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Gender differences in course of interventional and surgical treatment of cardiovascular diseases

Przebieg leczenia zabiegowego w chorobie zastawek oraz tętnic obwodowych i wieńcowych u kobiet i mężczyzn

Praca doktorska

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Pracę wykonano

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Dziękuję mojemu promotorowi,
profesorowi Stanisławowi Bartusiowi,
za nieocenioną pomoc i mentorstwo.

Dziękuję mojej rodzinie
za wsparcie i nieustanne motywowanie
do kontynuacji pracy naukowej.

Dziękuję mojej żonie Ani
za wyrozumiałość.

Spis treści:

1. Wprowadzenie

Choroby sercowo-naczyniowe nadal są główną przyczyną zgonów na świecie wśród kobiet i mężczyzn. W ostatnich dekadach nastąpił spadek częstości ich występowania, jednak w mniejszym stopniu u płci żeńskiej, a w grupie młodych kobiet trend ten w ogóle nie był obserwowany [1]. W krajach Europy Wschodniej zachorowalność na choroby układu krążenia należy do jednych z najwyższych. Ponadto, przeciwnie do Stanów Zjednoczonych i Europy Zachodniej, w ostatniej dekadzie w Europie Wschodniej zaobserwowano wzrost wystandaryzowanej do wieku częstości występowania chorób serca u kobiet [2]. Również polskie dane epidemiologiczne zaprzeczają powszechnie akceptowanemu mitowi o „męskim" charakterze miażdżycy. W 2019 roku na 100 000 kobiet w Polsce występowało 12 127 przypadków choroby sercowo-naczyniowej, podczas gdy analogiczna częstość u mężczyzn wynosiła 9855 przypadków. Niestety, zwiększona zapadalność na choroby sercowo-naczyniowe u kobiet idzie w parze z nierównością w ich diagnostyce i leczeniu. Wbrew obowiązującym wytycznym kobiety są rzadziej niż mężczyźni poddawane leczeniu farmakologicznemu i zabiegowemu [3-13]. Niektóre prace wskazują, iż mniej agresywne leczenie prowadzi do większej częstości ponownych zawałów serca i umieralności [14]. Na różnice w rozwoju, diagnostyce i leczeniu miażdżycy u kobiet i mężczyzn mają wpływ czynniki biologiczne (*sex differences*) oraz socjologiczne (*gender differences*). Te pierwsze odnoszą się do efektów wywieranych przez specyficzne dla płci hormony na układ sercowo-naczyniowy. W mechanizmach genomowych i niegenomowych estrogeny wpływają na funkcję śródbłonka, mięśni gładkich naczyń oraz profil lipidowy, hamując rozwój miażdżycy [15]. Korzystne działanie estrogenów opóźnia pojawienie się choroby wieńcowej u kobiet, jednak po menopauzie efekt zanika i kobiety zapadają na miażdżycę nie rzadziej niż mężczyźni. Ponadto, wśród kobiet panuje mniejsza świadomość ryzyka sercowo-naczyniowego i często przekładają

one obowiązki rodzinne ponad swoje zdrowie, w wyniku czego później zgłaszają się ze swoimi dolegliwościami do lekarza.

Choroba wieńcowa jest najczęstszą manifestacją miażdżycy, zarówno u kobiet jak i u mężczyzn. Przed 60 rokiem życia u kobiet ostre zespoły wieńcowe występują kilka razy rzadziej niż u mężczyzn, ale częściej mają odmienną manifestację. U młodych kobiet ostre zespoły wieńcowe częściej przebiegają bez istotnych zwężeń w tętnicach wieńcowych (ang. *myocardial infarction with non-obstructive coronary arteries* - MINOCA). Odmiennie niż w „typowej" postaci ze skrzepliną upośledzającą przepływ naczynia, w zawale bez widocznych przewężeń w tętnicach wieńcowych może dochodzić do erozji blaszki miażdżycowej i następczej dystalnej embolizacji, patologicznej wazoreaktywności tętnic wieńcowych i uszkodzenia mikrokrążenia [16,17]. Dla kobiet z ostrym zespołem wieńcowym w średnim wieku charakterystyczna jest spontaniczna dyssekcja tętnic wieńcowych wymagająca specyficznego postępowania i w razie nierozpoznania, mogąca prowadzić do katastrofalnych skutków.

Po 75 roku życia kobiety stanowią większość przypadków zawałów serca. Pomimo tego, w stosunku do mężczyzn rzadziej i później rozpoczyna się u nich leczenie [18-20]. Kobiety otrzymują mniej leczenia inwazyjnego, nawet po uwzględnieniu wieku, chorób współistniejących i ilości istotnych zwężeń w tętnicach wieńcowych [21,22]. Również kompleksowe zabiegi przezskórnej angioplastyki wieńcowej (ang. *percutaneous coronary intervention* – PCI) dotyczące złożonej anatomii tętnic wieńcowych z towarzyszącymi niekorzystnymi warunkami hemodynamicznymi (np. z obniżoną frakcją wyrzutową lewej komory) stanowią obecnie około 30% wszystkich zabiegów PCI, spośród których tylko 30% dotyczy kobiet [6]. Większa współchorobowość u płci żeńskiej zwiększa ryzyko zwapnień w tętnicach wieńcowych, które w trakcie PCI często są niepodatne na inflacje standardowych cewników balonowych i wymagają zastosowania dodatkowych technik modyfikujących

blaszkę miażdżycową, takich jak np. wysokociśnieniowe cewniki balonowe, litotrypsja wewnątrzwieńcowa czy aterektomia rotacyjna. Większość danych dotyczących kompleksowych zabiegów pochodzą z badań na kohortach złożonych głównie z mężczyzn, w wyniku czego odrębności między płciami w przebiegu oraz wynikach tych zabiegów są słabo poznane.

Podobnie jak w chorobie wieńcowej, kobiety stanowią większość objawowych i bezobjawowych przypadków choroby tętnic obwodowych (ang. *peripheral arterial disease* - PAD) [23]. Kobiety mają częściej nietypowe objawy PAD, prowadzące do zwiększonego ryzyka krytycznego niedokrwienia kończyny i większego ryzyka amputacji kończyny dolnej [24,25]. Pomimo tego rozpoznawalność PAD u kobiet pozostaje niska nawet w krajach rozwiniętych [1]. PAD wpływa zarówno na jakość życia, jak i rokowanie odległe. Leczenie farmakologiczne często pozostaje niewystarczające, szczególnie w przypadku przewlekłych okluzji tętnic obwodowych (ang. *chronic total occlusion* - CTO). Konwencjonalne techniki metodą *antegrade*, to znaczy próby przekroczenia okluzji od jej proksymalnej strony, w około 40-60% pozostają nieskuteczne [26]. Próby zaawansowanej rewaskularyzacji, m.in. od strony dystalnej do zmiany zwiększają szanse na powodzenie zabiegu, jednak dane dotyczące różnic między kobietami i mężczyznami w skuteczności i bezpieczeństwie tych zabiegów są znikome.

Stenoza aortalna jest najczęstszą wadą zastawkową w krajach rozwiniętych. Kobiety stanowią większość wśród pacjentów, jednak rozpoznawalność pozostaje niższa niż u mężczyzn. Wraz z wystąpieniem objawów ciężkiej stenozy aortalnej rokowanie znacznie się pogarsza. Dotychczasowe dane dotyczące różnic płciowych w wynikach chirurgicznej wymiany zastawki aortalnej (ang, *aortic valve disease* - AVR) pozostają sprzeczne z tendencją do gorszych wyników u kobiet w stosunku do mężczyzn [27-31]. W wyniku tego, pomimo równorzędnych wskazań do leczenia zabiegowego u obu płci w obowiązujących wytycznych, kobiety są kierowane do AVR rzadziej niż mężczyźni [32,33].

Wychodząc naprzeciw problemom pacjentek kardiologicznych, Roxana Mehran wraz z zespołem opracowała dokument dotyczący nieproporcjonalności reprezentacji kobiet w badaniach naukowych oraz leczeniu chorób sercowo-naczyniowych, który ukazał się na łamach *Europejskiego Towarzystwa Kardiologicznego* [34]. Podążając za tą ideą, niniejsza praca doktorska jest dedykowana zgłębianiu różnic płciowych w charakterystyce pacjentów poddawanych zabiegom kardiologicznym na przykładzie przezskórnych interwencji wieńcowych oraz obwodowych i operacyjnej wymiany zastawki aortalnej.

2. Publikacje zawarte w rozprawie doktorskiej

Treść niniejszej rozprawy doktorskiej powstała w oparciu o cykl trzech oryginalnych prac monotematycznych opublikowanych w bazie *PubMed*. Łączna wartość współczynnika oddziaływania (Impact Factor) dla wymienionych prac wynosi 7.696 oraz 45 punktów według wykazu czasopism naukowych Ministerstwa Nauki i Szkolnictwa Wyższego.

Na cykl monotematycznych publikacji składają się:

1. Pawlik A, Januszek R, Ruzsa Z, Óriás V, Kleczyński P, Wojtasik-Bakalarz J, Arif S, Nyerges A, Chyrchel M, Stanek A, Dudek D, Bartuś S. Gender differences and long-term clinical outcomes in patients with chronic total occlusions of infrainguinal lower limb arteries treated from retrograde access with peripheral vascular interventions. Adv Med Sci. 2020 Mar;65(1):197-201.
2. Januszek R, Pawlik A, Staszczak B, Jędrychowska M, Bartuś J, Legutko J, Dudek D, Surdacki A, Bartuś S. Age and gender differences in clinical outcomes of patients with heavy-calcified coronary artery lesions treated percutaneously with rotational atherectomy. Adv Clin Exp Med. 2020 Feb;29(2):225-233.
3. Pawlik A, Litwinowicz R, Kowalewski M, Suwalski P, Deja M, Widenka K, Tobota Z, Maruszewski B, Rzeszutko Ł, Januszek R, Plens K, Legutko J, Bartuś S, Kapelak B, Bartuś K. The impact of sex on in-hospital and long-term mortality rates in patients undergoing surgical aortic valve replacement: The SAVR and SEX study. Kardiol Pol. 2023;81(7-8):754-762

3. Cele badania

Wykazanie różnic w wynikach leczenia wewnątrzszpitalnego i odległego u kobiet i mężczyzn poddawanych zabiegom kardiologicznym na przykładzie choroby wieńcowej, choroby tętnic obwodowych oraz stenozy zastawki aortalnej.

Cele pomocnicze:

1. Wykazanie różnic w charakterystyce klinicznej kobiet i mężczyzn poddawanych zabiegom przezskórnym lub operacjom kardiochirurgicznym.
2. Wykazanie różnic w wynikach leczenia wewnątrzszpitalnego i w obserwacji odległej u kobiet i mężczyzn poddawanych zabiegom przezskórnego udrożnienia przewlekłej okluzji tętnic obwodowych techniką *retrograde*.
3. Wykazanie różnic w wynikach wewnątrzszpitalnych i odległych u kobiet i mężczyzn poddawanych zabiegom przezskórnej angioplastyki z użyciem rotablacji.
4. Wykazanie różnic w wynikach wewnątrzszpitalnych i odległych u kobiet i mężczyzn poddawanych chirurgicznej wymianie zastawki aortalnej.

4. Metodyka

Na niniejszą pracę doktorską składają się trzy publikacje dotyczące wpływu płci na przebieg leczenia chorób serca i naczyń obwodowych.

Pierwsza publikacja ma charakter retrospektywny i dotyczy pacjentów z przewlekłą okluzją tętnic kończyn dolnych poddawanych zabiegowi udrażniania techniką retrograde w dwóch ośrodkach referencyjnych. Określono charakterystykę kliniczną pacjentów, zebrano dane dotyczące przebiegu okołozabiegowego oraz powikłań wewnątrzszpitalnych i odległych, określonych jako poważne niepożądane zdarzenia sercowo-naczyniowe (ang. *major adverse cardiac and cerebrovascular events* – MACCE) i poważne kończynowe zdarzenia niepożądane (ang. *major adverse limb events* – MALE), na które składały się: śmierć, zawał serca, udar mózgu, przejściowe niedokrwienie mózgu (ang. *transient ischemic attack* – TIA), PCI lub chirurgiczne pomostowanie aortalno-wieńcowe (ang. *coronary artery bypass graft* - CABG), amputacja, re-interwencja w obrębie leczonej zmiany lub naczynia i konieczność ratującego zabiegu chirurgicznego. Obserwacja dotyczyła 939 pacjentów przez okres 5 lat.

Druga publikacja ma charakter jednoośrodkowy, retrospektywny i dotyczy pacjentów z ciężką chorobą wieńcową poddawaną zabiegowi PCI z użyciem techniki aterektomii rotacyjnej (ang. *rotational atherectomy* - RA). Scharakteryzowano grupę wyjściową 97 pacjentów i określono zdarzenia sercowo-naczyniowe jako MACCE, wśród których wyszczególniono: śmierć, reinterwencje, udar mózgu/TIA lub CABG.

Trzecia praca oryginalna jest jednoośrodkową, retrospektywną analizą ponad 4000 pacjentów poddanych chirurgicznej wymianie zastawki aortalnej (ang. *surgical aortic valve replacement* – SAVR). W publikacji określono charakterystykę wyjściową i porównano mężczyzn i kobiety pod względem przebiegu i powikłań wewnątrzszpitalnych.

5. Streszczenie prac

a. Artykuł 1

Tytuł: *Gender differences and long-term clinical outcomes in patients with chronic total occlusions of infrainguinal lower limb arteries treated from retrograde access with peripheral vascular interventions*

Autorzy: Artur Pawlik , Rafał Januszeka , Zoltan Ruzsa, Viktor Óriás , Paweł Kleczyński, Joanna Wojtasik-Bakalarz , Saleh Arif , Andras Nyerges , Michał Chyrchel , Agata Stanek , Dariusz Dudek , Stanisław Bartuś

Opublikowane w *Advances in Medical Science*s.

Cel badania:

Ocena różnic płciowych w wynikach leczenia pacjentów poddawanych przezskórnej angioplastyce (ang. *percutaneous vascular intervention* - PVI) przewlekłych okluzji tętnic obwodowych (ang. *chronic total occlusion* - CTO) metodą *retrograde*.

Materiał i metody:

Jest to badanie obserwacyjne prospektywne kolejnych pacjentów poddawanych PVI CTO metodą *retrograde* w zakresie tętnicy udowej wspólnej, podkonalnowej i tętnic podudzia. Warunkiem włączenia do badania była przynajmniej jedna nieskuteczna próba wykonania rekanalizacji metodą antegrade zdefiniowana jako nieudana próba przeprowadzenia prowadnika dystalnie za miejsce okluzji. Zebrano dane dotyczące chorób towarzyszących, czynników ryzyka, przyjmowanych leków, przebiegu leczenia wewnątrzszpitalnego oraz wyników odległych. Zaawansowanie choroby tętnic obwodowych było określone przez wskaźnik kostka-ramię oraz zaawansowanie objawów w skali Rutherforda oraz Fontaine'a.

Decyzja o zabiegu rekanalizacji była podejmowana na podstawie angiografii. Procedura odbywała się w znieczuleniu miejscowym i wymagała uzyskania dwóch dostępów naczyniowych: proksymalnego i dystalnego względem okluzji. Punkcje tętnic były wykonywano pod kontrolą USG lub angiografii. Proksymalnie do okluzji wsuwano koszulkę o średnicy 6 French, natomiast dystalnie używano koszulki 4 French. Okluzję z dostępu retrograde przekraczano miękkim nie-hydrofilowym 0.018"prowadnikiem V18 (Boston Scientific, Marlborough, Massachusetts, USA). Po przekroczeniu okluzji wykonywano predylatację cewnikiem balonowym. W zależności od lokalizacji oraz decyzji operatora u części chorych implantowano stent. Wszyscy chorzy byli leczeni podwójnym leczeniem przeciwpłytkowym przez 3 miesiące i heparyną niefrakcjonowaną przez miesiąc.

Wyniki:

Do badania włączono 939 pacjentów, z czego 62.6% stanowili mężczyźni. Kobiety częściej chorowały na nadciśnienie tętnicze (92% vs 86%, p = 0.001) oraz cukrzycę (54% vs 46%, p = 0.02). Mężczyźni częściej byli palaczami (60.4% vs 45%, p = 0.007), częściej chorowali na przewlekłą obturacyjną chorobę płuc (14.8% vs 6.8%, p = 0.0003) i chorobę wieńcową (45.4% vs 32.7%, p = 0.0001) oraz częściej byli po przebytych zabiegach na tętnicach obwodowych (25% vs 17%, p = 0.005). Kobiety miały bardziej zaawansowaną PAD według klasyfikacji TASC.

Techniczny sukces zabiegów wynosił 88.8% i nie różnił się statystycznie między płciami. Kobiety miały więcej komplikacji okołozabiegowych (7.93% vs 5.40%, p = 0.0094), w tym głównie dyssekcji (5.79% vs 2.58%, p = 0.02). Czas hospitalizacji u kobiet był istotnie dłuższy (5.7 ± 4.9dni vs 5.2 ± 5.2 dni, p=0.009).

Średni czas obserwacji wynosił 1149.9 ± 664.3 dni. 5-letnie przeżycie nie różniło się istotnie między kobietami i mężczyznami (p = 0.8), ale płeć męska była niezależnym predyktorem ponownego zabiegu PVI.

Wnioski:

1. W obserwacji odległej mężczyźni leczeni PVI metodą retrograde mają większe ryzyko reinterwencji.
2. PVI metoda retrograde jest związana z większą ilością powikłań okołozabiegowych u kobiet.
3. Kobiety poddawane zabiegom PVI metodą retrograde są starsze, mają więcej chorób towarzyszących i bardziej zaawansowane stadium choroby.

b. Artykuł 2

Tytuł: *Age and gender differences in clinical outcomes of patients with heavy-calcified coronary artery lesions treated percutaneously with rotational atherectomy*

Autorzy: Rafał Januszek, Artur Pawlik, Bartłomiej Staszczak, Magdalena Jędrychowska, Jerzy Bartuś, Jacek Legutko, Dariusz Dudek, Andrzej Surdacki, Stanisław Bartuś

Opublikowane w *Advances in Clinical and Experimental Medicine.*

Cel publikacji:

Ocena różnic płciowych w przebiegu i wynikach odległych przezskórnej angioplastyki z użyciem aterektomii rotacyjnej.

Materiały i metody:

Jest to jednoośrodkowe badanie obserwacyjne retrospektywne i częściowo prospektywne. Do badania włączano kolejnych pacjentów poddawanych zabiegowi PCI z użyciem aterektomii rotacyjnej. Zebrano informacje na temat czynników ryzyka, chorób współistniejących oraz przyjmowanych leków. Odnotowywano przebieg zabiegów, śmiertelność wewnątrzszpitalną oraz wyniki odległe. Na główny złożony punkt końcowy (MACCE) składały się: śmierć z jakiejkolwiek przyczyny, zawał serca, udar mózgu, przejściowe niedokrwienie mózgu, lub ponownej rewaskularyzacji w obrębie tej samej zmiany metodą chirurgiczną lub ponowną PCI.

Wyniki:

Włączono 97 pacjentów, u których przeprowadzono zabieg przezskórnej aterektomii rotacyjnej, spośród których mężczyźni stanowili 26.8%. Nie stwierdzono istotnej statystycznie różnicy między kobietami i mężczyznami w kwestii wieku (73.8 ±9.2 lat vs 70.8 ±10.0 lat; p=0.13), częstości występowania cukrzycy (60 % vs 49.3 %, p=0.36), nadciśnienia tętniczego

(100% vs 95.6%; p= 0.29), PAD (12% vs 27.9%; p=0.11), POChP (20% vs 13% p=0.40) wcześniej przebytego zawału serca, zabiegów PCI (61.9% vs 73.4%, p=0.31) lub CABG (16% vs 14.7%, p=0.87). Mężczyźni częściej byli palaczami (69.6% vs 40%, p=0.03) i mieli niższą frakcję wyrzutową lewej komory (43.9 ± 12.7, 51.4 ± 10.8, p=0.036), natomiast kobiety miały gorszą funkcję nerek wyrażoną jako GFR (80.0 ±33.2 ml vs 64.2 ± 29.4 ml; p=0.08). Punktacja w skali Euroscore II (3.3 ± 3.3% vs 9.4 ± 18.4%, p = 0.4) i Syntax (28.1 ±13.4 points vs 22.1 ±13 points, p = 0.06) nie różniła się statystycznie między płciami, nie było również różnicy w leczeniu przeciwzakrzepowym między płciami.

U obu płci najczęstszym wskazaniem do aterektomii rotacyjnej było niepełne rozprężenie cewnika balonowego (52.2% vs 58.2 %, p=0.61). U kobiet częściej niż u mężczyzn przed aterektomią nie udało się doprowadzić stentu do leczonej zmiany (13% vs 1.4%, p=0.02). Rozmiar użytych borów (1.49 ± 0.20 mm vs 1.43 ± 0.30 mm, p=0.26), ilość i długość stentów (24.0 ±8.5 vs 26.2 ±10.2, p=0.51) ilość użytego kontrastu (303 ±140 ml vs 271 ±106 ml, p=0.53) nie różniły się istotnie statystycznie między kobietami i mężczyznami. Również użycie obrazowania wewnątrznaczyniowego nie wykazało istotnych statystycznie różnic, jednak numerycznie u mężczyzn przeprowadzano zabiegi ponad dwukrotnie częściej pod kontrolą ultrasonografii wewnątrznaczyniowej. Kobiety dwukrotnie częściej niż mężczyźni miały wykonywany zabieg z dostępu promieniowego prawego.

Ilość komplikacji okołozabiegowych była istotnie statystycznie wyższa u kobiet niż u mężczyzn. Składały się na nie głównie dyssekcje tętnic, krwawienia oraz krwiaki.

W obserwacji odległej złożony punkt końcowy nie występował statystycznie częściej u kobiet niż u mężczyzn. Niemniej jednak numerycznie, śmierć występowała częściej u kobiet, natomiast ponowne zawały serca u mężczyzn.

Wnioski:

1. U kobiet poddawanych PCI z użyciem rotablacji częściej występowały powikłania okołozabiegowe, jednak częstość zgonu wewnątrzszpitalnego nie różniła się między płciami.
2. W obserwacji odległej złożony punkt końcowy (MACCE) nie występował istotnie częściej wśród kobiet, niż wśród mężczyzn.
3. Obecność powikłań okołozabiegowych oraz punktacja w skali Euroscore II były predyktorami MACCE.

c. Artykuł 3

Tytuł: *The impact of sex on in-hospital and long-term mortality rates in patients undergoing surgical aortic valve replacement: The SAVR and SEX study*

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Opublikowane w *Kardiologii Polskiej.*

Cel badania:

Ocena różnic płciowych w wynikach izolowanej chirurgicznej wymiany zastawki aortalnej.

Materiały i metody:

Jest to jednoośrodkowe retrospektywne badanie obserwacyjne obejmujące pacjentów skierowanych do chirurgicznej wymiany zastawki aortalnej. Pacjenci poddawani dodatkowemu zabiegowi chirurgicznemu obejmującemu tętnice wieńcowe lub aortę wstępującą oraz chorzy poddawani przezskórnej wymianie zastawki aortalnej byli wykluczeni z badania. Śmiertelność odległą oceniono na podstawie narodowego rejestru PESEL. Dodatkowo charakterystykę bazową, wyniki wewnątrzszpitalne i odległe poddano analizie metodą prepensity score matching (PSM).

Wyniki:

Do badania włączono 4510 pacjentów. Mężczyźni stanowili 58.5% kohorty. Kobiety były starsze (67.3 lat vs. 61.6 lat; P <0.001), częściej chorowały na otyłość (42.1% vs 30.8%, p <0.001), nadciśnienie tętnicze (84.8 vs 80.7, p <0.001), cukrzycę (23.4 vs 18.2, p <0.001) i miały wyższy wskaźnik w punktacji Euroscore II (1.2, IQR: 0.9–1.6 vs 0.8, IQR: 0.7–1.2,

p <0.001). Mężczyźni mieli niższą frakcję wyrzutową lewej komory, częściej chorowali na chorobę wieńcową i przewlekłą obturacyjną chorobę płuc. Mediana obserwacji wynosiła 2120 dni.

Długość hospitalizacji, ilość powikłań okołozabiegowych oraz śmiertelność wewnątrzszpitalna nie różniły się istotnie statystycznie między grupami. Po dopasowaniu mężczyzn i kobiet metodą PSM przeżywalność odległa była niższa u kobiet niż u mężczyzn.

Wnioski:

1. Śmiertelność wewnątrzszpitalna nie różniła się istotnie u mężczyzn i kobiet.
2. Po dopasowaniu charakterystyki bazowej przeżywalność w obserwacji odległej była lepsza u kobiet niż u mężczyzn.
3. Kobiety poddawane zabiegowi izolowanej wymiany zastawki aortalnej są starsze oraz mają więcej chorób towarzyszących.

6. Dyskusja

Najczęstszymi wskazaniami do leczenia rewaskularyzacyjnego w PAD są dolegliwości bólowe kończyn dolnych limitujące codzienną aktywność, takie jak ból wysiłkowy, ból spoczynkowy oraz zmiany troficzne kończyn dolnych. U płci żeńskiej prezentacja objawów jest bardzo nietypowa, co wynika m.in. z mniejszej aktywności fizycznej oraz mniejszej świadomości o ryzyku miażdżycy tętnic kończyn dolnych. Z tego powodu kobiety są rzadziej kierowane do leczenia zabiegowego [35]. Potwierdzają to dane z amerykańskiego rejestru 2.4 milionów przyjęć szpitalnych związanych z PAD [36]. Zaobserwowano również częstszą rewaskularyzację ze wskazań nagłych u płci żeńskiej. Podobna tendencja występuje w kohorcie z krytycznym niedokrwieniem tętnic kończyn dolnych będącym wskazaniem do rewaskularyzacji u 61.5% kobiet w porównaniu do 53.1% mężczyzn (p=0.01). Można więc wnioskować, iż miażdżyca tętnic kończyn dolnych rozwija się u kobiet w sposób bardziej utajony, a wraz z manifestacją objawów ma ona bardziej zaawansowany charakter. W prezentowanym badaniu kobiety w stosunku do mężczyzn były starsze i miały bardziej zaawansowaną PAD w klasyfikacji TASC II pomimo mniejszego nasilenia klasycznych czynników miażdżycy, takich jak nikotynizm i hiperlipidemia. Istotnym czynnikiem w kontekście leczenia zabiegowego jest również mniejsza średnica tętnic kończyn dolnych u płci żeńskiej [37]. W rezultacie u kobiet zabiegi rewaskularyzacyjne są technicznie trudniejsze i częściej powikłane jatrogenną dyssekcją oraz innymi naczyniowymi komplikacjami okołozabiegowymi. W niniejszym badaniu zjawiska te, mimo dłuższej hospitalizacji, nie przekładały się na twarde punkty końcowe, takie jak śmierć: z jakiejkolwiek przyczyny, zawał serca i udar mózgu. Występowały one równie często u kobiet i mężczyzn. Pomimo mniej korzystnej charakterystyki bazowej, częstość ponownych rewaskularyzacji była większa u mężczyzn niż u kobiet. Można zatem przypuszczać, że czynniki ryzyka, takie jak: POChP, hiperlipidemia, choroba wieńcowa i młodszy wiek, przeważają nad zaawansowaniem zmian,

obecnością cukrzycy i mają większy wpływ na ponowną rewaskularyzację w dalszej obserwacji.

Podobnie jak w przypadku zabiegów na tętnicach obwodowych zabiegi PCI są skojarzone z częściej występującymi komplikacjami u płci żeńskiej [38]. W przeciwieństwie do poprzednich badań dotyczących PCI z wykorzystaniem aterektomii rotacyjnej, w analizowanej kohorcie u kobiet częściej, w porównaniu do mężczyzn, stosowano naczyniowy dostęp promieniowy. Pomimo dobrze udokumentowanej redukcji powikłań naczyniowych w stosunku do dostępu udowego, w prezentowanym badaniu częstość powikłań okołozabiegowych pozostała istotnie częstsza u kobiet [39]. Dyssekcje i krwawienie z tętnic wieńcowych, które występują częściej u kobiet w trakcie PCI, niosą zagrażające życiu konsekwencje, co ma odzwierciedlenie w większej częstości transfuzji krwinek czerwonych, wstrząsów kardiogennych i konieczności rewaskularyzacji chirurgicznej. W prezentowanym przez nas badaniu powikłania okołozabiegowe, wraz z punktacją w skali Euroscore II oraz maksymalną średnicą boru, były również predyktorem MACCE. W obserwacji odległej częstość złożonego punktu końcowego nie różniła się istotnie statystycznie między kobietami i mężczyznami. Zatem, w trakcie kwalifikacji do kompleksowego zabiegu PCI z użyciem aterektomii rotacyjnej należy bardzo dokładnie przeanalizować bilans korzyści i ryzyka, szczególnie u kobiet. Należy również zwrócić uwagę na tendencję do częstszego kierowania kobiet, w stosunku do mężczyzn, do zaawansowanej angioplastyki wieńcowej ze wskazań ostrych i konieczności użycia dodatkowych technik zabiegowych dla otrzymania optymalnego efektu wymagającego odpowiedniego doświadczenia. W celu redukcji powikłań należy wykonywać te zabiegi w ośrodkach dysponujących odpowiednim zapleczem technicznym oraz doświadczeniem w ich stosowaniu [40].

Tradycyjnie uważa się, że dostępność do leczenia kardiochirurgicznego dla kobiet jest niższa niż u mężczyzn, a wyniki są gorsze [41]. Jest to związane z mniejszym wymiarem operowanych

struktur, bardziej rozsianym charakterem miażdżycy, mniej korzystnym profilem ryzyka u kobiet, nietypowym charakterem zgłaszanych objawów prowadzącym do późniejszego rozpoznania oraz częstszym wykonywaniem operacji ze wskazań nagłych. Bardziej aktualne rejestry wskazują, że ryzyko związane z CABG oraz AVR może się różnić między kobietami a mężczyznami. W dużym rejestrze na 72 000 pacjentów poddawanych operacjom kardiochirurgicznym śmiertelność wśród kobiet była wyższa niż u mężczyzn, ale dotyczyło to głównie operacji pomostowania tętnic wieńcowych. Wśród pacjentek poddawanych operacjom wymiany zastawek nie stwierdzono istotnych statystycznie różnic [42]. Również w przedstawionej przez nas pracy nie stwierdziliśmy istotnej statystycznie różnicy w śmiertelności wewnątrzszpitalnej między kobietami i mężczyznami (3.7 % vs 3.0%, p=0.15). W dalszej obserwacji śmiertelność wśród kobiet była niższa niż wśród mężczyzn również po dopasowaniu charakterystyki metodą PSM.

Przedstawione przez nas dobre wyniki leczenia chirurgicznego zwężenia zastawki aortalnej u kobiet są bardzo ważne z kilku powodów:

1) Jest to najczęstsza wada zastawkowa w krajach rozwiniętych, a kobiety są poddawane jej diagnostyce i leczeniu znacznie rzadziej niż mężczyźni.

2) W razie wystąpienia objawów, rokowanie pacjentów z ciężką wadą zastawkową drastycznie się pogarsza.

3) Alternatywna metoda leczenia, przezskórna implantacja zastawki aortalnej (ang. *transcatheter aortic valve implantation*, TAVI), pomimo coraz lepszych wyników dalej nie jest wystarczająco dostępna w Polsce.

Dotychczasowe badania wskazują na porównywalne wyniki TAVI i AVR, a w badaniu PARTNER wykazano nawet lepszą 2-letnią przeżywalność kobiet w grupie TAVI wykonywanego z dostępu przezudowego w stosunku do AVR. [41] Należy jednak pamiętać,

że większość badań nad przezskórnym leczeniem stenozy zastawki aortalnej dotyczyła osiemdziesięciolatków, więc nie odnoszą się do całości populacji pacjenótw z ciężką stenozą aortalna. Ponadto, nadal ilość wykonywanych procedur TAVI jest zbyt niska w stosunku do ilości pacjentów ze wskazaniami do tego zabiegu w Polsce. A zatem AVR nadal stanowi bardzo istotny, komplementarny do TAVI element leczenia populacji z ciężką stenozą aortalną i powinna być stosowana u kobiet w równym stopniu co u mężczyzn.

7. Ograniczenia

Dwie z trzech przytoczonych prac miały charakter jednoośrodkowy. Aterektomia rotacyjna i rekanalizacja metodą retrograde są technikami wysoce specjalistycznymi, których skuteczność i bezpieczeństwo zależą od doświadczenia operatorów je wykonujących. Tak więc wyniki tych badań mogą nie przekładać się na doświadczenia ośrodków bez operatorów dedykowanych do tego typu zabiegów. Ponadto, badania te miały charakter retrospektywny, więc ryzyko zakłócenia wyników przez czynniki nie ujęte w analizie jest trudne do oszacowania. Niemniej jednak, trendy ukazane w pracy są zgodne z trendami przedstawianymi w literaturze medycznej w zakresie innych rodzajów zabiegów kardiologicznych.

8. Podsumowanie

W niniejszej pracy przedstawiono przebieg leczenia zabiegowego u mężczyzn i kobiet na podstawie trzech różnych rodzajów zabiegów kardiologicznych. Kompleksowa przezskórna angioplastyka wieńcowa z użyciem aterektomii rotacyjnej nie wiązała się z większą częstością występowania złożonego punktu końcowego u kobiet w obserwacji odległej, niemniej jednak powikłania okołozabiegowe oraz śmiertelność odległa były wyższe u płci żeńskiej. Częściowo może być to spowodowane wyższym ryzykiem okołozabiegowym kobiet odzwierciedlonym wyższą punktacją w skali Euroscore II. Praca opisująca wyniki rewaskularyzacji przewlekłych okluzji tętnic kończyn dolnych metodą retrograde nie wykazała różnic w śmiertelności odległej między kobietami a mężczyznami. Co więcej, w trakcie obserwacji stwierdzono częstsze reinterwencje u mężczyzn, co można tłumaczyć słabszą kontrolą czynników ryzyka progresji miażdżycy u płci męskiej. W badaniu na dużej kilkutysięcznej kohorcie poddawanej izolowanej wymianie zastawki aortalnej kobiety nie cechowały się zwiększoną śmiertelnością w obserwacji wewnątrzszpitalnej i odległej. Po uwzględnieniu wieku oraz chorób współistniejących przeżywalność była lepsza u kobiet niż u mężczyzn.

Pomimo odrębnych technik zabiegowych powyższe prace nasuwają wspólne wnioski: kobiety poddawane zabiegom są starsze i mają więcej chorób towarzyszących, co prowadzi do większej ilości powikłań w okresie okołozabiegowym, jednak wyniki tych zabiegów przynoszą korzyści w równym stopniu mężczyznom, jak i kobietom, również w najbardziej zaawansowanych technikach zabiegowych, takich jak rewaskularyzacja metodą retrograde oraz z użyciem aterektomii rotacyjnej. Dlatego też, wbrew panującym trendom, kobiety powinny być kierowane do leczenia zabiegowego w równym stopniu co mężczyźni, zgodnie z obowiązującymi obecnie wytycznymi.

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10. Summary of Articles

a. Article 1

Title: *Gender differences and long-term clinical outcomes in patients with chronic total occlusions of infrainguinal lower limb arteries treated from retrograde access with peripheral vascular interventions*

Authors: Artur Pawlik , Rafał Januszeka , Zoltan Ruzsa, Viktor Óriás , Paweł Kleczyński, Joanna Wojtasik-Bakalarz , Saleh Arif , Andras Nyerges , Michał Chyrchel , Agata Stanek , Dariusz Dudek , Stanisław Bartuś

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Aim of the study: to evaluate gender differences in clinical outcomes of patients undergoing *percutaneous vascular interventions (PVI)* for *chronic total occlusions (CTO)* of peripheral arteries by *retrograde* approach.

Materials and methods:

This is a prospective study of consecutive patients undergoing PVI for CTOs by the *retrograde* method in the common femoral, popliteal and infrapopliteal arteries. The condition for inclusion in the study was at least one unsuccessful attempt at anterograde recanalisation, defined as a failed attempt to pass the guidewire distally beyond the point of occlusion. Data were collected on concomitant diseases, risk factors, medications taken, in-hospital course of treatment and long-term outcomes. The severity of peripheral arterial disease was defined by the ankle-brachial index (ABI) and the severity of symptoms according to Rutherford and Fontaine's classifications.

The decision for the recanalisation procedure was based on angiography. The procedure was carried out under local anaesthesia and required two vascular accesses: proximal and distal to

the occlusion. Arterial punctures were performed under ultrasound or angiography guidance. Proximal to the occlusion, a 6-French sheath was inserted, while distal to the occlusion, a 4-French sheath was used. The retrograde access occlusion was crossed with a soft non-hydrophilic 0.018" V18 guidewire (Boston Scientific, Marlborough, Massachusetts, USA). After crossing the occlusion, balloon catheter predilatation was performed. Depending on the location and the operator's decision, a stent was implanted in some patients. All patients received dual antiplatelet therapy for three months and unfractionated heparin for one month.

Outcomes:

A total of 939 patients were included in the study, 62.6% of whom were men. Women were more likely to suffer from hypertension (92% vs 86%, $p = 0.001$) and diabetes (54% vs 46%, $p = 0.02$). Men were more likely to be smokers (60.4% vs. 45%, $p = 0.007$), more likely to develop chronic obstructive pulmonary disease (14.8% vs 6.8%, $p = 0.0003$) and coronary artery disease (45.4% vs 32.7%, $p = 0.0001$), and more likely to have undergone peripheral artery surgery (25% vs 17%, $p = 0.005$). Women tended to have their PAD more advanced according to TASC classification.

The technical success rate of the procedures was 88.8% and was not statistically different between the genders. Women developed more perioperative complications (7.93% vs 5.40%, $p = 0.0094$), mostly dissections (5.79% vs 2.58%, $p = 0.02$). The period of hospitalisation was significantly longer for women (5.7 ± 4.9 days vs 5.2 ± 5.2 days, $p = 0.009$).

The mean follow-up time reached $1,1149.9 \pm 664.3$ days. The five-year survival rate was not considerably different between men and women ($p = 0.8$), but male gender was an independent predictor of re-PVI.

Conclusions:

1. Men treated with PVI in retrograde approach face a higher risk of re-intervention in the long-term follow-up.
2. Retrograde PVI is associated with more perioperative complications in women.
3. Women undergoing retrograde PVI are older, are affected by more concomitant diseases and present with a more advanced stage of disease.

b. Article 2

Title: *Age and gender differences in clinical outcomes of patients with heavy-calcified coronary artery lesions treated percutaneously with rotational atherectomy*

Authors: Rafał Januszek, Artur Pawlik, Bartłomiej Staszczak, Magdalena Jędrychowska, Jerzy Bartuś, Jacek Legutko, Dariusz Dudek, Andrzej Surdacki, Stanisław Bartuś

Journal: *Advances in Clinical and Experimental Medicine*

Purpose of publication: to evaluate gender differences in the course and long-term outcomes of percutaneous angioplasty (PCI) using rotational atherectomy.

Materials and methods:

This is a unicentric retrospective and partially prospective (cohort) study. Consecutive patients undergoing PCI with rotational atherectomy were included in the study. Information on risk factors, comorbidities and medications taken was collected. The course of the procedures, in-hospital mortality and long-term outcomes were recorded. The primary composite endpoint (MACCE) consisted of all-cause death, myocardial infarction, stroke, transient ischaemic attack (TIA), or repeat revascularisation within the same lesion by surgery or re-PCI.

Outcomes:

97 patients who underwent PCI with rotational atherectomy were included, of whom men accounted for 26.8 %. There was no statistically significant difference between men and women in terms of age (73.8 ± 9.2 years vs 70.8 ± 10.0 years; p=0.13), prevalence of diabetes (60% vs 49.3%, p=0. 36), hypertension (100% vs 95.6%; p= 0.29), PAD (12% vs 27.9%; p=0.11), COPD (20% vs 13% p=0.40) prior MI, PCIs (61.9% vs 73.4%, p=0.31) or CABG (16% vs 14.7%, p=0.87). Men were more likely to be smokers (69.6% vs 40%, p=0.03) and to show lower left ventricular ejection fraction (43.9 ± 12.7, 51.4 ± 10.8, p=0.036), while women tended

to have poorer renal function expressed as GFR (80.0 ± 33.2 ml vs 64.2 ± 29.4 ml; p=0.08). EuroSCORE II (3.3 ± 3.3% vs 9.4 ± 18.4%, p = 0.4) and Syntax (28.1 ± 13.4 points vs 22.1 ± 13 points, p = 0.06) scores were not statistically different between the genders, and there was also no difference in antithrombotic treatment between the genders.

Outcomes:

In both genders, the most common indication for rotational atherectomy was an incomplete expansion of the balloon catheter (52.2% vs 58.2%, p=0.61). Women were more likely than men to have failed to guide the stent to the treated lesion before atherectomy (13% vs 1.4%, p=0.02). The size of bores used (1.49 ± 0.20 mm vs 1.43 ± 0.30 mm, p=0.26), the number and length of stents (24.0 ±8.5 vs 26.2 ±10.2, p=0.51) the amount of contrast used (303 ±140 ml vs 271 ±106 ml, p=0.53) were not statistically significantly different between men and women. The use of intravascular imaging also showed no statistically significant differences, however, numerically men were more than twice as likely to have procedures performed under intravascular ultrasound (IVUS) guidance. Women were twice as likely as men to undergo the procedure from the right radial access (RRA).

The number of perioperative complications was statistically significantly higher in women than in men. These consisted mainly of arterial dissections, bleeding and haematomas.

In the long-term follow-up, the composite endpoint was not statistically more frequent in women than in men. Nevertheless, numerically, an incidence of death was more prevalent among women, while recurrent myocardial infarctions (re-MI) were more prevalent among men.

Conclusions:

1. Women undergoing PCI with rotablation showed a higher incidence of perioperative complications, but the incidence of in-hospital death did not differ between the genders.
2. In the long-term follow-up, the composite endpoint (MACCE) was not significantly more common among women than among men.
3. The occurrence of perioperative complications and EuroSCORE II scores were predictors of MACCE.

c. Article 3

Title: *The impact of sex on in-hospital and long-term mortality rates in patients undergoing surgical aortic valve replacement: The SAVR and SEX study*

Authors: Artur Pawlik, Radosław Litwinowicz, Mariusz Kowalewski, Piotr Suwalski, Marek Deja, Kazimierz Widenka, Zdzisław Tobota, Bohdan Maruszewski, Łukasz Rzeszutko, Rafał Januszek, Krzysztof Plens, Jacek Legutko, Stanisław Bartuś, Bogusław Kapelak, Krzysztof Bartuś

Journal: *Kardiologia Polska (Polish Cardiology)*

Aim of the study: to investigate gender differences in (clinical) outcomes of (isolated) surgical aortic valve replacement.

Materials and methods:

This is a unicentric retrospective (cohort) study including patients referred for surgical aortic valve replacement. Patients undergoing any additional surgical procedure involving the coronary arteries or ascending aorta and patients undergoing transcatheter aortic valve implantation (TAVI) were excluded from the study. Late mortality was determined based on the national PESEL (Personal Identification Number) registry. In addition, baseline characteristics, in-hospital and long-term outcomes were analysed by prepensity score matching (PSM).

Outcomes:

A total of 4510 patients were included in the study. Men made up 58.5% of the cohort. Women were older (67.3 years vs 61.6 years; P <0.001), more likely to suffer from obesity (42.1% vs 30.8%, p <0.001), hypertension (84.8 vs 80. 7, p <0.001), diabetes (23.4 vs 18.2, p <0.001) and tended to have higher EuroSCORE II scores (1.2, IQR: 0.9-1.6 vs 0.8, IQR: 0.7-1.2, p <0.001).

Men presented with a lower left ventricular ejection fraction and were more likely to develop coronary artery disease (CAD) and chronic obstructive pulmonary disease (COPD). The median follow-up was 2120 days.

The length of hospitalisation, number of perioperative complications and in-hospital mortality were not statistically significantly different between groups. After matching men and women by PSM, long-term survival was lower in women than in men.

Conclusions:

1. In-hospital mortality was not substantially different between men and women.
2. After adjusting for baseline characteristics, survival rate in the long-term follow-up was better in women than in men.
3. Women undergoing (isolated) surgical aortic valve replacement are older and have (developed) more concomitant diseases.

11. Thesis Summary

In this thesis, the surgical treatment course in men and women was presented based on three different types of cardiac surgeries. Complex percutaneous (transluminal) coronary angioplasty with rotational atherectomy did not involve a higher incidence of the composite endpoint in women at long-term follow-up, however, perioperative complications and long-term mortality were higher in the female gender. In part, this may be due to the higher perioperative risk in women reflected by higher EuroSCORE II scores. The work describing the results of revascularisation of chronic arterial occlusions of the lower extremities using the retrograde method has shown no differences in long-term mortality between men and women. Moreover, during follow-up, reinterventions were found to be more frequent in men, which may be explained by poorer control of risk factors for atherosclerosis progression in the male gender. In a study on a large cohort of several thousand subjects undergoing isolated aortic valve replacement, women were not characterised by increased in-hospital and long-term follow-up mortality. After accounting for age and comorbidities, survival was better in women than in men.

Despite the separate surgical techniques, the foregoing pieces of work yield common conclusions: women undergoing surgical procedures are older and suffer from more concomitant diseases, which leads to more complications in the perioperative period, yet the results of these procedures benefit men and women equally, including in the most advanced surgical techniques, such as revascularisation in retrograde approach and with rotational atherectomy. Therefore, contrary to prevailing trends, women should be referred for surgical treatment just as much as men, according to currently applicable guidelines.

12. Załącznik 1 – publikacje

a. Artykuł 1

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Original research article

Gender differences and long-term clinical outcomes in patients with chronic total occlusions of infrainguinal lower limb arteries treated from retrograde access with peripheral vascular interventions

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ABSTRACT

Purpose: We sought to investigate gender-related differences in clinical outcomes after peripheral vascular interventions (PVIs) from retrograde access in patients with chronic total occlusions (CTOs) of the infrainguinal arteries.

Patients and methods: A total of 939 consecutive patients undergoing PVI were enrolled in the study. Patients with peripheral artery diseases (PAD) and CTOs were treated with PVI from retrograde access according to the local protocol. The participants were divided according to gender. Retrograde access included distal puncturing to reach the CTO. The mean follow-up lasted 1,144.9 ± 664.3 days. Baseline characteristics, procedural and long-term outcomes were compared according to gender.

Results: Women represented 37.4% of the study population, and more frequently suffered from hypertension (92% vs. 86%, $p = 0.001$) and diabetes (54% vs. 46%, $p = 0.02$). Males more often presented with chronic obstructive pulmonary disease (14.8% vs. 6.8%, $p = 0.0003$), coronary artery disease (45.4% vs. 32.7%, $p = 0.0001$), smoking (60.4% vs. 45%, $p = 0.007$) and prior PVI (25% vs. 17%, $p = 0.005$). The Kaplan-Meier survival curves at 5 years did not reveal gender-related differences in mortality ($p = 0.8$), whereas men were at a significantly higher risk of re-PVI during the follow-up period ($p = 0.047$). Male gender was an independent predictor of re-PVI (Hazard ratio: 1.276; 95% confidence interval: 1.015–1.614, $p = 0.03$).

Conclusion: Males are at increased risk of re-PVI compared to females with PAD and CTOs of infrainguinal arteries treated with PVI from retrograde access.

1. Introduction

Peripheral artery disease (PAD) is an age-related, increasing social, economic and medical condition [1]. Although changing lifestyle plays an important role in PAD treatment, advanced stages of the disease often require peripheral vascular intervention (PVI). At many experienced academic centers, interventional methods have become the first-line of treatment allowing limb-salvage procedures in patients with an operative risk that precludes open surgery. The retrograde approach is used in selected cases when conventional endovascular techniques fail in occlusion management. Retrograde access includes distal puncturing to reach the obstruction, and depending on the location of the lesion, covering various locations, this includes pedal access. Publications are available regarding predictors of clinical outcomes in patients with PAD treated with angioplasty [2,3]. Clinical evaluation was mainly based on the frequency of amputations and revascularizations, which are referred to as major adverse lower-limb events (MALE), and mortality. Among the confirmed predictors of amputations in patients with PAD

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treated with antegrade access, we may find, for example: ulcerations, increased serum C-reactive protein level, diabetes mellitus or younger age [2]. While the predictors of survival include body-mass index, non-ambulatory status or lower left ventricle ejection fraction [2]. The relationship between gender and clinical presentation, treatment and outcomes in patients with PAD undergoing PVI, has been investigated in several studies [4]. Varying incidences of PAD among men and women depending on the age group have been reported [1]. Also, differences in the results of PAD treatment between woman and men are seen in many factors, such as the prevalence of comorbidities (including diabetes), the frequency of PAD diagnosis and endovascular treatment, vascular diameter, the age at treatment or procedural factors [1]. The published studies are not consistent in predicting outcomes after endovascular treatment in patients with PAD, and some of them revealed poorer outcomes in females [5,6], while the others showed no gender-related differences [6]. The relationship between gender and outcomes in patients with PAD and chronic total occlusions (CTOs), treated with PVI from retrograde access, is less investigated. Due to more advanced atherosclerosis, usually disseminated, multi-segmental, and in many cases, presented as critical lower limb ischemia, the results in this group of patients may differ significantly from those treated from antegrade access. The features mentioned above, including CTO of the infrainguinal arteries, different clinical image and other spectrums of atherosclerosis risk factors, may have an impact on the clinical outcomes and their relationship with gender. What is more, so far, they have not been analyzed in such a large group of patients.

The aim of the current study was to assess the relationship between gender and long-term clinical outcomes in patients with PAD and CTOs treated with endovascular interventions and retrograde access.

2. Patients and methods

2.1. Study population

This research was planned as a prospective observational study of consecutive patients who underwent retrograde recanalization of CTO localized in the superficial femoral artery (SFA), popliteal artery (PA) or below-the-knee arteries. At three experienced and collaborating centers, we enrolled all consecutive patients after at least one unsuccessful antegrade recanalization of CTO, qualified for the retrograde approach. The cohort of this study consisted of 939 consecutive patients, among whom 588 were men (62.6%). Females were significantly older in comparison to males (71 ± 10.8 years vs. 65.8 ± 10 years, $p < 0.0001$) (Table 1).

Antegrade failure was defined as inability to wire the distal part of the vessel after the occlusion via access site, located in the contralateral artery or proximal to the CTO lesion. According to the local protocol, patients were screened for concomitant diseases, risk factors and medication prior to the procedure. In all patients before the procedure, ankle-brachial index was examined and severity of PAD was assessed according to the Rutherford and/or Fontaine scales.

2.2. Methods

The decision regarding retrograde recanalization and access site was based on prior angiography. The procedure of retrograde recanalization was performed under local anesthesia and required two access sites: antegrade and retrograde. Both proximal and distal punctures were performed under the guidance of vascular ultrasound and/or fluoroscopy. The selection of antegrade access site type was determined by many factors, including anatomical conditioning, type of vascular lesions, technical possibilities, type of occlusion, its length and probability of blood flow restoration. For the proximal access site, the contralateral femoral artery was usually used, and 6 French (Fr) vascular sheaths were among the most popular. The distal access site was usually chosen in the reconnection area of the artery (needle: 12–15 mm, 21G). In some cases, 4 Fr vascular sheaths were needed to obtain support during the procedure. In a few cases, the distal access site was also used for the revascularization of more peripheral parts of the artery. A hydrophilic stiff, J-shaped 0.035" guidewire (Terumo Corporation, Shibuya, Tokyo, Japan) was used for the antegrade access site. Occlusions were crossed from the retrograde access site with a soft V18 non-hydrophilic 0.018" guidewire (Boston Scientific, Marlborough, Massachusetts, USA). After crossing the occlusion with a wire via the retrograde approach, predilatation was performed using a balloon catheter. Stent implantation was based on the decision of the operator. After the procedure, the distal sheet was immediately removed, and the proximal one was maintained up to 4 h when the femoral artery was punctured, which was conditioned by unfractionated heparin use. In periprocedural treatment, all patients received double antiplatelet therapy: aspirin 75 mg – permanently, and clopidogrel 75 mg for 3 months, a high dose of statin and according to local protocol, low-molecular-weight heparin for 4 weeks. Additional treatment was accordant with individual risk factors and comorbidities.

Table 1
Baseline clinical characteristics.

Variables	Female N = 351	Male N = 588	p
Age, years	71 ± 10.8	65.8 ± 10.0	< 0.0001
BMI, kg/m^2	26.8 ± 5	27.5 ± 5.4	0.33
Hypertension, %	91.4	86.4	0.02
Diabetes mellitus, %	54.1	46.3	0.02
Renal failure, %	16.2	15.6	0.81
Coronary artery disease, %	32.8	45.4	0.0001
Hyperlipidemia, %	77.8	87.8	0.15
Stroke/TIA, %	8.5	8.8	0.02
Smoking, %	45	60.4	0.008
COPD, %	6.8	14.8	0.0008
Prior PTA, %	17.1	25	0.005
Acute limb ischemia, %	6	4.4	0.28
Critical limb ischemia, %	61.5	53.1	0.01
Intermittent claudication, %	32.5	42.9	0.002
Fontaine scale, %			
1	0.3	0	0.002
2A	4.8	5.4	
2B	29.3	37.4	
3	15.7	18.4	
4	49.9	38.6	
Rutherford scale, %			
1	3.7	5.1	0.0002
2	12.2	19.7	
3	16.2	17.3	
4	17.1	18.9	
5	17.1	13.3	
6	33.6	25.7	

Abbreviations: COPD - chronic obstructive pulmonary disease; BMI - body mass index; PTA - percutaneous transluminal angioplasty; TIA - transient ischemic attacks.

2.3. Follow-up

In the long term follow-up, which lasted 1,144.9 ± 664.3 days, patients were evaluated for major adverse cardiac and cerebrovascular events (MACCE) as well as MALE. Data were collected between 2006 and 2016. In this study, MACCE were predefined as death, stroke/transient ischemic attack (TIA), myocardial infarction, percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG). MALE was defined as amputation, target lesion re-intervention, target vessel re-intervention and surgical treatment. Due to shortages in the available database, the level of amputation was not highlighted in the present study and alike high-, mid- and low-amputations, they were included in the overall amputation rate. The protocol complied with the Declaration of Helsinki, and all participants provided written informed consent before enrollment.

2.4. Statistical analysis

Continuous variables are expressed as mean ± standard deviation or median and interquartile range. Categorical variables are introduced as numbers and percentages. Normality of distribution was assessed with the Shapiro-Wilk test. The Mann Whitney U test was used for non-normally distributed continuous variables. Survival analyses were performed using the Kaplan-Meier method while univariate and multivariate Cox regression analyses were used to find significant predictors of re-PVI during the follow-up. All baseline characteristics and procedural data were tested as possible co-variates. Results are presented as hazard ratios (HR) with 95% confidence intervals (CI). All tests were two-tailed and the p-value < 0.05 was considered statistically significant. All analyses were performed with JMP®, Version 13.1.0 (SAS Institute INC., Cary, NC, USA). The sample size was not counted because the present study was based on the database registry, the original purpose of which was not to assess the impact of gender on clinical outcomes. All calculated analyzes were lesion-based. In the case of bilateral involvement, one limb was included in the analysis and this was recognized as one PVI, which in some cases, could be multi-segmental. The treated lesion concerned the limb which was clinically more affected by ischemia.

2.5. Ethical issues

The study protocol complied with the 1964 Declaration of Helsinki with its later amendments, and all participants provided informed written consent before enrollment. The protocol of the current study has not been approved by local bioethics committee, due to its retrospective nature, and no consent is required for such type of a study.

3. Results

3.1. Clinical features

In general, there were significant differences between genders when considering concomitant diseases. Men more frequently presented with coronary artery disease (45.4% vs. 32.7%, p = 0.0001), chronic obstructive pulmonary disease (COPD; 14.8% vs. 6.8%, p = 0.0003) and were more often smokers (60.4% vs. 45%, p = 0.007), while women more often suffered from hypertension (91.4% vs. 86.4%, p = 0.001) and diabetes (54.1% vs. 46.3%, p = 0.02). The baseline characteristics of the population are shown in Table 1.

3.2. Procedural indices and biochemical parameters

Hemoglobin and creatinine concentrations in the serum were statistically significantly lower in females compared to males (p = 0.0048 and p = 0.0005, respectively). There were no statistically significant differences between genders in procedure and fluoroscopy time, contrast volume or time from procedure to discharge, whereas the overall hospitalization time was statistically significantly longer in females (p = 0.0094). Females were qualified for the procedure with more advanced and disseminated atherosclerotic lesions according to the Trans-Atlantic Inter-Society Consensus (TASC) II classification. The procedural success rate attained 88.8% and there were no statistically significant differences between both groups. Women suffered from intraprocedural complications more often (7.93% vs. 5.40%, p = 0.0094), including residual dissection (5.79% vs. 2.58%, p = 0.02). This is presented in Table 2.

3.3. Clinical outcomes

There were no statistically significant differences between males and females in the frequency of particular study endpoints which included: strokes/TIA (p = 0.5), myocardial infarctions (p = 0.7), amputations (p = 0.07), deaths (p = 0.68), lower limb bypasses (p = 0.74) and percutaneous thrombectomies or thromboendarterectomies (p = 0.15). Also, the mean time to the first adverse event did not differ statistically significantly between males and females during the follow-up period for these particular study endpoints (Table 3). Men were at a higher risk of re-PVI at the 60-month follow-up (41.2% vs. 35.8%; p = 0.047). Re-PVI free survival probability for men and women is shown in Fig. 1. The male gender was found in univariate and multivariate Cox regression analysis to be an independent predictor of re-PVI (HR: 1.276; 95% CI: 1.015–1.614, p = 0.03). Univariate and multivariate Cox regression analyses confirmed that alongside gender, chronic occlusion of superficial femoral artery (HR: 1.71; 95% CI: 1.11–2.68, p = 0.013) and procedural failure (HR: 2.15; 95% CI: 1.06–3.96, p = 0.03) were also statistically significant predictors of re-PVI. After adjustment to male gender, re-PVI was statistically significantly associated with diabetes (HR:1.19; 95% CI 0.95–1.48, p = 0.03), COPD (HR: 0.75; 95% CI: 0.51–1.07, p = 0.03), prior PVI (HR: 1.34; 95% CI: 1.04–1.71, p = 0.008) and age (HR: 0.99; 95% CI: 0.98–1.001, p = 0.02).

Table 2
Biochemical, procedural and atherosclerotic lesion characteristics.

Variables	Female N = 351	Male N = 588	p
Hemoglobin, g/dL	12.9 ± 1.3	13.9 ± 1.7	0.005
Platelet count, *1000/μL	228.9 ± 59.2	209.3 ± 64.2	0.07
Creatinine, μmol/L	75.9 ± 23.8	91 ± 26.5	0.0005
eGFR mL/min/1.73 m^2	54.3 ± 12	57.5 ± 9.2	0.044
Procedure time, sec	2737.2 ± 1834.4	2768.2 ± 2039.4	0.6
Fluoroscopy time, sec	812.1 ± 584.1	832.9 ± 759.5	0.4
Contrast volume, mL	112.9 ± 69.7	126.1 ± 92.7	0.26
Intraprocedural complications, %	7.9	3.8	0.009
Time from PTA to discharge, days	3.5 ± 1.9	3.1 ± 2.3	0.53
Hospitalization time, days	5.7 ± 4.9	5.2 ± 5.2	0.009
TASC II classification, %			
A	14.6	21.6	0.003
B	17.7	21.6	
C	15.7	14.6	
D	52	42.2	

Abbreviations: GFR - glomerular filtration rate; PTA - percutaneous transluminal angioplasty; TASC - Trans-Atlantic Inter-Society Consensus.

Table 3
Clinical outcomes.

Variables	Female N = 351	Male N = 588	P
Re-PTA, %	30.86	36.93	0.059
Time to re-PTA, days	354.66 ± 456.6	331.33 ± 479.1	0.12
Stroke/TIA, %	3.14	2.44	0.52
Time to stroke/TIA, days	277.82 ± 359.9	703.86 ± 882.5	0.11
Myocardial infarction (MI), %	3.72	3.31	0.73
Time to MI, days	838.92 ± 640.6	773.11 ± 589.4	0.76
Death, %	14	13.07	0.68
Time to death, days	574.4 ± 657.8	616.68 ± 584.3	0.51
Amputation, %	19.94	15.26	0.07
Time to amputation, days	127.79 ± 193.4	184.53 ± 439.4	0.46
Lower extremity bypass (LEB), %	5.43	4.92	0.74
Time to LEB	231.88 ± 298.1	254.71 ± 299.78	0.9
PTE/TEA, %	0.32	1.43	0.15
Time to PTE/TEA, days	6 ± 0	76 ± 77.3	0.27

Abbreviations: PTA - percutaneous transluminal angioplasty; PTE - percutaneous thrombectomy; TEA - thromboendarterectomy; TIA - transient ischemic attacks.

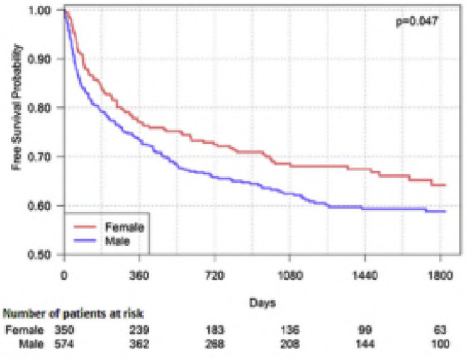

Fig. 1. Re-PVI free survival probability assessed at five years of the follow-up period.

4. Discussion

The main finding of the present study is that in the group of patients with PAD and CTOs treated with PVI from retrograde access, males were at a higher risk of re-PVI during the long-term follow-up period. According to the available database, there could be at least a few explanations for this observation. In our study, females represented 37.4% of the cohort, which remains in line with data presented in studies related to PAD treatment and is sanctioned by many factors [1]. Among them, we include age, poorer diagnosis of PAD in females, different symptoms which are related to a different spectrum of concomitant diseases such as diabetes and diabetic neuropathy [1]. Another issue is that the incidence of PAD rapidly increases during the climacteric period and after the fifth decade - it is at least equally frequent in both genders [7]. The disparity between epidemiological data and representation of the trial cohort may be rooted in sociological issues. The fact of the aging population as a progressive phenomenon is undeniable and its structure demonstrates the subpopulation of women as a majority [8]. In older age, it is common to confuse symptoms of PAD with osteoarthritis or osteoporosis. Females more often present asymptomatic PAD [9]. It has been suggested that women are less likely to be hospitalized or to undergo invasive procedures, and when they do, they are older and afflicted with a more advanced disease, which is concordant with the results of our study [10,11]. This explains why females undergo PVI at an older age and at more advanced stages of the disease. As confirmation, we may underline the fact that Rutherford's category III and IV occurred significantly more often in the female population than in males. Also, according to the TASC II classification, more advanced atherosclerosis was found in females. This is a consequence of differences in symptoms between genders. It can also be concluded that the consequence of this is greater difficulty with crossing the CTO in females, due to the fact that the atherosclerotic lesions are more advanced and occur at older age. Undoubtedly, it resulted in a greater number of peri-procedural complications. This, however, was not reflected in the frequency of retrograde access procedures among genders. Despite the factors mentioned above, the frequency of re-PVI was higher among men. Therefore, it can be suspected that there were other factors outweighing and determining the greater re-PVI rate in men. Both, diabetes and younger age, were confirmed as predictors of negative events in the group of patients with PAD undergoing PVI [12,13]. A similar relationship was demonstrated for TASC lesions and lower body-mass index, which is described as the obesity paradox [2,4]. It seems that factors such as coronary artery disease, younger age, smoking, COPD and hyperlipidemia prevail over the location of changes, clinical advancement or the presence of diabetes and have determined the higher frequency of re-PVI in the follow-up period in men. The other probable factors behind the lower re-PVI prevalence during follow-up among women are their compliance with post-treatment recommendations. More careful drug use and compliance with lifestyle modification recommendations, related to smoking, physical activity and diet, may be of crucial importance here. There are many studies assessing the need for reinterventions after PVI, but the presented results are often discrepant. Davies et al. [14] reported a higher frequency of repeated reinterventions in women. Similarly, DeRubertis et al. [6] noted an association between female gender and a higher incidence of reintervention. In a study investigating 3,338 patients undergoing peripheral vascular interventions, Ferranti et al. [10] found no significant differences between genders in terms of re-PVI. Analogic data related to a retrograde technique are scarce and do not include gender-related differences [15,16]. In the current study, male gender was linked to more frequent incidences of reintervention in comparison to women. It is an interesting finding regarding more advanced diseases in females, which remains in line with reports stating that women, despite more severe PAD, are less likely to undergo invasive procedures than men [1]. The presented results are burdened with a certain probability of bias and require further research among larger and more diverse populations.

Female gender has been recognized as a risk factor for periprocedural complications. There are many studies documenting wound issues after peripheral artery bypass surgery [17,18]. Development of PVI improved rates of procedural intricacies in both women and men and diminished the gap between these groups [19]. The results of our study remain in line with the findings in previously published papers [5,6,10]. In the present study, women had significantly higher incidences of intraprocedural complications and minor vascular complications compared to men. Based on the clinical data of the study in question, especially the age and stage of PAD, one may note that the greater number of peri-operative complications is associated with atherosclerotic lesions more challenging for the operator. This relationship seems to be crucial regarding the difference in the frequency of complications between women and men.

4.1. Limitations of the study

Several limitations could be attributed to the current study. One of them is the sample size which may bring some bias to the present study. Another potential factor is different completion time and shorter duration in selected patients during the follow-up period. Additional important limitation is the small number of procedural operators. There was also a significant possibility that more ill patients had out-of-hospital events and did not make it to follow-up.

5. Conclusions

Male gender was identified as an independent predictor of re-PVI in the group of patients with PAD and CTOs treated with percutaneous angioplasty from retrograde access. Chronic occlusion in the superficial femoral artery and procedural failure were associated with re-PVI in women. Further studies are needed to investigate gender disparities in outcomes after retrograde access procedures.

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The author contribution

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Declaration of competing interest

The authors declare no conflict of interests.

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b. Artykuł 2

Original papers

Age and gender differences in clinical outcomes of patients with heavy-calcified coronary artery lesions treated percutaneously with rotational atherectomy

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A – research concept and design; B – collection and/or assembly of data; C – data analysis and interpretation; D – writing the article; E – critical revision of the article; F – final approval of the article

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Abstract

Background. Rotational atherectomy (RA) used in elderly patients treated with percutaneous coronary interventions (PCI) could enable revascularization or the omission of cardiac surgery. Knowledge about factors affecting the prognosis may improve the results of treatment.

Objectives. We aimed to assess the relationship of gender and age with long-term clinical outcomes expressed as major adverse cardiac and cerebrovascular events (MACCEs).

Material and methods. The study included 97 consecutive patients treated with PCI and RA at the mean age of 71. The study group contained 73.2% men and 26.8% women, 36.1% of patients older than 75 and 63.9% younger than 75. The mean time of follow-up was 695.3 ±560.9 days. The rate of MACCEs (deaths, myocardial infarctions (MIs), reinterventions, coronary artery by-pass surgeries, or cerebral strokes (CSs)/transient ischemic attacks (TIAs)) in the overall group of patients was calculated at 33.7%.

Results. The comparison of Kaplan–Meier survival curves did not depict significant differences in the frequency of MACCEs for age ($p = 0.36$) and gender ($p = 0.07$). We noticed that the death rate was higher in females than in males and in patients older than 75 compared to those younger, and was statistically significant for age ($p = 0.04$). The rate of periprocedural complications was significantly higher among women than among men ($p = 0.005$) and in patients older than 75 compared to the younger ones ($p = 0.003$).

Conclusions. Age and gender are not significantly associated with an increased rate of MACCEs during follow-up in elderly patients treated with PCI and RA.

Key words: age, predictors, gender, clinical outcomes, rotational atherectomy

Cite as
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Introduction

In the era of population aging and the increase in the percentage of elderly patients, differences in the therapeutic approach among this group of patients are of special importance. A number of published studies have shown that age is associated with increased mortality and worse prognosis in the follow-up period among hospitalized patients.[1] Poorer prognosis in the elderly is associated with several factors reflecting the functional changes in their organisms. Some researchers even attempted to identify the most important independent risk factors and created a prognostic index for this group of patients to estimate the probability of mortality, and thus, the possibility of interfering with these factors to prolong life in this group of patients.[2] One of the independent risk factors of increased mortality in patients after hospitalization is ischemic heart disease. Previously published studies have shown differences in response to the established treatment regimens in the elderly group of patients, and that appropriate modification of the diagnostic and therapeutic processes in this group of patients may contribute to a significant improvement in treatment outcomes compared to younger patients.[3,4] Increased calcification in coronary arteries is associated with a higher risk of ischemic heart disease and cardiovascular events as well as mortality in elderly patients.[4] Rotational atherectomy (RA) as a device to facilitate percutaneous coronary interventions (PCI) is dedicated to patients with heavy calcified stenoses in the coronary arteries.[5] The RA is applicable to elderly patients, although the number of publications comparing the results of its use depending on age is limited. Several studies have shown that age is an independent risk factor for major adverse coronary events in this group of patients.[6] In comparative studies, the relationship of gender and long-term treatment results in the case of orbital atherectomy in the group of patients with heavy calcified lesions in coronary arteries has not been demonstrated, while the number of publications on RA is very limited.[7]

Therefore, in the current study, we aimed to assess the relationship of gender and age with long-term clinical outcomes in patients treated with PCI and RA expressed as major adverse cardiac and cerebrovascular events (MACCE).

Material and methods

Our study was a retrospective and partially prospective registry of 97 consecutive patients undergoing PCI with RA from 2002 to 2017 in the primary reference center. The majority of patients were included during the last 10 years. All patients were screened for risk factors, concomitant diseases, past PCI history, and medications. Procedural details, and in-hospital and long-term complications were collected. The maximum follow-up period was 2,315 days and the study endpoints were the rates of MACCE defined as the following: death (overall mortality), the requirement of target lesion revascularization expressed as endovascular reintervention or coronary artery by-pass grafting (CABG) operation, myocardial infarction (MI), and cerebral stroke (CS)/transient ischemic attack (TIA). All patients gave informed consent for the procedure. The study was approved by the institutional ethical board and conformed to the ethical principles for medical research involving human subjects of the 1975 Declaration of Helsinki.

Procedure

Patients were qualified for the procedure according to the current guidelines.[5] A Rotablator (Boston Scientific, Marlborough, USA) was used to perform the procedure. We evaluated the preprocedural risk with Euroscore II and Syntax score online calculators (http://euroscore.org/calc.html and http://www.syntaxscore.com/calculator/start.htm respectively). The risk was defined as: low (≤2%), intermediate (3–5%) and high (≥5%) for the EUROSCORE II and low (0–22 points), intermediate (23–32 points) and high (≥33 points) for the SYNTAX score.

Procedure-related complications

The rate of procedure-related complications consisted of the intraprocedural complications and periprocedural hospitalization, which occurred after the procedure until discharge from the hospital. The procedure-related MI was defined according to the 3rd universal definition of MI.[8] Coronary artery perforation was defined according to the most common and recognized definition proposed by Ellis at al.[9] The procedure-related hematoma was included in the analysis when it demanded surgical intervention or/and blood products transfusion. Cardiogenic shock was defined according to the current European Society Guidelines.[10] We included all the deaths that occurred during the procedure or after the procedure until discharge from the hospital into the current analysis as overall mortality. The allergic reaction was found to be significant when it demanded prolonged hospitalization and parenteral or oral therapy with antiallergic specifics. Contrast-induced nephropathy was recognized according to the definition published by Mehran et al.[11] Coronary artery dissection was defined according to the most common classification.[12] Other technical complications associated with the RA procedure itself were reported in accordance with current recommendations regarding the use of RA in Europe.[13] For periprocedural arrhythmias, we included persistent ventricular and supraventricular tachyarrhythmias, and atrioventricular conductive disorders requiring additional pharmacological or interventional treatment (pacing or cardioversion). Slow-flow or no-reflow was defined as TIMI (thrombolysis in myocardial infarction) flow grade 0 or 1.[14]

Statistical analysis

Normal distribution was assessed with the Shapiro–Wilk test. The χ^2 test was used to compare the categorical variables. For comparisons of continuous data, the Mann–Whitney U test or the Student's t-test were performed where applicable. The log-rank test was performed for comparisons of Kaplan–Meier survival curves in selected subgroups. Univariate analysis of selected potential predictors of clinical outcomes defined as MACEEs was also performed. A probability of $p < 0.05$ was considered statistically significant. The statistical analyses were conducted with STATISTICA v. 10.0 software (StatSoft, Inc., Tulsa, USA) and SPSS Statistics v. 24 (IBM Corp., Armonk, USA).

Results

The overall group of patients included 97 subjects in which successful rotablation was performed. Among them, there were 71 males (73.2%) and 26 females (26.8%), 62 individuals older than 75 (63.9%) and 35 patients younger than 75 (36.1%). The distribution of patients within particular age groups depending on gender is presented in Fig. 1.

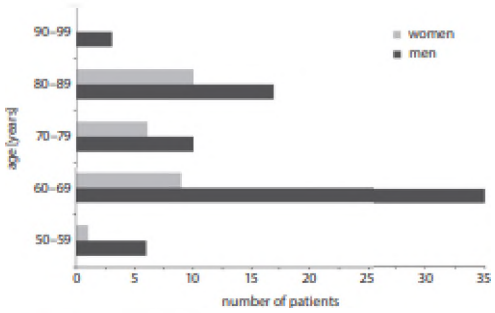

Fig. 1. Patient distribution in selected age intervals according to gender

General characteristics

The mean age of the males was 70.8 ±10 years and females 73.8 ±9.2 years. Males were significantly more often smokers (69.6% vs 10%, p = 0.03) and their mean ejection fraction of the left ventricle (LVEF) was smaller (43.9% vs 51.4%, p = 0.036), while the only 2 cases qualified for the RA in salvage mode were females (p = 0.01).

Patients older than 75 had significantly smaller mean body mass index (BMI) values (26.7 kg/m^2 vs 29.2 kg/m^2; p = 0.04), and presented at admission significantly more often with unstable angina (UA; 28.3% vs 53.1%, p = 0.019) or non-significantly less often with stable angina and non-ST segment elevation MI (NSTEMI). They also were qualified significantly more often for the procedure in emergency mode (26.5% vs 6.9%, p = 0.002) and non-significantly less often in elective and urgent mode. Moreover, the older group of patients characterized with greater mean serum creatinine level (p = 0.005) and smaller glomerular filtration rate (GFR) level (p < 0.001). All clinical data are presented in Table 1.

The mean EUROSCORE II value was higher in females compared to males; however, it was without statistical significance (3.3% ±3.3% vs 9.4% ±18.4%, p = 0.4). The higher mean EUROSCORE II value was attributed to the fact that among females there were 2 extremely high-risk patients treated in salvage mode, which increased the mean value. A similar relation was found when the overall group was divided according to age, where the 2 patients were placed in the group of patients older than 75. The difference in the mean EUROSCORE II value between patients younger and older than 75 was significant (9.2% ±15.2% vs 2.3% ±2.8%, p < 0.001). In the case of gender division, males were more often at low risk (44.6%) compared to moderate (35.4%) and high-risk patients (0.2%), and in comparison to women, each risk group did not differ significantly. Among women, the distribution in the low (34.8%), moderate (34.8%) and high-risk (30.4%) cases was more even.

In patients younger than 75, there were more patients in the low-risk group (58.2%) in comparison to moderate (50.9%) and high-risk (9.1%) groups. Not surprisingly, opposite distribution was shown in patients older than 75, among whom most patients were in the high-risk group (45.4%), while in the moderate (39.4%) and low-risk (15.1%) groups, their number was smaller. The difference between younger and older patients was significant for the low-risk group (p = 0.001) and high-risk group (p < 0.001).

Pharmacotherapy

There were no statistically significant differences in pharmacological treatment between males and females. Patients older than 75 were treated significantly more often with clopidogrel as a second antiplatelet drug (83% vs 100%, p = 0.01). This was mainly due to more frequent use of ticagrelor (8.3% vs 0%, p = 0.08) and prasugrel (6.7% vs 0%, p = 0.12) in younger patients. The frequency of other medications did not differ significantly between patients younger and older than 75. This is presented in Table 2.

Lesion characteristics and procedural indices

The mean SYNTAX Score I value did not differ significantly between males and females, and was greater in females (24.1 ±13 points vs 26.3 ±13.0 points, p = 0.45). Patients older than 75 were presented with greater mean SYNTAX Score I value compared to younger patients; however, the difference did not reach statistical significance (28.1 ±13.4 points vs 22.1 ±13 points, p = 0.06). When comparing SYNTAX Score I groups, there were

Table 1. General characteristics

Variable	Gender		p-value	Age [years]		p-value
	male	female		<75	≥75	
Age [years]	70.8 ±10.0	73.8 ±9.2	0.13	65.4 ±5.8	82.6 ±4.0	<0.000
BMI [kg/m^2]	27.9 ±6.3	28.9 ±4.6	0.50	29.2 ±7.0	26.7 ±3.1	0.04
Gender (males)	–	–		49 (79)	22 (62.8)	0.08
Diabetes	34 (49.3)	15 (60)	0.36	34 (56.7)	15 (44.1)	0.31
Hypertension	66 (95.6)	25 (100)	0.29	57 (95)	34 (100)	0.68
Hyperlipidemia	65 (94.2)	25 (100)	0.22	57 (95)	33 (97.1)	0.86
Obesity	18 (27.3)	6 (26.1)	0.91	18 (32.1)	6 (18.2)	0.27
Prior PCI	47 (73.4)	13 (61.9)	0.31	41 (75.9)	19 (61.3)	0.26
Prior MI	46 (66.7)	15 (65.2)	0.92	32 (59.2)	25 (73.5)	0.28
Prior CABG	10 (14.7)	4 (16)	0.87	11 (18.6)	3 (8.8)	0.43
PAD	19 (27.9)	3 (12)	0.11	16 (27.1)	6 (17.6)	0.44
COPD	9 (13)	5 (20)	0.40	7 (16.7)	7 (20.6)	0.24
CS/TIA	10 (14.5)	4 (16)	0.85	5 (8.3)	9 (26.5)	0.14
Heart failure	23 (33.3)	8 (32)	0.90	19 (31.7)	12 (35.3)	0.72
Smoking	48 (69.6)	10 (40)	0.03	38 (63.3)	20 (58.8)	0.71
Kidney failure	13 (18.8)	5 (20)	0.93	8 (13.3)	10 (29.4)	0.06
Clinical picture						
stable angina	36 (54.5)	9 (36)	0.11	32 (53.3)	14 (43.7)	0.38
UA	17 (25.7)	8 (32)	0.55	17 (28.3)	17 (53.1)	0.019
NSTEMI	13 (19.7)	7 (28)	0.39	9 (15.0)	1 (3.1)	0.08
STEMI	3 (4.5)	1 (4)	0.90	2 (1.7)	0 (0)	0.29
Mode						
elective	39 (56.5)	10 (40)	0.15	35 (60.3)	14 (41.2)	0.10
urgent	21 (30.4)	9 (36)	0.60	21 (36.2)	9 (26.5)	0.39
emergency	9 (13)	4 (16)	0.71	4 (6.9)	9 (26.5)	0.002
salvage	0 (0)	2 (8)	0.01	0 (0)	2 (5.9)	0.06
LVEF [%]	43.9 ±12.7	51.4 ±10.8	0.036	47.8 ±11.5	42.3 ±13.9	0.13
GFR [mL/min]	80.0 ±33.2	64.2 ±29.4	0.08	92.4 ±28.4	48.9 ±17.6	<0.000
Creatinine [µmol/L]	92.5 ±33.3	85.6 ±25.7	0.21	83.6 ±20.5	103.2 ±42.0	0.005

BMI – body mass index; CABG – coronary artery by-pass grafting; COPD – chronic obstructive pulmonary disease; CS – cerebral stroke; GFR – glomerular filtration rate; LVEF – left ventricle ejection fraction; MI – myocardial infarction; NSTEMI – non ST-segment elevation MI; PAD – peripheral artery disease; PCI – percutaneous coronary intervention; STEMI – ST-segment elevation MI; TIA – transient ischemic attacks; UA – unstable angina.

Table 2. Pharmacotherapy at discharge

Variable	Gender		p-value	Age [years]		p-value
	male	female		<75	≥75	
ASA	71 (100)	26 (100)	–	62 (100)	35 (100)	–
Antiplatelets						
clopidogrel	59 (88)	25 (96.2)	0.18	50 (83)	34 (97.1)	0.01
ticagrelor	4 (6)	1 (3.8)	0.69	5 (8.3)	0 (0)	0.08
prasugrel	4 (6)	0 (0)	0.20	4 (6.7)	0 (0)	0.12
ticlopidine	1 (1.5)	0 (0)	0.53	1 (1.7)	0 (0)	0.44
Oral antidiabetic	18 (26.1)	6 (25)	0.93	21 (35)	3 (9.1)	0.03
Insulin therapy	18 (26.1)	8 (32)	0.66	18 (30)	8 (23.5)	0.60
ACEis/ARB	33 (47.8)	10 (41.7)	0.65	27 (45)	16 (48.5)	0.78
Diuretic	34 (55.7)	10 (50)	0.95	23 (45.1)	21 (70)	0.28
β-blocker	64 (92.7)	24 (100)	0.59	56 (93.3)	32 (97)	0.77
Statin/fibrate	68 (98.5)	23 (95.8)	0.91	57 (96.6)	34 (100)	0.89
Anticoagulant	14 (20.3)	6 (25)	0.72	8 (13.3)	12 (36.4)	0.06
Nitrate	4 (5.8)	2 (8.3)	0.85	2 (3.3)	4 (12.1)	0.48
Ca-blocker	20 (29)	9 (37.5)	0.35	19 (31.7)	10 (30.3)	0.91

ASA – acetyl-salicylic acid; ACEi – angiotensin-converting enzyme inhibitors; ARB – aldosterone receptor blockers.

no significant differences between males and females in the low (45.6% vs 35.7%, p = 0.51), intermediate (28.2% vs 28.6%, p = 0.98) and advanced lesions (26.1% vs 35.7%, p = 0.48). While considering patients in terms of age, there were significantly more patients with less advanced atherosclerotic lesions in the coronary arteries among patients younger than 75 compared to older patients (54.3% vs 28%, p = 0.04), whereas there was not a significantly greater percentage of patients older than 75 in the intermediate (36% vs 22.8%, p = 0.26) and high (36% vs 22.8%, p = 0.26) SYNTAX Score I group compared to younger patients.

Both in the case of the division into women and men and into patients over and under the age of 75, atherosclerotic lesions in type C according to American Heart Association (AHA) classification were more frequent in comparison to type 2B lesions. Type C lesions occurred not significantly more often in males than in females (78.7% vs 71.4%, p = 0.56), and in patients older than 75 (84% vs 73.5%, p = 0.33), while type 2B lesions occurred more often in females (28.6% vs 21.3%, p = 0.56) and patients younger than 75 (26.5% vs 16%, p = 0.33).

Females were treated significantly more often from right radial access compared to males (50% vs 25.9%, p = 0.04), while patients older than 75 were treated significantly less often with single stent implantation compared to younger patients (80% vs 60%, p = 0.03), and insignificantly more often with 2 or 3 stents. Lesion characteristics and procedural indices are presented in Table 3.

Significantly more procedure-related complications occurred in females compared to males (46.1% vs 18.3%, p = 0.005). Also, older patients (>75 years) demonstrated a significantly higher frequency of procedure-related complications (42.8% vs 16.1%, p = 0.003). More detailed characteristics are presented in Table 4.

Table 3. Lesion characteristics and procedural indices

Variable	Gender		p-value	Age [years]		p-value
	male	female		<75	≥75	
Direct indication was inability to:						
cross with b.c.	27 (40.3)	8 (34.8)	0.63	21 (36.2)	14 (43.7)	0.48
dilate with b.c.	39 (58.2)	12 (52.2)	0.61	34 (58.6)	17 (53.1)	0.61
stent delivery	1 (1.4)	3 (13)	0.02	3 (5.2)	1 (3.1)	0.65
Mean burr diameter [mm]	1.49 ±0.20	1.43 ±0.30	0.26	1.47 ±0.20	1.47 ±0.20	0.57
Maximum burr diameter [mm]	1.5 ±0.20	1.4 ±0.20	0.27	1.48 ±0.20	1.48 ±0.30	0.69
Arteries						
1	56 (78.9)	16 (64)	0.13	49 (80.3)	23 (65.7)	0.11
2	12 (16.9)	7 (28)	0.23	10 (16.4)	9 (25.7)	0.26
3	3 (4.2)	2 (8)	0.46	2 (3.3)	3 (8.6)	0.46
Stents						
1	36 (54.5)	15 (60)	0.63	49 (80)	21 (60)	0.03
2	21 (31.8)	7 (28)	0.72	10 (16.4)	10 (28.6)	0.15
3	8 (12.1)	2 (8)	0.57	2 (3.3)	4 (11.4)	0.11
4	1 (1.5)	1 (3.6)	0.48	0 (0)	0 (0)	–
Stent length [mm]	26.2 ±10.2	24.0 ±8.5	0.51	26.6 ±11.0	24.1 ±7.6	0.49
Stent diameter [mm]	3.04 ±0.70	3.06 ±0.80	0.90	3.05 ±0.70	3.0 ±0.70	0.62
Balloon diameter before PCI [mm]	2.9 ±0.5	2.6 ±0.6	0.06	2.9 ±0.6	2.7 ±0.5	0.27
Post-dilatation	58 (87.9)	19 (76)	0.38	51 (89.5)	26 (76.5)	0.30
Balloon diameter after PCI [mm]	3.6 ±0.7	3.7 ±1.0	0.93	3.6 ±0.7	3.6 ±0.9	0.50
IVUS after PCI	18 (25.3)	3 (11.5)	0.29	15 (24.2)	6 (17.1)	0.56
Radiation dose [Gy]	1.97 ±1.20	1.9 ±1.2	0.77	2.04 ±1.40	1.8 ±0.8	0.89
Contrast volume [mL]	271 ±106	303 ±140	0.53	285 ±140	272.0 ±69.6	0.69
Type of PCI						
POBA/DEB	3 (4.4)	0 (0)	0.28	3 (5.2)	0 (0)	0.17
DES	64 (94.1)	24 (96)	0.72	55 (94)	33 (94.3)	0.91
BMS	1 (1.5)	1 (4)	0.45	0 (0)	2 (5.7)	0.06
Vascular access						
RRA	15 (25.9)	10 (50)	0.04	16 (34.8)	9 (28.1)	0.53
LRA	2 (3.4)	0 (0)	0.40	1 (2.2)	1 (3.1)	0.79
RFA	36 (62.1)	9 (45)	0.18	24 (52.2)	21 (65.6)	0.23
LFA	5 (8.6)	1 (5)	0.60	5 (10.9)	1 (3.1)	0.20

b.c. – balloon catheter; BMS – bare-metal stent; Cx – circumflex branch; DEB – drug-eluting balloon; DES – drug-eluting stent; Dg – diagonal branch; IVUS – intravascular ultrasound; LAD – left anterior descending branch; LFA – left femoral artery; LMCA – left main coronary artery; LRA – left radial artery; Mg – marginal branch; PCI – percutaneous coronary intervention; POBA – plain-old balloon angioplasty; RCA – right coronary artery; RFA – right femoral artery; RRA – right radial artery.

Table 4. Procedure-related complications

Variable	Gender		p-value	Age [years]		p-value
	male	female		<75	≥75	
Overall rate	13 (18.3)	12 (46.1)	0.005	10 (16.1)	15 (42.8)	0.003
AD	3 (4.2)	2 (7.7)	0.49	3 (4.8)	2 (5.7)	0.85
CS	1 (1.4)	3 (11.5)	0.02	2 (3.2)	2 (5.7)	0.55
MI	2 (2.8)	1 (3.8)	0.79	2 (3.2)	1 (2.8)	0.91
Death	0 (0)	1 (3.8)	0.09	0 (0)	1 (2.8)	0.18
Bleeding	1 (1.4)	2 (7.7)	0.11	1 (1.6)	2 (5.7)	0.27
Hematoma	1 (1.4)	2 (7.7)	0.11	0 (0)	3 (8.6)	0.02
Rotawire disruption	0 (0)	1 (3.8)	0.09	0 (0)	1 (2.8)	0.18
Arrhythmias	2 (2.8)	0 (0)	0.38	1 (1.6)	1 (2.8)	0.67
Allergic reaction	1 (1.4)	0 (0)	0.54	1 (1.6)	0 (0)	0.45
Slow flow	1 (1.4)	0 (0)	0.54	0 (0)	1 (2.8)	0.18
CIN	1 (1.4)	0 (0)	0.54	0 (0)	1 (2.8)	0.18

AD – arterial dissection; CIN – contrast-induced nephropathy; CS – cerebral stroke; MI – myocardial infarction.

Clinical outcomes and follow-up

Follow-up was completed among the overall study group in 78 (80.4%) patients included into the study. During the mean time to the MACCE or follow-up without MACCE (695 ±560 days), MACCEs occurred in 26 patients (33.7%). Among the MACCEs, there were 14 deaths (53.8%), 4 reinterventions (15.4%), 5 MIs (19.2%), 2 CS/TIA cases (7.7%), and 1 coronary artery by-pass grafting (CABG) operation (3.8%).

The frequency of MACCEs was greater among females compared to males, however, without statistical significance (45.4% vs 28.6%, p = 0.32). This was mainly due to greater rate of reinterventions (9.1% vs 3.6%, p = 0.7) and deaths (27.3% vs 14.3%, p = 0.37). Also, the MACCEs rate was greater in patients older than 75 compared to those younger than 75 (42.8% vs 28.6%, p = 0.38), and this was mainly the consequence of greater rate of deaths among older patients (35.7% vs 8%, p = 0.04). This is presented in Table 5.

The Kaplan–Meier survival curve comparison between males and females confirmed that, despite the fact that the frequency of MACCEs was higher in women, there was no significant difference between those 2 groups (p = 0.07). This is presented in Fig. 2.

Similarly, the greater rate of MACCEs in patients older than 75 compared to those younger did not meet statistical significance in comparison of the Kaplan–Meier survival curves (p = 0.36). This is presented in Fig. 3.

Predictors of clinical outcomes

Univariate analysis of several selected factors revealed that among them, statistically significant relationships with MACCEs were achieved for the maximal burr diameter (p = 0.03), the occurrence of procedure-related complications (p = 0.015), the mean EUROSCORE II value (p = 0.02), and borderline relationship with obesity (p = 0.052). Considering the fact that age and gender were

Table 5. Study endpoints and duration of follow-up in selected groups of patients

Variable	Gender		p-value	Age [years]		p-value
	male	female		<75	≥75	
Completed follow-up	56 (78.9)	22 (84.6)	0.90	50 (80.6)	28 (80)	0.88
Mean time of follow-up [days]	727 ±536	614 ±625	0.18	677 ±541	726 ±603	0.80
MACCE	16 (28.6)	10 (45.4)	0.32	14 (28.6)	12 (42.8)	0.38
Mean time to MACCE [days]	638 ±573	324 ±435	0.09	574 ±634	451 ±415	0.95
Re-PCI	2 (3.6)	2 (9.1)	0.70	4 (8)	0 (0)	0.55
Death	8 (14.3)	6 (27.3)	0.37	4 (8)	10 (35.7)	0.04
CS/TIA	1 (1.8)	1 (4.5)	0.85	1 (2)	1 (3.6)	0.90
MI	4 (7.1)	1 (4.5)	0.34	4 (8)	1 (3.6)	0.19
CABG	1 (1.8)	0 (0)	0.90	1 (2)	0 (0)	0.88

CABG – coronary artery by-pass grafting; CS – cerebral stroke; MACCE – major adverse cardiac and cerebrovascular events; MI – myocardial infarction; PCI – percutaneous coronary intervention; TIA – transient ischemic attack.

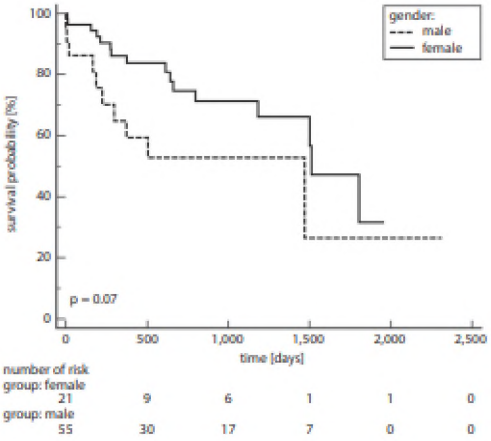

Fig. 2. The comparison of Kaplan–Meier survival curves according to gender

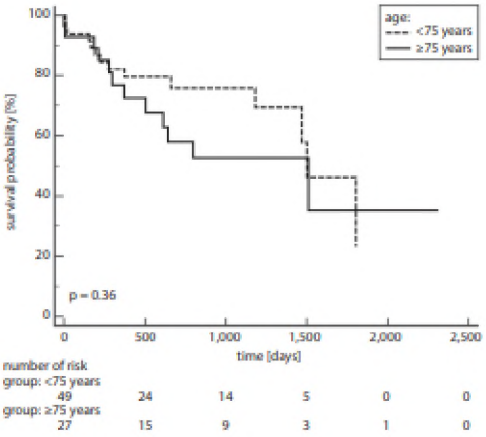

Fig. 3. The comparison of Kaplan–Meier survival curves according to the age of 75

not among the factors associated with the occurrence of MACCE in the follow-up period, a multivariate analysis was not performed.

Discussion

The crucial finding of the presented analysis is that gender and age greater than 75 were not found to be significantly related to poorer clinical outcomes expressed as MACCE rate during the long-term follow-up period compared with survival curves. However, it should be noted after the analysis of individual components of MACCEs, for both women and patients in the age group above 75, the incidence of deaths was higher, and in the case of age-related differences, mortality was statistically significantly greater in the group of older patients. The univariate analysis did not confirm the relationship of age and gender with MACCEs during the follow-up period. Instead, it revealed that the maximal burr diameter, EUROSCORE II value and the presence of procedure-related complications are associated with long-term clinical outcomes after RA. The relationship between the EUROSCORE II value and the length of the implanted stent was demonstrated in a previously published paper.[15] The level of perforations in the presented study was higher (3.1%) when compared to the published results based on large registries (0.3–1.1%).[16,17] However, coronary perforations observed in our analysis were not complicated by serious and life-threatening incidents, including cardiac tamponade and surgical treatment. They were treated successfully with an endovascular approach. Moreover, usually registries, including the Polish National Registry, underestimate the rate of procedure-related complications.[18,19] The frequency of the overall procedure-related complication rates was significantly greater in females and in the group of patients older than 75. In the case of age, this was mainly due to the greater number of arterial dissections, cardiogenic shocks and MIs, while in the case of the female gender, arterial dissections, cardiogenic shocks, arterial perforations, and hematomas demanding blood transfusion or surgical treatment were more frequent.

Some published studies estimating the relationship between age and long-term clinical outcomes in patients with heavy calcified coronary artery lesions demonstrated that age is an independent risk factor of poorer clinical outcomes expressed as MACCE.[6] However, most of them did not confirm a significant relationship between age and long-term clinical outcomes, and among the factors that have independent influence on the prognosis, they confirmed LVEF, diabetes, cardiogenic shock, acute coronary syndrome, kidney failure, SYNTAX score, neutrophil/lymphocyte ratio, burr to artery ratio, or prior PCIs.[20–23] Most of these studies involved several hundreds of patients. Considering the various components of MACCE, Abdel-Wahab et al. demonstrated that age was an independent predictor of target lesion revascularization.[20] Our study included only about 100 participants, which makes it one of the smaller studies among those discussed. As a consequence, the results are very susceptible to bias. One of the factors that certainly influenced the bias was the severe state of some patients qualified for RA at a young age for the present cohort of patients, which were the causes of MACCE occurrence during the hospital stay or shortly after discharge. Operators are less likely to perform heroic rotablation treatments in older patients with multiple risk factors, which undoubtedly influenced the artificial masking of mortality in the early periprocedural stage in patients over 75.

Moreover, we did not break down MACCE into individual components in order to assess the impact of age and gender in survival curve analysis on long-term treatment results due to an insufficient number of endpoints in individual groups of patients and the resulting high probability of error and bias. However, we performed such a comparison of study endpoints for both groups and showed almost twice as high mortality in the follow-up period in women and patients over the age of 75, although this difference was statistically significant only for older patients. Nonetheless, in the case of women, this relationship can be explained by the higher mean value of the initial EUROSCORE II, which was mainly associated with a greater number of salvage mode procedures, greater mean age and more procedure-related complications. On the other hand, it should also be noted that women initially had a statistically significantly higher mean LVEF and they smoked cigarettes less frequently, which in some way influenced mortality balance and made it statistically non-significant. In the case of older age, the mortality rate was statistically significantly higher in the group of patients older than 75, which was in line with other factors closely related to increased mortality as serum creatinine, GFR, mean SYNTAX score value, or mean EUROSCORE II value. In addition, the age of the patients and the aging of the body were also of great importance, as exemplified by the occurrence of deaths in patients above 90 years of age after a period of just over 200 days of the follow-up period. There are no publications attainable in the available literature that closely compare the long-term clinical outcomes of patients with severely calcified lesions of coronary arteries using RA. On the other hand, studies estimating the influence of individual factors on the results of treatment did not show that gender was related to treatment outcomes presented as MACCE prevalence. One of the few available studies on the treatment of similar coronary artery lesions, but undertaken with the use of another device, regards orbital atherectomy.[7] This study was conducted on a relatively large group of patients including 458 participants. The incidence of MACCE did not differ significantly between the 2 groups and was 0.7% and 2.7%, respectively, for women and men ($p = 0.14$). Admittedly, the incidence of MACCE in this study was higher in men than women. One of the factors that could have an impact on the incidence of MACCE in this study was higher mean length and diameter of stents in men compared to women, which was shown to be related to the incidence of MACCE in the follow-up period in other studies, including those published by our center.[15] On the other hand, in this study, the men were statistically significantly younger and less likely to have hypertension and hypercholesterolemia. Men were also insignificantly younger in our study, which certainly influenced the results.

Considering the relationship of procedure-related complications with gender and age, it turned out that the incidence of complications in both women and older individuals is greater. Already in a previously published publication by our center, we demonstrated on a large group of patients that the incidence of arterial perforations was related to age, and that age is an independent predictor of increased risk of their occurrence,[18] which is in contrast, for example, to acute coronary syndromes that have not been shown to be significantly associated with the incidence of procedure-related complications.[24] The increased rate of procedure-related complications is mainly caused by calcifications in the coronary arteries, which predispose to typical complications of RA such as dissections or perforations.[16,25] Previously published studies on the association of gender with periprocedural complications treated with PCI indicate a greater susceptibility of women to procedure-related complications.[26] This trend also seems to be sustained for PCI with RA.

Conclusions

The negative relationship of age and gender with clinical outcomes expressed as increased rate of MACCEs in elderly patients treated with PCI and RA does not have as much impact as in the case of patients in other age groups, which should encourage operators to reduce their concerns in the treatment of patients over 75 years of age with rotablation.

Study limitations

The results of the presented work should be received with great caution, because the influence of age on poorer results in the follow-up period seems to be evident in all groups of patients treated with percutaneous coronary angioplasty, although the purpose of this article is to show that well-prepared and stable patients among the elderly may achieve comparable benefits from the use of rotablation compared to younger patients. In the current work, apart from a very small group of patients as for this type of treatment and a relatively large number of patients lost in the follow-up period, there are a number of factors that artificially mask the actual impact of age and sex on long-term treatment results. One of the main factors is undoubtedly the greater willingness of the use of rotablation in the salvage mode, especially in younger and promising patients, compared to the older and less promising individuals burdened with many concomitant diseases, including cancer, heart failure and others, which artificially increased the number of deaths in the early periprocedural stage in patients under 75 years of age.

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c. Artykuł 3

ORIGINAL ARTICLE

The impact of sex on in-hospital and long-term mortality rates in patients undergoing surgical aortic valve replacement: The SAVR and SEX study

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ABSTRACT

Background: Surgical aortic valve replacement (SAVR) is among the most commonly performed valvular surgeries. Despite many previous studies conducted in this setting, the impact of sex on outcomes in patients undergoing SAVR is still unclear.

Aims: This study aimed to define sex differences in short- and long-term mortality in patients undergoing SAVR.

Methods: We analyzed retrospectively all the patients undergoing isolated SAVR from January 2006 to March 2020 in the Department of Cardiovascular Surgery and Transplantology in John Paul II Hospital in Kraków. The primary endpoint was in-hospital and long-term mortality. Secondary endpoints included the duration of hospital stay and perioperative complications. Groups of men and women were compared with regard to the prosthesis type. Propensity score matching was performed to adjust for differences in baseline characteristics.

Results: A total number of 4 510 patients undergoing isolated surgical SAVR were analyzed. A follow-up median (interquartile range [IQR]) was 2120 (1000–3452) days. Females made up 41.55% of the cohort and were older, displayed more non-cardiac comorbidities, and faced a higher operative risk. In both sexes, bioprostheses were more often applied (55.5% vs. 44.5%; $P < 0.0001$). In univariable analysis, sex was not linked to in-hospital mortality (3.7% vs. 3%; $P = 0.15$) and late mortality rates (23.37% vs. 23.52 %; $P = 0.9$). Upon adjustment for baseline characteristics (propensity score matching analysis) and considering 5-year survival, a long-term prognosis turned out to be better in women (86.8%) compared to men (82.7%, $P = 0.03$).

Conclusions: A key finding from this study suggests that female sex was not associated with higher in-hospital and late mortality rates compared to men. Further studies are needed to confirm long-term benefits in women undergoing SAVR.

Key words: mortality, SAVR, sex, TAVI

WHAT'S NEW?

Traditionally, female sex is considered a factor that worsens prognosis after heart surgeries. In this analysis, based on 4 510 patients undergoing isolated aortic valve replacement, in-hospital and late mortality did not differ significantly between men and women. In propensity score matching analysis, 5-year survival in women increased in comparison to men.

INTRODUCTION

Surgical aortic valve replacement (SAVR) is among the most commonly performed heart surgeries and most frequently conducted valvular interventions in Western countries [1]. The obvious indication for SAVR is aortic stenosis (AS), which has equal prevalence in elderly women and men [2]. With the onset of AS symptoms, the prognosis dramatically deteriorates as the disorder is resistant to pharmacological treatment [3]. On the other hand, surgery for AS reduces mortality and symptoms and increases the quality of life in both sexes [4, 5]. Nonetheless, sex differences in outcomes after SAVR are not unequivocally defined because of mixed results of previous studies, with greater evidence of worse prognosis for women [2, 6–11]. Unfavorable outcomes observed in women were explained by smaller anatomical structures rendering the procedure more technically demanding, more frequent frailty syndrome, and more comorbidities increasing the operative risk.

Recently, promising results of transcatheter aortic valve implantation (TAVI) in women were achieved [12, 13]. Nonetheless, the availability of this technique is not yet sufficient to include AS patients; therefore, improving results after the SAVR procedure is still of the utmost importance as surgery remains the gold standard of AS and aortic regurgitation (AR) treatment. This study aimed to assess sex differences in SAVR outcomes.

METHODS

We analyzed all patients undergoing SAVR in a single department of cardiac surgery from January 2006 to March 2020. To rule out the impact of other procedures on subjects undergoing TAVI, patients after annuloplasty and concomitant surgery were excluded. The baseline, clinical, and follow-up data were recorded, including demographic characteristics, concomitant diseases, course of hospitalization with procedural details, and possible complications. Late mortality was assessed with the Polish National PESEL database for the highest accuracy. A decision about the type and model of the prosthesis was made with patients. The primary study endpoints were in-hospital and late mortality. Secondary endpoints included length of hospital stay (LoHS) and periprocedural complications. Propensity score matching was applied for adjustment of baseline differences. All included characteristics are listed in Table 1. The study was conducted in accordance with the Declaration of Helsinki. Due to the retrospective nature of the collected data, patient consent was not required, and the bioethics committee approval was waived.

Study database

Data for this study were collected retrospectively based on the standardized form of the Polish National Database of Cardiac Surgery Procedures ("KROK" registry; www.krok.csioz.gov.pl). The registry is an ongoing, nationwide, multi-institutional record of cardiac surgery procedures in Poland, which was established on the initiative of the Club of Polish Cardiac Surgeons and compiled in cooperation with the Polish Ministry of Health. Centers enrolling patients in the KROK registry are required to transfer the data regarding every cardiac surgery to the central database in the National Center for Healthcare Information Systems at the Ministry of Health.

The data gathered included age, sex, body mass index (BMI), ejection fraction (EF), previous percutaneous coronary intervention (PCI), Canadian Cardiovascular Society (CCS) class, New York Heart Association (NYHA) class, smoking status, diabetes mellitus (DM), arterial hypertension, hypercholesterolemia, asthma, and chronic obstructive pulmonary disease (COPD). The follow-up time was defined as the period to the last observation or death. Data on late mortality were collected from the Polish National PESEL database to achieve the highest possible accuracy.

Based on the KROK registry form, a computer database was built for further statistical analysis.

Missing data in the database

We decided to exclude patients if records of outcomes (i.e., mortality/survivors) were missing. The completeness of each patient record was assessed: records were only analyzed if the percentage of complete data entered was higher than 90%. Records that were lower than 90% were excluded from this analysis. To handle missing data in propensity score matching (PSM), an additional level for the missing values was created for categorical data. In other words, the arbitrary value imputation technique was applied to those parameters. Cases with missing data in continuous parameters were excluded from PSM.

Statistical analysis

Categorical variables were presented as counts and percentages. Continuous variables were expressed as the mean with standard deviation (SD) or the median with the lower and upper quartile (interquartile range [IQR]). Normality was assessed by the Shapiro-Wilk test. Equality of variances was assessed using Levene's test. Differences between groups were compared using the Student's or Welch's t-test depending on the equality of variances for

Table 1. Baseline characteristics after propensity score matching (PSM)

		Men, n = 763	Women, n = 763	*P*-value
Age, years, median (IQR)		67 (58–74)	67 (60–73)	0.73
Body mass index, kg/m^2, median (IQR)		28.2 (25.1–31.5)	28.3 (25.1–32.4)	0.08
Overweight (BMI ≥25 kg/m^2), n (%)		574 (75.2)	577 (75.6)	0.86
Obesity (BMI ≥30 kg/m^2), n (%)		282 (37)	284 (37.2)	0.91
Body surface area, kg/m^2, mean (SD)		2 (0.2)	1.8 (0.2)	<0.001
LVEF, %, median (IQR)		60 (50–65)	60 (50–63)	0.22
AV gradient, mm Hg, median (IQR)		81 (66–96)	86.5 (73–104)	0.56
AR	None, n (%)	94 (12.3)	91 (11.9)	0.98
	Trivial, n (%)	281 (36.8)	279 (36.6)	
	Mild, n (%)	255 (33.4)	256 (33.6)	
	Moderate, n (%)	113 (14.8)	115 (15.1)	
	Severe, n (%)	20 (2.6%)	22 (2.9%)	
Smoking	None, n (%)	605 (79.3)	606 (79.4)	0.82
	Former, n (%)	107 (14)	101 (13.2)	
	Current, n (%)	51 (6.7)	56 (7.3)	
Last creatinine level, mg/dl, median (IQR)		0.9 (0.8–1.03)	0.8 (0.7–1)	<0.001*
CCS	N/A, n (%)	62 (8.1)	54 (7.1)	0.86
	I, n (%)	289 (37.9)	294 (38.5)	
	II, n (%)	344 (45.1)	341 (44.7)	
	III, n (%)	63 (8.3)	69 (9)	
	IV, n (%)	5 (0.7)	5 (0.7)	
NYHA	N/A, n (%)	62 (8.1)	54 (7.1)	0.96
	I, n (%)	142 (18.6)	138 (18.1)	
	II, n (%)	374 (49)	370 (48.5)	
	III, n (%)	208 (27.2)	212 (27.8)	
	IV, n (%)	30 (3.9)	34 (4.5)	
Prior MI, n (%)		57 (7.5)	62 (8.13)	0.63
Prior PCI, n (%)		26 (7.8)	32 (9.5)	0.82
Diabetes mellitus, n (%)		171 (22.4)	166 (21.8)	0.76
IDDM, n (%)		72 (9.4)	74 (9.7)	0.86
COPD	None, n (%)	611 (80.1)	615 (80.6)	0.56
	Treated, n (%)	150 (19.7)	148 (19.4)	
	Non-treated/untreated, n (%)	2 (0.3)	0 (0)	
Hypertension, n (%)		645(84.5)	637 (83.5)	0.57
Dyslipidemia, n (%)		290 (38)	280 (36.7)	0.61
EuroSCORE II, median (IQR)		0.9 (0.7–1.4)	1.1 (0.9–1.5)	<0.001*

Abbreviations: see Table 4

normally distributed variables. The Mann-Whitney U test was used for non-normally distributed continuous variables or ordinal variables. Categorical variables were compared by Pearson's χ^2 test or by Fisher's exact test if 20% of the cells had an expected count of less than 5. To evaluate the influence of sex on mortality (overall death), the Cox proportional-hazards model was created and adjusted for baseline covariates (age, prior myocardial infarction, current or former smoking status, DM, sinus rhythm before procedure, planned or emergency/urgent procedure, EuroSCORE II, hyperlipidemia and NYHA class). The multivariable model was fitted in backward stepwise regression with a *P*-value threshold of 0.05 stopping rule. Survival probabilities were presented using the Kaplan-Meier curves and compared with the log-rank test.

To avoid the potential influence of the non-randomized design and reduce bias, a propensity score was calculated using a multivariable logistic regression model with sex considered a dependent variable. The propensity score was calculated based on baseline variables (see Table 1 for details). Covariate balance was assessed using standardized mean differences (SMD) that were less than 5. Pairs of male and female patients were formed using 1:1 caliper matching. A caliper width of 0.07 was used. Unpaired patients were rejected from the analysis. Clinical outcomes (including mortality) for matched samples were compared using McNemar's test (Tables 2 and 3). Additionally, a matched pairs design of the win ratio method was applied for lifetime data [14]. The results of this method are presented on the forest plot (Figure 1).

The level of statistical significance was set at $P < 0.05$. Statistical analyses were performed with JMP®, version 16.2.0 (SAS Institute Inc, Cary, NC, US) and using R, Version 4.1.0 (R Core Team. R: A language and environment for statistical computing. R Foundation for Statistical Computing. Vienna, Austria, 2017, www.r-project.org/).

Table 2. Procedural and clinical outcomes after propensity score matching (PSM)

		Women, n = 763	Men, n = 763	*P*-value
Duration of hospitalization, days, median (IQR)		10 (8–14)	10 (8–14)	0.45
Valve type	Bioprosthesis, n (%)	457 (59.9)	453 (59.4)	0.83
	Mechanical, n (%)	306 (40.1)	310 (40.6)	
Valve diameter, mm, median (IQR)		23 (21–23)	23 (21–23)	0.14
Cardioplegia	Crystalloid, n (%)	469 (61.6)	497 (65.5)	0.11
	Blood, n (%)	293 (38.5)	262 (34.5)	
Re-operation	Re-sternotomy, n (%)	44 (9.4)	36 (7.8)	0.8
	Secondary sternal repair, n (%)	10 (2.2)	6 (1.3)	
Death in operating room, n (%)		1 (0.1)	2 (0.3)	0.56

Continuous variables were expressed as the median with the lower and upper quartile (IQR, interquartile range)

Table 3. In-hospital and late mortality after propensity score matching (McNemar's test)

	Female, n = 763	Male, n = 763	*P*-value
Procedural complications, n (%)	72 (9.5)	82 (10.8)	0.40
In-hospital mortality, n (%)	26 (3.4)	27 (3.5)	0.89
Death (within 1 year), n (%)	48 (6.3)	66 (8.7)	0.08
Death (within 2 years), n (%)	61 (8)	84 (11)	0.046
Death (within 3 years), n (%)	72 (9.4)	97 (12.7)	0.04
Death (within 4 years), n (%)	86 (11.3)	117 (15.3)	0.02
Death (within 5 years), n (%)	101 (13.2)	132 (17.3)	0.03
Overall death, n (%)	161 (21.1)	186 (24.4)	0.12

RESULTS

General characteristics

A total of 5035 consecutive patients undergoing invasive replacement of the aortic valve (AV) were included. Following exclusion, 4510 patients treated with isolated SAVR were analyzed (Supplementary material, *Figure S1*). Men formed 58.5 % of the cohort. Women were older (mean age 67.3 years vs. 61.6 years; $P < 0.001$) and more often overweight or obese (mean body mass index [BMI], 29.2 kg/m^3 vs. 28 kg/m^2; $P < 0.001$) with more non-cardiovascular concomitant diseases. Men were more often smokers (10.6% vs. 4.6%; $P < 0.001$), and they more often suffered from prior MI (11.2% vs. 5.4%; $P < 0.001$). The majority of patients were affected by aortic stenosis (85%). The maximal transvalvular (pressure) gradient was higher in women (89.2 vs. 79.4 mm Hg; $P < 0.001$). Men had more often moderate or severe aortic regurgitation. Symptoms assessed by the NYHA functional classification differed significantly in both groups, with female predominance in class III. The baseline patient characteristics are shown in Table 4.

Procedural outcomes

Except for 4 cases, all procedures were performed with the cardioplegic solution. The procedure was longer in men (214 vs. 208 min; $P = 0.002$), and they received bigger prostheses [23.7 vs. 21.3 mm; $P < 0.001$]. Also, the average time of extracorporeal circulation was longer in men (113.2 vs. 108.7 min; $P < 0.001$). Bioprostheses were chosen more often in both sexes, especially in women (61.6% vs. 51.2%; $P < 0.001$).

Clinical outcomes

A follow-up median (IQR) was 2120 (1000–3452) days, for men 2186 (1000–3568) days, and for women 2042 (1006–3270; $P = 0.01$) days. The frequency of complications did not differ between sexes (10.75% vs. 11.2%; $P = 0.67$). Univariate analysis did not show differences between women and men in terms of in-hospital mortality (3.7% vs. 3%; $P = 0.15$) and late mortality (23.37% vs. 23.52%; $P = 0.9$) (Table 5). Nonetheless, the propensity score analysis disclosed that after 1-year follow-up, the mortality rate in men was higher and remained so until the last observation period when we used McNemar's test for matched pairs (Table 3). The Kaplan-Meier estimate did not show significant differences between men and women in long-term follow-up (Figure 1). In the win ratio approach, a statistically significant mortality rate difference was observed only at 5 years; however, all analyses show similar win ratio results (Figure 2). At 5-year follow-up, women had 33% more wins over death (win ratio [WR], 1.33; 95% CI, 1.00–1.79; $P = 0.048$). Additionally, the multivariable Cox regression indicated that male sex was associated with higher risk of death (hazard ratio [HR], 1.22; 95% CI, 1.07–1.39; $P = 0.003$).

DISCUSSION

The key findings of this study led to the conclusion that women do not have higher in-hospital and long-term mortality than men. Traditionally, female sex was associated

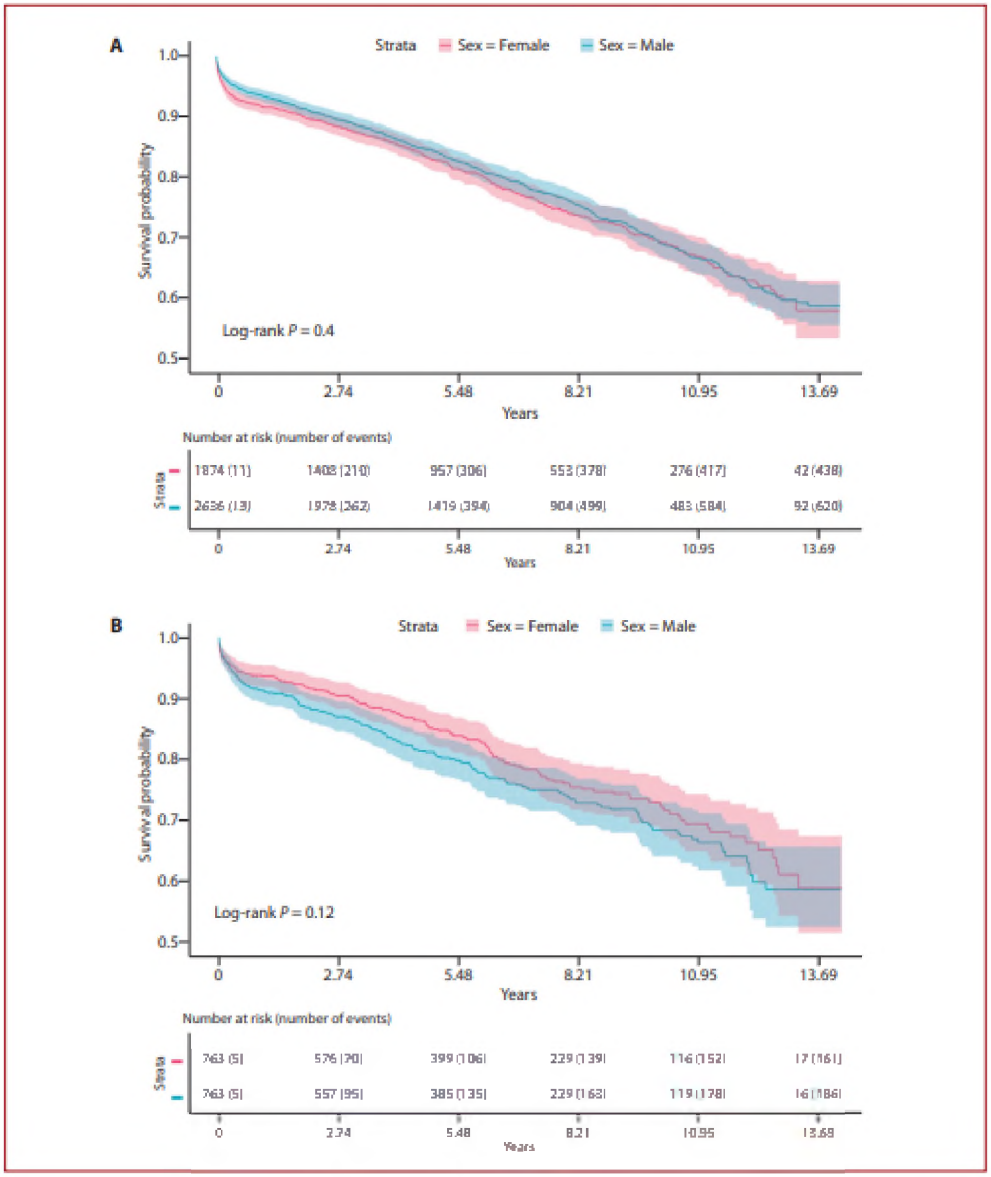

Figure 1. A. Kaplan-Meier curves before propensity score matching (PSM). **B.** Kaplan-Meier curves after PSM
Abbreviations: see Table 3

with worse clinical outcomes after heart surgeries. Female sex is embedded in the Society of Thoracic Surgeons (STS) and EuroSCORE II risk models as a factor worsening prognosis [15]. Nevertheless, it should be pointed out that these scales were designed based on data from coronary artery bypass grafting (CABG) procedures and might not accurately define an operative risk for SAVR.

In previous studies, despite more symptoms, females were treated conservatively for a longer time and were referred for SAVR more rarely; as a consequence, at the time of operation, they presented with worse baseline characteristics [2]. Similarly, in our study, women were older, more often with diabetes, hypertension, and higher operative risk.

Table 4. Baseline characteristics before propensity score matching (PSM)

		Women, n = 1874	Men, n = 2636	Total, n = 4510	*P*-value
Age, years, median (IQR)		69 (62–75)	63 (55–71)	66 (57–73)	<0.001
Body mass index, kg/m², median (IQR)		28.8 (25.4–32.5)	27.7 (24.8–30.9)	28.1 (25–31)	<0.001
Overweight (BMI ≥25 kg/m²), n (%)		1442 (77.2)	1904 (72.7)	3346 (74.6)	0.006
Obesity (BMI ≥30 kg/m²), n (%)		785 (42.1)	806 (30.8)	1591 (35.5)	<0.001
Body surface area, m², median (IQR)		1.8 (1.7–1.9)	2 (1.8–2.1)	1.9 (1.8–2)	<0.001
LVEF, %, median (IQR)		60 (50–65)	55 (45–60)	60 (50–63)	<0.001
AV mean gradient, mm Hg, median (IQR)		86.5 (73–104)	81 (66–96)	84 (70–100)	<0.001
AR	None, n (%)	205 (11)	240 (9.1)	445 (9.9)	<0.001
	Trivial, n (%)	692 (37)	793 (30.2)	1485 (33)	
	Mild, n (%)	649 (34.7)	762 (29)	1411 (31.4)	
	Moderate, n (%)	245 (13.1)	543 (20.7)	788 (17.5)	
	Severe, n (%)	79 (4.2)	287 (10.9)	366 (8.1)	
Smoking	None, n (%)	1604 (85.8)	1878 (71.6)	3482 (77.5)	<0.001
	Former, n (%)	179 (9.6)	469 (17.9)	648 (14.4)	
	Current, n (%)	86 (4.6)	277 (10.6)	363 (8.1)	
Last creatinine level, mg/dl, median (IQR)		0.85 (0.7–1)	0.95 (0.8–1)	0.9 (0.7–1)	<0.001
CCS	N/A, n (%)	144 (7.7)	209 (8)	353 (7.9)	0.77
	I, n (%)	690 (36.9)	962 (36.7)	1652 (36.8)	
	II, n (%)	852 (45.6)	1212 (46.2)	2064 (46)	
	III, n (%)	162 (8.7)	205 (7.8)	367 (8.2)	
	IV, n (%)	21 (1.1)	35 (1.3)	56 (1.3)	
NYHA	N/A, n (%)	21 (1.1)	25 (1)	46 (1)	0.03
	I, n (%)	311 (16.6)	497 (18.9)	808 (18)	
	II, n (%)	856 (45.8)	1255 (47.8)	2111 (47)	
	III, n (%)	606 (32.4)	719 (27.4)	1325 (29.5)	
	IV, n (%)	76 (4.1)	128 (4.9)	204 (4.5)	
Prior MI, n (%)		101 (5.4)	294 (11.2)	395 (8.8)	<0.001
Prior PCI, n (%)		56 (6.9)	122 (11.6)	178 (9.5)	0.001
Diabetes mellitus, n (%)		438 (23.4)	478 (18.2)	916 (20.4)	<0.001
IDDM, n (%)		183 (9.8)	200 (7.6)	383 (8.5)	0.01
COPD	None, n (%)	1548 (82.8)	2095 (79.9)	3643 (81.1)	0.04
	Treated, n (%)	320 (17.1)	526 (20.1)	846 (18.8)	
	Non-treated/untreated, n (%)	1 (0.1)	2 (0.1)	3 (0.1)	
Hypertension, n (%)		1585 (84.8)	2118 (80.7)	3703 (82.4)	0.001
Dyslipidemia, n (%)		676 (36.2)	966 (36.8)	1642 (36.6)	0.66
EuroSCORE II, median (IQR)		1.2 (0.9–1.6)	0.8 (0.7–1.2)	1 (0.7–1.4)	<0.001

Abbreviations: AV, aortic valve; AR, aortic regurgitation; COPD, chronic obstructive pulmonary disease; IDDM, insulin-dependent diabetes mellitus; IQR, interquartile range; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NYHA, New York Heart Association; PCI, percutaneous coronary intervention

Table 5. Procedural and clinical outcomes before propensity score matching (PSM)

		Women, n = 1874	Men, n = 2636	Total, n = 4510	*P*-value
Duration of hospitalization, days, median (IQR)		10 (8–14)	10 (8–14)	10 (8–14)	0.14
Valve type	Bioprosthesis	1155 (61.6)	1349 (51.2)	2504 (55.5)	<0.001
	Mechanical	719 (38.4)	1287 (48.8)	2006 (44.5)	
Valve diameter, mm, median (IQR)		21 (21–23)	23 (23–25)	23 (21–25)	<0.001
Cardioplegia	Crystalloid, n (%)	717 (38.5)	930 (35.5)	1647 (36.8)	0.04
	Blood, n (%)	1145 (61.5)	1689 (64.5)	2834 (63.2)	
Complications, n (%)		200 (10.8)	291 (11.1)	491 (11)	0.67
Re-operation	Re-sternotomy, n (%)	98 (5.5)	161 (6.9)	259 (6.3)	0.21
	Secondary sternal repair, n (%)	19 (1.7)	38 (2.3)	57 (2)	
In-hospital mortality, n (%)		70 (3.7)	78 (3)	148 (3.3)	0.15
Death in operating room, n (%)		6 (0.3)	7 (0.3)	13 (0.3)	0.74

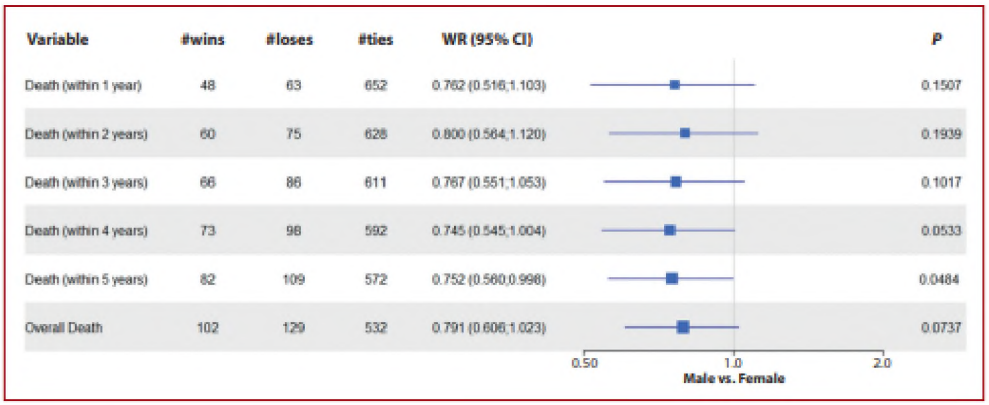

Figure 2. Differences in long-term mortality after surgical aortic valve replacement by sex shown on the forest plot of the win ratio method after propensity score matching

It was postulated that the later presentation of women for SAVR might be related to delayed development of AS in women. Older studies based on echocardiographic data showed that men are twice as likely to be diagnosed with AS [16]. Nonetheless, data from a large national registry from Sweden showed that the frequency of AS is nearly equivalent in elderly women and men [17]. As argued earlier [16], sex discrepancies among patients undergoing SAVR are probably caused by referral bias.

Sex-dependent pathophysiological development of AS was described previously [18]. Women face a greater risk of developing left ventricular concentric geometry in response to AS, decrease in ejection fraction, and fibrosis. As far as calcifications are concerned, women have a lower aortic valve calcium burden than men. Nonetheless, in women, calcifications have a more profound impact on AS severity. Therefore, sex is not associated with AS progression [19, 20].

The histogram representing the average 365-day survival for each year of the study period shows the mortality peak in 2015 with a subsequent tendency to decrease (Figure 3). This finding might be attributed to 240 patients who were qualified for TAVI mostly after 2015 (Supplementary material, *Figure S1*). Their risk profile based on EuroSCORE II was 2.55, higher than that of patients undergoing isolated SAVR. Therefore, we might assume that the transfer of the sickest patients to TAVI procedures has impacted SAVR outcomes. There are many studies supporting TAVI utilization in high- and medium-risk patients, given its favorable outcomes, especially in women. Nonetheless, the majority of TAVI studies were based on octogenarians, which raises doubts as longer life expectancy in women might influence these outcomes [21–26]. Moreover, the studies assessing sex differences in SAVR patients who were at least 80 years old also revealed better outcomes in the women's group [10, 17]. For all patients at that age, the newer generation bioprostheses might offer excellent outcomes [27–30]. In a post-hoc analysis of the SURTAVI study, van Mieghem et al. did not show significant sex differences between SAVR and TAVI groups in 2-year follow-up [9]. Similarly, in a recent analysis, Marzec et al. did not find a statistically significant difference in the 24-month mortality rate between the two methods [31]. Available meta-analyses comparing TAVI and SAVR show distinct benefits of each technique. TAVI seems to reduce the incidence of bleeding, new-onset atrial fibrillation, and acute kidney injury but has a higher rate of vascular complications, prosthesis-patient mismatch, and reinterventions. In terms of all-cause mortality, no significant differences between both methods were found [32, 33]. Noteworthy is the emergence of new surgical techniques that reduce the rate of cerebrovascular events and make SAVR more accessible for patients with COPD, which is a common contraindication for SAVR [34]. Comparable results of TAVI and SAVR in the mentioned studies suggest that both methods should be considered in patients suffering from aortic valve disease. Our study has demonstrated that SAVR is a reasonable option for women with outcomes comparable to men in short- and long-term follow-ups. There was a trend towards better results in women shown in PSM, but this needs to be confirmed in further studies. Also, in the presence of a growing body of evidence suggesting comparable outcomes in men and women after SAVR, female sex as a risk factor for SAVR should be reconsidered [35].

Limitations

This was a single-center retrospective study. Not all determinants of the outcomes could be recorded. The lack of comprehensive echocardiographic data prevented assessment of patient-prosthesis mismatch (PPM). In the case of

late mortality, it was not possible to distinguish between cardiac and non-cardiac causes of death.

CONCLUSIONS

In the present study, crude analysis demonstrated that female sex was not associated with higher in-hospital and late mortality rates after SAVR compared to men. Further studies are needed to confirm long-term benefits in women undergoing SAVR.

Supplementary material

Supplementary material is available at https://journals.viamedica.pl/kardiologia_polska.

Article information

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13. Załącznik 2 – Oświadczenia współautorów

Lek. Artur Pawlik

Kraków, 31.07.2023

OŚWIADCZENIE WSPÓŁAUTORA

Oświadczam, że mój wkład procentowy w powstanie publikacji: *„Gender differences and long-term clinical outcomes in patients with chronic total occlusions of infrainguinal lower limb arteries treated from retrograde access with peripheral vascular interventions"* wynosi *40%.*

Mój wkład polegał na:

- analizie danych
- napisaniu manuskryptu wraz z dyskusją

Artur Pawlik

(podpis współautora)

Dr n. med. Michał Chyrchel

Kraków, 03.01.2024

OŚWIADCZENIE WSPÓŁAUTORA

Oświadczam, że mój wkład procentowy w powstanie publikacji: „*Gender differences and long-term clinical outcomes in patients with chronic total occlusions of infrainguinal lower limb arteries treated from retrograde access with peripheral vascular interventions*" wynosi 5%.

Mój wkład polegał na:

- koncept pracy
- współudział w pisaniu dyskusji

Jednocześnie wyrażam zgodę na przedłożenie ww. pracy przez lekarza Artur Pawlika jako część rozprawy doktorskiej w formie spójnego tematycznie zbioru artykułów opublikowanych w czasopismach naukowych.

(podpis współautora)

Dr n. med. Joanna Wojtasik-Bakalarz Kraków, 31.07.2023

OŚWIADCZENIE WSPÓŁAUTORA

Oświadczam, że mój wkład procentowy w powstanie publikacji: „*Gender differences and long-term clinical outcomes in patients with chronic total occlusions of infrainguinal lower limb arteries treated from retrograde access with peripheral vascular interventions*" wynosi *5%.*

Mój wkład polegał na:

- redagowaniu manuskryptu

Jednocześnie wyrażam zgodę na przedłożenie ww. pracy przez lekarza Artur Pawlika jako część rozprawy doktorskiej w formie spójnego tematycznie zbioru artykułów opublikowanych w czasopismach naukowych.

Joanna Wojtasik-Bakalarz

(podpis współautora)

Prof. dr hab. n. med. Paweł Kleczyński Kraków, 18.12.2023

OŚWIADCZENIE WSPÓŁAUTORA

Oświadczam, że mój wkład procentowy w powstanie publikacji: „*Gender differences and long-term clinical outcomes in patients with chronic total occlusions of infrainguinal lower limb arteries treated from retrograde access with peripheral vascular interventions*" wynosi 5%.

Mój wkład polegał na:

- analizie danych
- pisaniu dyskusji

Jednocześnie wyrażam zgodę na przedłożenie ww. pracy przez lekarza Artur Pawlika jako część rozprawy doktorskiej w formie spójnego tematycznie zbioru artykułów opublikowanych w czasopismach naukowych.

.....
(podpis współautora)

Dr hab. Rafał Januszek

Kraków, 1.06.2023

OŚWIADCZENIE WSPÓŁAUTORA

Oświadczam, że mój wkład procentowy w powstanie publikacji: „*Gender differences and long-term clinical outcomes in patients with chronic total occlusions of infrainguinal lower limb arteries treated from retrograde access with peripheral vascular interventions*" wynosi *30%*.

Mój wkład polegał na:

- opracowywaniu danych
- krytycznych poprawek w zakresie napisanego manuskryptu

Jednocześnie wyrażam zgodę na przedłożenie ww. pracy przez lekarza Artur Pawlika jako część rozprawy doktorskiej w formie spójnego tematycznie zbioru artykułów opublikowanych w czasopismach naukowych.

.....
(podpis współautora)

Dr n. med. Salech Arif

Kraków, 3.01.2024

OŚWIADCZENIE WSPÓŁAUTORA

Oświadczam, że mój wkład procentowy w powstanie publikacji: „*Gender differences and long-term clinical outcomes in patients with chronic total occlusions of infrainguinal lower limb arteries treated from retrograde access with peripheral vascular interventions*" wynosi *5%*.

Mój wkład polegał na:

- współudział w pisaniu dyskusji

Jednocześnie wyrażam zgodę na przedłożenie ww. pracy przez lekarza Artur Pawlika jako część rozprawy doktorskiej w formie spójnego tematycznie zbioru artykułów opublikowanych w czasopismach naukowych.

.....
(podpis współautora)

Prof. dr hab. n. med. Stanisław Bartuś

Kraków, 29.12.2023

OŚWIADCZENIE WSPÓŁAUTORA

Oświadczam, że mój wkład procentowy w powstanie publikacji: *„Gender differences and long-term clinical outcomes in patients with chronic total occlusions of infrainguinal lower limb arteries treated from retrograde access with peripheral vascular interventions"* wynosi *10%*.

Mój wkład polegał na:

- koncept pracy
- redagowanie dyskusji

Jednocześnie wyrażam zgodę na przedłożenie ww. pracy przez lekarza Artur Pawlika jako część rozprawy doktorskiej w formie spójnego tematycznie zbioru artykułów opublikowanych w czasopismach naukowych.

.....

(podpis współautora)

Prof. dr hab. n. med. Agata Stanek

31.07.2023

OŚWIADCZENIE WSPÓŁAUTORA

Oświadczam, że mój wkład procentowy w powstanie publikacji: „*Gender differences and long-term clinical outcomes in patients with chronic total occlusions of infrainguinal lower limb arteries treated from retrograde access with peripheral vascular interventions*" wynosi *5%*.

Mój wkład polegał na:

- zbieranie danych

Jednocześnie wyrażam zgodę na przedłożenie ww. pracy przez lekarza Artur Pawlika jako część rozprawy doktorskiej w formie spójnego tematycznie zbioru artykułów opublikowanych w czasopismach naukowych.

.....

(podpis współautora)

Prof. dr hab. n. med. Dariusz Dudek Kraków, 3.11.2023

OŚWIADCZENIE WSPÓŁAUTORA

Oświadczam, że mój wkład procentowy w powstanie publikacji: *„Gender differences and long-term clinical outcomes in patients with chronic total occlusions of infrainguinal lower limb arteries treated from retrograde access with peripheral vascular interventions"* wynosi *5%*.

Mój wkład polegał na:

- krytyczne uwagi do treści manuskryptu.

Jednocześnie wyrażam zgodę na przedłożenie ww. pracy przez lekarza Artur Pawlika jako część rozprawy doktorskiej w formie spójnego tematycznie zbioru artykułów opublikowanych w czasopismach naukowych.

.....

(podpis współautora)

Prof. Zoltan Ruzsa 23.11.2023

OŚWIADCZENIE WSPÓŁAUTORA

Oświadczam, że mój wkład procentowy w powstanie publikacji: *„Gender differences and long-term clinical outcomes in patients with chronic total occlusions of infrainguinal lower limb arteries treated from retrograde access with peripheral vascular interventions"* wynosi *10%*.

Mój wkład polegał na:

- opracowywaniu danych i zbieraniu danych

Jednocześnie wyrażam zgodę na przedłożenie ww. pracy przez lekarza Artur Pawlika jako część rozprawy doktorskiej w formie spójnego tematycznie zbioru artykułów opublikowanych w czasopismach naukowych.

.....
(podpis współautora)

Prof. Viktor Orias 31.07.2023

OŚWIADCZENIE WSPÓŁAUTORA

Oświadczam, że mój wkład procentowy w powstanie publikacji: „*Gender differences and long-term clinical outcomes in patients with chronic total occlusions of infrainguinal lower limb arteries treated from retrograde access with peripheral vascular interventions*" wynosi *5%*.

Mój wkład polegał na:

- opracowywaniu danych i zbieraniu danych

Jednocześnie wyrażam zgodę na przedłożenie ww. pracy przez lekarza Artur Pawlika jako część rozprawy doktorskiej w formie spójnego tematycznie zbioru artykułów opublikowanych w czasopismach naukowych.

.....

(podpis współautora)

Lek. Artur Pawlik

Kraków, 23.11.2023

OŚWIADCZENIE WSPÓŁAUTORA

Oświadczam, że mój wkład procentowy w powstanie publikacji: *„Age and gender differences in clinical outcomes of patients with heavy-calcified coronary artery lesions treated percutaneously with rotational atherectom"*

wynosi *40%.*

Mój wkład polegał na:

- opracowaniu koncepcji pracy
- analizie danych
- współtworzeniu manuskryptu i dyskusji

Artur Pawlik

(podpis współautora)

Prof. dr hab. n. med. Andrzej Surdacki

Kraków, 22.12.2023

OŚWIADCZENIE WSPÓŁAUTORA

Oświadczam, że mój wkład procentowy w powstanie publikacji: *„Age and gender differences in clinical outcomes of patients with heavy-calcified coronary artery lesions treated percutaneously with rotational atherectom"*

wynosi *5%.*

Mój wkład polegał na:

- współudział w pisaniu dyskusji

Jednocześnie wyrażam zgodę na przedłożenie ww. pracy przez lekarza Artur Pawlika jako część rozprawy doktorskiej w formie spójnego tematycznie zbioru artykułów opublikowanych w czasopismach naukowych.

.....

(podpis współautora)

Lek. Bartłomiej Staszczak Kraków, 31.07.2023

OŚWIADCZENIE WSPÓŁAUTORA

Oświadczam, że mój wkład procentowy w powstanie publikacji: *„Age and gender differences in clinical outcomes of patients with heavy-calcified coronary artery lesions treated percutaneously with rotational atherectom"*

wynosi *5%*.

Mój wkład polegał na:

- opracowywaniu danych

Jednocześnie wyrażam zgodę na przedłożenie ww. pracy przez lekarza Artur Pawlika jako część rozprawy doktorskiej w formie spójnego tematycznie zbioru artykułów opublikowanych w czasopismach naukowych.

.....

(podpis współautora)

Prof. dr hab. n. med. Dariusz Dudek Kraków, 3.11.2023

OŚWIADCZENIE WSPÓŁAUTORA

Oświadczam, że mój wkład procentowy w powstanie publikacji: *„Age and gender differences in clinical outcomes of patients with heavy-calcified coronary artery lesions treated percutaneously with rotational atherectomy"*

wynosi 5%.

Mój wkład polegał na:

- krytyczne uwagi do manuskryptu.

Jednocześnie wyrażam zgodę na przedłożenie ww. pracy przez lekarza Artur Pawlika jako część rozprawy doktorskiej w formie spójnego tematycznie zbioru artykułów opublikowanych w czasopismach naukowych.

.....

(podpis współautora)

Prof. dr hab. n. med. Jacek Legutko

Kraków, 23.11.2023

OŚWIADCZENIE WSPÓŁAUTORA

Oświadczam, że mój wkład procentowy w powstanie publikacji: *„Age and gender differences in clinical outcomes of patients with heavy-calcified coronary artery lesions treated percutaneously with rotational atherectom"*

wynosi *5%*.

Mój wkład polegał na:

- współudziale w analizie danych i pisaniu dyskusji

Jednocześnie wyrażam zgodę na przedłożenie ww. pracy przez lekarza Artur Pawlika jako część rozprawy doktorskiej w formie spójnego tematycznie zbioru artykułów opublikowanych w czasopismach naukowych.

.....

(podpis współautora)

Lek. Jerzy Bartuś Kraków, 23.11.2023

OŚWIADCZENIE WSPÓŁAUTORA

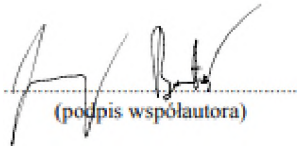
Oświadczam, że mój wkład procentowy w powstanie publikacji: *„Age and gender differences in clinical outcomes of patients with heavy-calcified coronary artery lesions treated percutaneously with rotational atherectom"*

wynosi *5%*.

Mój wkład polegał na:

- opracowywaniu danych

Jednocześnie wyrażam zgodę na przedłożenie ww. pracy przez lekarza Artur Pawlika jako część rozprawy doktorskiej w formie spójnego tematycznie zbioru artykułów opublikowanych w czasopismach naukowych.



(podpis współautora)

Dr n. med. Magdalena Jędrychowska

Kraków, 31.07.2023

OŚWIADCZENIE WSPÓŁAUTORA

Oświadczam, że mój wkład procentowy w powstanie publikacji: *„Age and gender differences in clinical outcomes of patients with heavy-calcified coronary artery lesions treated percutaneously with rotational atherectom"* wynosi *5%*.

Mój wkład polegał na:

- zbieraniu danych

Jednocześnie wyrażam zgodę na przedłożenie ww. pracy przez lekarza Artur Pawlika jako część rozprawy doktorskiej w formie spójnego tematycznie zbioru artykułów opublikowanych w czasopismach naukowych.

.....

(podpis współautora)

Prof. dr hab. n. med. Stanisław Bartuś Kraków, 29.12.2023

OŚWIADCZENIE WSPÓŁAUTORA

Oświadczam, że mój wkład procentowy w powstanie publikacji: *„Age and gender differences in clinical outcomes of patients with heavy-calcified coronary artery lesions treated percutaneously with rotational atherectom"*

wynosi *10%.*

Mój wkład polegał na:

- koncept pracy
- współudział w pisaniu dyskusji

Jednocześnie wyrażam zgodę na przedłożenie ww. pracy przez lekarza Artur Pawlika jako część rozprawy doktorskiej w formie spójnego tematycznie zbioru artykułów opublikowanych w czasopismach naukowych.

.....
(podpis współautora)

Dr hab. Rafał Januszek

Kraków, 1.06.2023

OŚWIADCZENIE WSPÓŁAUTORA

Oświadczam, że mój wkład procentowy w powstanie publikacji: *„Age and gender differences in clinical outcomes of patients with heavy-calcified coronary artery lesions treated percutaneously with rotational atherectom"*

wynosi *50%.*

Mój wkład polegał na:

- opracowywaniu danych
- pisaniu manuskryptu
- opublikowaniu pracu

Jednocześnie wyrażam zgodę na przedłożenie ww. pracy przez lekarza Artur Pawlika jako część rozprawy doktorskiej w formie spójnego tematycznie zbioru artykułów opublikowanych w czasopismach naukowych.

(podpis współautora)

Lek. Artur Pawlik

31.07.2023

OŚWIADCZENIE WSPÓŁAUTORA

Oświadczam, że mój wkład procentowy w powstanie publikacji: „*The impact of gender on in-hospital mortality and long-term mortality in patients undergoing surgical aortic valve replacement: SAVR and SEX Study*"
wynosi *40%*.

Mój wkład polegał na:

- opracowaniu koncepcji badania
- analizie danych
- napisaniu pracy wraz z dyskusją

Artur Pawlik
(podpis współautora)

Prof. dr hab. n. med. Bogusław Kapelak 29.11.2023

OŚWIADCZENIE WSPÓŁAUTORA

Oświadczam, że mój wkład procentowy w powstanie publikacji: *„The impact of gender on in-hospital mortality and long-term mortality in patients undergoing surgical aortic valve replacement: SAVR and SEX Study"*

wynosi *5%.*

Mój wkład polegał na:

- koncept badania
- krytyczne uwagi do końcowej wersji artykułu

Jednocześnie wyrażam zgodę na przedłożenie ww. pracy przez lekarza Artur Pawlika jako część rozprawy doktorskiej w formie spójnego tematycznie zbioru artykułów opublikowanych w czasopismach naukowych.

Klinika Chirurgii Serca, Naczyń
i Transplantologii UJ CM

prof. dr hab. med. Bogusław Kapelak
kierownik

.....
(podpis współautora)

Prof. dr hab. n. med. Bohdan Maruszewski 31.07.2023

OŚWIADCZENIE WSPÓŁAUTORA

Oświadczam, że mój wkład procentowy w powstanie publikacji: „*The impact of gender on in-hospital mortality and long-term mortality in patients undergoing surgical aortic valve replacement: SAVR and SEX Study*"

wynosi 5%.

Mój wkład polegał na:

- krytyczne uwagi do końcowej wersji artykuły

Jednocześnie wyrażam zgodę na przedłożenie ww. pracy przez lekarza Artur Pawlika jako część rozprawy doktorskiej w formie spójnego tematycznie zbioru artykułów opublikowanych w czasopismach naukowych.

.....
(podpis współautora)

Prof. dr hab. n. med. Jacek Legutko 29.11.2023

OŚWIADCZENIE WSPÓŁAUTORA

Oświadczam, że mój wkład procentowy w powstanie publikacji: *„The impact of gender on in-hospital mortality and long-term mortality in patients undergoing surgical aortic valve replacement: SAVR and SEX Study"*

wynosi *5%.*

Mój wkład polegał na:

- współudziale w analizie danych i pisaniu dyskusji

Jednocześnie wyrażam zgodę na przedłożenie ww. pracy przez lekarza Artur Pawlika jako część rozprawy doktorskiej w formie spójnego tematycznie zbioru artykułów opublikowanych w czasopismach naukowych.

.....
(podpis współautora)

Prof. dr hab. n. med. Kazimierz Widenka 31.07.2023

OŚWIADCZENIE WSPÓŁAUTORA

Oświadczam, że mój wkład procentowy w powstanie publikacji: *„The impact of gender on in-hospital mortality and long-term mortality in patients undergoing surgical aortic valve replacement: SAVR and SEX Study"*

wynosi *5%*.

Mój wkład polegał na:

- krytyczne uwagi do finalnej wersji manuskryptu

Jednocześnie wyrażam zgodę na przedłożenie ww. pracy przez lekarza Artur Pawlika jako część rozprawy doktorskiej w formie spójnego tematycznie zbioru artykułów opublikowanych w czasopismach naukowych.

KIEROWNIK
Kliniki Kardiochirurgii
z Pododdziałem Chirurgii Naczyniowej

dr hab. n. med. prof. UM Kazimierz Widenka

.....

(podpis współautora)

Mgr Krzysztof Plens 31.07.2023

OŚWIADCZENIE WSPÓŁAUTORA

Oświadczam, że mój wkład procentowy w powstanie publikacji: *„The impact of gender on in-hospital mortality and long-term mortality in patients undergoing surgical aortic valve replacement: SAVR and SEX Study"*

wynosi *10%*.

Mój wkład polegał na:

- analizę statystyczną

Jednocześnie wyrażam zgodę na przedłożenie ww. pracy przez lekarza Artur Pawlika jako część rozprawy doktorskiej w formie spójnego tematycznie zbioru artykułów opublikowanych w czasopismach naukowych.

Krzysztof Plens

.....

(podpis współautora)

Dr hab n. med. Łukasz Rzeszutko 27.12.2023

OŚWIADCZENIE WSPÓŁAUTORA

Oświadczam, że mój wkład procentowy w powstanie publikacji: *„The impact of gender on in-hospital mortality and long-term mortality in patients undergoing surgical aortic valve replacement: SAVR and SEX Study"*
wynosi *5%*.

Mój wkład polegał na:
- współudział w pisaniu dyskusji

Jednocześnie wyrażam zgodę na przedłożenie ww. pracy przez lekarza Artur Pawlika jako część rozprawy doktorskiej w formie spójnego tematycznie zbioru artykułów opublikowanych w czasopismach naukowych.

.....
(podpis współautora)

Prof. dr hab. n. med. Marek Deja

31.07.2023

OŚWIADCZENIE WSPÓŁAUTORA

Oświadczam, że mój wkład procentowy w powstanie publikacji: *„The impact of gender on in-hospital mortality and long-term mortality in patients undergoing surgical aortic valve replacement: SAVR and SEX Study"*
wynosi *5%.*

Mój wkład polegał na:

- analiza danych
- krytyczne uwagi do finalnej wersji manuskryptu

Jednocześnie wyrażam zgodę na przedłożenie ww. pracy przez lekarza Artur Pawlika jako część rozprawy doktorskiej w formie spójnego tematycznie zbioru artykułów opublikowanych w czasopismach naukowych.

.....
(podpis współautora)

dr hab. n. med. Mariusz Kowalewski, prof. UMK 31.07.2023

OŚWIADCZENIE WSPÓŁAUTORA

Oświadczam, że mój wkład procentowy w powstanie publikacji: *„The impact of gender on in-hospital mortality and long-term mortality in patients undergoing surgical aortic valve replacement: SAVR and SEX Study"*

wynosi *5%*.

Mój wkład polegał na:

- opracowywanie manuskryptu
- krytyczne uwagi do końcowej wersji artykuły

Jednocześnie wyrażam zgodę na przedłożenie ww. pracy przez lekarza Artur Pawlika jako część rozprawy doktorskiej w formie spójnego tematycznie zbioru artykułów opublikowanych w czasopismach naukowych.

Mariusz Kowalewski

.....

(podpis współautora)

Prof. dr hab. n. med. Piotr Suwalski 31.07.2023

OŚWIADCZENIE WSPÓŁAUTORA

Oświadczam, że mój wkład procentowy w powstanie publikacji: *„The impact of gender on in-hospital mortality and long-term mortality in patients undergoing surgical aortic valve replacement: SAVR and SEX Study"*
wynosi *5%.*

Mój wkład polegał na:
- opracowywanie manuskryptu
- krytyczne uwagi do finalnej wersji manuskryptu

Jednocześnie wyrażam zgodę na przedłożenie ww. pracy przez lekarza Artur Pawlika jako część rozprawy doktorskiej w formie spójnego tematycznie zbioru artykułów opublikowanych w czasopismach naukowych.

KIEROWNIK
KLINIKI KARDIOCHIRURGII I TRANSPLANTOLOGII
Państwowego Szpitala
prof. dr hab. n. med. Piotr Suwalski

.....
(podpis współautora)

Dr hab. n. med. Radosław Litwinowicz 23.11.2023

OŚWIADCZENIE WSPÓŁAUTORA

Oświadczam, że mój wkład procentowy w powstanie publikacji: *„The impact of gender on in-hospital mortality and long-term mortality in patients undergoing surgical aortic valve replacement: SAVR and SEX Study"*

wynosi *10%*.

Mój wkład polegał na:

- opracowywanie manuskryptu
- analiza danych

Jednocześnie wyrażam zgodę na przedłożenie ww. pracy przez lekarza Artur Pawlika jako część rozprawy doktorskiej w formie spójnego tematycznie zbioru artykułów opublikowanych w czasopismach naukowych.

Radosław Litwinowicz

(podpis współautora)

Dr hab. Rafał Januszek

Kraków, 1.06.2023

OŚWIADCZENIE WSPÓŁAUTORA

Oświadczam, że mój wkład procentowy w powstanie publikacji: „*The impact of gender on in-hospital mortality and long-term mortality in patients undergoing surgical aortic valve replacement: SAVR and SEX Study*"

wynosi *20%*.

Mój wkład polegał na:

- krytycznych uwag do opracowywanego manuskryptu
- opracowywanie rycin do pracy

Jednocześnie wyrażam zgodę na przedłożenie ww. pracy przez lekarza Artur Pawlika jako część rozprawy doktorskiej w formie spójnego tematycznie zbioru artykułów opublikowanych w czasopismach naukowych.

.....
(podpis współautora)

Prof. dr hab. n. med. Stanisław Bartuś 29.12.2023

OŚWIADCZENIE WSPÓŁAUTORA

Oświadczam, że mój wkład procentowy w powstanie publikacji: „*The impact of gender on in-hospital mortality and long-term mortality in patients undergoing surgical aortic valve replacement: SAVR and SEX Study*"

wynosi 5%.

Mój wkład polegał na:

- projektowanie badania

Jednocześnie wyrażam zgodę na przedłożenie ww. pracy przez lekarza Artur Pawlika jako część rozprawy doktorskiej w formie spójnego tematycznie zbioru artykułów opublikowanych w czasopismach naukowych.

.....

(podpis współautora)

Lekarz. Zdzisław Tobota 31.07.2023

OŚWIADCZENIE WSPÓŁAUTORA

Oświadczam, że mój wkład procentowy w powstanie publikacji: *„The impact of gender on in-hospital mortality and long-term mortality in patients undergoing surgical aortic valve replacement: SAVR and SEX Study"*

wynosi 5%.

Mój wkład polegał na:

- opracowywanie manuskryptu

Jednocześnie wyrażam zgodę na przedłożenie ww. pracy przez lekarza Artur Pawlika jako część rozprawy doktorskiej w formie spójnego tematycznie zbioru artykułów opublikowanych w czasopismach naukowych.

(podpis współautora)