0.002), platelet count (RR 0.99; 95% CI 0.98–0.99, p = 0.02), troponin index (RR 1.001; 95% CI 1.0001–1.002, p = 0.029), blood haemoglobin concentration (RR 0.74; 95% CI 0.55–0.98, p = 0.03), ST-segment depressions on admission to hospital (RR 2.96; 95% CI 1.05–8.88, p = 0.04), and hyperlipidaemia (RR 0.06; 95% CI 0.01–0.27, p < 0.0001) were independent predictors of death.

Univariate Cox regression analysis revealed that predictors of MACCE during the follow-up included the following: cardiac arrest on admission to hospital (HR 6.84; 95% CI 1.58–20.7, p = 0.01), treatment with GCSs (HR 9.01; 95% CI 2.88–24.01, p = 0.0006), smoking (HR 0.3; 95% CI 0.07–0.87, p = 0.02), age (HR 1.42; 95% CI 1.08–1.93, p = 0.01), BMI (HR 0.91; 95% CI 0.84–0.99, p = 0.04), serum creatinine concentration (HR 1.006; 95% CI 1.000–1.011; p = 0.04), GFR (HR 0.98; 95% CI 0.97–0.99; p = 0.002), troponin index (HR 1.002; 95% CI 1.001–1.002, p = 0.006), CK-MB level on admission to hospital (HR 1.006; 95% CI 1.002–1.008, p = 0.002), maximal CK-MB level (HR 1.002; 95% CI 1.001–1.003, p = 0.01), blood haemoglobin concentration (HR 0.77; 95% CI 0.63–0.94, p = 0.01), leucocyte count (HR 1.16; 95% CI 1.05–1.28, p = 0.007), total serum cholesterol concentration (HR 0.57; 95% CI 0.34–0.97, p = 0.04), and LDL-C level (HR 0.42; 95% CI 0.21–0.78, p = 0.006). After adjustment for male sex, the following predictors remained significant: cardiac arrest on admission, treatment with GCSs, age, GFR value, troponin index, CK-MB level on admission to hospital, maximal CK-MB level, blood haemoglobin concentration, leucocyte count, and LDL-C level. Proportional hazard multivariate analysis confirmed the following to be independent predictors of MACCE: troponin index (RR 1.002; 95% CI 1.0005–1.0026, p = 0.004), age (RR 1.04; 95% CI 1.008–1.065, p = 0.01), serum creatinine level (RR 1.01; 95% CI 1.001–1.01, p = 0.02), hyperlipidaemia (RR 0.26; 95% CI 0.07–0.75, p = 0.01) and prior venous thromboembolic disease (RR 8.28; 95% CI 1.15–38, p = 0.04).

Predictors of chest pain and rehospitalisation

Univariate logistic regression analysis revealed the following to be among the predictors of recurrent chest pain during the follow-up period: chest pain on admission to hospital (odds ratio [OR] 2.77; 95% CI 1.08–7.08, p = 0.03), hyperlipidaemia (OR 2.95; 95% CI 1.17–7.41, p = 0.02), treatment with acetylsalicylic acid (OR 4.38; 95% CI 1.59–12.2, p = 0.005), treatment with statins (OR 2.96; 95% CI 1.08–8.08, p = 0.04), troponin index at baseline (OR 0.99; 95% CI 0.99–1.00, p = 0.008), CK-MB level on admission to hospital (OR 0.97, 95% CI 0.95–1.005, p = 0.03), maximal CK-MB during hospitalisation (OR 0.97; 95% CI 0.94–1.002, p = 0.01), leucocyte count (OR 0.76; 95% CI 0.62–0.94, p = 0.003), and platelet count (OR 0.99; 95% CI 0.98–0.99, p = 0.02). After adjustment for male sex, none of the predictors remained significant.

Maximal CK-MB level during hospitalisation (OR 0.98; 95% CI 0.94–1.00, p = 0.03) and NT-proBNP level (OR 1.02; 95% CI 1.01–1.05, p = 0.005) were identified as predictors of rehospitalisation during follow-up in univariate logistic regression analysis. After adjustment for male sex, chest pain on admission, dual antiplatelet therapy, and left ventricular contractility disorders significantly correlated with rehospitalisation rate during the follow-up period.

DISCUSSION

One of the main findings of the presented study was that the rate of MINOCA among the overall MI population in our centre was 6.75%, and it was significantly higher in women than in men. Secondly, the most common diagnosis, both on admission to hospital and at discharge, was NSTEMI, whereas STEMI was observed less often. The most common known aetiology of MINOCA was takotsubo cardiomyopathy, followed by tachyarrhythmias. Thirdly, the clinical outcomes during the follow-up period were not significantly different between men and women. Also, the rate of recurrent chest pain and rehospitalisation during follow-up did not differ between the sexes.

According to current knowledge and recently published, large systematic reviews, the frequency of MINOCA is estimated at 6% with 95% CI 5%–7% [8]. However, a higher incidence of MINOCA (over 11%) was shown in a group of younger patients aged 18 to 55 years, consisting mostly of women [3]. In one of the recent large review articles, the ratio of men to women with MINOCA was different or even inverse (40% women) compared to our study, in which the percentage of women reached almost 60% [8]. Nevertheless, some publications support our results and report a higher incidence of MINOCA in women compared to men [9]. Similarly to our

analysis, the rate of MINOCA in a population-based registry study including patients with acute coronary syndromes without ST-segment elevation was more than twice as high in women as in men, although the overall rate of MINOCA was lower than reported herein (4.9%). Despite the fact that women included in our analysis were older and women included in the registry were more often hyperlipidaemic and former cigarette smokers, the frequency of diabetes and hypertension was comparable [10]. Similar findings have been confirmed in the analysis by Lansky et al. [11] performed in a group of patients with acute MI, in which women, despite being older and having more comorbid diseases, had less extensive CAD compared to men. Previously published studies revealed that the one-year mortality in MINOCA patients was 4.75%, while in our study, after almost two years of follow-up, it reached 15.4% in the overall group of patients [8]. Also, in the analysis performed on a large Swedish registry, which included over 12,000 patients with MINOCA, mortality rate during 2.6-year follow-up was 8% in STEMI patients and 5% in NSTEMI patients, which was significantly lower compared to our results [12].

In comparison to our analysis, studies in which the aetiology of MINOCA was determined based on magnetic resonance imaging (MRI) demonstrated greater rates of myocarditis (33%), arterial spasms (27%), and thrombophilia (14%) [8]. We were not able to compare these results due to the fact that MRI and blood tests for thrombophilia were performed only in a few of the analysed patients [13]. Young patients with suspected thrombophilia were referred to an outpatient clinic to be screened for hypercoagulable disorders. In the follow-up period, it turned out that almost none of the patients volunteered to perform the ordered tests. Therefore, it can be concluded that the most successful way to screen patients for this disease would be to perform the tests while they are at the clinic, although this is not recommended in the acute condition. Endovascular diagnostic tools, including optical coherence tomography and intravascular ultrasound (IVUS), were used in several patients. IVUS examination was performed in patients with suspected spontaneous coronary artery dissection and soft atherosclerotic plaque rupture. In the last year, the frequency of IVUS application significantly increased at our centre.

We did not observe significant differences in MACCE or death rate between men and women during the follow-up period; however, there was a tendency towards higher mortality in women. Similar results have been demonstrated for stable patients with non-obstructive CAD. It was shown that mortality in NSTEMI patients was higher in men, while in STEMI patients there was no significant difference in mortality between the sexes [6]. In the current study, the mean age of women who died during the follow-up period was 70.1 years (range, 40 to 90 years), while among male non-survivors it was 74.7 years (range, 51 to 90 years). This was significantly higher compared to patients who survived the follow-up period. Of the 19 patients who died in the follow-up period, four (21%) deaths occurred during hospitalisation. These patients were characterised by severe comorbidities such as sepsis, end-stage renal failure, cardiac tamponade in the course of hospitalisation, and the presence of sudden cardiac arrest on or before admission to hospital. However, the overall group of patients who died during the follow-up period was characterised by older age ($p < 0.001$), lower GFR value ($p < 0.001$), higher maximal CK-MB concentration ($p < 0.01$), lower haemoglobin concentration ($p < 0.001$), higher white blood cell count ($p = 0.03$), and higher levels of D-dimer ($p < 0.001$). What is more, the incidence of comorbidities was also higher in this group. It has been demonstrated that most of the predictors of adverse cardiovascular events following MINOCA are similar to the predictors of adverse events after regular acute MI with obstructive CAD. The WISE study identified hypertension, diabetes, and smoking as predictors of cardiovascular death and MI in women with signs of heart ischaemia during long-term follow-up, while in the current study, multivariate analysis did not confirm these factors as predictors of MACCE or death. Instead, the predictors identified in multivariate analysis were troponin level, age, serum creatinine level, and history of thromboembolic disease for MACCE, as well as leucocyte and platelet count, serum troponin level, blood haemoglobin concentration, and ST-segment depressions on admission to hospital for death [14]. In the current analysis, the increase in troponin and CK-MB levels at index procedure were found to be predictors of clinical outcomes expressed as the rate of MACCE and death, and troponin elevation was also associated with the occurrence of chest pain during the follow-up period, while the CK-MB level was associated with the rehospitalisation rate. The relationship between the extent of increase in markers of myocardial injury among patients with MINOCA and clinical outcomes expressed as the rate of MACE, all-cause mortality, cardiovascular mortality, and readmissions for heart failure during the follow-up period has been demonstrated in previously published studies [15]. However, the knowledge about the predictors of recurrent chest pains after MINOCA is smaller. It has been demonstrated that persistent chest pain after MINOCA is a predictor of adverse cardiovascular events [8]. Due to that reason and because of the unquestionable deterioration in quality of life that occurs after hospital discharge, we tried to identify potential predictors of recurrent chest pain on the basis of the information gathered during follow-up.

Available publications concerning the assessment of predictors of clinical outcomes after MINOCA are often based on large registries and do not include all biochemical data. Previously published studies, apart from the well-known predictors of MACCE such as older age, diabetes, hypertension, smoking, prior MI or cerebral stroke, chronic obstructive pulmonary disease, reduced LVEF or peripheral vascular disease,

and elevated serum creatinine level, identified a lower level of total cholesterol as a predictor, which was also confirmed in our study [10]. This finding was named "the cholesterol paradox" and it was observed in other populations of patients as well [11]. It was also shown that patients who did not receive statin therapy before an MINOCA incident and had low levels of cholesterol were at increased risk of MACCE during follow-up [16].

Due to manuscript length limitations we were not able to discuss all predictors of MACCE in the follow-up period, but attention was also paid to the influence of inflammatory markers, such as leucocyte count, and history of venous thromboembolism, on MACCE and mortality. The association of pro-inflammatory markers with clinical outcomes during follow-up is present in a great number of patients with myocarditis and other concomitant infectious diseases which are definitely more common in the MINOCA group than in patients with obstructive CAD. The association between clinical outcomes and thromboembolic diseases is undoubtedly connected to the fact that most of the MINOCA studies include a higher percentage of women, in whom hormonal changes are related to reproductive capacity.

In conclusion, the current analysis confirmed the significantly greater occurrence of MINOCA among women compared to men. Sex was not associated with worse clinical outcomes expressed as MACCE and mortality in patients with MINOCA during the follow-up period. The frequency of recurrent chest pain and rehospitalisation during follow-up was not related to sex either. The following factors can be identified as the predictors of MACCE and mortality during the follow-up period in patients after MINOCA: leucocyte and platelet count, troponin index, blood haemoglobin concentration and ST-segment depressions on admission to hospital, age, serum creatinine level, and history of venous thromboembolic disease.

References

1. Jespersen L, Hvelplund A, Abildstrøm SZ, et al. Stable angina pectoris with no obstructive coronary artery disease is associated with increased risks of major adverse cardiovascular events. Eur Heart J. 2012; 33(6): 734–744, doi: 10.1093/eurheartj/ehr331, indexed in Pubmed: 21911339.
2. Agewall S, Beltrame JF, Reynolds HR, et al. ESC working group position paper on myocardial infarction with non-obstructive coronary arteries. Eur Heart J. 2017; 38(3): 143-15, doi: 10.1093/eurheartj/ehw149, index in Pubmed: 28158518.
3. Thygesen K, Alpert JS, Jaffe AS, et al. Third universal definition of myocardial infarction. Eur Heart J. 2012; 33(20): 2551–2567.
4. Pasupathy S, Air T, Dreyer RP, et al. Systematic review of patients presenting with suspected myocardial infarction and nonobstructive coronary arteries. Circulation. 2015; 131(10): 861–870, doi: 10.1161/CIRCULATIONAHA.114.011201, indexed in Pubmed: 25587100.
5. Calvert PA, Obaid DR, O'Sullivan M, et al. Association between IVUS findings and adverse outcomes in patients with coronary artery disease: the VIVA (VH-IVUS in Vulnerable Atherosclerosis) Study. JACC Cardiovasc Imaging. 2011; 4(8): 894–901, doi: 10.1016/j.jcmg.2011.05.005, indexed in Pubmed: 21835382.
6. Pepine CJ, Ferdinand KC, Shaw LJ, et al. ACC CVD in Women Committee. Emergence of nonobstructive coronary artery disease: a woman's problem and need for change in definition on angiography. J Am Coll Cardiol. 2015; 66(17): 1918–1933, doi: 10.1016/j.jacc.2015.08.876, indexed in Pubmed: 26493665.
7. Gibson CM, Cannon CP, Daley WL, et al. TIMI frame count: a quantitative method of assessing coronary artery flow. Circulation. 1996; 93(5): 879–888, indexed in Pubmed: 8598078.
8. Johnson BD, Shaw LJ, Pepine CJ, et al. Persistent chest pain predicts cardiovascular events in women without obstructive coronary artery disease: results from the NIH-NHLBI-sponsored Women's Ischaemia Syndrome Evaluation (WISE) study. Eur Heart J. 2006; 27(12): 1408–1415, doi: 10.1093/eurheartj/ehl040, indexed in Pubmed: 16720691.
9. Leipsic J, Taylor CM, Gransar H, et al. Sex-based prognostic implications of nonobstructive coronary artery disease: results from the international multicenter CONFIRM study. Radiology. 2014; 273(2): 393–400, doi: 10.1148/radiol.14140269, indexed in Pubmed: 25028784.
10. Safdar B, Spatz ES, Dreyer RP, et al. Presentation, clinical profile, and prognosis of young patients with myocardial infarction with nonobstructive coronary arteries (MINOCA): results from the VIRGO study. J Am Heart Assoc. 2018; 7(13): e009174, doi: 10.1161/JAHA.118.009174, indexed in Pubmed: 29954744.
11. Lansky AJ, Ng VG, Maehara A, et al. Gender and the extent of coronary atherosclerosis, plaque composition, and clinical outcomes in acute coronary syndromes. JACC Cardiovasc Imaging. 2012; 5(3 Suppl): S62–S72, doi: 10.1016/j.jcmg.2012.02.003, indexed in Pubmed: 22421232.
12. Nordenskjöld AM, Baron T, Eggers KM, et al. Predictors of adverse outcome in patients with myocardial infarction with non-obstructive coronary artery (MINOCA) disease. Int J Cardiol. 2018; 261: 18–23, doi: 10.1016/j.ijcard.2018.03.056, indexed in Pubmed: 29563017.
13. Januszek R, Bartuś S. Does the use of rotational atherectomy procedure during percutaneous coronary interventions influence the frequency of procedure-related myocardial injury assessed by cardiac magnetic resonance? J Thorac Dis. 2018; 10(Suppl 26): S3050–S3052, doi: 10.21037/jtd.2018.07.104, indexed in Pubmed: 30370075.
14. Sharaf B, Wood T, Shaw L, et al. Adverse outcomes among women presenting with signs and symptoms of ischemia and no obstructive coronary artery disease: findings from the National Heart, Lung, and Blood Institute-sponsored Women's Ischemia Syndrome Evaluation (WISE) angiographic core laboratory. Am Heart J. 2013; 166(1): 134–141, doi: 10.1016/j.ahj.2013.04.002, indexed in Pubmed: 23816032.
15. Johnston N, Jönelid B, Christersson C, et al. Effect of gender on patients with ST-elevation and non-ST-elevation myocardial infarction without obstructive coronary artery disease. Am J Cardiol. 2015; 115(12): 1661–1666, doi: 10.1016/j.amjcard.2015.03.006, indexed in Pubmed: 25900352.
16. Cheng KH, Chu CS, Lin TH, et al. Lipid paradox in acute myocardial infarction — the association with 30-day in-hospital mortality. Crit Care Med. 2015; 43(6): 1255–1264, doi: 10.1097/CCM.0000000000000946, indexed in Pubmed: 25738856.

Cite this article as: Jędrychowska M, Januszek R, Plens K, et al. Impact of sex on the follow-up course and predictors of clinical outcomes in patients hospitalised due to myocardial infarction with non-obstructive coronary arteries: a single-centre experience. Kardiol Pol. 2019; 77(2): 198–206, doi: 10.5603/KP.a2018.0245.

WHAT IS NEW?

The present analysis confirmed that the occurrence of myocardial infarction with non-obstructive coronary arteries (MINOCA) is significantly greater among women compared to men. We showed that sex is not associated with clinical outcomes expressed as major cardiac and cerebrovascular events (MACCE) and death in patients with MINOCA during almost two years of follow-up. The study also demonstrated that the frequency of recurrent chest pains and rehospitalisations during the follow-up period is not significantly related to sex. White blood cell and platelet count, serum troponin index, haemoglobin concentration, ST-segment depressions on admission to hospital, age, serum creatinine level, hyperlipidaemia, and history of prior venous thromboembolic disease were identified as the predictors of MACCE and mortality during follow-up period in patients after MINOCA.

5. Artykuł nr 2

Jędrychowska M, Januszek R, Wańha W, Malinowski KP, Kunik P, Trznadel A, Bartuś J, Staszczak B, Januszek SM, Kameczura T, Wojakowski W, Surdacki A, Bartuś S.

Long-Term Prognostic Significance of High-Sensitive Troponin I Increase during Hospital Stay in Patients with Acute Myocardial Infarction and Non-Obstructive Coronary Arteries

Medicina (Kaunas), 2020

medicina

MDPI

Article

Long-Term Prognostic Significance of High-Sensitive Troponin I Increase during Hospital Stay in Patients with Acute Myocardial Infarction and Non-Obstructive Coronary Arteries

Magdalena Jędrychowska [1], Rafał Januszek [1,2,*], Wojciech Wańha [3], Krzysztof Piotr Malinowski [4], Piotr Kunik [3], Agata Trznadel [3], Joanna Bartuś [5], Bartłomiej Staszczak [6], Sławomir Mateusz Januszek [7], Tomasz Kameczura [8], Wojciech Wojakowski [3], Andrzej Surdacki [9,10] and Stanisław Bartuś [9,10]

1 Department of Cardiology and Cardiovascular Interventions, University Hospital, 30-688 Kraków, Poland; magdalena.mj.mj@gmail.com
2 Department of Clinical Rehabilitation, University of Physical Education, 31-571 Kraków, Poland
3 Department of Cardiology and Structural Heart Diseases, Medical University of Silesia, 40-055 Katowice, Poland; wojciech.wanha@gmail.com (W.W.); piotrkunik@gmail.com (P.K.); trznadelagata@gmail.com (A.T.); wwojakowski@sum.edu.pl (W.W.)
4 Institute of Public Health, Faculty of Health Sciences, Jagiellonian University Medical College, 31-008 Kraków, Poland; krzysztof.piotr.malinowski@gmail.com
5 Andrzej Frycz Modrzewski Kraków University, 30-705 Kraków, Poland; jbartus@babinski.pl
6 Jagiellonian University Medical College, 31-008 Kraków, Poland; bartlomiej.staszczak@gmail.com
7 Gynaecology and Obstetrics Clinic, Clinical District Hospital, 35-310 Rzeszow, Poland; versus_25@tlen.pl
8 Chair of Electroradiology, Faculty of Medicine, University of Rzeszow, 35-310 Rzeszow, Poland; tomasz_kameczura@yahoo.com
9 Department of Cardiology, Jagiellonian University Medical College, 40-055 Kraków, Poland; andrzej.surdacki@uj.edu.pl (A.S.); stanislaw.bartus@uj.edu.pl (S.B.)
10 Department of Cardiology and Cardiovascular Interventions, University Hospital, 40-055 Kraków, Poland
* Correspondence: jaanraf@interia.pl; Tel.: +48-12-400-2250; Fax: +48-12-400-2267

Received: 9 July 2020; Accepted: 25 August 2020; Published: 27 August 2020

Abstract: *Background and Objectives:* A topic already widely investigated is the negative prognostic value regarding the extent of high sensitive troponin I (hs-TnI) increases among patients with myocardial infarction (MI) and obstructive coronary atherosclerosis compared to a group of patients with MI and non-obstructive coronary atherosclerosis (MINOCA). Thus, the aim of this study was to evaluate the prognostic value concerning the extent of hs-TnI increase on clinical outcomes among patients with a MINOCA working diagnosis. *Materials and Methods:* We selected 337 consecutive patients admitted to hospital with a working diagnosis of MINOCA. The patients were divided in three groups according to the extent of hs-TnI increase during hospitalization (increase ≤5-times above the limit of the upper norm, >5 and ≤20-times, and >20-times). The study endpoints included all-cause mortality and major adverse cardiac and cerebrovascular events (MACCE; cerebral stroke and transient ischemic attacks, MI, coronary artery revascularization, either percutaneous coronary intervention or coronary artery bypass grafting and all-cause mortality). *Results:* During the mean follow-up period of 516.1 ± 239.8 days, using Kaplan–Meier survival curve analysis, significantly higher mortality rates were demonstrated among patients from the group with the greatest hs-TnI increase compared to the remaining groups ($p = 0.01$) and borderline values for MACCE ($p = 0.053$). Multivariable cox regression analysis did not confirm hs-TnI among factors related to increased MACCE or all-cause mortality rates. *Conclusion:* While a relationship between clinical outcomes and the extent of the hs-TnI increase among patients with a MINOCA working diagnosis remains, it does not seem to be not as strong as it is in patients with obstructive coronary atherosclerosis.

Keywords: clinical outcomes; myocardial infarction with non-obstructive coronary artery disease; predictors; troponin I

1. Introduction

Acute myocardial infarction (AMI) with non-obstructive coronary arteries defined as lack of relevant (over 50%) stenosis in coronary angiography has currently become an interesting topic [1]. The prevalence of myocardial infarction with non-obstructive coronary arteries (MINOCA) among patients admitted to hospital with acute coronary syndrome (ACS) is estimated to be at 6% [2,3]. Diagnosis of MINOCA is considered working, due to its various etiologies often requiring prolonged diagnostics and specific treatment [4]. During five years of observation, the mortality rate may even reach 10.9% in the group of patients with MINOCA [5]. In the ACUITY ("Acute Catheterization and Urgent Intervention Triage Strategy") trial patients with MINOCA, the 1-year death rate was higher than in the case of non-ST-segment elevation myocardial infarction (NSTEMI) patients with myocardial infarction and obstructive coronary artery disease (MI-CAD), mostly caused by non-cardiac mortality [6]. Various etiologies and complex pathomechanisms of MINOCA make identification of the underlying cause and selection of the proper clinical assessment as well as treatment extremely challenging. The negative predictive value of cardiac troponin in AMI is well-known, however, the impact of high-sensitivity troponin levels on MINOCA patients requires further investigation [7]. Therefore, the current study aimed to characterize patients with a working diagnosis of AMI. These patients demonstrated non-obstructive coronary arteries due to the extent of the high-sensitive troponin I (hs-TnI) increase. Furthermore, we aimed to assess clinical outcomes in terms of all-cause mortality and major adverse cardiac and cerebrovascular events (MACCE).

2. Materials and Methods

2.1. Study Population

We performed an observational cohort study involving patients hospitalized at two Polish academic cardiology centers. These patients had AMI with non-obstructive coronary arteries confirmed in angiography. The patients were included partially retrospectively and partially on an ongoing basis in a prospective manner. Patients and follow-up data were collected between January 2014 and December 2018. The diagnosis of AMI was made in accordance with the fourth universal definition of myocardial infarction and the 2017 working group position paper on myocardial infarction with non-obstructive coronary arteries by the European Society of Cardiology [8,9]. Also, type 2 myocardial infarction and its individual etiologies have been defined in accordance with the current European guidelines and recommended consensus [8,9]. In the current study, we included all consecutive patients with ACSs at baseline who were qualified for urgent coronary artery angiography. Its result confirmed non-obstructive coronary artery disease, and patients with unstable angina at baseline, based on subsequent determinations of myocardial necrosis markers, were reclassified to the AMI group. The exclusion criteria were qualification for coronary revascularization or the lack of confirmed AMI among patients initially diagnosed with unstable angina. Information on demographic features, cardiovascular risk factors, comorbidities, and medication were collected at admission based on detailed patient interview and medical documentation. Non-stenotic plaque was defined as stenosis in coronary artery angiography less than 50%, which was confirmed by at least two views. The plaque was defined as eccentric when the atherosclerotic plaque failed to involve the entire coronary artery circumference and left variable arc of the disease-free wall. Autoimmune and oncological diseases were diagnosed in the case of previous disease history. Previous or ongoing surgical, pharmacological, or radiation oncological treatment in the case of oncological diseases were diagnosed. Furthermore, confirmed diagnosis of the disease from autoimmunization or previous or toxic immunosuppressive

treatment associated with these diseases were also taken into consideration. Takotsubo cardiomyopathy was diagnosed according to the generally accepted recommendations [10]. Coronary artery spasm was defined as a reduction by >50% in luminal diameter assessed by coronary angiography with accompanying symptoms and/or ischemic ST-segment changes compared with post-intracoronary nitroglycerin. The study protocol was approved by the local Bioethics Committee and complied with the declaration of Helsinki. Ordinary written informed consent for coronary angiography and data collection was obtained from the patients.

2.2. Markers of Myocardial Injury

hs-TnI was determined using The ADVIA Centaur® TNIH assay (Siemens Healthcare GmbH, Erlagen, Germany), which is a device using dual-capture sandwich immunoassay using magnetic latex particles and a proprietary acridinium ester (tri-sulfo propyl acridinium ester) for chemiluminescence detection. Due to the fact that the troponin levels were estimated using different assays and upper limits, we calculated the troponin index based on the maximal troponin value measured during hospitalization in order to unify the results. The troponin index was calculated as the ratio of the maximal troponin concentration and the upper limit of the reference range for the particular assay which was based on calculating the 95% upper confidence level. We enrolled 337 consecutive patients and divided them into three groups according to troponin index. The first group included patients with mild (≤5-times above the upper normal limit), the second group with moderate (>5 to ≤20-times above the upper normal limit), and third group with a large hs-TnI increase (>20-times above the upper normal limit).

2.3. Working Diagnosis, Etiology, and Discharge Diagnosis

Working diagnosis of particular types of ACSs (AMI or unstable angina) is the concept used in the present work for patients qualified for coronary angiography (from admission to the department until the beginning of coronary angiography). Working diagnosis of MINOCA was set immediately after coronary angiography, when no significant stenosis was found in the coronary arteries, no further revascularization was required, and the diagnosis of AMI was confirmed according to the 4th universal definition of myocardial infarction. During further hospitalization, some patients changed the diagnosis depending on the clinical picture or the results of imaging and biochemical blood tests. Working etiology was set until the end of hospitalization, and it was not recognized as final or most probable etiology, due to the fact that some tests, e.g., cardiac magnetic resonance, blood tests (thrombophilia test package) or neoplastic tests (positron emission tomography) were performed after discharge from hospital and for various reasons were not considered in the final etiology. Discharge diagnosis was the diagnosis made on the discharge card, which was based on the entire clinical picture and research results collected until the patient was discharged from the hospital.

2.4. Echocardiography

All study participants underwent comprehensive two-dimensional echocardiography using Doppler and tissue Doppler imaging via commercially available ultrasound systems equipped with harmonic imaging (Vivid 9 or Vivid 95, GEHealthcare, General Electric Corp., Waukesha, WI, USA). The test was performed with the patient in left lateral decubitus position. The left ventricle ejection fraction was calculated based on the fraction area change in two dimensions. The function of the heart valves, the presence of fluid in the pericardial sac, the size of the heart cavities, and the presence of regional contractility disorders were also assessed.

2.5. Coronary Angiography

Selective coronary angiography was performed using a standard procedure via radial access. Intracoronary nitrate (100 or 200 mg) was administered before the angiographic views. Quantitative coronary angiography was performed under optimal projections with a computer-assisted coronary

angiographic analysis system (Siemens Artis Q with PURE, Siemens Healthcare GmbH, Erlagen, Germany). The coronary arteries were visualized in the left and right oblique planes with cranial and caudal angulations. The operators were not investigators. Qualification for the study was based on the description of the procedures (coronary angiography). Lesions considered angiographically non-qualifying for intravascular treatment, or in the case of borderline lesions, significance was ruled out by additional tests such as fractional coronary flow reserve measurement or intravascular ultrasound. Parietal lesions or smooth contours of the vessels were also considered eligible for the study.

2.6. Study Endpoints

Study endpoints were all-cause mortality and MACCE rates, where MACCE included all-cause mortality, cerebral stroke and transient ischemic attacks (TIA), myocardial infarction, coronary artery revascularization, either percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG). The all-cause, in-hospital mortality was assessed until discharge from hospital, while the overall all-cause mortality was calculated for the whole period (from admission to hospital until the end of follow-up period). The follow-up was carried out on the basis of documentation from the outpatient clinic, telephone calls and the database of the National Health Fund.

2.7. Statistical Analysis

Continuous variables in three selected groups of patients according to the extent of troponin increase were compared applying ANOVA, the Welch or Kruskal–Wallis test, when appropriate. Categorical variables were compared using Pearson's or Fisher's test, where applicable. Differences in all-cause mortality rates and the occurrence of MACCE between the three selected groups of patients according to the extent of troponin increase were assessed during the follow-up period via the Kaplan–Meier method and were compared using the log-rank test. All available variables were screened as potential predictors of all-cause mortality as well as MACCE. Multivariable models were constructed from all variables which were considered significant according to univariable analysis using stepwise regression with minimization of Bayes information criterion (BIC) as a target. BIC was chosen because it penalizes the complexity of models expressed as a number of parameters. Therefore, it favors less complex models with a smaller number of predictors and thus, provides some protection against over-parameterization. In a case of correlation of predictors, the stronger was favored for inclusion in the model. Multi collinearity was assessed using variance inflation factors (VIF). Assumptions of cox regression, i.e., proportional hazards were tested. The C-statistic was used as a measure of goodness-of-fit. Final models were validated using bootstraping with 1000 repetitions. Bootstrapped bias-corrected C-statistics were also presented. Results from all univariable as well as multivariable models were presented as risk ratios with 95% confidence intervals (CI). All of the analyses were performed using the SAS 9.1 system (SAS Institute Inc., Cary, NC, USA). All statistical tests were two-sided (the level of $p < 0.05$ was considered statistically significant).

3. Results

3.1. General Characteristics

The 337 patients with a working diagnosis of MINOCA were included in this study. According to the main assumption, all patients were divided into three groups, with regard to the extent of myocardial injury expressed by an increase in hs-TnI. The first group consisted of 87 (25.8%) consecutive patients with a mild hs-TnI increase. In the second group, we included 77 (22.8%) consecutive patients with a moderate hs-TnI increase. The third group comprised 173 patients (51.3%) with a severe hs-TnI increase. Considering the three selected groups of patients included in the study, the extent of troponin increase was inversely correlated with age. Patients assigned to the first group were significantly older in comparison to the other two groups (69.1 ± 10.62 years vs. 64 ± 12.91 years vs. 62.6 ± 16.37 years;

$p = 0.008$). There were no significant differences between groups in the rates obtained by females, although there was a remarkable over-representation of women.

3.2. Clinical Characteristics

Patients from the first group had a greater burden of cardiovascular risk factors, which included hyperlipidemia (66.3% vs. 45.5% vs. 35.9%; $p < 0.001$), arterial hypertension (83.7% vs. 83.1% vs. 67.8%; $p = 0.004$), and diabetes (34.9% vs. 20.8% vs. 22.2%; $p = 0.052$) when compared to the remaining two groups with greater troponin increases. Pharmacotherapy and other clinical indices are presented in Table 1.

Table 1. General patient characteristics and biochemical analysis according to the increase in high-sensitivity cardiac I troponin.

Clinical Characteristics	Concentration of High-Sensitivity Cardiac I Troponin (Increase—Times above the Upper Normal Limit)			*p*-Value
	≤5	>5 to ≤20	>20	
Age, years	69.1 ± 10.6	63.9 ± 12.9	62.6 ± 16.4	0.008
Hospitalization duration, days	4.58 ± 2.38	5.38 ± 3.45	6.06 ± 3.42	0.02
Gender, female	41 (47.1)	39 (50.6)	79 (45.7)	0.76
Arterial hypertension	72 (83.7)	64 (83,1)	116 (67.8)	0.004
Hyperlipidemia	57 (66.3)	35 (45.4)	61 (35.9)	<0.001
Diabetes	30 (34.9)	16 (20.8)	38 (22.2)	0.052
Kidney failure	15 (17.6)	7 (9.1)	19 (11.2)	0.2
Atrial fibrillation	17 (19.5)	15 (19.5)	25 (14.5)	0.46
COPD/Asthma	9 (10.5)	8 (10.4)	14 (8.2)	0.77
Autoimmune disease	2 (2,3)	5 (6.5)	7 (4.1)	0.45
Oncological disease	8 (9.3)	7 (9.1)	11 (6.5)	0.65
Hypercoagulable state	6 (7)	3 (3.9)	3 (1.8)	0.13
Smoking	22 (26.5)	19 (35.2)	12 (29.3)	0.55
Alcohol abuse	2 (2.3)	2 (2.6)	7 (4.3)	0.67
Prior myocardial infarction	30 (34.5)	16 (20.8)	37 (21.5)	0.04
Prior PCI	32 (36.8)	12 (15.6)	27 (15.8)	<0.001
Cardiac arrest	3 (3.4)	0 (0)	15 (8.8)	0.01
Prior cerebral stroke/TIA	6 (6.9)	4 (5.2)	12 (7)	0.86
Prior DVT/PE	2 (2.3)	0 (0)	4 (2.3)	0.4
Pharmacotherapy				
Acetyl salicylic acid	33 (55)	26 (42.6)	33 (22.9)	0.04
P_2Y_{12} blockers	14 (25)	8 (13.6)	10 (7)	0.002
Anticoagulants	17 (28.3)	15 (25)	14 (9.9)	0.001
Beta-blocker	38 (59.4)	28 (43.7)	42 (29.2)	<0.001
Statins	38 (59.4)	27 (44.3)	36 (25)	<0.001
Biochemical Analyses				
White blood cells, $10^3/\mu L$	8.18 ± 2.98	8.8 ± 3.12	9.98 ± 4.8	0.02
Platelet count, $10^3/\mu L$	225.9 ± 98	239.8 ± 79.8	220.5 ± 79.8	0.12
Hemoglobin, g/dL	13.5 ± 1.6	13.1 ± 1.8	12.9 ± 2.1	0.15
C-reactive protein, mg/L	13.3 ± 9.8	44.4 ± 53.9	41.1 ± 59.1	0.16
Total Cholesterol, mmol/L	4.15 ± 1.02	4.75 ± 1.1	4.5 ± 1.1	0.01
Cholesterol HDL, mmol/L	1.25 ± 0.4	1.34 ± 0.4	1.24 ± 0.4	0.45
Cholesterol LDL, mmol/L	2.24 ± 0.8	2.66 ± 1	2.58 ± 1.1	0.4
Triglycerides, mmol/L	1.48 ± 0.8	1.68 ± 1.1	1.49 ± 0.8	0.79
eGFR < 60 mL/min.	20 (25.6)	13 (19.1)	34 (25.9)	0.53
Creatinine, µmol/L	76.5 ± 34.6	68.9 ± 14.5	83.56 ± 43.9	0.23
CK-MB at admission, U/l	1.5 ± 3.1	11.7 ± 15.2	44 ± 75	<0.001
CK-MB max., U/l	30.4 ± 23.1	28.1 ± 16.4	68.6 ± 160	<0.001

CK-MB—creatine kinase myocardial band, COPD—chronic obstructive pulmonary disease, DVT—deep venous thrombosis, eGFR—estimated glomerular filtration rate, HDL—high-density lipoproteins, LDL—low-density lipoproteins, PCI—percutaneous coronary intervention, PE—pulmonary embolism, TIA—transient ischemic attack.

3.3. Biochemical Parameters

With regard to biochemical parameters, we noticed significantly greater white blood cells counts in the third group when compared to the remaining ones ($8.18 \pm 2.98 \cdot 10^3/\mu L$ vs. $8.8 \pm 3.12 \cdot 10^3/\mu L$ vs. $9.98 \pm 4.8 \cdot 10^3/\mu L$; $p = 0.02$). Total serum cholesterol concentration was significantly greater among patients from the groups characterized with higher troponin increases (4.15 ± 1.02 mmol/L vs. 4.75 ± 1.1 mmol/L vs. 4.5 ± 1.1 mmol/L; $p = 0.01$); Table 1.

3.4. Type of Acute Coronary Syndrome, Electrocardiography, and Echocardiography

The rate of patients with a STEMI working diagnosis was significantly greater in the third group compared to the other two groups (9.3% vs. 11.5% vs. 21.4%; $p < 0.001$). Significantly lower mean left ventricle ejection fraction (LVEF) was noticed in the first group in comparison to the second and third groups (43.6 ± 15.8% vs. 52.1 ± 11.8% vs. 47.8 ± 14.3%; $p < 0.001$; Table 2).

Table 2. Clinical presentation, electrocardiographic, echocardiographic, and coronary angiographic data.

	Concentration of High-Sensitivity Cardiac I Troponin (Increase—Times above the Upper Normal Limit)			***p*-Value**
	≤5	**>5 to ≤20**	**>20**	
Type of Myocardial Infarction at Admission—Working Diagnosis				
STEMI	8 (9.3)	9 (11.5)	37 (21.4)	<0.001
NSTEMI	69 (80.2)	68 (87.2)	136 (78.6)	
Unstable angina	9 (10.5)	0	0	
Electrocardiography				
ST segment elevation/LBBB	13 (15.3)	18 (23.4)	44 (25.6)	0.17
ST segment depression	21 (24.7)	20 (26)	29 (16.9)	0.16
T-wave inversion	15 (20.3)	14 (18.7)	34 (20.1)	0.95
Echocardiography				
LVEF ≥ 40%	49 (59.8)	60 (80)	114 (66,67)	0.02
Mean LVEF	43.6 ±15.8	52.1 ±11.8	47.8 ±14.3	0.001
Normal contractility	33 (39.8)	30 (40)	41 (24.4)	0.01
Present hypokinesis	32 (38.5)	26 (35.1)	72 (42.9)	0.05
Present akinesis	18 (21.7)	18 (24.3)	55 (32.7)	0.13
Pericardial effusion	2 (2.4)	5 (6.8)	15 (8.9)	0.15
Coronary Angiography				
Vascular access, radial	65 (75.6)	54 (76.1)	115 (78.8)	0.82
Non-stenotic plaques	65 (74.6)	59 (76.6)	119 (75.8)	0.95
Slow-flow contrasts	2 (2.3)	4 (5.2)	19 (11)	0.02
Eccentric plaque	2 (2.3)	3 (3.9)	1 (0.6)	0.17
Myocardial bridges	4 (4.6)	4 (5.2)	10 (5.8)	0.92
Arterial spasm	1 (1.1)	0 (0)	5 (2.9)	0.42
Thrombus	0 (0)	0 (0)	2 (1.1)	0.38

LBBB-left bundle branch block, LVEF—left ventricle ejection fraction, NSTEMI—non-ST-segment elevation myocardial infarction, STEMI—ST-segment elevation myocardial infarction.

3.5. Coronary Artery Angiography

We did not observe significant differences in the evaluated coronary artery angiography indices except for the contrast slow-flow phenomenon, which was found significantly more often in the third group than in the remaining two (2.3% vs. 2% vs. 11%; $p = 0.02$; Table 2).

3.6. Working Etiology and Discharge Diagnosis

For a significant number of patients in each group, the underlying cause of illness remained unclear, and the parentage of patients with unknown etiology was greatest in the third group when compared to the remaining two (16.1% vs. 23.4% vs. 33.4%; $p < 0.001$). The percentage of patients with type 2 myocardial infarction was significantly greater in the first, when compared to the second and third group (43.7% vs. 29.8% vs. 10.4%, $p < 0.001$) Nonetheless, the rate of patients with Takotsubo cardiomyopathy as the potential etiology of myocardial injury at admission was found most often in the third group when compared to the remaining two (0% vs. 5.2% vs. 15.5%; $p < 0.001$; Table 3).

Table 3. Working etiology of myocardial infarction determined during hospitalization according to increase in high-sensitivity cardiac I troponin.

Etiology	Concentration of High-Sensitivity Cardiac I Troponin (Increase—Times above the Upper Normal Limit)			*p*-Value
	≤5	>5 to ≤20	>20	
Unknown	14 (16.1)	18 (23.4)	58 (33.4)	0.008
Arterial spasm	0 (0)	1 (1.3)	4 (2.3)	0.34
Myocarditis	1 (1.2)	5 (6.5)	14 (8.1)	0.07
HCM	2 (2.3)	1 (1.3)	2 (1.2)	0.76
Takotsubo cardiomyopathy	0 (0)	4 (5.2)	27 (15.5)	<0.001
Slow-flow phenomenon	0 (0)	2 (2.6)	8 (4.6)	0.11
AV conduction disorders	3 (3.4)	3 (3.9)	2 (1.2)	0.31
Aortic dissection	0 (0)	1 (1.3)	1 (0.6)	0.55
Tachyarrhythmias	10 (12.6)	6 (7.8)	19 (11)	0.69
Atrial fibrillation	10 (12.6)	6 (7.8)	15 (8.7)	0.67
Arterial hypertension	13 (14.9)	9 (11.7)	4 (2.3)	<0.001
Anemia	0 (0)	0 (0)	2 (1.2)	0.38
Oncological embolization	1 (1.2)	1 (1.3)	3 (1.7)	0.92
Myocardial bridge	2 (2.3)	2 (2.6)	3 (1.7)	0.89
PE/DVT	0 (0)	0 (0)	1 (0.6)	0.62
Muscular dystrophy	0 (0)	0 (0)	1 (0.6)	0.62
Cerebral stroke	0 (0)	0 (0)	1 (0.6)	0.62
Alcoholic cardiomyopathy	0 (0)	0 (0)	1 (0.6)	0.62
Aortic valve stenosis	2 (2.3)	1 (1.3)	2 (1.2)	0.76
Antiphospholipid syndrome	0 (0)	0 (0)	1 (0.6)	0.62
Vasculitis	0 (0)	0 (0)	1 (0.6)	0.62

AV—atrio-ventricular, DVT—deep venous thrombosis, HCM—hypertrophic cardiomyopathy, PE—pulmonary embolism.

The percentage of patients with Takotsubo cardiomyopathy diagnosis at discharge from hospital remained most frequent in the third group in comparison to the others (12.1% vs. 1.3% vs. 0%; $p < 0.001$). The rate of patients with a final diagnosis of arterial hypertension (8.1% vs. 6.5% vs. 2.3%;

$p = 0.01$) and heart failure (31% vs. 3.9% vs. 11.5%; $p < 0.001$) was greatest in the first group of patients compared to the other groups (Table 4).

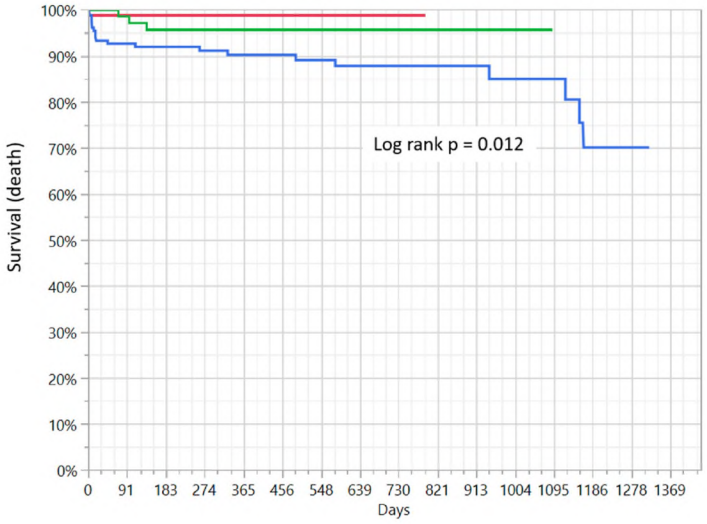
Table 4. Diagnosis at discharge and follow-up outcomes.

Selected Indices	Concentration of High-Sensitivity Cardiac I Troponin (Increase—Times above the Upper Normal Limit)			*p*-Value
	≤5	>5 to ≤20	>20	
Diagnosis at Discharge from Hospital				
Myocarditis	1 (1.1)	4 (5.2)	13 (7.5)	0.09
Takotsubo cardiomyopathy	0 (0)	1 (1.3)	21 (12.1)	<0.001
Arrhythmias	5 (5.8)	5 (6.5)	4 (2.3)	0.21
Atrial fibrillation	5 (5.8)	5 (6.5)	3 (1.7)	0.11
Arterial hypertension	7 (8.1)	5 (6.5)	2 (1.2)	0.01
Venous thromboembolic disease	0 (0)	0 (0)	1 (0.6)	0.62
NSTEMI	38 (43.7)	47 (61)	83 (48)	0.06
STEMI	3 (3.4)	4 (5.2)	14 (8.1)	0.31
Heart failure	27 (31)	3 (3.9)	20 (11.5)	<0.001
Type 2 myocardial infarction	5 (5.8)	6 (7.8)	12 (6.9)	0.87
Hypertrophic cardiomyopathy	1 (1.1)	1 (1.3)	1 (0.6)	0.81
Myocardial bridge	0 (0)	1 (1.3)	1 (0.6)	0.55
Cerebral stroke	0 (0)	0 (0)	1 (0.6)	0.62
Follow-Up				
Mean time of follow-up, days	482 ± 173	461 ± 245	566 ± 382	0.23
MACCE	4 (4.6)	7 (9.4)	28 (18.4)	0.005
Overall all-cause mortality	1 (1.1)	3 (4)	20 (13.1)	0.001
In-hospital all-cause mortality	1 (1.1)	1 (1.3)	6 (3.5)	0.39
Myocardial infarction	4 (4.6)	3 (4)	24 (15.8)	0.003
PCI	0 (0)	0 (0)	4 (2.6)	0.11
Cerebral stroke/TIA	0 (0)	3 (4)	0 (0)	0.007

MACCE—main adverse cardiac and cerebrovascular events, PCI—percutaneous coronary intervention, TIA—transient ischemic attack

3.7. Clinical Outcomes

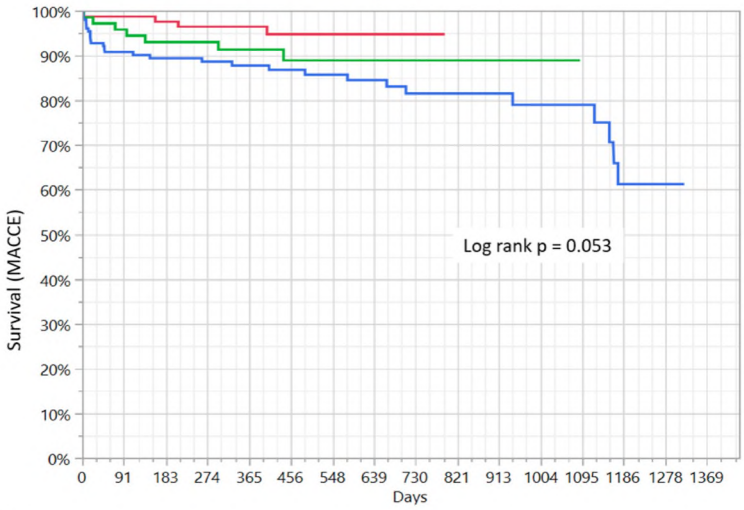
The mean duration of the follow-up period was 516.1 ± 299.9 days and did not differ significantly between groups (482 ± 173 days vs. 461 ± 245 days vs. 566 ± 382 days; $p = 0.23$). The follow-up was available for 94.5% of participants. The overall rate of MACCE was 12.1%, while the death rate was 7.5%, myocardial infarction rate was 9.5%, re-PCI 1.1% and cerebral stroke/TIA was 1.1%. The distribution of particular components of MACCE in the selected groups according to the increase in hs-TnI level is presented in Table 4. The overall incidence of MACCE was significantly greater in the third group compared to the other two (4.6% vs. 9.4% vs. 18.4%; $p = 0.005$). The overall all-cause mortality rate was also significantly greater in the third group in comparison to the first and second (1.1% vs. 4% vs. 13.1%; $p = 0.001$). Kaplan–Meier survival curves demonstrated that mortality rate during the follow-up period was significantly greater in the third group in comparison to the first and second ($p = 0.01$; Figure 1), while the MACCE rate was also greatest in the third group based on Kaplan–Meier curve analysis. However, its level did not reach statistical significance ($p = 0.053$; Figure 2).



Number of patients at risk

	0 days	180 days	360 days	540 days	720 days	900 days	1080 days	1260 days
≤5 x above ULN	86	84	61	36	10	-	-	-
>5≤20 x above ULN	73	64	44	26	11	4	2	-
>20 x above ULN	151	122	96	73	48	36	21	5
Combined	310	270	201	135	69	40	23	5

Figure 1. Comparison of Kaplan–Meier survival curves for three groups of patients depending on the extent of troponin I increase and presentation of mortality rates. ULN-upper limit of normal.



Number of patients at risk

	0 days	180 days	360 days	540 days	720 days	900 days	1080 days	1260 days
<5 x above ULN	87	85	62	36	10	-	-	-
>5<20 x above ULN	74	65	45	26	11	4	2	-
>20 x above ULN	152	123	97	74	49	37	22	5
Combined	313	273	204	136	70	41	24	5

Figure 2. Comparison of Kaplan–Meier survival curves for three groups of patients depending on the extent of troponin I increase and presentation of MACCE rates. MACCE-major adverse cardiac and cerebrovascular events, ULN-upper limit of normal.

3.8. Predictors of Clinical Outcomes

Univariate cox regression analysis demonstrated that the following were among predictors of increased risk of death rate during the follow-up period: age ($p = 0.02$); longer duration of hospitalization ($p = 0.003$); white blood cell (WBC) count ($p = 0.02$); serum creatinine concentration ($p = 0.01$); chronic kidney failure defined as estimated glomerular filtration rate (eGFR) <60 mL/min/1.72 m^2 ($p = 0.003$); cardiac arrest before admission ($p < 0.001$); chronic obstructive pulmonary disease (COPD)/bronchial asthma ($p = 0.03$); therapy with corticosteroids ($p = 0.001$); hormone replacement therapy ($p = 0.007$); alcohol abuse ($p < 0.001$); ST segment elevation/left bundle branch block when compared to other ischemic electrocardiographic changes or no changes ($p = 0.01$); presence of regional akinesis in echocardiography compared to other contractility disorders or lack thereof ($p = 0.04$); LVEF lower than 40% ($p = 0.01$); tachyarrhythmias/atrioventricular conduction disorders ($p = 0.03$); pericardial effusion ($p < 0.001$); and serum hs-TnI elevation more than 20-times above the upper normal limit compared to lower elevation greater than 5-times above the upper normal limit ($p = 0.02$). Among predictors of lower all-cause mortality rate, the following were found: chest pain at admission ($p < 0.001$); arterial hypertension ($p = 0.01$); hyperlipidemia ($p = 0.01$); therapy with beta-blockers ($p = 0.01$); body mass ($p = 0.008$); body mass index ($p = 0.02$); greater LVEF ($p = 0.02$); blood hemoglobin concentration ($p = 0.002$); higher platelet count ($p = 0.02$); and D-dimer concentration ($p = 0.01$).

Using univariate cox regression analysis, the following variables were identified as predictors of increased MACCE rate during the follow-up period: cardiac arrest before admission ($p < 0.001$); kidney failure assessed as eGFR < 60 mL/min. ($p = 0.02$); treatment with corticosteroids ($p = 0.02$); hormone replacement therapy ($p = 0.02$); alcohol abuse ($p = 0.01$); pericardial effusion ($p = 0.002$); serum hs-TnI level greater than 20-times above the upper norm in comparison to an hs-TnI level lower than 5-times above the upper normal limit ($p = 0.02$); duration of hospitalization ($p = 0.006$); serum creatinine concentration ($p < 0.001$); maximal level of creatinine kinase myocardial band ($p = 0.003$); and WBC count ($p = 0.04$). Predictors of lower MACCE rate were: presence of chest pain at admission ($p < 0.001$); hyperlipidemia ($p = 0.04$); body mass ($p = 0.01$); body mass index ($p = 0.04$); blood hemoglobin concentration ($p = 0.01$); and level of low-density lipoproteins ($p = 0.02$).

Multivariable analysis allowed to identify the following variables as significant independent predictors of increased death rate during the follow-up period: cardiac arrest at admission ($p < 0.001$); pericardial effusion ($p = 0.03$); and age ($p = 0.04$). Among the significant predictors of lower all-cause mortality rate, we found: chest pain at admission ($p < 0.001$); arterial hypertension ($p = 0.02$); and greater platelet count ($p = 0.04$). This information is presented in Figure 3A. The model was characterized by very high goodness-of-fit, with a C-statistic of 0.91 (bootstrap value of 0.88). Proportional hazard assumptions were met ($p = 0.31$).

Multivariable analysis confirmed the following to be among significant independent predictors of increased MACCE risk during the follow-up period: greater serum creatinine concentration ($p = 0.001$); greater WBC count ($p < 0.001$); and alcohol abuse ($p = 0.004$). Among the significant predictors of lower MACCE occurrence during the follow-up period the following were confirmed: higher hemoglobin concentration ($p = 0.04$) and presence of hyperlipidemia ($p = 0.02$). This is presented in Figure 3B. The model was characterized by high goodness-of-fit with a C-statistic of 0.73 (bootstrap value of 0.69). Proportional hazard assumptions were met ($p = 0.13$).

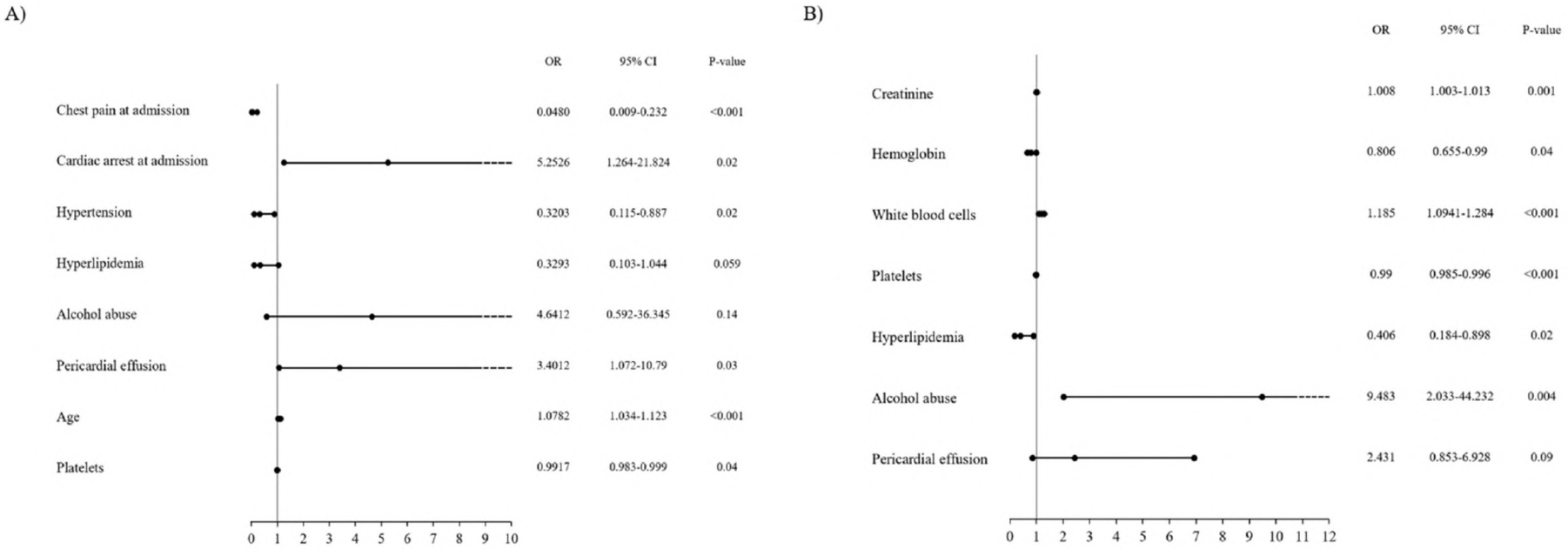


Figure 3. (**A**) Multivariable cox regression analysis regarding potential predictors of the occurrence of deaths during the follow-up period. (**B**) Multivariable cox regression analysis regarding potential predictors of the occurrence of MACCEs during the follow-up period. CI-confidence interval, OR-odds ratio.

4. Discussion

The main finding of the presented study, obtained on the basis Kaplan–Meier survival curve analysis, is that patients in the group with the greatest hs-TnI increase are related to significantly higher all-cause mortality rates during the follow-up period. A similar relationship was noted for the overall MACCE rate, however, it was not found to be statistically significant. Furthermore, this relationship was no longer significant for death and MACCE rates in multivariable analysis. Among the factors significantly related to all-cause mortality estimated in multivariable analysis during the follow-up period, we found cardiac arrest and chest pain at admission, pericardial effusion, age, arterial hypertension, and blood platelet count. Moreover, serum creatinine concentration, WBC count, alcohol abuse, hemoglobin concentration, and hyperlipidemia were found to be among the factors significantly related to MACCE rate during the follow-up. This was further confirmed in multivariate analysis.

As demonstrated in previously published studies, higher hs-TnI levels are associated with an underlying burden of coronary atherosclerosis, more rapid progression of coronary atherosclerosis, as well as higher risk of all-cause mortality and the incidence of cardiovascular events in patients undergoing cardiac catheterization and without evidence of ACS [11]. It has been observed that even a slight increase in troponin values above the upper normal limit is related to increased mortality rate during the follow-up period [12]. The extent of hs-TnI increase during hospitalization reflects the size of myocardial injury. It is simultaneously correlated with long-term prognosis, which is poorer in patients with a greater TnI increase during the first 24 h among patients with MI [13]. The duration of elevated TnI values persisting after MI is associated with increased follow-up mortality rate [1]. The role of TnI level prognostic value in patients hospitalized due to ACS with non-obstructive coronary artery disease has also been investigated [6]. Hs-TnT levels in MINOCA patients were found to be strong predictors of all-cause and cardiovascular mortality, as well as major adverse cardiac events (MACE) [6]. Hs-TnT value was demonstrated as a predictor of readmissions for heart failure but not non-fatal myocardial infarction or stroke [6]. In that study, patients with previously known coronary atherosclerosis or PCIs were excluded from the MINOCA group. The relationship between the extent of troponin increase and 1-year mortality in the MINOCA and MI-CAD groups suggested that hs-TnT was at least as prognostic in patients with MINOCA as in MI-CAD [6]. Despite the fact that the MINOCA group of patients differs in many aspects related to etiology compared to the MI-CAD group, in addition to the relationship between the degree of increase in peri-infarction TnI concentration and long-term clinical outcomes, such a relationship has been demonstrated for a number of other factors. These may include age or diabetes, which are typical follow-up risk factors among patients with MI-CAD [7]. Although a significant relationship between the degree of TnI increase and mortality was demonstrated in Kaplan–Meier curve analysis, in the current study, multivariable analysis did not confirm the significance of such a relationship, showing other factors as more important depending on the endpoint. Publications regarding long-term outcomes in patients with MINOCA predictors are less common than for patients with MI-CAD. Nevertheless, in another study, in which more than 9000 MINOCA patients were observed over a 4.5-year follow-up period, the mortality rate was 14%, while MACE was 24% [7]. We have confirmed older age, diabetes, hypertension, current smoking, previous MI, previous stroke, peripheral vascular disease, COPD, reduced LVEF, lower level of total cholesterol, and higher level of creatinine to be among the independent predictors of MACE [7]. In the case of independent predictors for all-cause deaths, age, current smoking, diabetes, cancer, COPD, previous stroke, reduced LVEF, lower level of total cholesterol, and higher levels of creatinine and c-reactive protein were found [7].

The negative impact of anemia on long-term mortality among 2011 patients with MI-CAD treated with PCIs was demonstrated in the study published by Colombo et al. [14]. Similar results were presented by Wańha et al. in a study including 1916 consecutive patients with coronary artery disease treated with PCI and stent implantation [15]. In comparison, in the current study, anemia was found to be a significant predictor of MACCE, but not death.

Furthermore, in this study, thrombocytopenia is another significant predictor of MACCE also mentioned in other studies concerning patients with MI-CAD [16]. However, in some studies, it has been shown that among patients with STEMI, an increased platelet count also worsens long-term prognosis within the context of a higher incidence of target lesion revascularizations (thrombotic complications) and the overall rate of MACE [17]. These results may indicate that, in patients with MI, the relationship between platelet counts and distant results may be U-shaped for patients with MI-CAD, whereas in the case of MINOCA, the frame considering the negative impact of increased platelet counts on distant results may have less significant impact [18].

Systemic inflammatory response is observed in ACS. A relationship between proinflammatory markers and clinical outcomes was found in patients with STEMI [19]. It has been proven that higher blood leukocyte levels are associated with higher mortality rate and in-hospital complications [20]. The higher WBC count notably correlated with intra-hospital deaths as well as long-term mortality [20]. Additionally, neutrophilia at admission was related to the significantly greater rate of adverse cardiac events in 228 patients with ACS during the mean follow-up period of 52 months [21].

In this study, higher cholesterol level appears to have had a protective effect in the MINOCA group of patients and is associated with fewer adverse events. Hypercholesterolemia is an established cardiovascular risk factor of CAD and future MACCE occurrence. Despite this fact, in the literature, we can find the so-called "hypercholesterolemia paradox", in which blood serum cholesterol levels positively correlate with the beneficial influence of remnant-like lipoprotein particles [22]. This can be partially explained by their large share in the MINOCA group and the subgroup with more severe myocardial damage expressed as greater concentration of hs-TnI in patients with moderately and severely decreased LVEF. The presence of the hypercholesterolemia paradox in the group of patients with heart failure is already sanctioned [23,24].

There are no specific publications on pericardial effusion as a predictor of MACCE. In one published study, conducted among a group of 1732 patients with STEMI, it was observed that the presence of pericardial effusion in the period following primary PCI was not independently associated with mortality [25]. To the contrary, in another study, it was demonstrated that moderate-to-large pericardial effusion complicating STEMI was a common finding (almost 25%) and is related to more severe infarcts with subsequently significantly increased MACE rates during the 1-year follow-up period. As a consequence, moderate-to-large pericardial effusion was found to be a marker of poor outcomes in patients with STEMI [26]. In the current study, pericardial effusion was an independent predictor of increased all-cause mortality during the follow-up. This could be explained, at least in part, by the presence of patients with myocarditis and concomitant pericarditis, and their influence on clinical outcomes.

Although there are reports on the positive effects of moderate alcohol consumption due to the so-called U-shape relationship of its consumption with MACCE, alcohol abuse seems to have a negative impact on both MINOCA and MI-CAD patients in terms of higher MACCE rates during the follow-up period [27]. In patients with a MINOCA diagnosis, this is mainly attributed to the negative effect of alcohol consumption on the higher rate of heart failure and related admissions to hospital due to exacerbations [28].

Renal failure expressed as elevated markers of kidney function impairment in the serum is a well-known factor related to poorer clinical outcomes in patients with MI-CAD and treated with primary PCI. Furthermore, this relationship was also confirmed in the current study on MACCE rate [29].

In patients with AMI, age seems to have greater negative impact on long-term clinical outcomes in older patients, and this was confirmed to be a predictor of increased mortality during the follow-up period in the present analysis [30].

The group of patients with MINOCA is a specific cohort, and one of the typical features of this cohort of patients is greater percentage of females in comparison to male patients with MI-CAD. It has been demonstrated that women with chest pain and suspected coronary atherosclerosis less often

present confirmed coronary atherosclerosis compared to males [31]. Johnson et al. demonstrated that females presenting non-obstructive coronary arteriosclerosis and recurrent chest pain during post-angiography 1-year follow-up, were at a higher risk of cardiovascular events [32]. Patients with recurrent chest pain and no relevant obstructive coronary atherosclerosis were found to more frequently present impaired coronary flow reserve flow and more advanced atherosclerosis with positive remodeling in intra-vascular ultrasound [33,34]. However, the lower all-cause mortality rate in patients presenting chest pain at admission in the group of patients with MINOCA is probably mostly related to delayed diagnosis and less advanced impairment of myocardial injury in terms of LVEF and microvascular circulation.

5. Conclusions

While the relationship between clinical outcomes and the extent of hs-TnI increase during hospitalization in patients with a working diagnosis of MINOCA remains visible, it is not as strong as it is in patients with obstructive coronary atherosclerosis. Prognosis in the group of patients with a working diagnosis of MINOCA at baseline is different and depends on many factors, which is mainly determined by the very diverse etiology and pathomechanisms responsible for ACS in this group of patients. Therefore, in the case of prognosis assessment in this group of patients and the decision to introduce the most appropriate treatment in order to improve its results, multi-faceted diagnostics is used to determine the dominant etiology and pathomechanism of myocardial infarction.

The use of the troponin conversion factor relative to their upper limit of the norm, in exchange for their continuous values, could have introduced bias, but in our opinion, unification of the results. Taking into account different methods of determining troponins depending on the centers and time of determination, was a priority. The use of the working MINOCA diagnosis to calculate all-cause mortality and MACCE predictors may introduce some distortions or inaccuracies, because one of these patients will eventually be removed from the MINOCA group to other groups, e.g., myocarditis or takotsubo cardiomyopathy. However, in order to carry out diagnostics in the MINOCA group, it would have to be limited to patients who have been diagnosed with other potential causes of myocardial injury. Such adiagnosis often takes several months and includes a number of tests, including those for hypercoagulability. A great limitation regarding interpretation of the research results is also associated with the relatively small group of patients, but on the other hand, in this manner, it is possible to achieve conclusions on local trends and tendencies which may contribute to determining the appropriate treatment and care over this group of patients, while improving long-term treatment results. In the present publication, we do not present the exact results of the physiological studies on coronary circulation (fractional flow reserve), intravascular ultrasound, or the exact division depending on the thickness of the atherosclerotic lesion walls and the degree of their dissemination within the coronary arteries. This may be significantly related to the assessed study endpoints, introducing significant bias.

Author Contributions: Conceptualization, R.J. and M.J.; methodology, R.J., M.J. and W.W. (Wojciech Wańha); software, K.P.M.; validation, R.J., M.J. and W.W. (Wojciech Wańha); formal analysis, K.P.M.; investigation, R.J., M.J.; resources, P.K., A.T., M.J., S.M.J. and J.B.; data curation, T.K., S.M.J., A.T., J.B. and P.K.; writing—original draft preparation, R.J., M.J. and W.W. (Wojciech Wańha); writing—review and editing, S.B., A.S. and W.W. (Wojciech Wojakowski); visualization, R.J.; supervision, A.S., W.W. (Wojciech Wojakowski), S.B. and R.J.; project administration, M.J. and R.J.; funding acquisition, S.J., A.T., P.K., T.K., B.S. and J.B. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Acknowledgments: In this section you can acknowledge any support given which is not covered by the author contribution or funding sections. This may include administrative and technical support, or donations in kind (e.g., materials used for experiments).

Conflicts of Interest: The authors declare that there are no potential conflict of interest regarding the publication of this article.

References

1. Adamson, D.P.; McAllister, D.; Pilbrow, A.; Pickering, W.J.; Poppe, K.; Shah, A.; Whalley, G.; Ellis, C.; Mills, L.N.; Newby, E.D.; et al. Convalescent troponin and cardiovascular death following acute coronary syndrome. *Heart* **2019**, *105*, 1717–1724. [CrossRef] [PubMed]
2. Chapman, A.R.; Fujisawa, T.; Lee, K.K.; Andrews, J.P.; Anand, A.; Sandeman, D.; Ferry, A.V.; Stewart, S.; Marshall, L.; Strachan, F.E.; et al. Novel high-sensitivity cardiac troponin I assay in patients with suspected acute coronary syndrome. *Heart* **2019**, *105*, 616–622. [CrossRef] [PubMed]
3. Chapman, A.R.; Lee, K.K.; McAllister, D.A.; Cullen, L.; Greenslade, J.H.; Parsonage, W.; Worster, A.; Kavsak, P.A.; Blankenberg, S.; Neumann, J.; et al. Association of high-sensitivity cardiac troponin I concentration with cardiac outcomes in patients with suspected acute coronary syndrome. *JAMA* **2017**, *318*, 1913–1924. [CrossRef] [PubMed]
4. Pasupathy, S.; Air, T.; Dreyer, R.P.; Tavella, R.; Beltrame, J.F. Systematic review of patients presenting with suspected myocardial infarction and nonobstructive coronary arteries. *Circulation* **2015**, *131*, 861–870. [CrossRef] [PubMed]
5. Chapman, A.R.; Hesse, K.; Andrews, J.; Ken Lee, K.; Anand, A.; Shah, A.S.; Sandeman, D.; Ferry, A.V.; Jameson, J.; Piya, S.; et al. High-Sensitivity cardiac troponin I and clinical risk scores in patients with suspected acute coronary syndrome. *Circulation* **2018**, *138*, 1654–1665. [CrossRef] [PubMed]
6. Hjort, M.; Lindahl, B.; Baron, T.; Jernberg, T.; Tornvall, P.; Eggers, K.M. Prognosis in relation to high-sensitivity cardiac troponin T levels in patients with myocardial infarction and non-obstructive coronary arteries. *Am. Heart J.* **2018**, *200*, 60–66. [CrossRef] [PubMed]
7. Nordenskjöld, A.M.; Baron, T.; Eggers, K.M.; Jernberg, T.; Lindahl, B. Predictors of adverse outcome in patients with myocardial infarction with non-obstructive coronary artery (MINOCA) disease. *Int. J. Cardiol.* **2018**, *261*, 18–23. [CrossRef] [PubMed]
8. Agewall, S.; Beltrame, J.F.; Reynolds, H.R.; Niessner, A.; Rosano, G.; Caforio, A.L.; De Caterina, R.; Zimarino, M.; Roffi, M.; Kjeldsen, K.; et al. WG on cardiovascular pharmacotherapy. ESC working group position paper on myocardial infarction with non-obstructive coronary arteries. *Eur. Heart J.* **2017**, *38*, 143–153. [CrossRef] [PubMed]
9. Thygesen, K.; Alpert, J.S.; Jaffe, A.S.; Chaitman, B.R.; Bax, J.J.; Morrow, D.A.; White, H.D.; Mickley, H.; Crea, F.; Van de Werf, F.; et al. ESC scientific document group. Fourth universal definition of myocardial infarction (2018). *Eur. Heart J.* **2019**, *40*, 237–269. [CrossRef] [PubMed]
10. Tsuchihashi, K. Angina pectoris-myocardial infarction investigations in Japan. Transient left ventricular apical ballooning without coronary arterystenosis: A novel heart syndrome mimicking acute myocardial infarction. Angina pectoris-myocardial infarction investigations in Japan. *J. Am. Coll. Cardiol.* **2001**, *38*, 11–18. [CrossRef] [PubMed]
11. Samman Tahhan, A.; Sandesara, P.; Hayek, S.S.; Hammadah, M.; Alkhoder, A.; Kelli, H.M.; Topel, M.; O'Neal, W.T.; Ghasemzadeh, N.; Ko, Y.A.; et al. High sensitivity troponin I Levels and coronary artery disease severity, progression, and long-term outcomes. *J. Am. Heart Assoc.* **2018**, *7*, e007914. [CrossRef] [PubMed]
12. Kaura, A.; Panoulas, V.; Glampson, B.; Davies, J.; Mulla, A.; Woods, K.; Omigie, J.; Shah, A.D.; Channon, K.M.; Weber, J.N.; et al. Association of troponin level and age with mortality in 250,000 patients: Cohort study across five UK acute care centres. *BMJ* **2019**, *367*, l6055. [CrossRef] [PubMed]
13. Lindahl, B.; Venge, P.; Wallentin, L. Relation between troponin T and the risk of subsequent cardiac events in unstable coronary artery disease. The FRISC study group. *Circulation* **1996**, *93*, 1651–1657. [CrossRef] [PubMed]
14. Colombo, M.G.; Kirchberger, I.; Amann, U.; Heier, M.; Thilo, C.; Kuch, B.; Peters, A.; Meisinger, C. Association between admission anemia and long-term mortality in patients with acute myocardial infarction: Results from the MONICA/KORA myocardial infarction registry. *BMC Cardiovasc. Disord.* **2018**, *18*, 50. [CrossRef] [PubMed]
15. Wańha, W.; Kawecki, D.; Roleder, T.; Pluta, A.; Marcinkiewicz, K.; Dola, J.; Morawiec, B.; Krzych, Ł.; Pawłowski, T.; Smolka, G.; et al. Impact of anaemia on long-term outcomes in patients treated with first-and second-generation drug-eluting stents; Katowice-Zabrze Registry. *Kardiol. Pol.* **2016**, *74*, 561–569. [CrossRef] [PubMed]

16. Sinkovič, A.; Majal, M. The impact of thrombocytopenia on outcome in patients with acute coronary syndromes: A single center retrospective study. *BioMed Res. Int.* **2015**, *2015*, 907304. [CrossRef] [PubMed]
17. Kaplan, S.; Kaplan, S.T.; Kiris, A.; Gedikli, O. Impact of initial platelet count on baseline angiographic finding and end-points in ST-elevation myocardial infarction referred for primary percutaneous coronary intervention. *Int. J. Clin. Exp. Med.* **2014**, *7*, 1064–1070. [PubMed]
18. Mueller, C.; Neumann, F.J.; Hochholzer, W.; Trenk, D.; Zeller, T.; Perruchoud, A.P.; Buettner, H.J. The impact of platelet count on mortality in unstable angina/non-ST-segment elevation myocardial infarction. *Am. Heart J.* **2006**, *151*, 1214-e1. [CrossRef] [PubMed]
19. Milwidsky, A.; Ziv-Baran, T.; Letourneau-Shesaf, S.; Keren, G.; Taieb, P.; Berliner, S.; Shacham, Y. CRP velocity and short-term mortality in ST segment elevation myocardial infarction. *Biomarkers* **2017**, *22*, 383–386. [CrossRef] [PubMed]
20. Pesaro, A.E.P.; Nicolau, J.C.; Serrano, C.V., Jr.; Truffa, R.; Gaz, M.V.B.; Karbstein, R.; Giraldez, R.R.; Kalil Filho, R.; Ramires, J.A. Influence of leukocytes and glycemia on the prognosis of patients with acute myocardial infarction. *Arq. Bras. Cardiol.* **2009**, *92*, 88–93. [CrossRef] [PubMed]
21. Takahashi, T.; Hiasa, Y.; Ohara, Y.; Miyazaki, S.I.; Ogura, R.; Suzuki, N.; Hosokawa, S.; Kishi, K.; Ohtani, R. Relationship of admission neutrophil count to microvascular injury, left ventricular dilation, and long-term outcome in patients treated with primary angioplasty for acute myocardial infarction. *Circ. J.* **2008**, *72*, 867–872. [CrossRef] [PubMed]
22. Martin, S.S.; Faridi, K.F.; Joshi, P.H.; Blaha, M.J.; Kulkarni, K.R.; Khokhar, A.A.; Maddox, T.M.; Havranek, E.P.; Toth, P.P.; Tang, F.; et al. Remnant lipoprotein cholesterol and mortality after acute myocardial infarction: Further evidence for a hypercholesterolemia paradox from the TRIUMPH registry. *Clin. Cardiol.* **2015**, *38*, 660–667. [CrossRef] [PubMed]
23. Velavan, P.; Huan Loh, P.; Clark, A.; Cleland, J.G. The cholesterol paradox in heart failure. *Congest. Heart Fail.* **2007**, *13*, 336–341. [CrossRef] [PubMed]
24. Jędrychowska, M.; Januszek, R.; Plens, K.; Surdacki, A.; Bartuś, S.; Dudek, D. Impact of sex on the follow-up course and predictors of clinical outcomes in patients hospitalised due to myocardial infarction with non-obstructive coronary arteries: A single-centre experience. *Kardiol. Pol.* **2019**, *77*, 198–206. [CrossRef] [PubMed]
25. Albani, S.; Fabris, E.; Stolfo, D.; Falco, L.; Barbati, G.; Aquaro, G.D.; Vitrella, G.; Rakar, S.; Korcova, R.; Lardieri, G.; et al. Prognostic relevance of pericardial effusion in STEMI patients treated by primary percutaneous coronary intervention: A 10-year single-centre experience. *Eur. Heart J. Acute Cardiovasc. Care* **2019**, 2048872619884858. [CrossRef] [PubMed]
26. Jobs, A.; Eitel, C.; Pöss, J.; Desch, S.; Thiele, H.; Eitel, I. Effect of pericardial effusion complicating st-elevation myocardial infarction as predictor of extensive myocardial damage and prognosis. *Am. J. Cardiol.* **2015**, *116*, 1010–1016. [CrossRef] [PubMed]
27. Pai, J.K.; Mukamal, K.J.; Rimm, E.B. Long-Term alcohol consumption in relation to all-cause and cardiovascular mortality among survivors of myocardial infarction: The health professionals follow-up study. *Eur. Heart J.* **2012**, *33*, 1598–1605. [CrossRef] [PubMed]
28. Maisch, B. Alcoholic cardiomyopathy: The result of dosage and individual predisposition. *Herz* **2016**, *41*, 484–493. [CrossRef] [PubMed]
29. Homorodean, C.; Iancu, A.C.; Dregoesc, I.M.; Spînu, M.; Ober, M.C.; Tătaru, D.; Leucuța, D.; Olinic, M.; Olinic, D.M. Renal failure impact on the outcomes of ST-segment elevation myocardial infarction patients due to a left main coronary culprit lesion treated using a primary percutaneous coronary intervention. *J. Clin. Med.* **2019**, *8*, 565. [CrossRef] [PubMed]
30. Plakht, Y.; Shiyovich, A.; Gilutz, H. Predictors of long-term (10-year) mortality post myocardial infarction: Age-related differences. Soroka Acute Myocardial Infarction (SAMI) Project. *J. Cardiol.* **2015**, *65*, 216–223. [CrossRef] [PubMed]
31. Sullivan, A.K.; Holdright, D.R.; Wright, C.A.; Sparrow, J.L.; Cunningham, D.; Fox, K.M. Chest pain in women: Clinical, investigative, and prognostic features. *BMJ* **1994**, *308*, 883–886. [CrossRef] [PubMed]
32. Johnson, B.D.; Shaw, L.J.; Pepine, C.J.; Reis, S.E.; Kelsey, S.F.; Sopko, G.; Rogers, W.J.; Mankad, S.; Sharaf, B.L.; Bittner, V.; et al. Persistent chest pain predicts cardiovascular events in women without obstructive coronary artery disease: Results from the NIH-NHLBI-sponsored Women's Ischaemia Syndrome Evaluation (WISE) study. *Eur. Heart J.* **2006**, *27*, 1408–1415. [CrossRef] [PubMed]

33. Khuddus, M.A.; Pepine, C.J.; Handberg, E.M.; Baireymerz, C.N.; Sopko, G.; Bavry, A.A.; Denardo, S.J.; McGorray, S.P.; Smith, K.M.; Sharaf, B.L.; et al. An intravascular ultrasound analysis in women experiencing chestpain in the absence of obstructive coronary artery disease: A substudy from the National Heart, Lung and Blood Institute-Sponsored Women's Ischemia Syndrome Evaluation (WISE). *J. Interv. Cardiol.* **2010**, *23*, 511–519. [CrossRef] [PubMed]
34. Mygind, N.D.; Michelsen, M.M.; Pena, A.; Frestad, D.; Dose, N.; Aziz, A.; Faber, R.; Høst, N.; Gustafsson, I.; Hansen, P.R.; et al. Coronary microvascular function and cardiovascular risk factors in women with angina pectoris and no obstructive coronary artery disease: The iPOWER study. *J. Am. Heart Assoc.* **2016**, *5*, e003064. [CrossRef] [PubMed]

6. Artykuł nr 3

Jędrychowska M, Januszek R, Wańha, Malinowski KP, Wojakowski W, Bartuś K, Surdacki A, Dudek D, Bartuś S.

Long-term prognosis in patients suffering from myocardial infarction with non-obstructive coronary arteries, ST segment elevation myocardial infarction, infective myocarditis and tako-tsubo cardiomyopathy – all-cause mortality comparison

Archives of Medical Science, 2021

Long-term prognosis in patients suffering from myocardial infarction with non-obstructive coronary arteries, ST-segment elevation myocardial infarction, infective myocarditis and tako-tsubo cardiomyopathy – all-cause mortality comparison

Magdalena Jędrychowska[1], Rafał Januszek[2], Wojciech Wańha[3], Krzysztof Piotr Malinowski[4], Wojciech Wojakowski[3], Krzysztof Bartuś[5], Andrzej Surdacki[6], Dariusz Dudek[6], Stanisław Bartuś[6]

[1]Department of Cardiology and Cardiovascular Interventions, University Hospital, Kraków, Poland
[2]University of Physical Education, Department of Clinical Rehabilitation, Kraków, Poland Department of Cardiology and Cardiovascular Interventions, University Hospital, Kraków, Poland
[3]Department of Cardiology and Structural Heart Diseases, Medical University of Silesia, Katowice, Poland
[4]Institute of Public Health, Faculty of Health Sciences, Jagiellonian University Medical College, Kraków, Poland
[5]Department of Cardiovascular Surgery and Transplantology, Jagiellonian University Medical College, John Paul II Hospital, Krakow, Poland
[6]Department of Cardiology, Jagiellonian University Medical College, Kraków, Poland; Department of Cardiology and Cardiovascular Interventions, University Hospital, Kraków, Poland

Corresponding author:
Rafał Januszek MD, PhD
Department of Cardiology and Cardiovascular Interventions
University Hospital in Kraków
ul. Jakubowskiego 2
30-688 Kraków, Poland
Phone: 0048 12 400 22 50
Fax: 0048 12 400 22 67
E-mail: jaanraf@interia.pl

Submitted: 19 April 2020
Accepted: 2 August 2020

Arch Med Sci
DOI: https://doi.org/10.5114/aoms/125934

Abstract

Introduction: Myocardial infarction with non-obstructive coronary arteries (MINOCA), tako-tsubo cardiomyopathy (TTC), infective myocarditis (IM) and acute ST-segment elevation myocardial infarction (STEMI) of anterior wall being a heterogeneous group, may occur in very similar clinical presentations. In this study, it was aimed to compare the prognosis and identify predictors of major adverse cardiac and cerebrovascular events (MACCE) and all-cause mortality in these groups of patients.

Material and methods: At 2 Polish Academic Cardiology Centres among 596 patients, we compared clinical characteristics and outcomes in 4 groups: MINOCA (318, 53.3%), TTC (31, 5.2%), IM (22, 3.7%) and STEMI (225, 37.7%). MACCE were defined as myocardial infarction (MI), revascularisation (either percutaneous or surgical), all-cause death and stroke/transient ischemic attacks. Survival curves were presented using Kaplan-Meier estimator and compared using log-rank test.

Results: Kaplan-Meier survival analysis demonstrated that in the 3-year follow-up period, patients with anterior wall STEMI were at the highest risk of MACCE ($p < 0.001$). During the follow-up period, the greatest mortality rate was observed in the TTC group, however, this was without statistical significance. Multivariable regression analysis showed that long-term mortality was significantly related to age ($p < 0.001$), creatinine level ($p < 0.001$), platelet count ($p < 0.001$), white blood cells ($p < 0.001$) and hyperlipidaemia ($p = 0.001$).

Conclusions: During the 3 years of follow-up, anterior wall STEMI had significantly poorer prognosis in terms of MACCE when compared to the TTC,

IM and MINOCA groups. TTC was related to the greatest all-cause mortality, however, without statistical significance.

Key words: anterior wall STEMI, clinical outcomes, infective myocarditis, MINOCA, tako-tsubo cardiomyopathy.

Introduction

Myocardial infarction with non-obstructive coronary arteries (MINOCA), tako-tsubo cardiomyopathy (TTC), infective myocarditis (IM) and acute ST-segment elevation myocardial infarction (STEMI) of the anterior wall, being in fact a heterogeneous group, may occur in very similar clinical presentations. The MINOCA working diagnosis, which is made at the beginning of hospitalisation, includes a heterogeneous group of diseases, which is depleted in favour of other disease entities, identified after deeper diagnostics [1]. These include, among others, imaging tests such as cardiac echocardiography, magnetic resonance imaging, a thorough family and occasional interview, and specialised biochemical blood tests.

One of the first groups of patients who are separated from the MINOCA group after performing initial tests during primary hospitalisation, such as coronary angiography, are patients with IM and TTC. Due to the fact that the clinical and echocardiographic image of patients with anterior wall STEMI is often similar to that observed in TTC, we selected patients with this diagnosis for long-term observation within the aspect of all-cause mortality, as well as major adverse cardiac and cerebrovascular events (MACCE) [2]. It has been suggested that TCC is not such a trivial condition and patients with TTC, especially males, have poor prognosis compared to STEMI and non-ST-segment elevation myocardial infarction (NSTEMI) patients [3–5]. Also, comparisons between MINOCA and TTC patients have been reported [3–5]. In several studies, the survival of MINOCA patients has been compared to those experiencing myocardial infarction with obstructive coronary arteries (MI-CAD), showing poorer outcomes in the latter group, mainly due to repeated revascularisation [6–9].

Therefore, based on patients gathered at 2 academic centres, we focused to compare clinical outcomes expressed as all-cause mortality and MACCE between patients with MINOCA, TTC, IM and anterior wall STEMI during a 3-year follow-up period. Also, we aimed to compare the results obtained with the results of other analyses that have been published so far.

Material and methods

We conducted an observational cohort study involving patients hospitalised at 2 Polish Academic Cardiology Centres. We selected 596 consecutive patients admitted to hospital with a working diagnosis of MINOCA and STEMI of the anterior wall. Then, we separated patients with TTC and IM from the MINOCA group. The differential diagnosis was based, among others, on clinical symptoms, coronary angiography, electrocardiography, echocardiography presentation, biochemical parameters and magnetic reasons imaging when necessary. Information on demographic features, risk factors, comorbidities and medication at admission was collected in a detailed patient interview and based on previous medical documentation. Patients and follow-up data were collected between January 2014 and December 2018.

The diagnosis of acute myocardial infarction was made in accordance with the fourth universal definition of myocardial infarction and the working group position paper on MINOCA published by the European Society of Cardiology [10, 11]. Pharmacological and interventional treatment were in accordance with current European Guidelines [12, 13]. Study endpoints were all-cause mortality and MACCE. The study protocol was approved by the local Bioethics Committee and complied with the declaration of Helsinki. All participants provided their written informed consent for percutaneous coronary angiography and/or percutaneous coronary intervention (PCI), when applicable.

Study endpoints

The primary study endpoint was all-cause mortality and MACCE defined as hospitalisation for myocardial infarction, re-intervention within the coronary arteries (PCI or/and coronary artery by-pass grafting) and cerebral stroke/transient ischaemic attack. We assessed all-cause mortality as well as MACCE rates at 30-days, 12- and 36-months.

Statistical analysis

Categorical variables are presented as numbers and percentages. Continuous variables are expressed as mean standard deviation or median interquartile range, where applicable. Normality was assessed using the Shapiro-Wilk test. Equality of variance was assessed via Levene's test. The Mann-Whitney U-test was used for non-normally distributed continuous variables. Categorical var-

iables were compared with Pearson's χ^2 test or Fisher's exact test if 20% of cells had an expected count of less than 5 (the Monte Carlo simulation for Fisher's test was used for tables of a higher dimension than 2 x 2). Multiple group comparisons were performed using analysis of variance or the Kruskal-Wallis test. Survival curves were presented using Kaplan-Meier estimator and compared using log-rank test. Univariable and multivariable Cox proportional hazard models were implemented to identify predictors of MACCE and death. All statistical analyses were performed with JMP®, Version 14.2.0 (SAS Institute INC., Cary, NC, USA). All statistical tests were 2-sided (the level of $p < 0.05$ was considered statistically significant).

Results

In our study, we enrolled 596 patients, among them there were 318 patients with MINOCA, 31 patients with TTC, 22 patients with IM and 225 with acute STEMI of the anterior wall.

General patient characteristics

The mean age in the overall group of patients included in the current analysis was 63.3 ±13.8 years, while in the MINOCA group: 65.1 ±13.4; TTC group: 70.7 ±13.0; IM group: 43.7 ±16.2 and STEMI group: 61.6 ±12.2 ($p < 0.001$). Women were more prevalent in the STEMI group in comparison to other groups ($p < 0.001$). These and other clinical characteristics of indices are presented in Table I.

Biochemical indices

Considering all of the assessed groups of patients, the peak serum troponin I concentrations were highest in the STEMI group and the lowest in MINOCA group (157.1 vs. 14.0 x above upper limit of normal, $p < 0.001$). The mean blood haemoglobin concentration in the TTC and MINOCA groups was significantly lower when compared to other groups ($p < 0.001$). Biochemical analyses in the selected groups of patients are presented in Table II.

Electrocardiography, echocardiography and procedural indices

Assessing the frequency of the type of myocardial infarction diagnosed at admission, we revealed that patients from MINOCA and TTC group were more likely to present as NSTEMI rather than STEMI ($p < 0.001$). Patients from TTC and STEMI group had significantly lower left ventricle ejection fraction (LVEF) compered to MINOCA and IM group ($p < 0.001$). These and other electrocardiographic, echocardiographic and procedural indices are presented in Table III.

Study endpoints

The 30-day all-cause mortality was the highest in TTC group (7.4%) and was followed by the MINOCA (3.3%) and STEMI group (2.2%), nonetheless, this difference remained without statistical significance. Also, 1-year mortality was the greatest in the TTC group (11.1%) compared to the STEMI (6.7%) and MINOCA groups (5.3%), and was also without statistical significance. At 3 years, the all-cause mortality remained the highest in the TTC group, however, it become comparable to the anterior STEMI group (11.1% vs. 9.8%), and did not differ statistically significantly between all 4 groups of patients (Table IV). Lack of significance was also confirmed by Kaplan-Meier curves analysis (Figure 1). Considering MACCE rates, at 30 days, the highest MACCE incidence was present in the TTC (7.4%) and STEMI groups (6.7%), and there were no statistically significant differences between the 4 analysed groups. At 1 year, the MACCE rate was significantly greater in the STEMI group (25.8%) in comparison to the TTC (14.8%), MINOCA (8.3%) and IM groups (0%, $p < 0.001$). At 3 years, the MACCE rate was the highest in the STEMI group (32%) when compared to the TTC (14.8%), MINOCA (11.3%) and IM groups (0%, $p < 0.001$). This is presented in Table IV. The significance of MACCE rate differences was also confirmed by Kaplan-Meier curves analysis (Figure 2). When considering particular components of MACCE after 3 years of follow-up in the STEMI group, the values reached 42% for re-PCIs, 23% regarding deaths, 27% for MIs and 8% concerning cerebral stroke. In the MINOCA group, deaths totalled 38%, 6.6% re-PCIs, 6.6% cerebral strokes and 49% MIs. In the TTC group, deaths comprised 37.5%, 12.5% re-PCIs and 50% MIs. There were no MACCEs at the time of the 3-year follow-up period in the IM group.

Predictors of all-cause mortality and major adverse cardiac and cerebrovascular events

The results of univariable and multivariable analysis used to identify variables as significant predictors of the frequency of MACCEs during the 3-year long follow-up period in the overall group of patients are presented in Table V.

While evaluating predictors of all-cause mortality, the results of univariable and multivariable analysis are presented in Table V.

Discussion

The main finding of the current analysis is that the frequency of MACCEs was significantly higher in the STEMI group at 1 and 3 years of follow-up when compared to other groups, and this was confirmed by Kaplan-Meier survival curves anal-

Table I. General patient characteristics in selected groups of patients at baseline

Clinical parameter	Overall *N* = 596	MINOCA *n* = 318	TCC *n* = 31	IM *n* = 22	STEMI – anterior wall *n* = 225	*P*-value
Age [years]	63.3 ±13.8	65.1 ±13.4	70.7 ±13.0	43.7 ±16.2	61.6 ±12.2	< 0.001
Hospitalisation time (days)	5.6 ±3.2 5 (4 ÷ 7)	5.2 ±3.3 5 (3 ÷ 6)	6.4 ±2.5 7 (4 ÷ 8)	6.8 ±1.5 7 (5.75 ÷ 8)	5.9 ±3.3 5 (4 ÷ 7)	0.007
Gender, female	333/596 (55.9)	154/318 (48.4)	7/31 (22.6)	13/22 (59.1)	159/225 (70.7)	< 0.001
Arterial hypertension	423/584 (72.4)	243/314 (77.4)	22/31 (70.8)	10/22 (45.4)	148/217 (68.2)	0.007
Hyperlipidemia	281/583 (48.2)	151/314 (48.1)	12/31 (38.7)	2/21 (9.5)	116/217 (53.4)	0.001
Diabetes	157/584 (26.7)	87/314 (27.7)	4/31 (12.9)	0/22 (0)	66/217 (30.4)	0.001
COPD/bronchial asthma	42/494 (8.5)	33/314 (10.5)	2/31 (6.4)	1/22 (4.5)	6/127 (4.7)	0.22
Autoimmune disease	20/588 (3.4)	13/314 (4.1)	1/31 (3.2)	0/21 (0)	6/222 (2.7)	0.79
Prior oncological disease	42/587 (7.2)	27/313 (8.6)	2/31 (6.4)	1/21 (4.7)	12/222 (5.4)	0.53
Smoking	151/423 (35.7)	57/189 (30.1)	2/7 (28.6)	5/11 (45.4)	87/216 (40.3)	0.14
Prior-MI	126/589 (21.4)	76/317 (24.0)	8/31 (25.8)	2/22 (9.1)	40/219 (18.2)	0.18
Prior-PCI	108/588 (18.4)	72/316 (22.8)	5/31 (16.1)	0/22 (0)	31/219 (14.2)	0.005
Cardiac arrest at baseline	44/594 (7.4)	23/316 (7.3)	2/31 (6.4)	0/22 (0)	19/225 (8.4)	0.66
Prior cerebral stroke/TIA	27/398 (6.8)	22/317 (6.9)	2/31 (6.4)	0/22 (0)	3/28 (10.7)	0.57

COPD – chronic obstructive pulmonary disease, MI – myocardial infarction, MINOCA – myocardial infarction with non-obstructive coronary arteries, TCC – tako-tsubo cardiomyopathy, IM – infective myocarditis, PCI – percutaneous coronary intervention, STEMI – ST-segment elevation myocardial infarction, TIA – transient ischemic attack.

Table II. Biochemical analysis in selected groups of patients at baseline

Selected laboratory tests	Overall *N* = 596	MINOCA *n* = 318	TCC *n* = 31	IM *n* = 22	STEMI – anterior wall *n* = 225	*P*-value
White blood cells [*10^3/µl]	10.5 ±6.4	9.1 ±4.3	10.4 ±3.1	9.2 ±2.6	12.5 ±8.4	< 0.001
Platelet count [*10^3/µl]	228.7 ±77.4	224.3 ±86.9	228.4 ±59.4	240.2 ±48.3	233.4 ±68.1	< 0.001
Haemoglobin [g/dl]	13.6 ±1.9	13.1 ±1.9	12.7 ±2.0	13.7 ±1.7	14.4 ±1.6	< 0.001
eGFR < [60 ml/min.]	93/529 (17.6)	58/261 (22.2)	10/21 (47.6)	1/22 (4.5)	24/225 (10.7)	< 0.001
Creatinine [µmol/l]	81.4 ±36.7	81.8 ±39.8	87.8 ±60.5	76.4 ±20.7	80.6 ±28.9	0.95
Maximum troponin [µg/l x above ULN]	166.4 ±267.6 54.8 (9.4 ÷ 213.6)	73.29 ±258.08 14 (3.1 ÷ 66)	175.3 ±294.38 83.5 (49 ÷ 206.5)	289.3 ±402.1 120.8 (14.8 ÷ 404.1)	271.6 ±513.7 157.1 (51.3 ÷ 400.1)	< 0.001
Troponin increase:						< 0.001
≤ 3 * above ULN	72/564 (12.8)	70/288 (24.3)	0/31 (0)	1/20 (5)	2/225 (0.9)	
> 3 ≤ * 10 above ULN	69/564 (12.2)	55/288 (19.1)	1/31 (3.2)	5/20 (25)	10/225 (4.4)	
> 10 * above ULN	423/564 (75)	163/288 (56.6)	30/31 (96.8)	14/20 (75)	213/225 (94.7)	
Troponin increase:						< 0.001
≤ 5 * above ULN	91/562 (16.2)	86/286 (30.1)	0/31 (0)	1/20 (5)	4/225 (1.8)	
> 5 ≤ 20 * above ULN	96/562 (17.1)	68/286 (23.8)	4/31 (12.9)	5/20 (25)	19/225 (8.4)	
> 20 * above ULN	375/562 (66.7)	132/286 (46.1)	27/31 (87.1)	14/20 (75)	202/225 (89.8)	
CK-MB max. [ng/ml]	116.6 ±170.2 48 (28 ÷ 130.2)	60.7 ±153.8 29.5 (20 ÷ 52.5)	37.9 ±24.3 29 (25 ÷ 42.5)	56.4 ±38.2 52 (32 ÷ 70)	168.7 ±179.7 98 (43 ÷ 233)	< 0.001

MINOCA – myocardial infarction with non-obstructive coronary arteries, TCC – tako-tsubo cardiomyopathy, IM – infective myocarditis, CK-MB – creatine kinase myocardial band, GFR – glomerular filtration rate, STEMI – ST-segment elevation myocardial infarction, ULN – upper limit of normal.

Table III. Clinical echocardiographic procedure-related indices at baseline according to selected group

Selected indices	Overall *N* = 596	MINOCA *n* = 318	TCC *n* = 31	IM *n* = 22	STEMI – anterior wall *n* = 225	*P*-value
Clinical presentation at admission						
NSTEMI	297/595 (49.9)	262/317 (82.6)	22/31 (71)	13/22 (59.1)	0/225 (0)	< 0.001
STEMI	289/595 (48.6)	46/317 (14.5)	9/31 (29)	9/22 (40.9)	225/225 (100)	
Unstable angina	9/595 (1.5)	9/317 (2.8)	0/31 (0)	0/22 (0)	0/225 (0)	
Echocardiography						
LVEF ≥ 40%	319/580 (55)	291/307 (71.3)	9/31 (29)	17/22 (77.3)	74/220 (33.6)	< 0.001
Mean LVEF	44.3 ±13.6	48.4 ±14.3	36.9 ±13.3	51.3 ±10.1	38.9 ±10.3	< 0.001
Coronary angiography						
Vascular access (radial)	272/540 (50.4)	218/293 (74.4)	22/25 (88)	17/18 (94.4)	15/204 (7.3)	< 0.001

LVEF – left ventricle ejection fraction, MINOCA – myocardial infarction with non-obstructive coronary arteries, TCC – takotsubo cardiomyopathy, IM – infective myocarditis, NSTEMI – non-ST-segment elevation myocardial infarction, STEMI – ST-segment elevation myocardial infarction.

Table IV. Study endpoints

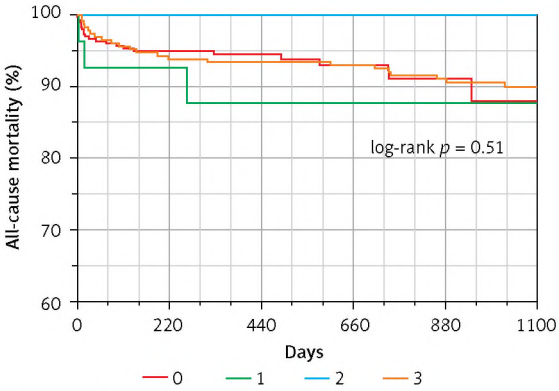
Laboratory tests	Overall *N* = 596	MINOCA *n* = 318	TCC *n* = 31	IM *n* = 22	STEMI – anterior wall *n* = 225	*P*-value
MACCE 30 days	30/575(5.2)	13/301 (4.3)	2/27 (7.4)	0/22 (0)	15/225 (6.7)	0.26
MACCE 365 days	87/575 (15.1)	25/301 (8.3)	4/27 (14.8)	0/22 (0)	58/225 (25.8)	< 0.001
MACCE 1,100 days	110/575 (19.1)	34/301 (11.3)	4/27 (14.8)	0/22 (0)	72/153 (32)	< 0.001
Overall mortality 30 days	17/575 (2.9)	10/301 (3.3)	2/27 (7.4)	0/22 (0)	5/225 (2.2)	0.35
Overall mortality 365 days	34/575 (5.9)	16/301 (5.3)	3/27 (11.1)	0/22 (0)	15/225 (6.7)	0.24
Overall mortality 1,100 days	45/575 (7.8)	20/301 (6.6)	3/27 (11.1)	0/22 (0)	22/225 (9.8)	0.12

MACCE – major adverse cardiac and cerebrovascular events, MINOCA – myocardial.infarction with non-obstructive coronary arteries, TCC – tako-tsubo cardiomyopathy, IM – infective myocarditis, STEMI – ST-segment elevation myocardial infarction.

ysis. While all-cause mortality was the greatest in TTC group when compared to other groups at following time points of the observation period, the difference did not reach statistical significance. The main component of MACCE in the STEMI group, which outweighed the significance, were reinterventions. Prior-PCI, maximal creatine kinase myocardial band (CK-MB), haemoglobin concentration, white blood cells, platelet count, age and serum creatinine concentration were among the independent predictors of all-cause mortality and MACCE.

Although MINOCA, TTC, IM and acute anterior wall STEMI have different pathogenesis, they may be visible as very similar clinical presentations, posing some difficulties in differentiating diagnosis. In recent years, the number of STEMIs has slightly decreased, whereas the number of cases of other acute cardiovascular diseases including TTC, MINOCA or viral myocarditis have experienced an increase [14, 15]. This process is associated with the general trend of decreasing STEMI infarction rates for NSTEMI, but also the prevalence of additional diagnostic imaging tests such as cardiac magnetic resonance imaging, which is recently being more frequently used in the diagnosis of MINOCA [16]. Discussing the all-cause mortality, although there were no statistically significant differences among the 4 examined groups, surprisingly enough, the highest death rates in short- (30 days) and long-term (3 years) follow-up were visible in the TCC group.

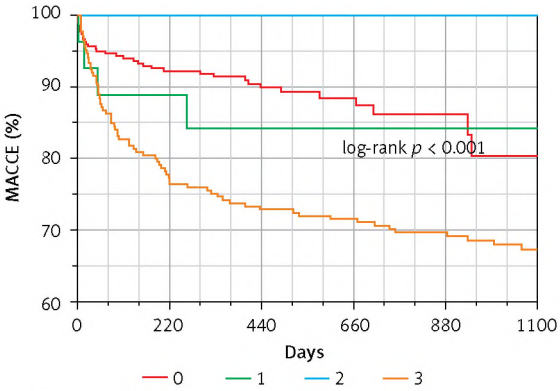
Referring to the results of other studies, in a recent, broad systematic review and meta-regression study, the overall mortality rate was calculated during the median follow-up of 28 months at 10.2% [17]. Comparing these results to those obtained in our study, long-term, all-cause mortality among patients with TCC was at the level of 11.1% after 3 years of follow-up. While in the report from the SWEDEHEART registry published by Redfors *et al*., 30-day mortality among TCC patients totalled 4.1% and was comparable to the STEMI and NSTEMI groups [2]. In our study, the 30-day mortality rate in the TCC group was higher than that reported by Redfors *et al*,. and the



Number at risk by time

Group 0 – MINOCA						
297	263	169	85	31	18	
Group 1 – Takotsubo cardiomyopathy						
27	19	14	10	7	2	
Group 2 – Myocarditis						
22	19	12	7	4	1	
Group 3 – Anterior wall STEMI						
225	211	210	209	176	132	

Figure 1. Comparison of Kaplan-Meier survival curves of all-cause mortality between selected groups of patients (myocardial infarction with non-obstructive coronary arteries, tako-tsubo cardiomyopathy, ST-segment elevation myocardial infarction and infective myocarditis) during the 3-year follow-up period



Number at risk by time

Group 0 – MINOCA						
297	263	169	85	32	18	
Group 1 – Takotsubo cardiomyopathy						
27	19	14	10	7	2	
Group 2 – Myocarditis						
22	19	12	7	4	1	
Group 3 – Anterior wall STEMI						
225	175	164	161	129	91	

Figure 2. Comparison of Kaplan-Meier survival curves of MACCE incidence between selected groups of patients (myocardial infarction with non-obstructive coronary arteries, tako-tsubo cardiomyopathy, ST-segment elevation myocardial infarction and infective myocarditis) during the 3-year follow-up period

rate for anterior-wall STEMI patients included in the current analysis (7.4 % vs. 2.2%). Subjectivity of the results may have partially been affected by the very small group of patients with TCC in our study compared to the study published by Redfors *et al.* (302 patients) or Pellicia *et al.* (4,679 patients). Another important factor that could have influenced the results was significant over-representation of males in the group of patients with TCC in our study. Comparing men and women, Misumida *et al.* indicated that in-hospital mortality rate among males with TCC was slightly higher than among women (8.4 % vs. 3.6%) [18]. In yet another analysis, a higher in-hospital mortality, longer intensive care stay and higher frequency of sever heart failure was demonstrated among men with TCC compared to women [19]. According to subgroup analysis from the Tokyo Cardiovascular Care Unite network registry, patients with physically triggered TCC, which appeared more often among men, had higher non-cardiac mortality rates than patients with acute anterior myocardial infarction (7% vs. 1.1%) [1, 20].

Interestingly, in gender-based comparisons of TCC vs. myocardial infarction, the mortality of male patients with TCC was significantly higher compared to acute coronary syndrome in MI-CAD patients [21]. Inversely, in acute STEMI, women seem to have poorer outcomes than men [22]. However, in our analysis, the majority of patients for the anterior wall STEMI group were females. It may be suspected that if the gender ratio were inversed in the anterior wall STEMI group, then all-cause mortality in TCC group would became significantly greater than in the anterior wall STEMI group. But also, in case of higher frequency of females in the TCC group, which is usually observed in other studies, then this relationship would also became balanced.

In long-term observation (5 years), the all-cause death rate in STEMI patients was at the level of 20.7% [23]. In our study, it reached 9.8% among patients in the anterior wall STEMI group. This may be the result of the shorter follow-up duration (3 years) [23]. Another factor is the specifics of the group, which was burdened to anterior wall STEMI patients, and not all STEMI patients. Whereas the short- and long-term mortality rates presented in our study were lower among anterior wall STEMI than TCC patients; in long-term observation, the MACCE rate was statistically significantly higher in the anterior wall STEMI group (32% vs. 14.8%). While assessing the burden of cardiovascular risk factors in the present study, the frequency of patients with arterial hypertension was similar in all groups. There was statistically more patients with hyperlipidaemia and diabetes in the anterior wall STEMI group compared to other groups, which may be directly related to a greater number MACCEs during follow-up. This could be related to the higher rate of re-interventions in the anterior wall STEMI group when compared to other groups. This remains with agreement with other results reported in published studies [6]. Overall mortality in the MINOCA group in our study ranged from 3.3% at 30 days of observation to 6.6% in at the 3-year

Table V. Predictors of long-term mortality and major adverse cardiac and cerebrovascular events in the overall group of patients

Predictor	Univariable		Multivariable	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
MACCE				
Gender: female vs. male	1.493 (1.004–2.218)	0.047		
Body mass index > 30 kg/m^2	0.35 (0.175–0.702)	0.003		
STEMI vs. NSTEMI at baseline	2.519 (1.641–3.865)	< 0.001		
STEMI ant. vs. MINOCA	2.511 (1.66–3.798)	< 0.001		
STEMI ant. vs. TCC	1.848 (0.674–5.065)	< 0.001		
MINOCA vs. TCC	0.735 (0.261–2.074)	< 0.001		
Duration of hospitalisation (days)	1.09 (1.043–1.133)	< 0.001		
Cardiac arrest at baseline	2.112 (1.205–3.702)	0.009		
Prior percutaneous coronary intervention	1.511 (0.977–2.336)	0.063	1.843 (1.124–3.023)	0.015
Femoral vs. radial access	2.159 (1.398–3.336)	< 0.001		
LVEF (%)	0.974 (0.96–0.988)	< 0.001		
LVEF < 40%	2.101 (1.423–3.102)	< 0.001	1.68 (1.066–2.646)	0.025
Hs-TnI (times above ULN)	1.001 (1.0006–1.0014)	< 0.001		
Hs-TnI increase, group 3 vs. 2	1.79 (0.868–3.69)	0.004		
Hs-TnI increase, group 2 vs. 1	3.123 (0.828–11.773)	0.004		
Hs-TnI increase, group 3 vs. 1	5.591 (1.769–17.67)	0.004		
Hs-TnI increase, group 6 vs. 4	3.651 (1.593–8.365)	0.001		
Hs-TnI increase, group 6 vs. 5	2.049 (1.093–3.837)	0.001		
Hs-TnI increase, group 5 vs. 4	1.781 (0.658–4.8190	0.001		
CK-MB max.	1.0017 (1.0008–1.0025)	< 0.001	1.001 (1.000–1.002)	0.044
Creatinine [µmol/l]	1.003 (0.999–1.006)	0.039		
Haemoglobin [g/dl]	1.009 (0.912–1.122)	0.853	0.89 (0.796–0.996)	0.044
White blood cells, × 10^3	1.013 (0.992–1.027)	0.107	1.053 (0.998–1.111)	0.055
Platelet count, × 10^3	0.997 (0.994–1.0005)	0.127	0.995 (0.992–0.999)	0.016
All-cause mortality				
Age (years)	1.042 (1.017–1.068)	< 0.001	1.049 (1.023–1.075)	< 0.001
Age > 70 years	2.236 (1.242–4.026)	0.007		
Duration of hospitalisation (days)	1.12 (1.055–1.177)	< 0.001		
Creatinine [µmol/l]	1.005 (0.999–1.009)	0.017	1.009 (0.99–1.004)	< 0.001
Glomerular filtration rate [ml/min.]	0.978 (0.967–0.99)	< 0.001		
Glomerular filtration rate < 60 ml/min.	3.765 (1.907–7.434)	< 0.001		
LVEF (%)	0.954 (0.933–0.976)	< 0.001		
LVEF < 40%	3.375 (1.704–6.685)	< 0.001		
Hs-TnI (times above ULN)	1.0008 (1.000–1.0015)	0.026		
Hyperlipidemia	0.353 (0.182–0.684)	0.002	0.3 (0.146–0.616)	0.001
White blood cells, × 10^3	1.014 (0.974–1.034)	0.3	1.121 (1.05–1.198)	< 0.001
Haemoglobin [g/dl]	0.814 (0.71–0.944)	0.004		
Platelet count, × 10^3	0.994 (0.989–0.999)	0.024	0.991 (0.985–0.996)	< 0.001
Cardiac arrest at baseline	2.592 (1.155–5.819)	0.02		

MACCE – major adverse cardiac and cerebrovascular events, LVEF – left ventricle ejection fraction, TCC – takotsubo cardiomyopathy, ULN – upper limit of normal, CK-MB – maximal creatine kinase myocardial band, hs-TnI – high-sensitivity troponin I, group 1 – hs-TnI ≤ 3 × above ULN, group 2 – hs-TnI > 3 ≤ 10 × above ULN, group 3 – > 10 × above ULN, group 4 – hs-TnI ≤ 5 × above ULN, group 5 – hs-TnI > 5 ≤ 20 × above ULN, group 6 –hs-TnI > 20 × above ULN.

follow-up, which seems to be in accordance with recent publications in which the1-year follow-up mortality rate was estimated at 4.7% [24]. The group of patients with the best outcomes in which we did not observe deaths or MACCEs in the long-term, 3-year follow-up, was the group of patients with infectious myocarditis. In comparison to the results of other published studies, one of the retrospective multicentre registries reported cardiac mortality in uncomplicated cases to be at 0%, and there were no AM-related cardiac events after 5 years of follow-up among these patients [25].

Another issue worth mentioning in the current study is that higher body-mass index values and presence of hyperlipidaemia were found to be statistically significant predictors of better clinical outcomes in the overall group of assessed patients. Although it has been previously reported in MINOCA patients as the so-called "cholesterol paradox", reports involving patients with TCC or STEMI patients are rare [26]. In one such study, no differences were demonstrated in mortality among obese or non-obese TCC patients [27]. In another study, the all-cause mortality was lower in older, overweight and obese patients with myocardial infarction in comparison to normal-weight patients [28].

Among other significant predictors of all-cause mortality, we also found increased level of creatinine, which is a well-known and sanctioned predictor of poorer clinical outcomes in this group of patients and was also confirmed in another study which revealed that GFR < 60 ml/min. was an independent predictor of 5-year mortality [19].

Similarly to the previously published study by our team, female gender was found to be an independent predictor of MACCE (p = 0.047) in univariable analysis, nonetheless, its significance was not confirmed by multivariable analysis [29]. Somehow, it has to be mentioned that the ratio of males vs. females in the current analysis is different when compared the previous one.

Among further independent predictors of all-cause mortality and MACCE rate, we found prior-PCI, maximal serum CK-MB level, blood haemoglobin concentration, white blood cell and platelet count. Lower haemoglobin concentration seems to be especially meaningful among MINOCA patients who presented significantly lower blood haemoglobin concentration in comparison to other groups. This can be mainly driven by its association with the supply/demand mismatch accountable for myocardial infarction type 2. That was also confirmed by Jesus Espinosa Pascal *et al.* in a vast study conducted among MINOCA patients [30]. Patients with myocarditis were younger and had fewer traditional risk factors for coronary heart disease, which undoubtedly influenced MACCE and all-cause mortality during the follow-up period.

In conclusion, during the 3-year follow-up period, anterior wall STEMI had significantly poorer prognosis in terms of MACCE when compared to the TTC, IM and MINOCA groups. TTC was related to the greatest all-cause mortality, however, this was without statistical significance. The analysis allowed to compare the results of treatment between selected groups of patients limited to 2 academic centres and to confront them with the results of other studies, as well as to identify subgroups of patients with the worst prognosis in terms of predictors. Local data often differ significantly from data obtained in multicentre studies, which allows adjusting the care of patients in selected groups of patients and thus improving treatment results in dedicated centres.

Conflict of interest

The authors declare no conflict of interest.

References

1. Rakowski T, De Luca G, Siudak Z, et al. Characteristics of patients presenting with myocardial infarction with non-obstructive coronary arteries (MINOCA) in Poland: data from the ORPKI National Registry. J Thromb Thrombolysis 2019; 47: 462-6.
2. Isogai T, Yoshikawa T, Ueda T, et al. Apical tako-tsubo syndrome versus anterior acute myocardial infarction: findings from the Tokyo Cardiovascular Care Unit network registry. Eur Heart J Acute Cardiovasc Care 2019; 8: 86-95.
3. Redfors B, Vedad R, Angerås O, et al. Mortality in tako-tsubo syndrome is similar to mortality in myocardial infarction – a report from the SWEDEHEART registry. Int J Cardiol 2015; 185: 282-9.
4. Zalewska-Adamiec M, Malyszko J, Bachórzewska-Gajewska H, et al. Tako-tsubo syndrome – fatal prognosis of patients with low Body Mass Index in 5-year follow-up. Arch Med Sci 2019; 16: 282-8.
5. Zandecki Ł, Janion M, Sadowski M, et al. Associations of changes in patient characteristics and management with decrease in mortality rates of men and women with ST-elevation myocardial infarction – a propensity score-matched analysis. Arch Med Sci 2020; 16: 772-80.
6. Dastidar AG, Baritussio A, De Garate E, et al. Prognostic role of CMR and conventional risk factors in myocardial infarction with nonobstructed coronary arteries. JACC Cardiovasc Imaging 2019; 12: 1973-82.
7. Y-Hassan S. Most of the patients classified under "Myocardial infarction with non-obstructive coronary arteries (MI-NOCA)" have either no MI or no NOCA. Int J Cardiol 2019; 294: 54.
8. Pathik B, Raman B, Mohd Amin NH, et al. Troponin-positive chest pain with unobstructed coronary arteries: incremental diagnostic value of cardiovascular magnetic resonance imaging. Eur Heart J Cardiovasc Imaging 2016; 17: 1146-52.
9. Choo EH, Chang K, Lee KY, et al. KAMIR-NIH Investigators. Prognosis and predictors of mortality in patients

suffering myocardial infarction with non-obstructive coronary arteries. J Am Heart Assoc 2019; 8: e011990.
10. Thygesen K, Alpert JS, Jaffe AS, et al. ESC Scientific document group. Fourth universal definition of myocardial infarction (2018). Eur Heart J 2019; 40: 237-69.
11. Agewall S, Beltrame JF, Reynolds HR, et al. WG on cardiovascular pharmacotherapy. ESC working group position paper on myocardial infarction with non-obstructive coronary arteries. Eur Heart J 2017; 38: 143-53.
12. Ibanez B, James S, Agewall S, et al. ESC Scientific Document Group. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: the task force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). Eur Heart J 2018; 39: 119-77.
13. Roffi M, Patrono C, Collet JP, et al. ESC Scientific Document Group. 2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: task force for the management of acute coronary syndromes in patients presenting without persistent ST-Segment elevation of the European Society of Cardiology (ESC). Eur Heart J 2016; 37: 267-315.
14. Sugiyama T, Hasegawa K, Kobayashi Y, et al. Differential time trends of outcomes and costs of care for acute myocardial infarction hospitalizations by ST-elevation and type of intervention in the United States, 2001–2011. J Am Heart Assoc 2015; 4: e001445.
15. McManus DD, Gore J, Yarzebski J, et al. Recent trends in the incidence, treatment, and outcomes of patients with STEMI and NSTEMI. Am J Med 2011; 124: 40-7.
16. Heidecker B, Ruedi G, Baltensperger N, et al. Systematic use of cardiac magnetic resonance imaging in MINOCA led to a five-fold increase in the detection rate of myocarditis: a retrospective study. Swiss Med Wkly 2019; 149: w20098.
17. Pelliccia F, Pasceri V, Patti G, et al. Long-term prognosis and outcome predictors in tako-tsubo syndrome: a systematic review and meta-regression study. JACC Heart Fail 2019; 7: 143-54.
18. Misumida N, Ogunbayo GO, Kim SM, et al. Clinical Outcome of tako-tsubo cardiomyopathy diagnosed with or without coronary angiography. Angiology 2019; 70: 56-61.
19. Pérez-Castellanos A, Martínez-Sellés M, Mejía-Rentería H, et al. Tako-tsubo Syndrome in Men: rare, but with poor prognosis. Rev Esp Cardiol (Engl Ed) 2018; 71: 703-8.
20. Uribarri A, Núñez-Gil IJ, Conty DA, et al. RETAKO investigators. Short- and long-term prognosis of patients with tako-tsubo syndrome based on different triggers: importance of the physical nature. J Am Heart Assoc 2019; 8: e013701.
21. Giannakopoulos K, El-Battrawy I, Gietzen T, et al. Gender-based comparison of tako-tsubo syndrome versus myocardial infarction. QJM 2019; 112: 355-62.
22. Pancholy SB, Shantha GP, Patel T, Cheskin LJ. Sex differences in short-term and long-term all-cause mortality among patients with ST-segment elevation myocardial infarction treated by primary percutaneous intervention: a meta-analysis. JAMA Intern Med 2014; 174: 1822-30.
23. Yaku H, Shiomi H, Morimoto T, et al. Comparison of short- and long-term mortality between ST-segment elevation and non-ST-segment elevation myocardial infarction. J Am Coll Cardiol 2016; 67, Suppl. 13.
24. Pasupathy S, Air T, Dreyer RP, Tavella R, Beltrame JF. Systematic review of patients presenting with suspected myocardial infarction and nonobstructive coronary arteries. Circulation 2015; 131: 861-70.
25. Ammirati E, Cipriani M, Moro C, et al. Clinical presentation and outcome in a contemporary cohort of patients with acute myocarditis: multicenter lombardy registry. Circulation 2018; 138: 1088-99.
26. Nordenskjöld AM, Baron T, Eggers KM, et al. Predictors of adverse outcome in patients with myocardial infarction with non-obstructive coronary artery (MINOCA) disease. Int J Cardiol 2018; 261: 18-23.
27. Desai R, Singh S, Baikpour M, et al. Does obesity affect the outcomes in tako-tsubo cardiomyopathy? Analysis of the Nationwide Inpatient Sample database, 2010-2014. Clin Cardiol 2018; 41: 1028-34.
28. O'Brien EC, Fosbol EL, Peng SA, et al. Association of body mass index and long-term outcomes in older patients with non-ST-segment-elevation myocardial infarction: results from the CRUSADE Registry. Circ Cardiovasc Qual Outcomes 2014; 7: 102-9.
29. Jędrychowska M, Januszek R, Plens K, et al. Impact of sex on the follow-up course and predictors of clinical outcomes in patients hospitalised due to myocardial infarction with non-obstructive coronary arteries: a single-centre experience. Kardiol Pol 2019; 77: 198-206.
30. Jesus Espinosa Pascual M, Lopez Pais J, Izquierdo Coronel B, et al. Predictors of myocardial infarction with non-obstructive coronary arteries (MINOCA). Eur Heart J 2019; 40: ehz747.0479.