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Rola kopeptyny w stratyfikacji ryzyka zgonu i dekompensacji niewydolności serca

Rozprawa na stopień doktora w dziedzinie nauk medycznych i nauk o zdrowiu,
w dyscyplinie nauki medyczne

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1. **Wykaz skrótów**

AF	migotanie przedsionków (*atrial fibrilation*)
ACEI	inhibitor konwertazy angiotensyny (*angiotensyn converting enzyme inhibitors*)
ALP	fosfataza alkaliczna *(alkaline phosphatase)*
ALT	aminotransferaza alaninowa (*alanine aminotransferase)*
ARB	bloker receptora angiotensyny II (*angiotensin receptor blocker)*
ARNI	połączenie sakubitrylu (antagonista receptora dla neprilizyny) z walsartanem
ASA	kwas acetylosalicylowy *(acetylsalicylic acid)*
AST	aminotransferaza asparaginianowa (*asparate aminotransferase)*
AUC	pole powierzchni pod krzywą ROC (*area under curve*)
BMI	indeks masy ciała (*body mass index*)
CI	przedział ufności (*confidence interval*)
CRT-D	kardiowerter-defibrylator z funkcją resynchronizacji *(cardiac resynchronization therapy–defibrillator)*;
HBA1c	hemoglobina glikozylowana *(glycosylated hemoglobin)*
HF	niewydolność serca (*heart failure*)
HT	transplantacja serca *(heart transplantation)*
HR	rytm serca *(heart rate)*
hsCRP	wysoko czułe białko C-reaktywne *(high-sensitivity C-reactive protein)*
GFR	wskaźnik filtracji kłębuszkowej *(glomerular filtration rate)*
GGTP	gamma glutamylotranspeptydaza *(gammaglutamyltranspeptidase)*
ICD	kardiowerter-defibrylator (*implantable cardioverter-defibrillator*)
LA	lewy przedsionek *(left atrium)*
LDL	lipoproteiny o niskiej gęstości (*low-density lipoproteins)*
LVEDD	wymiar końcoworozkurczowy lewej komory *(left ventricular end-diastolic diameter)*
LVEF	frakcja wyrzutowa lewej komory *(left ventricular ejection fraction*)
LVH	przerost lewej komory (*left ventricular hypertrophy)*
LVOT	droga odpływu lewej komory (*left ventricular outflow tract*)
MCS	mechaniczne wspomaganie krążenia (*mechanical circulatory support*)
MRA	antagonista receptora mineralokortykosteroidowego *(mineralocorticosteroid receptor antagonist)*

NOAC	doustne leki przeciwkrzepliwe niebędące antagonistami witaminy K
nsVT	nieutrwalony częstoskurcz komorowy (*nonsustained ventricular tachycardia)*
NT-proBNP	N-końcowy fragment mózgowego peptydu natriuretycznego typy B *(N-terminal pro-B-type natriuretic peptide)*
NYHA	Nowojorskie Towarzystwo Serca (*New York Heart Association*)
OR	iloraz szans (*odds ratio*)
POCHP	przewlekła obturacyjna choroba płuc *(chronic obstructive pulmonary disease)*
RVEDD	wymiar końcoworozkurczowy prawej komory *(right ventricular dimension at end- diastole*)
RVSP	ciśnienie skurczowe w prawej komorze (*right ventricular systolic pressure*)
SGLT2	kotransporter sodowo glukozowy 2

2. **Wykaz publikacji, na podstawie których oparta jest rozprawa doktorska**

   a. Nadziakiewicz Paulina, Wioletta Szczurek-Wasilewicz and Bożena Szyguła-Jurkiewicz. Heart Failure in Elderly Patients: Medical Management, Therapies and Biomarkers. Pharmaceuticals 2025; 18 (1); 1-13. **IF: 4.8, MNiSW: 100**

   b. Nadziakiewicz Paulina, Wioletta Szczurek-Wasilewicz, Michał Jurkiewicz, Michał Skrzypek, Agnieszka Gorzkowska, Mariusz Gąsior i Bożena Szyguła-Jurkiewicz. Copeptin, Routine Laboratory Parameters, and Ischemic Etiology of Heart Failure Predict Outcomes in Elderly Patients with Decompensated Heart Failure. Biomedicines 2025; 13(9); 2048. **IF: 3.9 MNiSW: 100**

3. **Wykaz tabel i rycin**

Tabela I. Podstawowa charakterystyka badanej populacji.

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Tabela V. Podsumowanie krzywych ROC.

Rycina 1. Krzywe ROC dla kopeptyny (A), bilirubiny (B), sodu (C), CRP (D), kwasu moczowego (E).

III. **Wstęp**

Ustalenie rozpoznania i ocena rokowania u chorych w podeszłym wieku (>65 rż.) z niewydolnością serca (HF) są trudne, przede wszystkim ze względu na nietypowe objawy, obecność schorzeń współistniejących i ograniczoną wartość diagnostyczną peptydów natriuretycznych [1,2]. Z tego powodu istnieje potrzeba poszukiwania nowych biomarkerów, pozwalających na stratyfikację ryzyka zgonu i dekompensacji układu krążenia w tej niejednorodnej etiologicznie i funkcjonalnie grupie chorych. Uczucie zmęczenia lub osłabienia stwierdzane u chorych w podeszłym wieku (>65 roku życia) często wiąże się z zaostrzeniem lub progresją HF, ale może być także spowodowane brakiem kondycji, utratą masy mięśniowej będącej następstwem niewystarczającej aktywności fizycznej, działaniami niepożądanymi leków, niedokrwistością, zaburzeniami funkcji tarczycy, a także zaburzeniami snu i depresją [3,4]. U osób w podeszłym wieku konieczne jest skuteczne leczenie chorób współistniejących, stosowanie regularnego, dostosowanego do możliwości wysiłku aerobowego oraz unikanie dużej liczby leków, które wchodzą wzajemnie ze sobą w interakcje i powodują działania niepożądane [2, 3].

Populacja chorych w podeszłym wieku różni się zasadniczo od populacji ogólnej. W wieloośrodkowych, prospektywnych, randomizowanych badaniach klinicznych osoby starsze nie są na ogół uwzględniane i dlatego uzyskane wyniki, które stanowią podstawę do ustalania wytycznych postępowania w HF nie odzwierciedlają ani ich charakterystyki klinicznej, ani odmienności leczenia ani też metod stratyfikacji ryzyka zgonu i zaostrzeń choroby [1,2]. Często nie jest możliwe stosowanie u osób starszych zalecanych dawek wszystkich leków rekomendowanych w HF. Mogą one bowiem nasilać dolegliwości związane ze schorzeniami współistniejącymi oraz powodować objawową hipotonię, prowadząc do obniżenia jakości i długości trwania życia. Z tych powodów konieczne jest poszukiwanie biomarkerów, które adekwatnie określą rokowanie u chorych w podeszłym wieku [5-7].

Z punktu widzenia patofizjologicznego przydatnym narzędziem służącym do stratyfikacji ryzyka u chorych w podeszłym wieku z zaawansowaną HF mogłaby być kopeptyna [7,8,9]. Jest to stabilny i łatwy do oznaczenia C-końcowy fragment prekursora arginino-wazopresyny syntetyzowany i wydzielany przez tylny płat przysadki w ilościach równoważnych w stosunku do wazopresyny. Ze względu na to, że kopeptyna jest bardziej stabilna od wazopresyny, może być ona stosowana jako marker aktywności wazopresyny. Zmiany stężenia kopeptyny odzwierciedlają aktywację układu renina-angiotensyna-aldosteron w HF i wzrost stężenia angiotensyny II. Z kolei podwyższone stężenie angiotensyny II

u chorych z HF powoduje stymulację sekrecji arginino-wazopresyny w odpowiedzi na stres hemodynamiczny i zaburzenia równowagi neurohormonalnej. Ponadto uwalnianie wazopresyny i kopeptyny jest również stymulowane przez zmniejszony rzut serca w zaawansowanej HF, prowadząc do słabszego wypełnienia tętnic szyjnych i następczej aktywacji baroreceptorów zatoki szyjnej i łuku aorty, co z kolei ponownie zwiększa sekrecję kopeptyny i wazopresyny. Zwiększone uwalnianie wazopresyny jest również związane z nadmiernym obciążeniem wstępnym i następczym oraz podwyższonym ciśnieniem napełniania lewej komory serca, co prowadzi do dalszej progresji HF [10,11].

W populacji chorych w podeszłym wieku powyższe procesy mogą być nasilone ze względu na zmniejszone rezerwy fizjologiczne, upośledzone mechanizmy kompensacyjne i obecność chorób współistniejących. Ponadto występująca często u pacjentów w podeszłym wieku dysfunkcja nerek może również zwiększać sekrecję wazopresyny i nasilać jej działanie. Ekspresja wazopresyny u chorych z niewydolnością nerek jest zwiększona i wazopresyna nie może prawidłowo działać przez receptory V2, co prowadzi do zwiększonej aktywacji receptorów V1a i V1b. Poprzez receptory V1a wazopresyna stymuluje produkcję fibroblastów promując włóknienie mięśnia sercowego i zwiększenie syntezy białek miocytów, a także nasila przerost kardiomiocytów i zmniejsza kurczliwość lewej komory. Kopeptyna może odzwierciedlać układowy stres i zapalenie, które są powszechne u pacjentów w stanach ostrych takich jak zaostrzenie HF. U pacjentów w podeszłym wieku mechanizmy sekrecji kopeptyny i wazopresyny mogą być istotnie zaburzone poprzez zmiany fizjologiczne, które pojawiają się w następstwie procesów starzenia, takie jak stres osmotyczny i hemodynamiczny, upośledzona odpowiedź nerek na diurezę oraz zaburzenia funkcji baroreceptorów [12-17].

IV. **Założenia i cele pracy:**

Założeniem i celem głównym pracy jest określenie czynników związanych z występowaniem złożonego punktu końcowego (obejmującego zgon ze wszystkich przyczyn i zaostrzenie HF wymagające hospitalizacji) z uwzględnieniem kopeptyny, u pacjentów w podeszłym wieku ze zdekompensowaną niewydolnością serca.

V. **Materiały i metody:**

W niniejszym prospektywnym badaniu poddano analizie kolejnych 279 chorych w podeszłym wieku hospitalizowanych w latach 2018-2023 w III Katedrze i Klinice Kardiologii Wydziału Nauk Medycznych w Zabrzu, Śląskiego Uniwersytetu Medycznego w Katowicach z powodu dekompensacji HF. Punktem końcowym badania był zgon ze wszystkich przyczyn lub zaostrzenie HF wymagające hospitalizacji w okresie 6 miesięcy obserwacji.

Kryteriami włączenia do badania był wiek>65 lat, HF rozpoznana co najmniej dwa lata przed hospitalizacją z powodu dekompensacji HF oraz frakcja wyrzutowa lewej komory (LVEF) niższa niż 40% w badaniu echokardiograficznym wykonanym przy przyjęciu do szpitala. Kryteria wykluczenia obejmowały: aktualną infekcję, nieodwracalną niewydolność nerek (eGFR<30 ml/min/1,73 m^2), przewlekłą chorobę wątroby, nowotwory złośliwe, udary mózgu, choroby hematologiczne i autoimmunologiczne. U wszystkich pacjentów określano charakterystykę kliniczną, przeprowadzono badanie przedmiotowe i podmiotowe, pomiary antropometryczne, rutynowe badania laboratoryjne, badanie elektrokardiograficzne i echokardiograficzne.

Protokół badania zatwierdziła Komisja Bioetyczna Śląskiego Uniwersytetu Medycznego (Zgody nr: KNW/0022/KB1/53/18, PCN/0022/KB1/20/I/21, PCN/CBN/0052/ KB1/20/II/21/22). Badanie przeprowadzono zgodnie z Deklaracją Helsińską. Wszyscy uczestnicy wyrazili pisemną świadomą zgodę przed włączeniem do badania.

Próbki krwi żylnej zostały pobrane przy przyjęciu od pacjentów będących na czczo przez 12 godzin. Pomiary wskaźników hematologicznych, morfologii krwi, stężenia hemoglobiny i hematokrytu zostały wykonane za pomocą automatycznych liczników krwinek czerwonych Sysmex XS-1000i lub XE-2100 (Sysmex Corporation, Kobe, Japonia). Parametry biochemiczne takie jak stężenie w surowicy krwi kreatyniny, bilirubiny całkowitej, albumin, transaminaz, glukozy i NT-proBNP zostały ocenione za pomocą analizatora COBAS 600 (Roche Diagnostics, Bazylea, Szwajcaria). Do pomiaru stężenia białka C-reaktywnego (hs-CRP) został wykorzystany wysoko czuły, oparty na lateksie test immunologiczny wykonywany za pomocą Cobas Integra 70 (Roche Diagnostics, Bazylea, Szwajcaria). Stężenie NT-proBNP w osoczu zmierzono za pomocą systemu testów immunologicznych Elecsys 2010 (Roche Diagnostics). Do pomiaru stężenia kopeptyny użyto testu immunoenzymatycznego ELISA

(*Enzyme-linked Immunosorbent Assay)* (Human Copeptin ELISA kit, Sunred Biological Technology Co, Shanghai, China)

Weryfikację zgonów pacjentów przeprowadzono na podstawie dokumentacji medycznej i oficjalnego rejestru Narodowego Funduszu Zdrowia. W trakcie 6 miesięcznego okresu obserwacji analizowano częstość występowania dekompensacji HF oraz zgonów ze wszystkich przyczyn. Wszystkie dane laboratoryjne i dane z obserwacji odległej były kompletne.

Analiza statystyczna

Analizę statystyczną przeprowadzono przy użyciu oprogramowania SAS w wersji 9.4. Zmienne jakościowe zostały wyrażone w postaci częstości i wartości procentowych (%) i były porównywane pomiędzy grupami za pomocą testu chi-kwadrat Pearsona. Zmienne ciągłe o rozkładzie normalnym przedstawiono jako średnią ± odchylenie standardowe. Dane odbiegające od rozkładu normalnego przedstawiono jako medianę (IQR - rozstęp międzykwartylowy). Istotność statystyczną różnic między zmiennymi o rozkładzie normalnym analizowano za pomocą testu t-Studenta, a w przypadku rozkładu innego niż normalny stosowano test U Manna-Whitneya. Normalność rozkładu oceniano za pomocą testu Shapiro-Wilka.

Analiza proporcjonalnego hazardu Coxa była stosowana w celu określenia współczynnika hazardu (HR-hazard ratio) i 95% przedziału ufności dla złożonego punktu końcowego. Jednoczynnikową analizę regresji Coxa wykorzystano do wyróżnienia potencjalnych czynników prognostycznych złożonego punktu końcowego (zgon ze wszystkich przyczyn lub zaostrzenie niewydolności serca wymagające hospitalizacji), które zostały następnie użyte w analizie wieloczynnikowej. Uwzględniono następujące dane: wiek, bilirubina, kreatynina, białko C-reaktywne (hs-CRP), fibrynogen, kwas moczowy, kopeptyna, wskaźnik masy ciała, albumina i sód, obecność dyslipidemii i cukrzycy typu 2, etiologia niedokrwienna HF, frakcja wyrzutowa lewej komory serca (LVEF) i wymiar końcowo-rozkurczowy lewej komory (LVEDD). Zależności między zmiennymi obliczono za pomocą współczynnika korelacji rang Spearmana, a współliniowość oceniono za pomocą współczynnika tolerancji i współczynnika inflacji wariancji. Obliczano współczynniki hazardu (HR), a wyniki prezentowano jako HR i 95% współczynnik ufności.

Ocenę wartości predykcyjnej zmiennych niezależnych dokonano za pomocą analizy krzywych ROC (Receiver Operating Characteristic). Dla każdego parametru obliczono pole pod krzywą (AUC) w celu oceny jego mocy dyskryminacyjnej. Optymalne wartości progowe

dla analizowanych zmiennych określono za pomocą wskaźnika Youdena. Wartość $p < 0.05$ uznano za statystycznie istotną.

VI. **Wyniki**

Podstawową charakterystykę badanej populacji w całości i z podziałem na grupy przedstawiono w tabeli 1.

Tabela I. Podstawowa charakterystyka badanej populacji

	Wszyscy badani pacjenci N=279	**Pacjenci bez MACE* N=169 (60.6%)**	**Pacjenci z MACE* N=110 (39.4%)**	**P**
Wiek, lata	77.0 (69.0 - 79.0)	72.0 (68.0 - 77.0)	79.0 (77.0 - 81.0)	<0.0001
Mężczyźni, n (%)	221 (79.2)	132 (78.1)	89 (80.9)	0.5729
Etiologia niedokrwienna HF, n (%)	156 (55.9)	70 (41.4)	86 (78.2)	<0.0001
BMI, kg/m2	26.6 (23.8 - 29.5)	27.1 (23.8 - 30.4)	26.1 (24.3 - 28.1)	0.0376
NYHA III, n (%)	123 (44.1)	105 (62.1)	18 (16.4)	<0.0001
NYHA IV, n (%)	156 (55.9)	64 (37.9)	92 (83.6)	<0.0001
Nadciśnienie, n (%)	185 (66.3)	106 (62.7)	79 (71.8)	0.1162
Cukrzyca typu II, n (%)	144 (51.6)	66 (39.1)	78 (70.9)	<0.0001
Utrwalone AF, n (%)	138 (49.5)	83 (49.1)	55 (50.0)	0.8848
POCHP, n (%)	70 (25.1)	35 (20.7)	35 (31.8)	0.0365
LA, mm	45.0 (45.0 - 50.0)	45.0 (45.0 - 49.0)	45.0 (45.0 - 50.0)	0.7206
RVEDd, mm	35.00 (32.0 - 38.0)	35.0 (31.0 - 37.0)	35.0 (32.0 - 39.0)	0.0563
LVEDd, mm	75.0 (70.0 - 78.0)	71.0 (69.0 - 77.0)	77.0 (75.0 - 79.0)	<0.0001

LVEF, %	25.0 (23.0 - 30.0)	27.0 (25.0 - 30.0)	23.5 (20.0 - 26.0)	<0.001

* zgon lub dekompensacja niewydolności serca w ciągu 6 miesięcy od włączenia do badania.

Skróty: AF, migotanie przedsionków; BMI, indeks masy ciała; POCHP, przewlekła obturacyjna choroba płuc; niewydolność serca; LA, lewy przedsionek; LVEDd, wymiar końcoworozkurczowy lewej komory serca; LVEF, frakcja wyrzutowa lewej komory; MACE, złożony punkt końcowy; NYHA, New York Heart Association; RVEDd, wymiar końcoworozkurczowy prawej komory serca.

Tabela II. Wyniki badań laboratoryjnych przy przyjęciu do szpitala

	Wszyscy badani pacjenci N=279	**Pacjenci bez MACE* N=169 (60.6%)**	**Pacjenci z MACE* N=110 (39.4%)**	**P**
Kopeptyna, pmol/l	4.66 (3.05 - 8.77)	3.46 (2.28 - 4.58)	9.11 (7.36 - 11.80)	<0,001
Leukocyty, x 10^9/l	7.3 (6.1 - 8.4)	6.58 (5.40 - 7.92)	5.6 (4.70 - 6.73)	0.0007
Płytki krwi, x 10^9/l	194.0 (171.0 - 225.0)	179.0 (152.0- 210.00)	157.5 (143.0- 206.0)	0.0048
Hemoglobina, mmol/l	8.8 (8.2-9.7)	8.8 (8.3 - 9.7)	8.9 (8.2- 10.0)	0.5572
Glukoza, mmol/l	5.7 (5.3-6.1)	5.6 (5.2-6.1)	5.8 (5.4-6.1)	0.2183
HBA_{1c}, %	5.8 (5.4-6.3)	5.8 (5.5-6.3)	5.8 (5.4-6.4)	0.5946
Kreatynina, µmol/l	117.0 (90.0 - 134.0)	98.0 (87.0 - 126.0)	125.0 (111.0- 146.0)	<0.0001
GFR, ml/min/1,73 m²	58.5 (50.3-71.4)	65.1 (54.0-78.6)	53.9 (45.1-60.1)	<0.0001
Bilirubina, µmol/l	22.9 (17.3 - 28.6)	19.4 (13.3 - 23.0)	27.8 (25.1 - 32.2)	<0.0001
Albuminy, g/l	44.0 (41.0 - 46.0)	44.0 (41.0 - 46.0)	45.0 (41.0 - 47.0)	0.0946
Kwas moczowy, µmol/l	440.0 (378.0 – 515.0)	400.5 (341.0- 465.00)	512.00 (433.0- 603.0)	<0.0001
Mocznik, µmol/l	7.7 (5.8 - 11.3)	7.6 (5.9 - 11.9)	7.7 (5.7 - 11.3)	0.6649
Fibrynogen,	329.0 (380.0 - 436.0)	347.0(306.0- 398.00)	420.0 (345.0- 51.0)	<0.0001

mg/dl				
AST, U/l	32.0 (26.0 - 35.0)	31.0 (23.2 - 34.0)	30.0 (21.0 - 35.0)	0.8003
ALT, U/l	25.0 (20.0 - 33.0)	23.0 (18.1 - 31.5)	29.0 (19.0 - 33.1)	0.0598
ALP, U/l	79.0 (64.0 - 93.0)	78.0 (62.0 - 97.0)	80.5 (72.0 - 91.0)	0.1266
GGTP, U/l	80.0 (49.0 - 125.0)	71.0 (43.0 - 121.0)	89.0 (75.0 - 132.0)	0.0081
Cholesterol, mmol/l	4.3 (3.9-4.9)	4.2 (3.8-4.8)	4.5 (4.1-5.3)	<0.0001
hs-CRP, mg/l	2.3 (1.9 - 5.1)	2.95 (1.88 - 4.36)	4.5 (3.76 – 5.60)	<0.0001
Sód, mmol/l	135.0 (133.0 - 138.0)	137.0(134.0- 139.0)	133.5 (132.0- 135.0)	<0.0001
NT-proBNP, pg/ml	4832 (3491.0 -7191.0)	4625.0 (3500.0-7089.0)	5563.0 (3491.0-7191.0)	0.6488

* zgon lub dekompensacja niewydolności serca w ciągu 6 miesięcy od włączenia do badania.

Skróty: ALP, fosfataza alkaliczna; ALT, transaminaza alaninowa; AST – transaminaza asparaginianowa; GGTP, gammaglutamylotranspeptydaza; GFR, wskaźnik filtracji kłębuszkowej; hs-CRP, wysokoczułe białko C-reaktywne; MACE, złożony punkt końcowy; NT-proBNP, N-końcowy fragment propeptydu natriuretycznego typu B.

Tabela III. Leczenie farmakologiczne i za pomocą urządzeń wszczepialnych przy przyjęciu

	Wszyscy badani pacjenci **N=279**	**Pacjenci bez MACE*** **N=169 (60.6%)**	**Pacjenci z MACE*** **N=110 (39.4%)**	**P**
β-blokery, n (%)	219 (78.5)	139 (82.2)	80 (72.7)	0.05
Bisoprolol, mg/dobę	5.0 (2.5-5.0)	5.0 (2.5-5.0)	5.0 (5.0-5.0)	0.13
Nebiwolol, mg/dobę	5.0 (2.5-5.0)	2.50 (2.5-5.0)	5.0 (2.5-5.0)	0.6
Karwedilol, mg/dobę	25.0 (25.0-25.0)	25.0 (25.0-25.0)	25.0 (12.5- 25.0)	0.2
Bursztynian metoprololu, mg/dobę	90.0 (47.5-90.0)	90.0 (47.5-90.0)	90.0 (47.5-90.0)	0.4
ACEI, n (%)	148 (53)	89 (52.7)	59 (53.6)	0.87
Ramipryl, mg/dobę	5.0 (2.5-5.0)	5.0 (2.5-5.0)	3.75 (2.5-5.0)	0.2
Perindopryl, mg/dobę	5.0 (2.5-5.0)	5.0 (2.5-5.0)	5.0 (2.5-5.0)	0.3

Sartany (ARB), n (%)	51 (18.3)	37 (21.9)	14 (12.7)	0.05
Walsartan, mg/dobe	80.0 (80.0-160.0)	80.0 (80.0-160.0)	80.0 (80.0-160.0)	>0.9
Telmisartan, mg/dobę	40.0 (40.0-40.0)	40.0 (30.0-40.0)	40.0 (40.0-40.0)	0.2
ARNI, n (%)	56 (20.1)	27 (16)	29 (26.4)	0.03
ARNI, sakubitryl, mg/dobę	48.6 (24.3-48.6)	48.6 (24.3-48.6)	48.6 (48.6-48.6)	0.4
ARNI, walsartan, mg/dobę	51.4 (25.7-51.4)	51.4 (25.7-51.4)	51.4 (51.4-51.4)	0.5
Diuretyki pętlowe, n (%)	273 (97.8%)	168 (99.4%)	105 (95.5%)	0.037
Furosemid #, mg/dobę	80.0 (80.0-160.0)	90.0 (80.0-160.0)	80.0 (40.0-120.0)	0.062
MRA, n (%)	101 (36.2)	89 (52.7)	12 (10.9)	<0.001
Spironolakton/ eplerenon, mg/dobe	25.0 (25.0-50.0)	25.0 (12.5-50.0)	25.0(25.0-50.0)	0.4
SGLT2, n (%)	129 (46.2)	63 (37.3)	66 (60)	0.0002
NOAC, n (%)	141 (50.5)	82 (48.5)	59 (53.6)	0.40
Digoksyna, n (%)	76 (27.2)	39 (23.1)	37 (33.6)	0.05
Statyna, n (%)	167 (59.9)	101 (59.8)	66 (60)	0.96
ASA , n (%)	95 (34.1)	66 (39.1)	29 (26.4)	0.03
ICD/CRT-D, n (%)	238 (85.3)	144 (85.2)	94 (85.5)	0.95

#Dawki leków moczopędnych zostały przeliczone na odpowiedniki furosemidu.(10 mg torasemidu = 40 mg furosemidu)
Skróty: ACEI, inhibitor konwertazy angiotensyny; ASA, kwas acetylosalicylowy; ARB, antagonista receptora angiotensyny; ARNI, sakubitryl-walsartan, antagonista receptora dla neprilizyny; CRT-D, stymulator resynchronizujący z funkcją kardiowertera - defibrylatora; ICD, wszczepialny kardiowerter-defibrylator; MRA, antagonista receptora mineralokortykoidowego; NOAC, doustne leki przeciwkrzepliwe niebędące antagonistami witaminy K; SGLT-2, kotransporter sodowo glukozowy 2

Jednoczynnikowa analiza proporcjonalnego hazardu Coxa wykazała, że wiek, indeks masy ciała, wymiar końcoworozkurczowy lewej komory (LVEDD), frakcja wyrzutowa lewej komory, wieńcowa etiologia HF i cukrzyca, a także stężenie w surowicy krwi kopeptyny, bilirubiny, kreatyniny, kwasu moczowego, hsCRP, fibrynogenu, albuminy i sodu były związane z występowaniem złożonego punktu końcowego w okresie 6 miesięcznej obserwacji. Wieloczynnikowa analiza proporcjonalnego hazardu Coxa wykazała, że niezależnymi czynnikami ryzyka złożonego punktu końcowego były: kopeptyna, bilirubina, hsCRP, kwas

moczowy, sód i etiologia niedokrwienna HF. Wyniki analizy jednoczynnikowej i wieloczynnikowej przedstawiono w tabeli 3.

Tabela IV. Wyniki analizy jednoczynnikowej i wieloczynnikowej proporcjonalnego hazardu Coxa

	Analiza jednoczynnikowa		**Analiza wieloczynnikowa**	
Parametr	HR (95% CI)	P	HR (95% CI)	P
Wiek	1.317 [1.239-1.400]	<0.0001		
Bilirubina	1.119 [1.096-1.144]	<0.0001	1.085 [1.057-1.114]	<0.0001
Kreatynina	1.019 [1.012-1.025]	<0.0001		
CRP	1.357 [1.252-1.470]	<0.0001	1.208 [1.088-1.342]	<0.0001
Fibrynogen	1.011 [1.009-1.013]	<0.0001		
Kwas moczowy	1.006 [1.005-1.008]	<0.0001	1.005 [1.003-1.006]	<0.0001
Kopeptyna	1.025 [1.016-1.035]	<0.0001	1.053 [1.042-1.064]	<0.0001
BMI ↓	1.067 [1.012-1.126]	0.017		
Albuminy	1.052 [1.014-1.092]	0.007		
Sód ↓	1.341 [1.246-1.444]	<0.0001	1.111 [1.025-1.1203]	0.01
LVEDD	1.162 [1.115-1.213]	<0.0001		
EF ↓	1.238 [1.177-1.302]	<0.0001		
Etiologia niedokrwienna	3.738 [2.375-5.884]	<0.0001	3.969 [2.396-6.575]	<0.0001
Cukrzyca typu 2	2.858 [1.892-4.317]	<0.0001		

Skróty: patrz tabela 1 i 2.

Analiza krzywych ROC wykazała, że kopeptyna miała najwyższą wartość prognostyczną (AUC = 0,866; 95% CI: 0.816–0.916; $p < 0.001$), a następnie bilirubina (AUC = 0.857; 95% CI: 0.811–0.902; $p < 0.001$), sód (AUC = 0.821; 95% CI: 0.774–0.868; $p < 0.001$), kwas

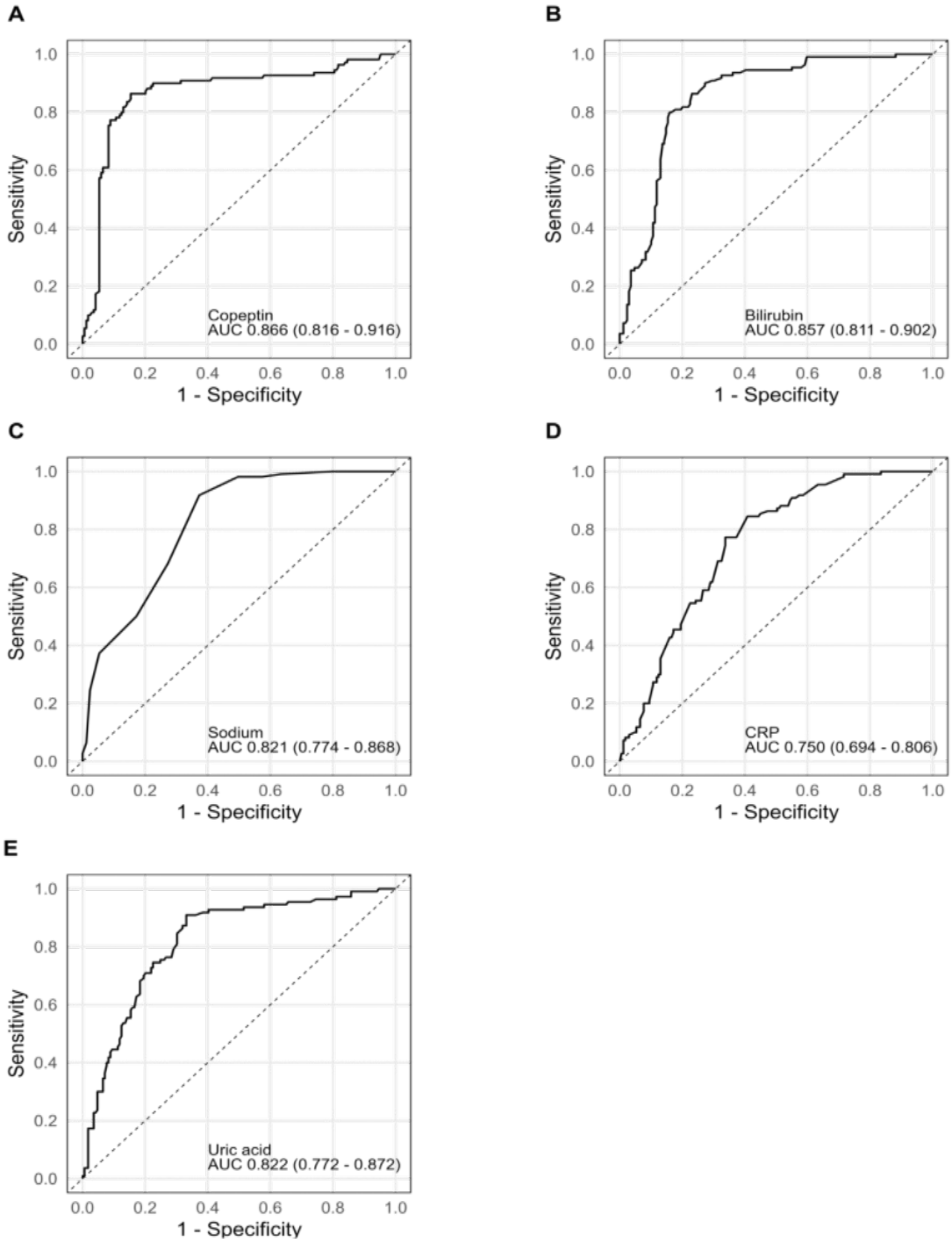
moczowy (AUC = 0.822; 95% CI: 0.772–0.872; p < 0,001) oraz hs-CRP (AUC = 0.750; 95% CI: 0.694–0.806; p < 0.001). Krzywe ROC przedstawiono na rycinie 1 A-E, a podsumowanie znajduje się w tabeli 4.

Tabela V: Podsumowanie krzywych ROC

	AUC [±95 CI]	**Punkt odcięcia**	**Czułość [±95 CI]**	**Specyficzność [±95 CI]**
Kopeptyna	0.866 [0.816 - 0.916]	5.365	0.864 [0.785 - 0.922]	0.846 [0.783 - 0.897]
Bilirubina	0.857 [0.811 - 0.902]	24.7	0.800 [0.713 - 0.87]	0.84 [0.776 - 0.892]
Sód	0.821 [0.774 - 0.868]	135	0.918 [0.85 - 0.962]	0.627 [0.55 - 0.7]
hs-CRP	0.75 [0.694 - 0.806]	3.4	0.845 [0.764 - 0.907]	0.592 [0.514 - 0.667]
Kwas moczowy	0.822 [0.772 - 0.872]	425	0.909 [0.839 - 0.956]	0.669 [0.592 - 0.739]

Skróty: AUC, pole pod krzywą; CI, przedział ufności; hs-CRP białko CRP wysokiej czułości.

Rycina 1: Krzywe ROC dla kopeptyny (A), bilirubiny (B), sodu (C), hs-CRP (D), kwasu moczowego (E)


A
Sensitivity
1 - Specificity
Copeptin
AUC 0.866 (0.816 - 0.916)
B
Sensitivity
1 - Specificity
Bilirubin
AUC 0.857 (0.811 - 0.902)
C
Sensitivity
1 - Specificity
Sodium
AUC 0.821 (0.774 - 0.868)
D
Sensitivity
1 - Specificity
CRP
AUC 0.750 (0.694 - 0.806)
E
Sensitivity
1 - Specificity
Uric acid
AUC 0.822 (0.772 - 0.872)

VII. **Dyskusja:**

Niniejsze jednoośrodkowe badanie obserwacyjne wykazało, że wyższe stężenia kopeptyny, bilirubiny, hsCRP i kwasu moczowego, niższe stężenia sodu i niedokrwienna etiologia HF są związane ze śmiertelnością ze wszystkich przyczyn oraz hospitalizacją w okresie 6 miesięcy obserwacji u pacjentów w podeszłym wieku ze zdekompensowaną niewydolnością serca.

Spośród wszystkich analizowanych parametrów kopeptyna wykazywała najwyższą wartość prognostyczną w przewidywaniu złożonego punktu końcowego w badanej populacji. Jednakże kopeptyna może być traktowana jedynie jako dodatkowy, uzupełniający element prognostyczny w połączeniu z innymi wskaźnikami klinicznymi i laboratoryjnymi. Przeprowadzona w niniejszym badaniu analiza wykazała przydatność kopeptyny jako czynnika prognostycznego wystąpienia złożonego punktu końcowego (zgon i hospitalizacja z powodu zaostrzenia HF) w okresie 6 miesięcy obserwacji. Poprzednie badania różnych grup pacjentów z niewydolnością serca wykazały, że wyższe stężenia kopeptyny wiązały się z gorszym rokowaniem u chorych z HF [11-13]. Istnieją ograniczone dane dotyczące znaczenia prognostycznego kopeptyny u pacjentów w podeszłym wieku ze zdekompensowaną HF [14, 15]. Alehagen i wsp. oraz Holmström i wsp. wykazali wprawdzie, że podwyższone stężenia kopeptyny były związane ze zwiększonym ryzykiem zgonu ze wszystkich przyczyn u pacjentów w podeszłym wieku, jednakże analizowane przez wymienionych autorów populacje różniły się od niniejszej grupy w kilku aspektach [14, 15]. W wymienionych analizach pacjenci byli istotnie młodsi i niewielki odsetek spośród nich miał zredukowaną frakcję wyrzutową lewej komory oraz objawy zaawansowanej HF (NYHA III-IV). W niniejszym badaniu analizowano chorych w podeszłym wieku ze znacznie obniżoną frakcją wyrzutową lewej komory (mediana LVEF 25%) w III i IV klasie czynnościowej wg NYHA. Kopeptyna odzwierciedla aktywację układu wazopresynowego w odpowiedzi na obciążenie hemodynamiczne i zaburzenia neurohormonalne w HF. Wskaźnik ten jest stabilnym markerem arginino-wazopresyny wydzielanym w ilościach równoważnych (ekwiwalentnych) przez przysadkę. Podwyższone stężenia kopeptyny są związane ze stopniem nasilenia choroby i aktywacją neurohumoralną w HF będącą następstwem zmniejszonego rzutu serca i zwiększonymi ciśnieniami napełniania lewej komory [16-19]. U pacjentów w podeszłym wieku upośledzona funkcja nerek, zmniejszona czułość baroreceptorów i schorzenia współistniejące nasilają sekrecję arginino-wazopresyny i kopeptyny [18-21]. Ponadto stężenie kopeptyny koreluje z układowym stresem i zapaleniem co sprawia, że może być ona

adekwatnym potencjalnym biomarkerem w zdekompensowanej HF [22, 23]. W populacji chorych w podeszłym wieku powyższe efekty mogą być bardziej nasilone ze względu na upośledzone rezerwy fizjologiczne i mechanizmy kompensacyjne oraz liczne schorzenia współistniejące. Ponadto dysfunkcja nerek u pacjentów w podeszłym wieku z HF może odzwierciedlać podwyższoną sekrecję arginino-wazopresyny. W populacji chorych w podeszłym wieku powyższe procesy mogą być nasilone ze względu na zmniejszone rezerwy fizjologiczne, upośledzone mechanizmy kompensacyjne i obecność chorób współistniejących [18-21]. Ponadto występująca często u pacjentów w podeszłym wieku dysfunkcja nerek może również zwiększać sekrecję wazopresyny i nasilać jej działanie [20]. Ekspresja wazopresyny u chorych z niewydolnością nerek jest zwiększona i wazopresyna nie może prawidłowo działać przez receptory V2, co prowadzi do zwiększonej aktywacji receptorów V1a i V1b. Poprzez receptory V1a wazopresyna stymuluje produkcję fibroblastów promując włóknienie mięśnia sercowego i zwiększenie syntezy białek miocytów, a także nasila przerost kardiomiocytów i zmniejsza kurczliwość lewej komory. Kopeptyna może odzwierciedlać układowy stres i zapalenie, które są powszechne u pacjentów w stanach ostrych takich jak zaostrzenie HF. U pacjentów w podeszłym wieku mechanizmy sekrecji kopeptyny i wazopresyny mogą być istotnie zaburzone poprzez zmiany fizjologiczne, które pojawiają się w następstwie procesów starzenia, takie jak stres osmotyczny i hemodynamiczny, upośledzona odpowiedź nerek na diurezę oraz zaburzenia funkcji baroreceptorów [20].

Niniejsze badanie potwierdziło znaczenie prognostyczne innych dobrze znanych czynników ryzyka niekorzystnych zdarzeń sercowych u pacjentów w podeszłym wieku takich jak stężenie sodu, hsCRP, bilirubiny i kwasu moczowego w surowicy krwi.

Hiponatremia jest uznanym wskaźnikiem dekompensacji i niekorzystnego rokowania w HF niezależnie od grupy wiekowej pacjentów [24-27]. Odzwierciedla aktywację układu współczulnego i osi renina-angiotensyna-aldosteron. Jest również pośrednim wskaźnikiem podwyższonej aktywności wazopresyny, co może być odzwierciedlone przez poziom kopeptyny. U osób starszych zmniejszone przesączanie kłębuszkowe i upośledzona synteza prostaglandyn w nerkach ograniczają wydalanie wody i nasilają hiponatremie [27-28]. Ponadto leki moczopędne pętlowe i tiazydowe, powszechnie stosowane w niewydolności serca, przyczyniają się do hiponatremii i zaburzeń równowagi wodno-elektrolitowej [28-30].

Innym czynnikiem związanym z punktem końcowym w niniejszej analizie jest stężenie białka hsCRP w surowicy, które odzwierciedla tlący się stan zapalny w HF [31-33]. CRP jest syntetyzowane w wątrobie w odpowiedzi na obecność interleukiny-6 i innych cytokin prozapalnych cytokiny, a jego stężenie rośnie podczas dekompensacji niewydolności serca.

Dokładny mechanizm tlącej się zapalnej reakcji ogólnoustrojowej w niewydolności serca nie jest w pełni poznany. Uważa się, że nasila ona stan zapalny śródbłonka naczyń włosowatych i sprzyja ekspresji cząsteczek adhezyjnych, które przyciągają krążące leukocyty, co prowadzi do odkładania się kolagenu w tkance śródmiąższowej i niekorzystnej przebudowy serca. Ponadto mikrouszkodzenia śródbłonka prowadzą do zwiększonego uwalniania reaktywnych form tlenu (ROS) i zmniejszenia dostępności tlenku azotu (NO) [32-34]. Dodatkowo choroby współistniejące, takie jak cukrzyca, nadciśnienie i przewlekła obturacyjna choroba płuc nasilają stan zapalny, pobudzając w ten sposób komórki śródbłonka do dalszej produkcji reaktywnych form tlenu, które uszkadzają inne komórki, tworząc dodatnie sprzężenie zwrotne [35]. Chociaż rutynowe badanie poziomu hs-CRP nie jest obecnie zalecane w wytycznych, wyniki uzyskane na podstawie niniejszej analizy, zgodne z wynikami poprzednich badań, sugerują jego potencjalną przydatność w ocenie pacjentów z HF.

Kolejnym czynnikiem związanym ze zwiększonym ryzykiem niekorzystnych zdarzeń sercowych w badanej grupie chorych było stężenie bilirubiny w surowicy krwi, co stwierdzono również w badaniach innych autorów [36-38]. Zastoinowa hepatopatia jest częstym objawem niewyrównanej HF występującym w około 70% przypadków [36], a jej najczulszym markerem jest jest nieznacznie podwyższone stężenie bilirubiny w surowicy [39]. Z patofizjologicznego punktu widzenia hiperbilirubinemia w zaostrzonej niewydolności serca jest głównie spowodowana zastojem żylnym, prowadzącym do biernego przekrwienia wątroby, a w konsekwencji do upośledzenia funkcji hepatocytów [40, 41]. Ponadto zmniejszony rzut serca w przebiegu HF prowadzi do hipoksji wątroby, co nasila zaburzenia metaboliczne hepatocytów i powoduje dalszy wzrost poziomu bilirubiny w surowicy [40,42].

Innym niezależnym czynnikiem ryzyka niekorzystnego rokowania w analizowanej populacji osób starszych z zaostrzoną niewydolnością serca był podwyższony poziom kwasu moczowego, którego rola jako czynnika ryzyka sercowo-naczyniowego jest szeroko omawiana od dziesięcioleci. Wiele dużych badań populacyjnych wykazało, że podwyższone poziomy kwasu moczowego były niezależnymi predyktorami śmiertelności w niewyrównanej niewydolności serca [35, 43-45]. Kwas moczowy wykazuje właściwości przeciwutleniające i prooksydacyjne. W hydrofilnym środowisku zewnątrzkomórkowym działa jako silny wychwytywacz wolnych rodników, natomiast wewnątrzkomórkowo wywiera szkodliwy wpływ, działając jako prooksydant. Kwas moczowy, poprzez swoje działanie stymulujące produkcję reaktywnych form tlenu, wywiera szczególnie niekorzystny wpływ na śródbłonek naczyniowy, powodując zmniejszenie biodostępności NO, hamowanie migracji i proliferacji komórek. Ponadto kwas moczowy, poprzez aktywację szlaków prozapalnych, stymuluje

proliferację komórek mięśni gładkich naczyń, włóknienie śródbłonka, a także skurcz naczyń krwionośnych [35, 41, 43-45].

Ostatnim czynnikiem związanym z ponownym przyjęciem do szpitala z powodu niewydolności serca lub zgonem w ciągu 6 miesięcy obserwacji była etiologia niedokrwienna HF [46-49]. W krajach europejskich niedokrwienie mięśnia sercowego jest główną przyczyną niewydolności serca. Odgrywa znaczącą rolę w przebudowie mięśnia sercowego, który obejmuje zmiany kształtu i wielkości serca, a także zmniejszenie przepływu krwi do mięśnia sercowego i zmniejszenie frakcji wyrzutowej [48, 49]. Ponadto niedokrwienie mięśnia sercowego może zarówno powodować, jak i przyspieszać dekompensację niewydolności serca [47, 48].

Ograniczenia badania:

Badanie to ma kilka ograniczeń. Po pierwsze, jest to badanie jednoośrodkowe z relatywnie małą grupą pacjentów, co może powodować pewne ograniczenia przy uogólnianiu wyników do całej populacji. Po drugie, poziom kopeptyny w surowicy krwi mierzono tylko w momencie przyjęcia do szpitala i nie oceniano zmian w okresie obserwacji. Prawdopodobnie dynamiczne zmiany poziomu kopeptyny w czasie mogłyby dostarczyć dodatkowych informacji prognostycznych. Co ważne, niewielki był odsetek kobiet w badanej populacji (około 20% populacji objętej badaniem), co ogranicza zastosowanie wyników do starszych pacjentek i podkreśla potrzebę przyszłych badań dotyczących różnic związanych z płcią w działaniu biomarkerów i rokowaniu. Wreszcie, nasze badanie miało charakter obserwacyjny, dlatego nie można jednoznacznie ustalić związku przyczynowo skutkowego między podwyższonym poziomem kopeptyny, a niekorzystnym rokowaniem.

VIII. **Wnioski**

Niniejsze badanie wykazało, że wyższe stężenia kopeptyny, bilirubiny, hs-CRP i kwasu moczowego, a także niższe stężenia sodu w surowicy krwi i niedokrwienna etiologia niewydolności serca są związane ze śmiertelnością z jakiejkolwiek przyczyny lub ponownym przyjęciem do szpitala w ciągu sześciu miesięcy u starszych pacjentów ze zdekompensowaną niewydolnością serca. Najwyższą wartość prognostyczną w analizowanej grupie chorych miała kopeptyna.

Wyniki te podkreślają przydatność kopeptyny i innych biochemicznych markerów jako potencjalnych narzędzi do stratyfikacji ryzyka u pacjentów w podeszłym wieku ze zdekompensowaną niewydolnością serca. Jednakże konieczne byłoby przeprowadzenie dużych badań wieloośrodkowych, aby potwierdzić te wyniki i ustalić, czy rutynowe stosowanie kopeptyny i innych biomarkerów może poprawić wyniki kliniczne lub pomóc w prowadzeniu terapii w przypadku dekompensacji serca u osób starszych.

IX. Piśmiennictwo

1. Sunayama T, Matsue Y, Dotare T, Maeda D, Iso T, Morisawa T, i in. Multidomain Frailty as a Therapeutic Target in Elderly Patients with Heart Failure. International Heart Journal. 2022 Jan 29;63(1):1–7.
2. Liu E, Lampert BC. Heart Failure in Older Adults: Medical Management and Advanced Therapies. Geriatrics. 2022 Mar 23;7(2):36.
3. Nadziakiewicz P, Szczurek-Wasilewicz W, Szyguła-Jurkiewicz B. Heart Failure in Elderly Patients: Medical Management, Therapies and Biomarkers. Pharmaceuticals. 2024 Dec 30;18(1):32.
4. Clemente G, Soldano JS, Tuttolomondo A. Heart Failure: Is There an Ideal Biomarker? Reviews in Cardiovascular Medicine. 2023 Nov 19;24(11):310.
5. Candeloro M, Di Nisio M, Balducci M, Genova S, Valeriani E, Pierdomenico SD, i in. Prognostic nutritional index in elderly patients hospitalized for acute heart failure. ESC Heart Failure. 2020 Jun 26;7(5):2479–84.
6. Manzano L, Babalis D, Roughton M, Shibata M, Anker SD, Ghio S, i in. Predictors of clinical outcomes in elderly patients with heart failure. European Journal of Heart Failure. 2011 Feb 18;13(5):528–36.
7. Pacho C, Domingo M, Núñez R, Lupón J, Núñez J, Barallat J, i in. Predictive biomarkers for death and rehospitalization in comorbid frail elderly heart failure patients. BMC Geriatrics. 2018 May 9;18(1):109.
8. Mu D, Cheng J, Qiu L, Cheng X. Copeptin as a Diagnostic and Prognostic Biomarker in Cardiovascular Diseases. Frontiers in Cardiovascular Medicine. 2022 Jul 4;9:901990.
9. Balling L, Goetze JP, Jung MH, Rossing K, Boesgaard S, Gustafsson F. Copeptin Levels and Invasive Hemodynamics in Patients with Advanced Heart Failure. Biomarkers in Medicine. 2018 Jul 30;12(8):861–70.
10. Stoiser B, Mörtl D, Hülsmann M, Berger R, Struck J, Morgenthaler NG, i in. Copeptin, a fragment of the vasopressin precursor, as a novel predictor of outcome in heart failure. European Journal of Clinical Investigation. 2006 Oct 9;36(11):771–8.
11. Yoshikawa Y, Shiomi H, Kuwahara K, Sowa N, Yaku H, Yamashita Y, i in. Utility of copeptin for predicting long-term clinical outcomes in patients with heart failure. Journal of Cardiology. 2019 Dec 24;73(5):379–85.
12. Ianos RD, Iancu M, Pop C, Lucaciu RL, Hangan AC, Rahaian R, i in. Predictive Value of NT-proBNP, FGF21, Galectin-3 and Copeptin in Advanced Heart Failure in Patients with Preserved and Mildly Reduced Ejection Fraction and Type 2 Diabetes Mellitus. Medicina. 2024 Nov 8;60(11):1841.

13. Zimodro JM, Gasecka A, Jaguszewski M, Amanowicz S, Szkiela M, Denegri A, i in. Role of copeptin in diagnosis and outcome prediction in patients with heart failure: a systematic review and meta-analysis. Biomarkers. 2022 Nov 17;27(8):720–6.
14. Alehagen U. Association of Copeptin and N-Terminal proBNP Concentrations With Risk of Cardiovascular Death in Older Patients With Symptoms of Heart Failure. JAMA. 2011 May 25;305(20):2088.
15. Holmström A, Sigurjonsdottir R, Fu MLX, Gustafsson D, Petzold M, Hammarsten O. Levels of copeptin among elderly patients in relation to systolic heart failure and heart failure with normal ejection fraction. European Geriatric Medicine. 2013 Mar 26;4(3):139–44.
16. Zhang P, Wu X, Li G, Sun H, Shi J. Prognostic role of copeptin with all-cause mortality after heart failure: a systematic review and meta-analysis. Therapeutics and Clinical Risk Management. 2017 Jan 5;Volume 13:49–58.
17. Dobsa L, Cullen Edozien K. Copeptin and its potential role in diagnosis and prognosis of various diseases. Biochemia Medica. 2013 Jun 15;23:172–92.
18. Strait JB, Lakatta EG. Aging-Associated Cardiovascular Changes and Their Relationship to Heart Failure. Heart Failure Clinics. 2012 Jan;8(1):143–64.
19. Regan JA, Kitzman DW, Leifer ES, Kraus WE, Fleg JL, Forman DE, i in. Impact of Age on Comorbidities and Outcomes in Heart Failure With Reduced Ejection Fraction. JACC: Heart Failure. 2019 Nov 25;7(12):1056–65.
20. Krane V, Genser B, Kleber ME, Drechsler C, März W, Delgado G, i in. Copeptin Associates with Cause-Specific Mortality in Patients with Impaired Renal Function: Results from the LURIC and the 4D Study. Clinical Chemistry. 2017 May 1;63(5):997–1007.
21. Fukuzawa J, Haneda T, Kikuchi K. Arginine vasopressin increases the rate of protein synthesis in isolated perfused adult rat heart via the V1 receptor. Molecular and Cellular Biochemistry. 1999 May;195(1/2):93–8.
22. Smaradottir MI, Andersen K, Gudnason V, Näsman P, Rydén L, Mellbin LG. Copeptin is associated with mortality in elderly people. European Journal of Clinical Investigation. 2021 Jul;51(7):e13516.
23. Morgenthaler NG, Müller B, Struck J, Bergmann A, Redl H, Christ-Crain M. Copeptin, a stable peptide of the arginine vasopressin precursor, is elevated in hemorrhagic and septic shock. Shock. 2007 Aug;28(2):219–26.
24. Klein L, O'Connor CM, Leimberger JD, Gattis-Stough W, Piña IL, Felker GM, i in. Lower Serum Sodium Is Associated With Increased Short-Term Mortality in Hospitalized Patients With Worsening Heart Failure: Results From the Outcomes of a

Prospective Trial of Intravenous Milrinone for Exacerbations of Chronic Heart Failure (OPTIME-CHF) Study. Circulation. 2005 May 17;111(19):2454–60.
25. Herrero-Puente P, Marino-Genicio R, Martín-Sánchez FJ, Vázquez-Alvarez J, Jacob J, Bermudez M, i in. Characteristics of acute heart failure in very elderly patients — EVE study (EAHFE very elderly). European Journal of Internal Medicine. 2014 Jun;25(5):463–70.
26. Greenberg B. Managing hyponatremia in patients with heart failure. Journal of Hospital Medicine. 2010 Aug 5, 5:35-39.
27. Filippatos TD, Makri A, Elisaf MS, Liamis G. Hyponatremia in the elderly: challenges and solutions. Clinical Interventions in Aging. 2017 Nov 14;Volume 12:1957–65.
28. Clark BA, Shannon RP, Rosa RM, Epstein FH. Increased susceptibility to thiazide-induced hyponatremia in the elderly. Journal of the American Society of Nephrology. 1994 Oct;5(4):1106–11.
29. Gheorghiade M, Abraham WT, Albert NM, Gattis Stough W, Greenberg BH, O'Connor CM, i in. Relationship between admission serum sodium concentration and clinical outcomes in patients hospitalized for heart failure: an analysis from the OPTIMIZE-HF registry. European Heart Journal. 2007 Apr 2;28(8):980–8.
30. Maisel A, Xue Y, Shah K, Mueller C, Nowak R, Peacock WF, i in. Increased 90-Day Mortality in Patients With Acute Heart Failure With Elevated Copeptin: Secondary Results From the Biomarkers in Acute Heart Failure (BACH) Study. Circulation: Heart Failure. 2011 Sept;4(5):613–20.
31. Kalogeropoulos AP, Tang WHW, Hsu A, Felker GM, Hernandez AF, Troughton RW, i in. High-Sensitivity C-Reactive Protein in Acute Heart Failure: Insights From the ASCEND-HF Trial. Journal of Cardiac Failure. 2014 May;20(5):319–26.
32. Zhang L, He G, Huo X, Tian A, Ji R, Pu B, i in. Long-Term Cumulative High-Sensitivity C-Reactive Protein and Mortality Among Patients With Acute Heart Failure. Journal of the American Heart Association. 2023 Oct 3;12(19):e029386.
33. Santas E, Villar S, Palau P, Llàcer P, De La Espriella R, Miñana G, i in. High-sensitivity C-reactive protein and risk of clinical outcomes in patients with acute heart failure. Scientific Reports. 2024 Sep 17;14(1):21672.
34. Habibi D, Daneshpour MS, Asgarian S, Kohansal K, Hadaegh F, Mansourian M, i in. Effect of C-reactive protein on the risk of Heart failure: a mendelian randomization study. BMC Cardiovascular Disorders. 2023 May 7;23(1):112.
35. Huang G, Qin J, Deng X, Luo G, Yu D, Zhang M, i in. Prognostic value of serum uric acid in patients with acute heart failure: A meta-analysis. Medicine. 2019 Feb;98(8):e14525.

36. Chintanaboina J, Haner MS, Sethi A, Patel N, Tanyous W, Lalos A, i in. Serum bilirubin as a prognostic marker in patients with acute decompensated heart failure. The Korean Journal of Internal Medicine. 2013 May 1;28(3):300.
37. Okada A, Sugano Y, Nagai T, Honda Y, Iwakami N, Nakano H, i in. Usefulness of the Direct and/or Total Bilirubin to Predict Adverse Outcomes in Patients With Acute Decompensated Heart Failure. The American Journal of Cardiology. 2017 Jun 15;119(12):2035–41.
38. Shinagawa H, Inomata T, Koitabashi T, Nakano H, Takeuchi I, Naruke T, i in. Prognostic Significance of Increased Serum Bilirubin Levels Coincident With Cardiac Decompensation in Chronic Heart Failure. Circulation Journal. 2008 Feb 25;72(3):364–9.
39. Allen LA, Felker GM, Pocock S, McMurray JJV, Pfeffer MA, Swedberg K, i in. Liver function abnormalities and outcome in patients with chronic heart failure: data from the Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity (CHARM) program. European Journal of Heart Failure. 2009 Feb;11(2):170–7.
40. Nikolaou M, Parissis J, Yilmaz MB, Seronde MF, Kivikko M, Laribi S, i in. Liver function abnormalities, clinical profile, and outcome in acute decompensated heart failure. European Heart Journal. 2013 Mar 2;34(10):742–9.
41. Samsky MD, Patel CB, DeWald TA, Smith AD, Felker GM, Rogers JG, i in. Cardiohepatic Interactions in Heart Failure. Journal of the American College of Cardiology. 2013 Jun;61(24):2397–405.
42. Lau GT, Tan HC, Kritharides L. Type of liver dysfunction in heart failure and its relation to the severity of tricuspid regurgitation. The American Journal of Cardiology. 2002 Dec 15;90(12):1405–9.
43. Huang G, Qin J, Deng X, Luo G, Yu D, Zhang M, i in. Prognostic value of serum uric acid in patients with acute heart failure: A meta-analysis. Medicine. 2019 Feb;98(8):e14525.
44. Alimonda AL, Núñez J, Núñez E, Husser O, Sanchis J, Bodí V, i in. Hyperuricemia in acute heart failure. More than a simple spectator? European Journal of Internal Medicine. 2009 Jan;20(1):74–9.
45. Kumrić M, Borovac JA, Kurir TT, Božić J. Clinical Implications of Uric Acid in Heart Failure: A Comprehensive Review. Life. 2021 Jan 14;11(1):53.
46. Remme WJ. Overview of the relationship between ischemia and congestive heart failure. Clinical Cardiology. 2000 Jul;23(S4):IV-4-IV–8.
47. Canepa M, Anastasia G, Ameri P, Vergallo R, O'Connor CM, Sinagra G, i in. Characterization of ischemic etiology in heart failure with reduced ejection fraction

randomized clinical trials: A systematic review and meta-analysis. European Journal of Internal Medicine. 2025 Apr;134:51–8.

48. Kajimoto K, Minami Y, Sato N, Kasanuki H. Etiology of Heart Failure and Outcomes in Patients Hospitalized for Acute Decompensated Heart Failure With Preserved or Reduced Ejection Fraction. The American Journal of Cardiology. 2016 Dec 15;118(12):1881–7.
49. Flaherty JD, Bax JJ, De Luca L, Rossi JS, Davidson CJ, Filippatos G, i in. Acute Heart Failure Syndromes in Patients With Coronary Artery Disease. Journal of the American College of Cardiology. 2009 Jan 13;53(3):254–63.

X. **Streszczenie polskie**

Wprowadzenie: Diagnostyka i ocena rokowania u starszych pacjentów z niewydolnością serca (HF) są trudne ze względu na nietypowe objawy i ograniczoną wartość peptydów natriuretycznych, co podkreśla potrzebę poszukiwania nowych biomarkerów stratyfikacji ryzyka w tej populacji.

Cel: Celem pracy była analiza czynników związanych ze złożonym punktem końcowym (śmiertelność z jakiejkolwiek przyczyny lub hospitalizacja związana z dekompensacją niewydolności serca) w ciągu sześciu miesięcy obserwacji u pacjentów w podeszłym wieku z dysfunkcją skurczową lewej komory i dekompensacją niewydolności serca, ze szczególnym naciskiem na stężenie kopeptyny.

Metody: W tym jednoośrodkowym badaniu wzięło udział 279 kolejnych pacjentów w podeszłym wieku hospitalizowanych w latach 2018–2023 z powodu dekompensacji niewydolności serca. Kryteria włączenia obejmowały: wiek>65 lat, rozpoznanie niewydolności serca co najmniej dwa lata przed hospitalizacją oraz frakcję wyrzutową lewej komory < 40% w echokardiografii w chwili przyjęcia. Poziomy kopeptyny w surowicy mierzono za pomocą testu immunoenzymatycznego (ELISA) (Human Copeptin ELISA kit, Sunred Biological Technology Co, Szanghaj, Chiny). Główny punkt końcowy obejmował śmiertelność z jakiejkolwiek przyczyny lub hospitalizację z powodu niewydolności serca w okresie sześciu miesięcy obserwacji.

Wyniki: Mediana wieku badanej populacji wynosiła 77 lat (IQR: 69–79), a 221 (79,2%) stanowili mężczyźni. Złożony punkt końcowy wystąpił u 110 pacjentów (38,1%). Analiza wieloczynnikowa wykazała, że stężenia w surowicy krwi kopeptyny (iloraz szans [HR] 1,053 [1,042-1,064], p<0,0001), bilirubiny (HR 1,085 [1,057-1,114], p<0,0001), kwasu moczowego (HR 1,005 [1,003-1,006], p<0,0001), białka C-reaktywnego o wysokiej czułości (hs-CRP) (HR 1,208 [1,088-1,342], p<0,0001) oraz sodu (HR 1,111 [1,025-1,203], p=0,01), a także niedokrwienna etiologia niewydolności serca (HR 3,969 [2,396 – 6,575], p<0,0001) były niezależnie związane z gorszym rokowaniem.

Wnioski: Niniejsze badanie wykazało, że wyższe stężenia kopeptyny,, hs-CRP i kwasu moczowego oraz niższe stężenie sodu w surowicy krwi a także niedokrwienna etiologia niewydolności serca są związane ze śmiertelnością ze wszystkich przyczyn i hospitalizacją z powodu zaostrzenia niewydolności serca w okresie 6 miesięcy obserwacji w analizowanej grupie chorych w podeszłym wieku ze zdekompensowaną niewydolnością serca.

XI. **Abstrakt:**

Background: Diagnosing and predicting outcomes in elderly patients with heart failure (HF) is challenging due to atypical symptoms and limited value of natriuretic peptides, highlighting the need to search for new risk stratification biomarkers in this population.

Aim: We aimed to analyze factors associated with composite endpoint (all-cause mortality or decompensated HF related hospitalization) within six months of follow-up in elderly patients with left ventricular systolic dysfunction and decompensated HF, with particular emphasis on copeptin concentration.

Methods: This single-center study included 279 consecutive elderly patients hospitalized between 2018 and 2023 due to decompensated HF. Inclusion criteria were: age>65 years, history of HF diagnosed at least two years before the index hospitalization and left ventricular ejection fraction <40% on admission echocardiography. Serum copeptin levels were measured using an Enzyme-Linked Immunosorbent Assay (ELISA) (Human Copeptin ELISA kit, Sunred Biological Technology Co, Shanghai, China). The composite endpoint was all-cause mortality or decompensated HF-related hospitalization during the six-month follow-up.

Results: The median age of the study population was 77 years (IQR: 69-79) and 221 (79.2%) were male. The composite endpoint occurred in 110 patients (38.1%). Multivariable analysis showed that serum concentrations of copeptin [hazard ratio (HR) 1.053 (1.042-1.064), p<0.0001], bilirubin [HR 1.085 (1.057-1.114), p<0.0001], uric acid [HR 1.005 (1.003-1.006), p<0.0001], high-sensitivity C-reactive protein (hs-CRP) [HR 1.208 (1.088-1.342), p<0.0001], and sodium [HR 1.111 (1.025-1.203), p=0.01], as well as ischemic etiology of HF [HR 3.969 (2.396 – 6.575), p<0.0001] were independently associated with worse outcomes.

Conclusions: Our study demonstrated that higher concentrations of copeptin, bilirubin, hs-CRP, and uric acid, as well as lower sodium levels and ischemic etiology of HF, are independently associated with all-cause mortality or HF-related hospitalization during a six-month follow-up in elderly patients with decompensated HF.

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Review

Heart Failure in Elderly Patients: Medical Management, Therapies and Biomarkers

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Abstract: Heart failure (HF) is a common condition and one of the main morbidity and mortality factors in elderly patients. The incidence of HF progressively increases with age, reaching >10% in those aged 70 years or over. In the elderly population, both the diagnosis and the management of HF prove challenging, often requiring specialized care and a multidisciplinary approach. In seniors, atypical presentation of HF is much more common than in younger patients; thus, a holistic assessment with biomarkers related to HF allows for early diagnosis and accurate risk stratification in this group of patients. This article reviews the clinical and diagnostic differences in elderly patients with HF, highlighting the presence of comorbidities, frailty, cognitive impairment, and polypharmacy, as well as discussing potential biomarkers that may have clinical application in this population.

Keywords: heart failure; biomarkers; elderly patients; pharmacological treatment; comorbidities

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1. Introduction

Heart failure (HF) is a major public health problem, generating high healthcare-related costs. It can be defined as a clinical syndrome associated with cardiac abnormalities affecting structure and/or function. In the natural course of the condition, reduced cardiac output can be observed with elevated intracardiac filling pressures [1]. The prevalence of HF is strongly associated with age, increasing from around 1% in patients aged <55 years up to >10% in elderly aged over 70 years [2]. The number of elderly patients with HF is steadily growing due to better medical care and increasing life expectancy.

Elderly patients with HF are a varied group, including both patients with reduced, mildly reduced, and preserved ejection fractions (HFrEF: HF with reduced ejection fraction, HFpEF: HF with preserved ejection fraction, HFmrEF: HF with mildly reduced ejection fraction). Study shows that in patients over 60 years old, diastolic left ventricular dysfunction is more common, with a median prevalence of 36.0% (range 15.8–52.8%), while systolic dysfunction has a median of 5.5% (range 3.3–9.2%) in this group [2]. Thus, elderly patients with HF constitute an etiologically and functionally heterogeneous group of patients that requires an interdisciplinary approach due to comorbidities, which may additionally complicate the course of the HF. Furthermore, the clinical course of this condition may often be difficult to predict in the elderly population. This article reviews the clinical and diagnostic differences in elderly patients with chronic HF (CHF), highlighting the presence

of comorbidities, frailty, cognitive impairment, and polypharmacy, as well as discussing potential biomarkers that may have clinical applications in this population.

2. Heart Failure in Elderly

In the group of patients with CHF aged over 65 years old, the overall course of the condition varies from other age groups. In older patients, the percentage of women affected is higher and the ratio of genders is more balanced [3]. Moreover, they usually suffer from diastolic HF. In the younger age group, however, most patients suffer from systolic HF [1], and men are affected more frequently. The most common causes of HF overall are coronary artery disease and hypertension. Opposed to the general population, HF etiology in the elderly is more likely to be related to valvular heart disease (VHD), with the most common VHD affecting the elderly being aortic stenosis. Other factors that contribute to the development of HF can also be observed in the elderly, like left ventricular hypertrophy and diastolic dysfunction [4]. HF characteristics vary across the elderly population. Patients aged 65 to 74 years more frequently had lower left ventricular ejection fraction (LVEF), with an ischemic etiology of HF. Before and during index hospitalization, they oftentimes required percutaneous coronary intervention or coronary artery bypass grafting. In turn, patients aged over 75 years old had a lower percentage of ischemic etiology and a higher average LVEF when compared to the other group [5]. Those patients may also vary regarding the prevalence of HFrEF and HFpEF. HFrEF was more common in men, while HFpEF occurred more frequently in women. Research also showed a declining trend of HFrEF incidence in the elderly [4]. When it comes to prognosis, among elderly patients hospitalized with HF, median survival is approximately 2.5 years, with 25% of patients dying within 1 year. While for all types of HF patients indiscriminately, 1-year and 5-year mortality rates after diagnosis were 20% and 53%, respectively [1]. The mortality rate in patients aged over 65 was greater than in younger patients, and the prognosis was significantly worse for patients over 75 [5].

Diagnosis of HF in the elderly is challenging, as the condition may have an unusual presentation in this group. Patients instead of typical symptoms that include dyspnea, fatigue, ankle swelling, and edema present with atypical, nonspecific symptoms distorting the clinical manifestation of the disease. These symptoms include tiredness, altered mental status, depression, and loss of appetite [6]. In the study conducted in a geriatric outpatient clinic in the Netherlands on 206 patients, the diagnosis could be confirmed in only 46% of geriatric patients with suspected HF. Only one-third of the patients with HF presented with typical symptoms [6].

Elderly patients are more likely to have multiple comorbidities, which play an important role in the treatment, prognosis, and diagnosis of HF. In the Interdisziplinäres Netzwerk Herzinsuffizienz registry, seven or more comorbidities were present in approximately 50% of the patients [3]. Another study investigating patients aged over 65 years old found that around 90% of participants had at least 3 comorbidities, and over 60% had at least 5 [7]. Furthermore, patients with a higher number of comorbidities were at a higher risk for all-cause mortality in patients with HF [8]. The Charlson Comorbidity Index (CCI) is the most extensively studied comorbidity index validated to assess the presence and degree of comorbidity in the elderly, currently used in geriatric practice [9]. It has been reported to be reliable and to provide a good correlation with mortality and survival outcomes, and it accounts for the effect of age [10]. However, studies provide conflicting evidence for CCI index in elderly patients with CHF. The 'Osservatorio Geriatrico Regione Campania' study finds that CCI does not predict long-term mortality in elderly subjects with CHF [11]. Another study states that high CCI, along with reduced EF and poor physical functionality, was associated with high mortality [12].

Atrial fibrillation (AF) is one of the most common comorbidities coexisting with HF. The proportion of patients with HF who develop AF increases with age and HF severity, making it especially prevalent in the elderly. Studies conducted on the Polish population show that nearly 40% of patients with HF also have AF [13,14]. Patients with AF have higher short- and long-term mortality after hospital discharge and a higher risk of readmission. The mean age of studied patients with both AF and HF was 72 (62–79) [5]. In a group of patients aged over 75 years old, AF often leads to stroke, which has a higher incidence in this group. Moreover, those patients are frequently undertreated with anticoagulants because of a higher risk of bleeding [13].

Another important comorbidity in elderly patients with HF is diabetes mellitus type 2 (DM-2). DM-2 and HF, due to their pathophysiology, are inclined to coexist, with each disease independently increasing the risk for the other. In HF cohorts, including patients with HFrEF and HFpEF, the co-occurrence of DM-2 ranges from 10% to 47% in different studies. The pathophysiological mechanism of this incidence is based on the acceleration of atherosclerosis via vascular smooth muscle cell proliferation and inflammation that is directly connected with hyperglycemia and hyperinsulinemia [15]. DM-2 can also cause cardiovascular autonomic neuropathy, which has potentially life-threatening complications including arrhythmias and silent myocardial ischemia [16].

Chronic kidney disease (CKD) is highly prevalent in the elderly, with renal dysfunction affecting as many as 60% of HF patients $\geq$ 75 years [17]. CKD and HF have a bidirectional interaction; CKD may worsen cardiovascular function, causing hypertension and vascular calcification, while HF may worsen renal function through the effects of neurohormonal and inflammatory activation, increased venous pressure, and hypoperfusion. Furthermore, CKD has been consistently associated with worse HF prognosis and is commonly recognized as a major independent determinant of increased mortality and morbidity in HF [1]. When it comes to the elderly with chronic HF and CKD, the one-year prognosis is different depending on the presence of frailty. Patients with CKD present a worse clinical profile, with more advanced HF, comorbidities, and frailty. However, CKD was found to be associated with a worse prognosis only in non-frail patients [17].

3. Frailty Syndrome in Elderly Patients

Frailty is a clinical syndrome associated with age and characterized by a decrease in physiological reserve under stressful conditions, leading to a state of vulnerability that entails an increased likelihood of adverse events [18]. Frailty has over 70% prevalence in patients aged over 70 years old hospitalized for HF [19]. Furthermore, frail patients affected with CHF have an overall increased risk of hospitalization and mortality. Studies also suggest that stratifying patients with HF based on frailty status offers valuable prognostic insights and can help guide priorities for HF interventions and management [20]. Thus, identifying and accurately characterizing frailty status in patients with HF is crucial in order to minimize the significant negative impact of frailty on CHF. Geriatric assessment can be useful to identify the main factors of frailty from the outset. There are multiple scales for frailty assessment, and the major ones [frailty index by Rockwood and Mitnitski, Fried phenotype from the Cardiovascular Health Study, FRAIL (Fatigue, Resistance, Ambulation, Illnesses, & Loss of Weight) scale, and the Hubbard modified frailty score] have comparable accuracy in predicting death and physical limitation in geriatric patients [21]. Cardiovascular rehabilitation plays an important role in evaluating and treating frailty. Its proven beneficial effects on muscle mass and strength, as well as mobility, habitual physical activity, social interaction, cognitive performance, mood, and vitality, were significant enough to be regarded as one of the best comprehensive therapies available in clinical practice with the potential to mitigate frailty and its downstream effects [22].

4. Pharmacotherapy in Elderly

Elderly patients are underrepresented in most trials investigating drug treatment for HF. Therefore, the recommendations for treatment in this group are more or less based on subgroup analysis and expert opinions. However, the majority of trials have not demonstrated age-dependent heterogeneity in the efficacy or safety of medical treatment for HF [23]. The pre-specified subgroup analyses in the major clinical trials investigating angiotensin-converting enzyme inhibitors (ACEI) [24], beta-blockers (BB) [25], mineralocorticoid receptor antagonists (MRA) [26], and sodium-glucose cotrasporter2 inhibitors (SGLT2i) [27,28] show that in patients with HFrEF, both in elderly and other age groups, the therapy yields similar results. Thus, pharmacotherapy in the elderly is recommended to follow the guidelines established for other age groups.

The current treatment regimen assumes the fastest possible initiation and rapid escalation of ACEI, BB, and MRA dosages simultaneously with the initial optimal dose of SGLT2i [1,29]. Simultaneous initiation takes place at the initial (low) doses recommended for HFrEF (except for SGLT2i, which are dosed from the beginning at the optimal dose) [1,29]. Especially in older patients, monitoring of potency and side effects (including kidney function) is of great importance in establishing the optimal regimen for each individual.

Out of the four main groups of drugs used in HF treatment, ACEIs were the first class of drugs shown to reduce mortality and morbidity in patients with HFrEF. They are recommended in all patients unless contraindicated or not tolerated. However, the 2021 guidelines strengthen the indication for angiotensin receptor-nephrilysin inhibitor (ARNI) as a replacement in ambulatory patients with HFrEF who remain symptomatic despite optimal treatment with ACEI/angiotensin receptor blockers (ARB) [1]. It is important to note that no randomized controlled studies that focused on elderly patients with ACEI or ARB were conducted. A meta-analysis of five randomized controlled trials with ACEI in patients with ischemic etiology of HF or left ventricular systolic dysfunction reported that there was a nonsignificant age-by-treatment interaction for mortality, reinfraction, and rehospitalization [30]. Few observational studies were conducted on this topic. An older review of multiple observational studies concurs with the results from the sub-analysis, validating the effectiveness of ACEI in the elderly [31]. Another observational study on elderly people with HFrEF and CKD concluded that treatment with ACEI/ARB was associated with a lower rate of cardiovascular events [32]. When it comes to angiotensin receptor-neprilysin inhibitors (ARNI), a subgroup analysis of the PARADIGM—HF (Prospective Comparison of ARNI With ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure) trial demonstrated consistent risk reduction in the primary endpoint of cardiovascular mortality or hospitalization for HF regardless of age. The trial enrolled almost 20% of patients aged $\geq$75 years, including 7.0% aged $\geq$80 years and 1.4% aged $\geq$85 years. It found that even in very elderly patients, the effect of ARNI on heart failure hospitalization seemed qualitatively and quantitatively similar to its effect in younger patients [33].

BBs play a major role in HF treatment. Controlled prospective clinical studies documented the efficacy of bisoprolol, carvedilol (and prolonged-release metoprolol succinate, as included in both the European and American guidelines [1,29]. Another beta-blockerused in HF is nebivolol; similarly to carvedilol, it has a vasodilatory effect. Interestingly, nebivolol is included as an evidence-based beta-blocker in the ESC guidelines but not the CCS or AHA/ACC/HFSA guidelines [1,29]. All of those drugs are eligible for treatment in elderly patients, as stated in the following trials. In the SENIORS (Study of Effects of Nebivolol Intervention on Outcomes and Rehospitalization in Seniors with Heart Failure) trial, therapy with nebivolol was compared with placebo in patients aged $\geq$70 years. Therapy with nebivolol led to a significant reduction of the primary endpoint all-cause mortality and

cardiovascular hospitalizations regardless of the ejection fraction value [34]. A similar trial, including a considerable percentage of elderly patients, was conducted with metoprolol succinate, comparing its effect with placebo. A retrospective subgroup analysis found a comparable reduction regarding mortality and morbidity in patients aged over 69 and younger participants [35]. The CIBIS-ELD (Cardiac Insufficiency Bisoprolol Study in Elderly) trial was a superiority trial comparing therapy with the beta-blockers bisoprolol and carvedilol in older patients. It found no difference regarding tolerance or achieved target dose between the two [36]. However, patients with bisoprolol more often suffered from bradycardia, whereas carvedilol led to a reduction in the forced expiratory volume [36]. It shows the importance of individual approach to pharmacotherapy, as the choice of suitable BB should be tailored to patients' needs and comorbidities.

Since the release of 2021 ESC guidelines, MRA (eplerenone and spironolactone) are recommended in all patients with HFrEF. Their use is associated with a reduction in HF symptoms, the risk of hospitalization for HF, and mortality. MRAs block receptors that bind aldosterone and other steroid hormones (e.g., corticosteroid and androgen) receptors, with different degrees of affinity. Eplerenone is more selective to the aldosterone receptor, thus causing less gynecomastia than spironolacton [1]. Similarly to ACEI, their impact on the elderly is based on prespecified subgroup analyses. Both in the RALES (The Randomized Aldactone Evaluation Study) and in the EMPHASIS-HF (Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure), the analyses concluded that older HF patients benefit from treatment with an MRA to a similar extent as younger patients [37,38]. In a meta-analysis including 1756 patients $\geq$ 75 years old (352 from the RALES trial, 657 from the EMPHASIS trial, and 747 from the TOPCAT (Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist trial), MRAs were associated with lower cardiovascular mortality, morbidity, and hospitalization. The beneficial effect observed was higher in elderly patients with reduced LVEF [39]. The most important adverse effect of MRAs treatment is hyperkaliemia, which is more common in the elderly, especially with concomitant medication with an ACEIs or an ARBs; thus, in this group, renal function and electrolytes should be controlled regularly.

SGLT2i were introduced to the pharmacotherapy of HF fairly recently. They were initially observed to reduce the HF hospitalization rate in diabetic patients and, after multiple trials, became an important pharmacological group in HF treatment even in patients without DM-2 [1]. The current guidelines [1,29] strongly recommend (class I) dapagliflozin or empagliflozin in patients with HF (New York Heart Association class II–IV) with reduced left ventricular ejection fraction (LVEF $\leq$ 40%) to reduce the risk of hospitalization for HF and death. Elderly patients were widely represented in SGLT2i clinical trials, and sub-analysis has confirmed the benefit of these drugs in this specific population [27,28].

Diuretics are considered the basis of symptomatic HF treatment. In everyday clinical practice, they are used in acute HF treatment for patients with volume overload and in patients with compensated HF to maintain a stable state [1]. Especially loop diuretics frequently are the only drugs that can adequately control fluid retention in HF. Whereas thiazide diuretics may be considered in patients with hypertension, HF, and mild fluid retention, loop diuretics are the preferred diuretic agents [29]. However, the quality of the evidence regarding diuretics is lacking, and their effects on morbidity and mortality have not been extensively studied in randomized controlled trials [1]. Loop diuretics have been studied among older patients hospitalized for decompensated HF who were not taking diuretics before hospitalization. It concluded that loop diuretic prescription at discharge is associated with a significantly lower risk of 30-day all-cause mortality and HF readmission [40]. Loop diuretics were not extensively studied in CHF in elderly patients.

Despite the proven benefits of guidelines-based pharmacotherapy and the reassuring safety profile of most drugs, the issue of undertreatment in the elderly population still prevails. In the Euro Heart Failure Survey II, underuse and underdosage of medications recommended for HF were common in patients over 80 years old with HFrEF [41]. Other studies report similar results showing that drugs such as BBs and ACEIs are less prescribed in eligible patients over 75 years of age [42,43]. Therapy management may prove difficult in this group, as elderly individuals have lower tolerance and a greater propensity for developing adverse drug reactions. The homoeostatic systems of elderly subjects are very fragile, and the management of HF accompanied by numerous comorbidities requires a holistic approach toward the patient. It is prudent to start HF pharmacotherapy in older patients at lower doses, then slowly and carefully up-titrate to target doses to prevent intolerance and adverse drug reactions while providing adequate treatment [44].

Due to the complexity of pharmacotherapy, patients with HF are at higher risk of adverse reactions. Furthermore, there are a number of commonly used medications that are relatively or absolutely contraindicated in patients with HF because they can cause exacerbations of HF or harmful interactions with the administered drugs [45]. That makes drug-induced exacerbation or decompensation of established HF a relatively common occurrence. It is important to acknowledge the usual mechanisms by which drugs can exacerbate HF, which are sodium retention, negative inotropic effect, and direct cardiotoxicity. Nonsteroidal anti-inflammatory drugs deserve special attention, as they are one of the most common groups taken by patients worldwide. They are relatively contraindicated as they may precipitate acute decompensation in patients with HF [46]. As some patients with HF may also suffer from angina, it is important to note that verapamil and diltiazem increase HF-related events in patients with HFrEF and therefore should be substituted by other safer alternatives such as ivabradine and trimetazidine [1,47]. In the treatment of hypertension, aside from non-dihydropyridine calcium channel blockers (diltiazem and verapamil), centrally acting agents, such as moxonidine, are contraindicated as they are associated with worse outcomes [48]. On the other hand, alpha-blockers according to ESC guidelines have no effects on survival and are therefore not indicated, while 2022 AHA guidelines indicate that they may cause or exacerbate HF and should be avoided [1,29]. In cases of diabetes and HF coincidence, treatment should avoid thiazolidinediones (glitazones), as they cause sodium and water retention and an increased risk of worsening HF and hospitalization [49]. Also, sulfonylureas were associated with a higher risk of HF events in some analyses [1].

5. Polypharmacy and Its Impact on Elderly

In HF, the gradual incorporation of multiple medications and a complex treatment regimen is common and recommended by ESC guidelines for the treatment of acute and chronic HF [50]. Adequate pharmacotherapy is also crucial to controlling comorbidities, lowering mortality, and potentially improving the quality of life. In the elderly, where the number of comorbidities is usually greater, each could require additional specific treatment, thus further increasing the number of drugs prescribed. Study shows that the vast majority (84% at admission and 95% at discharge) of older patients take at least 5 different medications, and nearly half of the investigated population (42% at admission and 55%) at discharge took over 10 different ones [51]. Elderly patients are highly susceptible to the adverse effects of polypharmacy due to age-related transformation in pharmacokinetics and pharmacodynamics [52] and coexisting conditions like frailty and mental impairment.

Among the drugs used in elderly patients with HF, warfarin could be especially harmful in polypharmacy due to its multiple potential interactions [53]. The last guidelines for atrial fibrillation [54] recommend direct oral anticoagulants as a first-line drugs, but many elderly patients are still taking warfarin due to its high price point [55]. Furthermore,

there are also some conditions that still require vitamin K antagonists usage. Patients with mechanical valves or left ventricular assist devices are treated with vitamin K antagonists in long-term oral anticoagulation therapy. Both patients with those conditions or atrial fibrillation make up for a significant number of elderly patients still taking warfarin, therefore at higher risk of adverse drug reactions [56]. Unfortunately, in Poland, almost 50% of optimally treated elderly HF patients were taking additional medications and supplements for self-treatment, such as analgetics, herbal products, and mineral products, further increasing the probability of interactions [57]. A similar situation was observed in the USA, where more than half of the HF patients used at least one dietary supplement [58].

Another important issue is adherence to therapy. A study by Giardini et al. shows that adherence is usually low in the elderly (below 45%) and further decreases with an increasing number of medications administered [59]. This problem is exacerbated in patients with dementia. According to a study conducted in the Polish population, nearly 60% of patients forget to take their medications. Among them, 70% of patients omitted the medication dose that had been forgotten, and 29% declared that they took such a dose as soon as they remembered. It may potentially lead to reduced levels of the active substance, which in turn reduces treatment efficiency or leads to adverse reactions when the level of the active substance increases beyond the safety threshold [57]. The complexity of the treatment regimen and introduction of non-pharmacological guidelines may also pose a problem. Geriatric patients often do not abide by physicians' guidelines due to an overly complex treatment regimen, prolonged treatment duration, or the introduction of constant changes that are difficult to memorize for the elderly. Furthermore, patients are required to change their previous lifestyles and to introduce recommended modifications such as a limited intake of salt and fluids, tobacco smoking cessation, reduced alcohol consumption, performing physical exercises of moderate activity, and daily body weight monitoring [60]. Those non-pharmacological recommendations are usually negatively received by patients as difficult to introduce or hardly significant, which is a challenge, especially in elderly patients who have been accustomed to their own lifestyle for many years. However, it should be underlined that social support and loneliness are often negative predictors of compliance, especially among older patients. Studies report that living alone was an independent determinant of follow-up appointment-keeping, medication-taking, lifestyle changes, and overall compliance scores. Cognate social support provided by family members and other informal caregivers in the care of HF patients have a positive effect on adherence [61].

6. Neurohormones in HF

6.1. Natriuretic Peptides

Neurohormones play a major role in cardiology, primarily due to their role in diagnosis and prognosis of various cardiovascular conditions, including acute coronary syndromes and CHF. Among neurohormones, both natriuretic peptides, including N-terminal pro-brain natriuretic peptide (NT-proBNP) and brain natriuretic peptide (BNP), have become established diagnostic and prognostic markers [62]. Measurement of plasma concentrations of natriuretic peptides is recommended as a diagnostic test in patients with symptoms indicative of HF to rule out the diagnosis [1]. However, levels of natriuretic peptides tend to increase with age and may be labile in the presence of comorbidities such as obesity, kidney disease, thyroid disease, or atrial fibrillation [3]. Therefore, the usefulness of natriuretic peptides in elderly patients may be limited. The BED (BNP Usefulness in Elderly Dyspnoeic Patients) study reported that brain natriuretic peptide did not discriminate adequately between cardiac and respiratory origin of acute dyspnea in patients $\geq$ 60 years [63]. In a meta-analysis of brain natriuretic peptide -guided therapy in patients with HF, where two cohorts divided by age were investigated and compared, similar correlation was observed.

A study reported that in patients under 75 years old, therapy guided by NT-proBNP decreased mortality and hospitalization rates; there was no improvement in patients over 75 years of age [64]. While data from the TIME-CHF (Trial of Intensified versus Standard Medical Therapy in Elderly Patients with Congestive Heart Failure) study showed that NT-proBNP-guided therapy is safe in elderly and highly co-morbid HF patients [65].

6.2. Copeptine in Elderly Patients

Neurohormones of the arginine vasopressin (AVP) system, including AVP and its surrogate marker copeptin, have also been investigated in elderly patients with HF as potentially useful in clinical practice. AVP is a conventional neurohormone released from the hypothalamus in response to hypovolemia and increased plasma osmolarity. High osmolarity is partially responsible for the increase in AVP concentration in patients with CHF. AVP release in HF is primarily triggered by reduced cardiac output, which leads to insufficient filling of arteries that activates carotid sinus and aortic baroreceptors. Hyponatremia, which is a common occurrence in patients with HF, might further stimulate the release of AVP. Concentration of AVP can also be increased due to other factors, such as angiotensin II [66].

Copeptin, the C-terminal portion of provasopressin, is a novel neurohormone of the AVP system co-secreted with AVP from the hypothalamus; it reflects vasopressin concentration in human plasma and serum. Because of its equimolar secretion with AVP and greater stability, it has been consistently replacing AVP in the clinical setting [47], and accordingly, copeptin has been focused on in studies investigating the co-relation between the AVP system and various clinical conditions [67]. A previous study showed that copeptin was an independent predictor of mortality and rehospitalization in patients with advanced HF [68]. Similar findings were reported in a study on elderly patients, showing an association between copeptin levels and mortality [69].

Combining copeptin with other biomarkers may enhance prognostic capabilities in older patients. A study on 470 elderly patients exhibiting symptoms of HF examined the association between plasma concentrations of copeptin, in combination with concentrations of the NT-proBNP, and mortality. The study found that in this age group elevated copeptin levels, as well as the combination of increased copeptin and NT-proBNP levels, were correlated with the increase in all-cause mortality risk during a median period of 13 years [69]. Similarly, among 172 patients suffering from chronic HF, copeptin and high-sensitivity cardiac troponin T were highly effective in predicting outcomes during long-term follow-up [70].

6.3. Other Biomarkers

New biomarkers are under evaluation for their potential to advance the management of patients with HF, but only a few have shown their usefulness for elderly patients.

Suppression of tumorigenicity 2 (ST2) is a member of the interleukin 1 receptor family found in 2 main isoforms: transmembrane or cellular (ST2L) and soluble or circulating (sST2) forms. ST2 is a marker associated with inflammatory disease and fibrosis, and its concentration was found to not be affected by age, renal function, or body mass index [71]. ST2L is a membrane-bound receptor with IL-33 as its functional ligand. IL-33/ST2L signaling triggers the transcription of inflammatory genes, leading to the production of inflammatory cytokines and chemokines and the activation of the immune response. Depending on the circumstances, IL-33 can exhibit a pro- or anti-inflammatory cytokine effect. IL-33 has also been demonstrated to have cardioprotective effects. sST2 is released into the circulation, where it acts as a decoy receptor for IL-33, suppressing the effects of IL-33/ST2L signaling. Thus, elevated circulating sST2 levels diminish the systemic biological effects of

IL-33 [72]. ST2 demonstrates predictive value for 30-day and 1-year outcomes in comorbid frail elderly patients with HFpEF in a study comparing four different markers. This study evaluated the prognostic significance of early post-discharge circulating levels of ST2, NT-proBNP, cancer antigen 125 (CA125), and high-sensitivity cardiac troponin T (hs-cTnT). ST2 demonstrated superior predictive capability compared to NT-proBNP for risk prediction of the composite primary endpoint, comprising all-cause mortality and heart HF-related rehospitalization. Thus, establishing its role as a predictive marker in high-risk HFpEF [71].

Another marker that could be useful in the elderly is hs-cTnT; as mentioned earlier, its combined use with copeptin was an excellent prognostic marker for patients with stable HF. It is a marker reflecting myocardial injury, associated with various cardiovascular conditions, including heart failure and myocardial infarction. Plasma concentration of hs-cTnT is routinely checked in patients with HF, particularly in acute HF syndromes. Measurement of cardiac troponin I (cTnI) or cTnT is recommended to identify type 1 myocardial infarction (MI) or acute HF-related injury [72]. However, sensitive troponin levels have also been linked to prognosis in patients with CHF. Longitudinal changes in cTnT concentrations assessed using hs-cTnT have been shown to predict cardiovascular events in these patients. In elderly people, hs-cTn has also shown its usefulness. In the CORONA (Controlled Rosuvastatin Multinational Trial in Heart Failure) trial, elevated hs-cTnT levels in elderly patients with chronic HF of ischemic cause provided independent prognostic and discriminating information beyond that of established risk markers [73].

Although new biomarkers such as growth differentiation factor 15, soluble urokinase-type plasminogen activator receptor, and fibroblast growth factor-23 were observed to have clinical significance in patients with HF and their pathophysiology shows correlation with aging, their usefulness in the elderly population is disputable [74–76]. Currently, the data regarding patients over 65 years of age is scarce, and the results are nonconclusive. To properly establish their role in the elderly, further research is needed.

7. Conclusions

HF in the elderly is a nuanced and varied problem in clinical practice. The clinical profiles of elderly patients differ from those of younger ones, and non-specific symptoms of HF in this group of patients are associated with a later diagnosis and consequently significantly worse prognosis. To improve the prognosis, a holistic approach is recommended. Addressing the issue of polypharmacy, undertreatment, specific and frequent aging particularities such as frailty and other geriatric conditions, and proper management of comorbidities are vital steps in HF treatment in this group. Special care should be applied to pharmacotherapy to ensure effective and safe treatment for elderly patients. Natriuretic peptides commonly used in HF have limited clinical utility in elderly patients. Other biomarkers, including copeptin, ST2, and high-sensitive troponin, may be useful prognostic tools in this population.

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References

1. McDonagh, T.A.; Metra, M.; Adamo, M.; Gardner, R.S.; Baumbach, A.; Böhm, M.; Burri, H.; Butler, J.; Čelutkienė, J.; Chioncel, O.; et al. 2021 ESC Guidelines for the Diagnosis and Treatment of Acute and Chronic Heart Failure. *Eur. Heart J.* **2021**, *42*, 3599–3726. [CrossRef]
2. Van Riet, E.E.S.; Hoes, A.W.; Wagenaar, K.P.; Limburg, A.; Landman, M.A.J.; Rutten, F.H. Epidemiology of Heart Failure: The Prevalence of Heart Failure and Ventricular Dysfunction in Older Adults over Time. A Systematic Review. *Eur. J. Heart Fail.* **2016**, *18*, 242–252. [CrossRef]

3. Berliner, D.; Bauersachs, J. Drug Treatment of Heart Failure in the Elderly. *Herz* **2018**, *43*, 207–213. [CrossRef] [PubMed]
4. Heart Failure Society of America. HFSA 2010 Comprehensive Heart Failure Practice Guideline. *J. Card. Fail.* **2010**, *16*, e1–e2. [CrossRef]
5. Ozierański, K.; Balsam, P.; Tymińska, A.; Peller, M.; Kapłon-Cieślicka, A.; Marchel, M.; Drożdż, J.; Filipiak, K.J.; Opolski, G. Heart Failure in Elderly Patients: Differences in Clinical Characteristics and Predictors of 1-Year Outcome in the Polish ESC-HF Long-Term Registry. *Pol. Arch. Intern. Med.* **2016**, *126*, 502–513. [CrossRef] [PubMed]
6. Oudejans, I.; Mosterd, A.; Bloemen, J.A.; Valk, M.J.; Van Velzen, E.; Wielders, J.P.; Zuithoff, N.P.; Rutten, F.H.; Hoes, A.W. Clinical Evaluation of Geriatric Outpatients with Suspected Heart Failure: Value of Symptoms, Signs, and Additional Tests. *Eur. J. Heart Fail.* **2011**, *13*, 518–527. [CrossRef]
7. Lochner, K.A.; Shoff, C.M. County-Level Variation in Prevalence of Multiple Chronic Conditions Among Medicare Beneficiaries, 2012. *Prev. Chronic Dis.* **2015**, *12*, 140442. [CrossRef]
8. Angermann, C.E. Comorbidities in Heart Failure: A Key Issue. *Eur. J. Heart Fail. Suppl.* **2009**, *8*, i5–i10. [CrossRef]
9. Degroot, V.; Beckerman, H.; Lankhorst, G.; Bouter, L. How to Measure Comorbiditya Critical Review of Available Methods. *J. Clin. Epidemiol.* **2003**, *56*, 221–229. [CrossRef]
10. Charlson, M.; Szatrowski, T.P.; Peterson, J.; Gold, J. Validation of a Combined Comorbidity Index. *J. Clin. Epidemiol.* **1994**, *47*, 1245–1251. [CrossRef]
11. Testa, G.; Cacciatore, F.; Galizia, G.; Della-Morte, D.; Mazzella, F.; Russo, S.; Ferrara, N.; Rengo, F.; Abete, P. Charlson Comorbidity Index Does Not Predict Long-Term Mortality in Elderly Subjects with Chronic Heart Failure. *Age Ageing* **2009**, *38*, 734–740. [CrossRef] [PubMed]
12. Weng, S.-C.; Lin, C.-S.; Tarng, D.-C.; Lin, S.-Y. Physical Frailty and Long-Term Mortality in Older People with Chronic Heart Failure with Preserved and Reduced Ejection Fraction: A Retrospective Longitudinal Study. *BMC Geriatr.* **2021**, *21*, 92. [CrossRef]
13. Ozierański, K.; Kapłon-Cieślicka, A.; Peller, M.; Tymińska, A.; Balsam, P.; Galas, M.; Marchel, M.; Crespo-Leiro, M.; Maggioni, A.P.; Drożdż, J.; et al. Clinical Characteristics and Predictors of One-Year Outcome of Heart Failure Patients with Atrial Fibrillation Compared to Heart Failure Patients in Sinus Rhythm. *Kardiol. Pol.* **2016**, *74*, 251–261. [CrossRef] [PubMed]
14. Rewiuk, K.; Wizner, B.; Fedyk-Łukasik, M.; Zdrojewski, T.; Opolski, G.; Dubiel, J.; Gąsowski, J.; Grodzicki, T. Epidemiology and Management of Coexisting Heart Failure and Atrial Fibrillation in an Outpatient Setting. *Pol. Arch. Intern. Med.* **2013**, *121*, 392–399. [CrossRef]
15. Dunlay, S.M.; Givertz, M.M.; Aguilar, D.; Allen, L.A.; Chan, M.; Desai, A.S.; Deswal, A.; Dickson, V.V.; Kosiborod, M.N.; Lekavich, C.L.; et al. Type 2 Diabetes Mellitus and Heart Failure: A Scientific Statement From the American Heart Association and the Heart Failure Society of America: This Statement Does Not Represent an Update of the 2017 ACC/AHA/HFSA Heart Failure Guideline Update. *Circulation* **2019**, *140*, e294–e324. [CrossRef]
16. Verrotti, A.; Prezioso, G.; Scattoni, R.; Chiarelli, F. Autonomic Neuropathy in Diabetes Mellitus. *Front. Endocrinol.* **2014**, *5*, 205. [CrossRef]
17. Díez-Villanueva, P.; Jiménez-Méndez, C.; Pérez-Rivera, Á.; Barge Caballero, E.; López, J.; Ortiz, C.; Bonanad, C.; Goirigolzarri, J.; Esteban Fernández, A.; Cobo, M.; et al. Different Impact of Chronic Kidney Disease in Older Patients with Heart Failure According to Frailty. *Eur. J. Intern. Med.* **2024**, *in press*. [CrossRef]
18. Díez-Villanueva, P.; Arizá-Solé, A.; Vidán, M.T.; Bonanad, C.; Formiga, F.; Sanchis, J.; Martín-Sánchez, F.J.; Ruiz Ros, V.; Sanmartín Fernández, M.; Bueno, H.; et al. Recomendaciones de la Sección de Cardiología Geriátrica de la Sociedad Española de Cardiología para la valoración de la fragilidad en el anciano con cardiopatía. *Rev. Española Cardiol.* **2019**, *72*, 63–71. [CrossRef]
19. Vidán, M.T.; Sánchez, E.; Fernández-Avilés, F.; Serra-Rexach, J.A.; Ortiz, J.; Bueno, H. FRAIL-HF, a Study to Evaluate the Clinical Complexity of Heart Failure in Nondependent Older Patients: Rationale, Methods and Baseline Characteristics. *Clin. Cardiol.* **2014**, *37*, 725–732. [CrossRef]
20. Yang, X.; Lupón, J.; Vidán, M.T.; Ferguson, C.; Gastelurrutia, P.; Newton, P.J.; Macdonald, P.S.; Bueno, H.; Bayés-Genís, A.; Woo, J.; et al. Impact of Frailty on Mortality and Hospitalization in Chronic Heart Failure: A Systematic Review and Meta-Analysis. *J. Am. Heart Assoc.* **2018**, *7*, e008251. [CrossRef]
21. Woo, J.; Leung, J.; Morley, J.E. Comparison of Frailty Indicators Based on Clinical Phenotype and the Multiple Deficit Approach in Predicting Mortality and Physical Limitation. *J. Am. Geriatr. Soc.* **2012**, *60*, 1478–1486. [CrossRef] [PubMed]
22. Afilalo, J. Evaluating and Treating Frailty in Cardiac Rehabilitation. *Clin. Geriatr. Med.* **2019**, *35*, 445–457. [CrossRef]
23. Masoudi, F.A.; Havranek, E.P.; Wolfe, P.; Gross, C.P.; Rathore, S.S.; Steiner, J.F.; Ordin, D.L.; Krumholz, H.M. Most Hospitalized Older Persons Do Not Meet the Enrollment Criteria for Clinical Trials in Heart Failure. *Am. Heart J.* **2003**, *146*, 250–257. [CrossRef] [PubMed]
24. The Consensus Trial Study Group. Effects of Enalapril on Mortality in Severe Congestive Heart Failure. *N. Engl. J. Med.* **1987**, *316*, 1429–1435. [CrossRef]
25. Ibrahim, N.E.; Gaggin, H.K.; Turchin, A.; Patel, H.K.; Song, Y.; Trebnick, A.; Doros, G.; Maya, J.F.; Cannon, C.P.; Januzzi, J.L. Heart Rate, Beta-Blocker Use, and Outcomes of Heart Failure with Reduced Ejection Fraction. *Eur. Heart J.—Cardiovasc. Pharmacother.* **2019**, *5*, 3–11. [CrossRef]
26. Ferreira, J.P.; Mentz, R.J.; Pizard, A.; Pitt, B.; Zannad, F. Tailoring Mineralocorticoid Receptor Antagonist Therapy in Heart Failure Patients: Are We Moving Towards a Personalized Approach? *Eur. J. Heart Fail.* **2017**, *19*, 974–986. [CrossRef]

27. McMurray, J.J.V.; Solomon, S.D.; Inzucchi, S.E.; Køber, L.; Kosiborod, M.N.; Martinez, F.A.; Ponikowski, P.; Sabatine, M.S.; Anand, I.S.; Bělohlávek, J.; et al. Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction. *N. Engl. J. Med.* **2019**, *381*, 1995–2008. [CrossRef] [PubMed]
28. Packer, M.; Anker, S.D.; Butler, J.; Filippatos, G.; Pocock, S.J.; Carson, P.; Januzzi, J.; Verma, S.; Tsutsui, H.; Brueckmann, M.; et al. Cardiovascular and Renal Outcomes with Empagliflozin in Heart Failure. *N. Engl. J. Med.* **2020**, *383*, 1413–1424. [CrossRef]
29. Heidenreich, P.A.; Bozkurt, B.; Aguilar, D.; Allen, L.A.; Byun, J.J.; Colvin, M.M.; Deswal, A.; Drazner, M.H.; Dunlay, S.M.; Evers, L.R.; et al. 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Circulation* **2022**, *145*, e263–e421. [CrossRef]
30. Flather, M.D.; Yusuf, S.; Køber, L.; Pfeffer, M.; Hall, A.; Murray, G.; Torp-Pedersen, C.; Ball, S.; Pogue, J.; Moyé, L.; et al. Long-Term ACE-Inhibitor Therapy in Patients with Heart Failure or Left-Ventricular Dysfunction: A Systematic Overview of Data from Individual Patients. *Lancet* **2000**, *355*, 1575–1581. [CrossRef]
31. Dobre, D.; Van Veldhuisen, D.J.; DeJongste, M.J.L.; Van Sonderen, E.; Klungel, O.H.; Sanderman, R.; Ranchor, A.V.; Haaijer-Ruskamp, F.M. The Contribution of Observational Studies to the Knowledge of Drug Effectiveness in Heart Failure. *Brit. J. Clin. Pharmacol.* **2007**, *64*, 406–414. [CrossRef]
32. Martínez-Milla, J.; García, M.C.; Urquía, M.T.; Castillo, M.L.; Arbiol, A.D.; Monteagudo, A.L.R.; Mariscal, M.L.M.; Figuero, S.B.; Franco-Pelaéz, J.A.; Tuñón, J. Blockade of Renin–Angiotensin–Aldosterone System in Elderly Patients with Heart Failure and Chronic Kidney Disease: Results of a Single-Center, Observational Cohort Study. *Drugs Aging* **2019**, *36*, 1123–1131. [CrossRef]
33. Jhund, P.S.; Fu, M.; Bayram, E.; Chen, C.-H.; Negrusz-Kawecka, M.; Rosenthal, A.; Desai, A.S.; Lefkowitz, M.P.; Rizkala, A.R.; Rouleau, J.L.; et al. Efficacy and Safety of LCZ696 (Sacubitril-Valsartan) According to Age: Insights from PARADIGM-HF. *Eur. Heart J.* **2015**, *36*, 2576–2584. [CrossRef] [PubMed]
34. Flather, M.D.; Shibata, M.C.; Coats, A.J.S.; Van Veldhuisen, D.J.; Parkhomenko, A.; Borbola, J.; Cohen-Solal, A.; Dumitrascu, D.; Ferrari, R.; Lechat, P.; et al. Randomized Trial to Determine the Effect of Nebivolol on Mortality and Cardiovascular Hospital Admission in Elderly Patients with Heart Failure (SENIORS). *Eur. Heart J.* **2005**, *26*, 215–225. [CrossRef] [PubMed]
35. Hjalmarson, Å.; Goldstein, S.; Fagerberg, B.; Wedel, H.; Waagstein, F.; Kjekshus, J.; Wikstrand, J.; El Allaf, D.; Vítovec, J.; Aldershvile, J.; et al. Effects of Controlled-Release Metoprolol on Total Mortality, Hospitalizations, and Well-Being in Patients with Heart Failure: The Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure (MERIT-HF). *JAMA* **2000**, *283*, 1295. [CrossRef] [PubMed]
36. Düngen, H.-D.; Apostolović, S.; Inkrot, S.; Tahirović, E.; Töpper, A.; Mehrhof, F.; Prettin, C.; Putniković, B.; Nešković, A.N.; Krotin, M.; et al. Titration to Target Dose of Bisoprolol vs. Carvedilol in Elderly Patients with Heart Failure: The CIBIS-ELD Trial. *Eur. J. Heart Fail.* **2011**, *13*, 670–680. [CrossRef]
37. Eschalier, R.; McMurray, J.J.V.; Swedberg, K.; Van Veldhuisen, D.J.; Krum, H.; Pocock, S.J.; Shi, H.; Vincent, J.; Rossignol, P.; Zannad, F.; et al. Safety and Efficacy of Eplerenone in Patients at High Risk for Hyperkalemia and/or Worsening Renal Function. *J. Am. Coll. Cardiol.* **2013**, *62*, 1585–1593. [CrossRef] [PubMed]
38. Pitt, B.; Zannad, F.; Remme, W.J.; Cody, R.; Castaigne, A.; Perez, A.; Palensky, J.; Wittes, J. The Effect of Spironolactone on Morbidity and Mortality in Patients with Severe Heart Failure. *N. Engl. J. Med.* **1999**, *341*, 709–717. [CrossRef] [PubMed]
39. Ferreira, J.P.; Rossello, X.; Eschalier, R.; McMurray, J.J.V.; Pocock, S.; Girerd, N.; Rossignol, P.; Pitt, B.; Zannad, F. MRAs in Elderly HF Patients. *JACC Heart Fail.* **2019**, *7*, 1012–1021. [CrossRef] [PubMed]
40. Faselis, C.; Arundel, C.; Patel, S.; Lam, P.H.; Gottlieb, S.S.; Zile, M.R.; Deedwania, P.; Filippatos, G.; Sheriff, H.M.; Zeng, Q.; et al. Loop Diuretic Prescription and 30-Day Outcomes in Older Patients with Heart Failure. *J. Am. Coll. Cardiol.* **2020**, *76*, 669–679. [CrossRef]
41. Komajda, M.; Hanon, O.; Hochadel, M.; Lopez-Sendon, J.L.; Follath, F.; Ponikowski, P.; Harjola, V.-P.; Drexler, H.; Dickstein, K.; Tavazzi, L.; et al. Contemporary Management of Octogenarians Hospitalized for Heart Failure in Europe: Euro Heart Failure Survey II. *Eur. Heart J.* **2008**, *30*, 478–486. [CrossRef] [PubMed]
42. Maison, P.; Cunin, P.; Hemery, F.; Fric, F.; Elie, N.; Del'Volgo, A.; Dubois-Randé, J.L.; Hittinger, L.; Macquin-Mavier, I. Utilisation of Medications Recommended for Chronic Heart Failure and the Relationship with Annual Hospitalisation Duration in Patients over 75 Years of Age. A Pharmacoepidemiological Study. *Eur. J. Clin. Pharmacol.* **2005**, *61*, 445–451. [CrossRef] [PubMed]
43. Muntwyler, J.; Cohen-Solal, A.; Freemantle, N.; Eastaugh, J.; Cleland, J.G.; Follath, F. Relation of Sex, Age and Concomitant Diseases to Drug Prescription for Heart Failure in Primary Care in Europe. *Eur. J. Heart Fail.* **2004**, *6*, 663–668. [CrossRef] [PubMed]
44. Komajda, M.; Cowie, M.R.; Tavazzi, L.; Ponikowski, P.; Anker, S.D.; Filippatos, G.S.; on behalf of the QUALIFY Investigators. Physicians' Guideline Adherence Is Associated with Better Prognosis in Outpatients with Heart Failure with Reduced Ejection Fraction: The QUALIFY International Registry. *Eur. J. Heart Fail.* **2017**, *19*, 1414–1423. [CrossRef] [PubMed]
45. Amabile, C.M.; Spencer, A.P. Keeping Your Patient with Heart Failure Safe: A Review of Potentially Dangerous Medications. *Arch. Intern. Med.* **2004**, *164*, 709–720. [CrossRef]
46. Arfè, A.; Scotti, L.; Varas-Lorenzo, C.; Nicotra, F.; Zambon, A.; Kollhorst, B.; Schink, T.; Garbe, E.; Herings, R.; Straatman, H.; et al. Non-Steroidal Anti-Inflammatory Drugs and Risk of Heart Failure in Four European Countries: Nested Case-Control Study. *BMJ* **2016**, *354*, i4857. [CrossRef]

47. Goldstein, R.E.; Boccuzzi, S.J.; Cruess, D.; Nattel, S. Diltiazem Increases Late-Onset Congestive Heart Failure in Postinfarction Patients with Early Reduction in Ejection Fraction. The Adverse Experience Committee; and the Multicenter Diltiazem Postinfarction Research Group. *Circulation* **1991**, *83*, 52–60. [CrossRef] [PubMed]
48. Cohn, J.N.; Pfeffer, M.A.; Rouleau, J.; Sharpe, N.; Swedberg, K.; Straub, M.; Wiltse, C.; Wright, T.J.; for the MOXCON Investigators. Adverse Mortality Effect of Central Sympathetic Inhibition with Sustained-release Moxonidine in Patients with Heart Failure (MOXCON). *Eur. J. Heart Fail.* **2003**, *5*, 659–667. [CrossRef] [PubMed]
49. Lago, R.M.; Singh, P.P.; Nesto, R.W. Congestive Heart Failure and Cardiovascular Death in Patients with Prediabetes and Type 2 Diabetes given Thiazolidinediones: A Meta-Analysis of Randomised Clinical Trials. *Lancet* **2007**, *370*, 1129–1136. [CrossRef] [PubMed]
50. McDonagh, T.A.; Metra, M.; Adamo, M.; Gardner, R.S.; Baumbach, A.; Böhm, M.; Burri, H.; Butler, J.; Čelutkienė, J.; Chioncel, O.; et al. 2023 Focused Update of the 2021 ESC Guidelines for the Diagnosis and Treatment of Acute and Chronic Heart Failure. *Eur. Heart J.* **2023**, *44*, 3627–3639. [CrossRef]
51. Unlu, O.; Levitan, E.B.; Reshetnyak, E.; Kneifati-Hayek, J.; Diaz, I.; Archambault, A.; Chen, L.; Hanlon, J.T.; Maurer, M.S.; Safford, M.M.; et al. Polypharmacy in Older Adults Hospitalized for Heart Failure. *Circ. Heart Fail.* **2020**, *13*, e006977. [CrossRef] [PubMed]
52. Mangoni, A.A.; Jackson, S.H.D. Age-related Changes in Pharmacokinetics and Pharmacodynamics: Basic Principles and Practical Applications. *Brit. J. Clin. Pharmacol.* **2004**, *57*, 6–14. [CrossRef]
53. Ageno, W.; Gallus, A.S.; Wittkowsky, A.; Crowther, M.; Hylek, E.M.; Palareti, G. Oral Anticoagulant Therapy. *Chest* **2012**, *141*, e44S–e88S. [CrossRef]
54. Van Gelder, I.C.; Rienstra, M.; Bunting, K.V.; Casado-Arroyo, R.; Caso, V.; Crijns, H.J.G.M.; De Potter, T.J.R.; Dwight, J.; Guasti, L.; Hanke, T.; et al. 2024 ESC Guidelines for the Management of Atrial Fibrillation Developed in Collaboration with the European Association for Cardio-Thoracic Surgery (EACTS). *Eur. Heart J.* **2024**, *45*, 3314–3414. [CrossRef] [PubMed]
55. Boursiquot, B.C.; Jackson, L.R.; Essien, U.R. Advancing Pharmacoequity in Atrial Fibrillation—The Case for Direct Oral Anticoagulants. *JAMA Netw. Open* **2024**, *7*, e249403. [CrossRef]
56. Lund, J.; Saunders, C.L.; Edwards, D.; Mant, J. Anticoagulation Trends in Adults Aged 65 Years and over with Atrial Fibrillation: A Cohort Study. *Open Heart* **2021**, *8*, e001737. [CrossRef]
57. Makarewicz-Wujec, M.; Janas, E.; Kozłowska-Wojciechowska, M. Health Behaviour of Elderly Patients with Heart Failure in Poland Associated with Pharmacotherapy and Non-Pharmacological Treatment. *Acta Pol. Pharm.—Drug Res.* **2019**, *76*, 367–374. [CrossRef]
58. Fan, X.; Lee, K.S.; Frazier, S.K.; Lennie, T.A.; Moser, D.K. The Use of, and Perceptions about, Dietary Supplements among Patients with Heart Failure. *Eur. J. Cardiovasc. Nurs.* **2014**, *13*, 311–319. [CrossRef] [PubMed]
59. Giardini, A.; Martin, M.T.; Cahir, C.; Lehane, E.; Menditto, E.; Strano, M.; Pecorelli, S.; Monaco, A.; Marengoni, A. Toward Appropriate Criteria in Medication Adherence Assessment in Older Persons: Position Paper. *Aging Clin. Exp. Res.* **2016**, *28*, 371–381. [CrossRef] [PubMed]
60. Van Der Wal, M.H.L.; Jaarsma, T. Adherence in Heart Failure in the Elderly: Problem and Possible Solutions. *Int. J. Cardiol.* **2008**, *125*, 203–208. [CrossRef] [PubMed]
61. Jankowska-Polańska, B.; Świątoniowska-Lonc, N.; Sławuta, A.; Krówczyńska, D.; Dudek, K.; Mazur, G. Patient-Reported Compliance in Older Age Patients with Chronic Heart Failure. *PLoS ONE* **2020**, *15*, e0231076. [CrossRef]
62. Yalta, K.; Sıvrı, N.; Yalta, T.; Geyik, B.; Aksoy, Y.; Yetkın, E. Copeptin (C-Terminal Provasopressin): A Promising Marker of Arrhythmogenesis in Arrhythmia Prone Subjects? *Int. J. Cardiol.* **2011**, *148*, 105. [CrossRef] [PubMed]
63. Plichart, M.; Orvoën, G.; Jourdain, P.; Quinquis, L.; Coste, J.; Escande, M.; Friocourt, P.; Paillaud, E.; Chedhomme, F.; Labourée, F.; et al. Brain Natriuretic Peptide Usefulness in Very Elderly Dyspnoeic Patients: The BED Study. *Eur. J. Heart Fail.* **2017**, *19*, 540–548. [CrossRef] [PubMed]
64. Troughton, R.W.; Frampton, C.M.; Brunner-La Rocca, H.-P.; Pfisterer, M.; Eurlings, L.W.M.; Erntell, H.; Persson, H.; O'Connor, C.M.; Moertl, D.; Karlstrom, P.; et al. Effect of B-Type Natriuretic Peptide-Guided Treatment of Chronic Heart Failure on Total Mortality and Hospitalization: An Individual Patient Meta-Analysis. *Eur. Heart J.* **2014**, *35*, 1559–1567. [CrossRef] [PubMed]
65. Łukaszyk, E.; Małyszko, J. Copeptin: Pathophysiology and Potential Clinical Impact. *Adv. Med. Sci.* **2015**, *60*, 335–341. [CrossRef] [PubMed]
66. Sanders-van Wijk, S.; Muzzarelli, S.; Neuhaus, M.; Kiencke, S.; Maeder, M.; Estlinbaum, W.; Tobler, D.; Mayer, K.; Erne, P.; Pfisterer, M.E.; et al. Safety and Tolerability of Intensified, N-terminal pro Brain Natriuretic Peptide-guided Compared with Standard Medical Therapy in Elderly Patients with Congestive Heart Failure: Results from TIME-CHF. *Eur. J. Heart Fail.* **2013**, *15*, 910–918. [CrossRef]
67. Yalta, K.; Yalta, T.; Sivri, N.; Yetkin, E. Copeptin and Cardiovascular Disease: A Review of a Novel Neurohormone. *Int. J. Cardiol.* **2013**, *167*, 1750–1759. [CrossRef] [PubMed]
68. Stoiser, B.; Mörtl, D.; Hülsmann, M.; Berger, R.; Struck, J.; Morgenthaler, N.G.; Bergmann, A.; Pacher, R. Copeptin, a Fragment of the Vasopressin Precursor, as a Novel Predictor of Outcome in Heart Failure. *Eur. J. Clin. Investig.* **2006**, *36*, 771–778. [CrossRef]
69. Alehagen, U. Association of Copeptin and N-Terminal proBNP Concentrations with Risk of Cardiovascular Death in Older Patients with Symptoms of Heart Failure. *JAMA* **2011**, *305*, 2088–2095. [CrossRef]

70. Tentzeris, I.; Jarai, R.; Farhan, S.; Perkmann, T.; Schwarz, M.A.; Jakl, G.; Wojta, J.; Huber, K. Complementary Role of Copeptin and High-sensitivity Troponin in Predicting Outcome in Patients with Stable Chronic Heart Failure. *Eur. J. Heart Fail.* **2011**, *13*, 726–733. [CrossRef]
71. Pacho, C.; Domingo, M.; Núñez, R.; Lupón, J.; Núñez, J.; Barallat, J.; Moliner, P.; De Antonio, M.; Santesmases, J.; Cediel, G.; et al. Predictive Biomarkers for Death and Rehospitalization in Comorbid Frail Elderly Heart Failure Patients. *BMC Geriatr.* **2018**, *18*, 109. [CrossRef]
72. Meijers, W.C.; Bayes-Genis, A.; Mebazaa, A.; Bauersachs, J.; Cleland, J.G.F.; Coats, A.J.S.; Januzzi, J.L.; Maisel, A.S.; McDonald, K.; Mueller, T.; et al. Circulating Heart Failure Biomarkers beyond Natriuretic Peptides: Review from the Biomarker Study Group of the Heart Failure Association (HFA), European Society of Cardiology (ESC). *Eur. J. Heart Fail.* **2021**, *23*, 1610–1632. [CrossRef]
73. Gravning, J.; Askevold, E.T.; Nymo, S.H.; Ueland, T.; Wikstrand, J.; McMurray, J.J.V.; Aukrust, P.; Gullestad, L.; Kjekshus, J. Prognostic Effect of High-Sensitive Troponin T Assessment in Elderly Patients with Chronic Heart Failure: Results from the CORONA Trial. *Circ. Heart Fail.* **2014**, *7*, 96–103. [CrossRef] [PubMed]
74. Bradley, J.; Schelbert, E.B.; Bonnett, L.J.; Lewis, G.A.; Lagan, J.; Orsborne, C.; Brown, P.F.; Black, N.; Naish, J.H.; Williams, S.G.; et al. Growth Differentiation Factor-15 in Patients with or at Risk of Heart Failure but before First Hospitalisation. *Heart* **2024**, *110*, 195–201. [CrossRef] [PubMed]
75. Hayek, S.S.; Tahhan, A.S.; Ko, Y.-A.; Alkhoder, A.; Zheng, S.; Bhimani, R.; Hartsfield, J.; Kim, J.; Wilson, P.; Shaw, L.; et al. Soluble Urokinase Plasminogen Activator Receptor Levels and Outcomes in Patients with Heart Failure. *J. Card. Fail.* **2023**, *29*, 158–167. [CrossRef]
76. Leidner, A.S.; Cai, X.; Zelnick, L.R.; Lee, J.; Bansal, N.; Pasch, A.; Kansal, M.; Chen, J.; Anderson, A.H.; Sondheimer, J.H.; et al. Fibroblast Growth Factor 23 and Risk of Heart Failure Subtype: The CRIC (Chronic Renal Insufficiency Cohort) Study. *Kidney Med.* **2023**, *5*, 100723. [CrossRef]

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Article

Copeptin, Routine Laboratory Parameters, and Ischemic Etiology of Heart Failure Predict Outcomes in Elderly Patients with Decompensated Heart Failure

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Abstract

Background: Diagnosing and predicting outcomes in elderly patients with heart failure (HF) is challenging due to atypical symptoms and the limited value of natriuretic peptides, highlighting the need to search for new risk stratification biomarkers in this population. **Aim**: We aimed to analyze factors associated with the composite endpoint (all-cause mortality or decompensated HF-related hospitalization) within six months of follow-up in elderly patients with left ventricular systolic dysfunction and decompensated HF, with particular emphasis on copeptin concentration. **Methods**: This is a retrospective observational study based on prospectively collected data of 279 consecutive elderly patients hospitalized between 2018 and 2023 due to decompensated HF. Inclusion criteria were age > 65 years, history of HF diagnosed at least two years before the index hospitalization, and left ventricular ejection fraction < 40% on admission echocardiography. Serum copeptin levels were measured using an Enzyme-Linked Immunosorbent Assay (ELISA) (Human Copeptin ELISA kit, Sunred Biological Technology Co, Shanghai, China). The primary endpoint was all-cause mortality or decompensated HF-related hospitalization during the six-month follow-up. **Results**: The median age of the study population was 77 years (IQR: 69–79), and 221 (79.2%) were male. The composite endpoint occurred in 110 patients (38.1%). Multivariable analysis showed that serum concentrations of copeptin [hazard ratio (HR) 1.053 (1.042–1.064), $p < 0.0001$], bilirubin [HR 1.085 (1.057–1.114), $p < 0.0001$], uric acid [HR 1.005 (1.003–1.006), $p < 0.0001$], high-sensitivity C-reactive protein (hs-CRP) [HR 1.208 (1.088–1.342), $p < 0.0001$], and sodium [HR 1.111 (1.025–1.203), $p = 0.01$], as well as ischemic etiology of HF [HR 3.969 (2.396–6.575), $p < 0.0001$], were independently associated with worse outcomes. **Conclusions**: Our study demonstrated that higher concentrations of copeptin, bilirubin, hs-CRP, and uric acid, as well as lower sodium levels and ischemic etiology of HF, were independently associated with all-cause mortality or HF-related hospitalization during a six-month follow-up in elderly patients with decompensated HF.

Keywords: biomarkers; copeptin; heart failure; elderly patients

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1. Introduction

Heart failure (HF) is the final stage of many cardiovascular diseases and is associated with high morbidity and mortality. With increasing life expectancy and advances in interventional and pharmacological treatments, the population of elderly patients with advanced HF is gradually increasing. Among patients hospitalized with decompensated HF, more than 50% are over 75 years of age [1,2]. In this group, clinical symptoms of HF in the elderly are often atypical and reflect not only cardiac dysfunction but also the impact of multiple comorbidities [2]. Most clinical trials evaluate much younger cohorts, and older patients are underrepresented in clinical registries, despite the growing population of elderly patients with HF. Furthermore, guideline-directed medical therapies are largely based on younger populations, and their findings may not be directly applicable to elderly patients, who differ substantially in clinical profile, multimorbidity, and prognosis [2,3].

In clinical practice, optimal management and accurate risk stratification in elderly HF patients remain challenging [1,2,4]. It seems that an integrated approach using multiple biomarkers reflecting different pathophysiological pathways of HF may improve risk stratification [5–8]. One of the promising indicators in HF is copeptin, which is a stable C-terminal fragment of provasopressin that plays a crucial role in the regulation of the water and electrolyte balance [9,10]. Elevated copeptin levels have been linked to greater disease severity, reduced cardiac index, and an increased risk of death or rehospitalization [9–12]. Moreover, the combination of copeptin with other biomarkers, such as N-terminal pro b-type natriuretic peptide (NT-proBNP), may further improve risk stratification in patients with HF [9–11]. However, the utility of copeptin in elderly patients is not fully understood. This study aims to identify factors associated with a composite endpoint of death or HF decompensation, with a particular focus on copeptin, in elderly patients with decompensated HF during a 6-month follow-up.

2. Materials and Methods

The research was conducted in accordance with the Declaration of Helsinki, and the study protocols were approved by the Ethics Committee of Medical University of Silesia (specific ethics codes KNW/0022/KB1/53/18, date of approval 19 June 2018; PCN/0022/KB1/20/I/21, date of approval 4 May 2021; PCN/CBN/0052/KB1/20/II/21/22, date of approval 20 September 2022). All participants provided written informed consent prior to inclusion in the study.

This is a retrospective observational study based on prospectively collected data of 279 consecutive elderly patients hospitalized between 2018 and 2023 due to decompensated HF. The inclusion criteria were age > 65 years, HF diagnosed at least two years prior to the index hospitalization, and left ventricular ejection fraction (LVEF) < 40% on admission echocardiography. The exclusion criteria included recent infection, irreversible kidney disease (eGFR < 30 mL/min/1.73 m^2), chronic liver disease, malignancies, cerebrovascular accidents, and hematologic and autoimmune diseases. In all patients, physical examinations, clinical characteristics, anthropometric measurements, laboratory tests, and echocardiography were performed during the index hospitalization.

Peripheral venous blood samples were collected after 12 h of fasting at the time of enrollment. Laboratory assessments were performed using validated automated analyzers. Hematological indicators were determined with Sysmex XS-1000i or XE-2100 systems (Sysmex Corporation, Kobe, Japan). Biochemical parameters—including serum creatinine, total bilirubin, albumin, transaminases, glucose, and NT-proBNP—were assessed using a COBAS 6000 analyzer (Roche Diagnostics, Basel, Switzerland), while high-sensitivity C-reactive protein (hs-CRP) was measured via latex-enhanced immunoassay on the Cobas

Integra 70 platform (Roche Diagnostics, Basel, Switzerland). NT-proBNP levels were measured with the Elecsys 2010 immunoassay system (Roche Diagnostics).

The Enzyme-Linked Immunosorbent Assay (ELISA) technique was used to measure copeptin serum levels (Human Copeptin ELISA kit, Sunred Biological Technology Co, Shanghai, China).

Patient deaths were verified based on medical records and the official registry of the National Health Fund. During the 6 months from inclusion in the study, patients were followed for HF decompensation and all-cause mortality. All laboratory and follow-up data were complete, and no patients were lost to follow-up.

Statistical Analysis

Categorical variables were expressed as frequencies and percentages (%) and were compared between groups using Pearson's chi-square test. Continuous variables were presented as median (interquartile range [IQR]) or mean (standard deviation), and comparisons between groups were made using the Mann–Whitney U test or Student's *t*-test, depending on the distribution of the data. Normality of distribution was assessed using the Shapiro–Wilk test.

The Cox proportional hazards model was utilized to compute the hazard ratio (HR) and the 95% confidence interval (CI) for the composite endpoint between the analyzed groups. Cox's univariable proportional hazard analysis was used to select potential independent predictive factors of the composite endpoint for inclusion in the multivariable analysis. The examined covariates included age, bilirubin, creatinine, highly sensitive C-reactive protein (hs-CRP), fibrinogen, uric acid, copeptin, body mass index, albumin and sodium, the presence of dyslipidemia and diabetes mellitus type 2, ischemic etiology, LVEF, and left ventricular end-diastolic dimension. The relationships between explanatory variables were calculated by the Spearman rank correlation coefficient, and multicollinearity was evaluated using tolerance and variance inflation factors. HRs were calculated, and the findings were presented with 95% confidence intervals (CIs). Receiver Operating Characteristic (ROC) curve analysis was performed to assess the predictive ability of independent variables identified in the multivariable analysis. The area under the curve (AUC) was calculated for each parameter to evaluate its discrimination power. Optimal cut-off values were determined using the Youden index, and corresponding sensitivity and specificity were reported. A p-value of <0.05 was considered statistically significant. All data analyses were conducted using SAS software version 9.4.

3. Results

Baseline characteristics of the population are shown in Table 1. The median age of the entire population was 77 years [IQR: 69–79], and 79.2% were male. During the 6-month follow-up period, the composite endpoint occurred in 110 patients (39.4%). All-cause mortality was 14.7% (n = 41), while 69 patients (24.7%) experienced episodes of HF decompensation.

Patients who met the composite endpoint were older, more likely to be classified as New York Heart Association (NYHA) class IV, and had a higher prevalence of comorbidities (type 2 diabetes and chronic obstructive pulmonary disease) than patients without the composite endpoint.

The baseline characteristics of pharmacological and device therapy are presented in Table 2.

Table 1. Baseline characteristics of the study population.

	All Included Patients N = 279	**Without Composite Endpoint * N = 169 (60.6%)**	**With Composite Endpoint * N = 110 (39.4%)**	***p***
Baseline data				
Age, years	77.0 (69.0–79.0)	72.0 (68.0–77.0)	79.0 (77.0–81.0)	<0.0001
Male, n (%)	221 (79.2)	132 (78.1)	89 (80.9)	0.5729
Ischemic etiology of HF, n (%)	156 (55.9)	70 (41.4)	86 (78.2)	<0.0001
BMI, kg/m^2	26.6 (23.8–29.5)	27.1 (23.8–30.4)	26.1 (24.3–28.1)	0.0376
NYHA III, n (%)	123 (44.1)	105 (62.1)	18 (16.4)	<0.0001
NYHA IV, n (%)	156 (55.9)	64 (37.9)	92 (83.6)	<0.0001
Comorbidities				
Hypertension, n (%)	185 (66.3)	106 (62.7)	79 (71.8)	0.1162
Type 2 diabetes, n (%)	144 (51.6)	66 (39.1)	78 (70.9)	<0.0001
Persistent AF, n (%)	138 (49.5)	83 (49.1)	55 (50.0)	0.8848
COPD, n (%)	70 (25.1)	35 (20.7)	35 (31.8)	0.0365
Laboratory parameters				
Copeptin, pmol/L	4.66 (3.05–8.77)	3.46 (2.28–4.58)	9.11 (7.36–11.80)	<0.001
WBC, $\times 10^9$/L	7.3 (6.1–8.4)	6.58 (5.40–7.92)	5.6 (4.70–6.73)	0.0007
Platelets, $\times 10^9$/L	194.0 (171.0–225.0)	179.0 (152.0–210.00)	157.5 (143.0–206.0)	0.0048
Hemoglobin, mmol/L	8.8 (8.2–9.7)	8.8 (8.3–9.7)	8.9 (8.2–10.0)	0.5572
Glucose, mmol/L	5.7 (5.3–6.1)	5.6 (5.2–6.1)	5.8 (5.4–6.1)	0.2183
HbA1c, %	5.8 (5.4–6.3)	5.8 (5.5–6.3)	5.8 (5.4–6.4)	0.5946
Creatinine, µmol/L	117.0 (90.0–134.0)	98.0 (87.0–126.0)	125.0 (111.0–146.0)	<0.0001
GFR, mL/min/1.73 m^2	58.5 (50.3–71.4)	65.1 (54.0–78.6)	53.9 (45.1–60.1)	<0.0001
Total bilirubin, µmol/L	22.9 (17.3–28.6)	19.4 (13.3–23.0)	27.8 (25.1–32.2)	<0.0001
Albumin, g/L	44.0 (41.0–46.0)	44.0 (41.0–46.0)	45.0 (41.0–47.0)	0.0946
Uric acid, µmol/L	440.0 (378.0–515.0)	400.5 (341.0–465.00)	512.00 (433.0–603.0)	<0.0001
Urea, µmol/L	7.7 (5.8–11.3)	7.6 (5.9–11.9)	7.7 (5.7–11.3)	0.6649
Fibrinogen, mg/dL	329.0 (380.0–436.0)	347.0(306.0–398.00)	420.0 (345.0–51.0)	<0.0001
AST, U/L	32.0 (26.0–35.0)	31.0 (23.2–34.0)	30.0 (21.0–35.0)	0.8003
ALT, U/L	25.0 (20.0–33.0)	23.0 (18.1–31.5)	29.0 (19.0–33.1)	0.0598
ALP, U/L	79.0 (64.0–93.0)	78.0 (62.0–97.0)	80.5 (72.0–91.0)	0.1266
GGTP, U/L	80.0 (49.0–125.0)	71.0 (43.0–121.0)	89.0 (75.0–132.0)	0.0081
Cholesterol, mmol/L	4.3 (3.9–4.9)	4.2 (3.8–4.8)	4.5 (4.1–5.3)	<0.0001
hs-CRP, mg/L	2.3 (1.9–5.1)	2.95 (1.88–4.36)	4.5 (3.76–5.60)	<0.0001
Sodium, mmol/L	135.0 (133.0–138.0)	137.0(134.0–139.0)	133.5 (132.0–135.0)	<0.0001
NT-proBNP, pg/mL	4832 (3491.0–7191.0)	4625.0 (3500.0–7089.0)	5563.0 (3491.0–7191.0)	0.6488

Table 1. *Cont.*

	All Included Patients N = 279	Without Composite Endpoint * N = 169 (60.6%)	With Composite Endpoint * N = 110 (39.4%)	*p*
Echocardiographic parameters				
LA, mm	45.0 (45.0–50.0)	45.0 (45.0–49.0)	45.0 (45.0–50.0)	0.7206
RVEDd, mm	35.00 (32.0–38.0)	35.0 (31.0–37.0)	35.0 (32.0–39.0)	0.0563
LVEDd, mm	75.0 (70.0–78.0)	71.0 (69.0–77.0)	77.0 (75.0–79.0)	<0.0001
LVEF, %	25.0 (23.0–30.0)	27.0 (25.0–30.0)	23.5 (20.0–26.0)	<0.001

* Death or HF decompensation within 6 months of inclusion in the study. Data are presented as medians (25th–75th percentile) or numbers (percentage) of patients. Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; COPD, chronic obstructive pulmonary disease glomerular filtration rate; GGTP, gamma-glutamyl transpeptidase; HbA1c, glycated hemoglobin; HF, heart failure; hs-CRP, high-sensitivity C-reactive protein; LA, left atrium; LVEDd, left ventricular end-diastolic dimension; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; RVEDd, right ventricular end-diastolic dimension; WBC, white blood cell.

Table 2. Baseline characteristics of pharmacological and device therapy.

	All Included Patients N = 279	Without Composite Endpoint * N = 169 (60.6%)	With Composite Endpoint * N = 110 (39.4%)	*P*
B-blockers, n (%)	219 (78.5)	139 (82.2)	80 (72.7)	0.05
Bisoprolol, mg/day	5.00 (2.50–5.00)	5.00 (2.50–5.00)	5.00 (5.00–5.00)	0.13
Nebivolol, mg/day	5.00 (2.50–5.00)	2.50 (2.50–5.00)	5.00 (2.50–5.00)	0.6
Carvedilol, mg/day	25.00 (25.00–25.00)	25.00 (25.00–25.00)	25.00 (12.50–25.00)	0.2
Metoprolol succinate, mg/day	90.00 (47.50–90.00)	90.00 (47.50–90.00)	90.00 (47.50–90.00)	0.4
ACEI, n (%)	148 (53)	89 (52.7)	59 (53.6)	0.87
Ramipril, mg/day	5.00 (2.50–5.00)	5.00 (2.50–5.00)	3.75 (2.50–5.00)	0.2
Perindopril, mg/day	5.00 (2.50–5.00)	5.00 (2.50–5.00)	5.00 (2.50–5.00)	0.3
ARB, n (%)	51 (18.3)	37 (21.9)	14 (12.7)	0.05
Valsartan, mg/day	80.00 (80.00–160.00)	80.00 (80.00–160.00)	80.00 (80.00–160.00)	>0.9
Telmisartan, mg/day	40.00 (40.00–40.00)	40.00 (30.00–40.00)	40.00 (40.00–40.00)	0.2
ARNI, n (%)	56 (20.1)	27 (16)	29 (26.4)	0.03
Sacubitril/valsartan, sacubitril, mg/day	48.60 (24.30–48.60)	48.60 (24.30–48.60)	48.60 (48.60–48.60)	0.4
Sacubitril/valsartan, valsartan, mg/day	51.40 (25.70–51.40)	51.40 (25.70–51.40)	51.40 (51.40–51.40)	0.5
Loop diuretics, n (%)	273 (97.8%)	168 (99.4%)	105 (95.5%)	0.037
Furosemide #, mg/day	80.00 (80.00–160.00)	90.00 (80.00–160.00)	80.00 (40.00–120.00)	0.062
MRA, n (%)	101 (36.2)	89 (52.7)	12 (10.9)	<0.001
Spironolactone/eplerenone, mg/day	25.00 (25.00–50.00)	25.00 (12.50–50.00)	25.00 (25.00–50.00)	0.4
SGLT2, n (%)	129 (46.2)	63 (37.3)	66 (60)	0.0002
NOAC, n (%)	141 (50.5)	82 (48.5)	59 (53.6)	0.40

Table 2. *Cont.*

	All Included Patients N = 279	Without Composite Endpoint * N = 169 (60.6%)	With Composite Endpoint * N = 110 (39.4%)	*P*
Digoxin, n (%)	76 (27.2)	39 (23.1)	37 (33.6)	0.05
Statin, n (%)	167 (59.9)	101 (59.8)	66 (60)	0.96
ASA, n (%)	95 (34.1)	66 (39.1)	29 (26.4)	0.03
ICD/CRT-D, n (%)	238 (85.3)	144 (85.2)	94 (85.5)	0.95

* Death or HF decompensation within 6 months of inclusion in the study. Data are presented as numbers (percentages) of patients. # Diuretic doses have been converted to furosemide equivalents (10 mg of torasemide = 40 mg of furosemide). Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ASA, acetylsalicylic acid; ARB, angiotensin receptor blocker; ARNI, angiotensin-receptor neprilysin inhibitor; CRT-D, cardiac resynchronization therapy-defibrillator; ICD, implantable cardioverter-defibrillator; MRA, mineralocorticoid receptor antagonist; NOAC, non-vitamin K antagonist oral anticoagulant; SGLT2, sodium–glucose transport protein 2.

Multivariable Cox proportional hazards analysis demonstrated that copeptin [HR 1.053 (1.042–1.064), $p < 0.0001$], bilirubin [HR 1.085 (1.057–1.114), $p < 0.0001$], uric acid [HR 1.005 (1.003–1.006), $p < 0.0001$], CRP [HR 1.208 (1.088–1.342), $p < 0.0001$], and sodium [HR 1.111 (1.025–1.203), $p = 0.01$] serum concentrations, as well as ischemic etiology of HF [HR 3.969 (2.396–6.575 $p < 0.0001$], are independently associated with the composite endpoint.

The results of the univariable and multivariable analyses are presented in Table 3.

Table 3. Univariable and multivariable analyses of factors.

	Univariable Analysis		Multivariable Analysis	
Parameter	HR (95% CI)	*p*	HR (95% CI)	*p*
Age	1.317 [1.239–1.400]	<0.0001		
Bilirubin	1.119 [1.096–1.144]	<0.0001	1.085 [1.057–1.114]	<0.0001
Creatinine	1.019 [1.012–1.025]	<0.0001		
CRP	1.357 [1.252–1.470]	<0.0001	1.208 [1.088–1.342]	<0.0001
Fibrinogen	1.011 [1.009–1.013]	<0.0001		
Uric acid	1.006 [1.005–1.008]	<0.0001	1.005 [1.003–1.006]	<0.0001
Copeptin	1.025 [1.016–1.035]	<0.0001	1.053 [1.042–1.064]	<0.0001
BMI ↓	1.067 [1.012–1.126]	0.017		
Albumin	1.052 [1.014–1.092]	0.007		
Sodium ↓	1.341 [1.246–1.444]	<0.0001	1.111 [1.025–1.203]	0.01
LVEDD	1.162 [1.115–1.213]	<0.0001		
EF ↓	1.238 [1.177–1.302]	<0.0001		
Ischemic etiology	3.738 [2.375–5.884]	<0.0001	3.969 [2.396–6.575]	<0.0001
Diabetes mellitus	2.858 [1.892–4.317]	<0.0001		

Abbreviations: see Table 1. ↓ per one unit decrease.

ROC curve analysis demonstrated that copeptin had the highest prognostic value (AUC = 0.866; 95% CI: 0.816–0.916; $p < 0.001$), followed by bilirubin (AUC = 0.857; 95% CI: 0.811–0.902; $p < 0.001$), sodium (AUC = 0.821; 95% CI: 0.774–0.868; $p < 0.001$), uric acid (AUC = 0.822; 95% CI: 0.772–0.872; $p < 0.001$), and hs-CRP (AUC = 0.750; 95% CI: 0.694–0.806; $p < 0.001$). The ROC curves are shown in Figure 1A–E, and a summary is provided in Table 4.

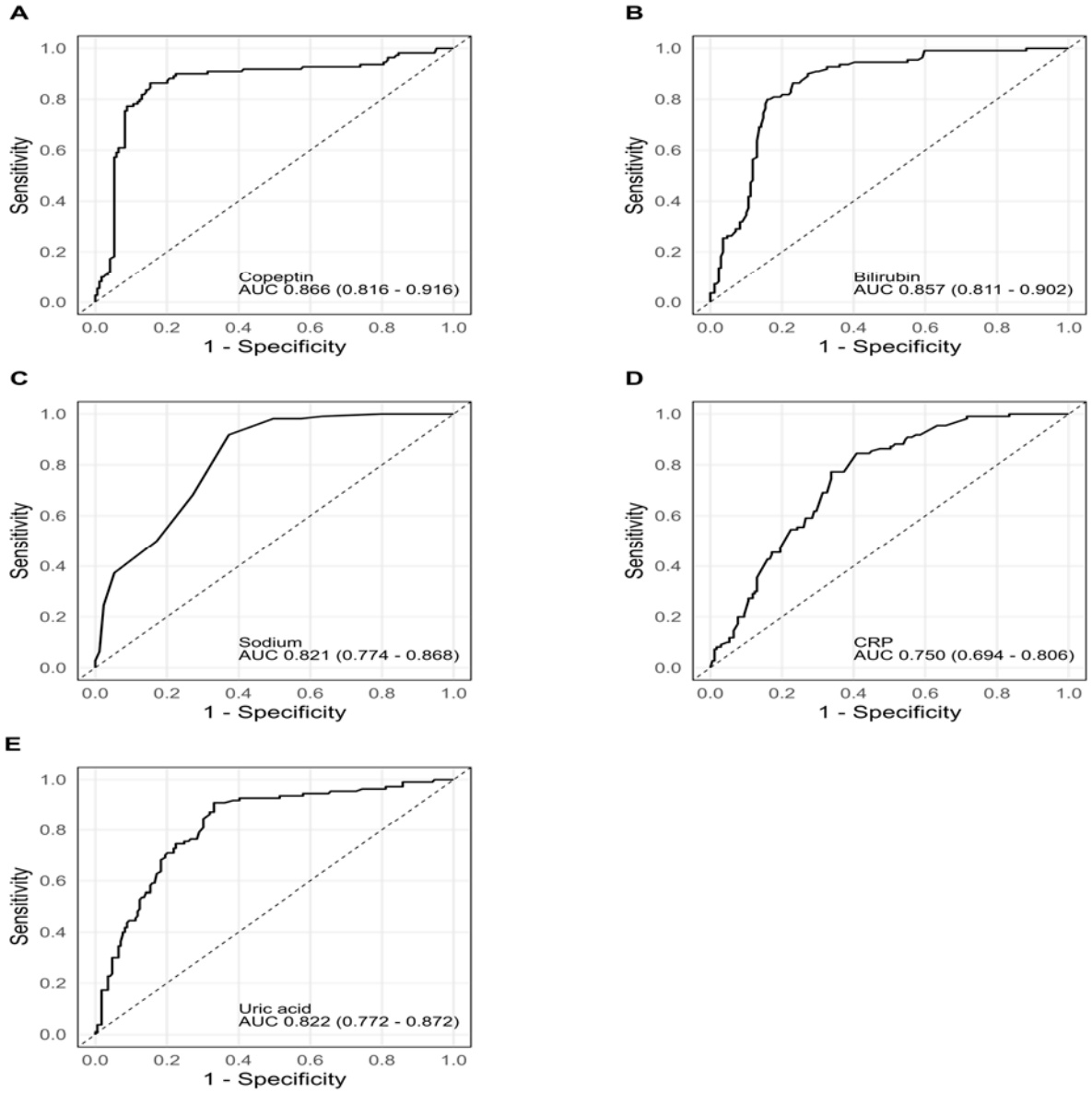

Figure 1. ROC curves for copeptin (**A**), bilirubin (**B**), sodium (**C**), hs-CRP (**D**), and uric acid (**E**).

Table 4. Summary of the ROC curves analysis for selected biomarkers.

	AUC [±95 CI]	Cut-off	Sens. [±95 CI]	Spec. [±95 CI]
Copeptin	0.866 [0.816–0.916]	5.365	0.864 [0.785–0.922]	0.846 [0.783–0.897]
Bilirubin	0.857 [0.811–0.902]	24.7	0.800 [0.713–0.87]	0.84 [0.776–0.892]
Sodium	0.821 [0.774–0.868]	135	0.918 [0.85–0.962]	0.627 [0.55–0.7]
hs-CRP	0.75 [0.694–0.806]	3.4	0.845 [0.764–0.907]	0.592 [0.514–0.667]
Uric acid	0.822 [0.772–0.872]	425	0.909 [0.839–0.956]	0.669 [0.592–0.739]

Abbreviations: AUC, area under the curve; CI, confidence interval; see Table 1.

4. Discussion

This single-center study demonstrated that higher copeptin, bilirubin, hs-CRP, and uric acid concentrations, as well as lower sodium concentrations and ischemic etiology of HF, are associated with all-cause mortality or rehospitalization during a six-month follow-

up in elderly patients with decompensated HF. Among the analyzed parameters, copeptin demonstrated the highest prognostic value for predicting the composite endpoint in this population. However, copeptin should be considered an important component of the risk model rather than a standalone predictor, as it contributes to overall prognostic accuracy in combination with other clinical and laboratory parameters.

Our study provides new data on the utility of copeptin in assessing the composite endpoint over a six-month follow-up period in elderly patients with decompensated HF. Previous studies have shown that higher copeptin concentrations are associated with a worse prognosis in different groups of patients with HF [12–14]. However, the data regarding the clinical significance of copeptin in elderly patients with decompensated HF have been limited [15,16]. Alehagen et al. showed that elevated copeptin levels, along with the combination of elevated copeptin and NT-proBNP levels, were associated with an increased risk of all-cause mortality in elderly patients with HF during the long-term follow-up [15]. Holmström et al. also demonstrated that copeptin levels are elevated in elderly patients with normal LVEF and systolic HF [16]. However, the populations analyzed in those studies [15,16] differed from ours in several aspects. Their cohorts included younger patients, and only a small proportion had advanced HF with LVEF < 30% in NYHA classes III–IV. In contrast, our analysis focused exclusively on patients with end-stage HF with a median LVEF of 25% in NYHA classes III and IV. Copeptin reflects activation of the vasopressin system in response to hemodynamic stress and neurohormonal imbalance in HF, and its elevation is associated with the severity of the disease [17–20]. In elderly patients, impaired renal function, diminished baroreceptor sensitivity, and comorbidities may further enhance copeptin secretion [19–22], especially during an episode of decompensation [23,24]. In addition, impaired regulation of fluid volume due to a decrease in the kidneys' ability to concentrate urine increases the dependence on vasopressin in maintaining water–electrolyte homeostasis [21].

Our study also confirms the prognostic importance of several other well-known risk factors in this elderly HF population. Lower sodium concentrations, as well as higher hs-CRP, bilirubin, and uric acid concentrations, were associated with all-cause mortality or rehospitalization during the six-month follow-up in the elderly patients with decompensated HF.

Hyponatremia is a common marker of HF decompensation and is associated with poor prognosis in HF, regardless of the patient's age group [25–28]. In the elderly, reduced GFR and impaired intrarenal prostaglandin synthesis also limit water excretion [28,29], whereas diuretic use contributes to dilutional hyponatremia and fluctuations in water–electrolyte balance [29,30]. Hyponatremia is also an indirect marker of elevated AVP activity, which can be reflected by copeptin levels [31].

Another factor associated with the composite endpoint in our analysis was hs-CRP, which reflects smoldering inflammation in HF. Previous studies have also shown a strong association of hs-CRP with the severity of disease, worse prognosis, and decompensation of HF [32–34]. CRP levels increase during HF decompensation, reflecting systemic inflammation. The exact mechanism of the smoldering systemic inflammation in HF is not fully understood. However, studies suggest that it may increase microvascular endothelial inflammation and promote myofibroblast formation and interstitial collagen deposition, leading to adverse cardiac remodeling and progression of HF [33–35]. Moreover, comorbidities such as diabetes, hypertension, and COPD are common in the elderly population and induce a systemic pro-inflammatory state, which damages other cells, creating a positive feedback loop [36]. Although routine hs-CRP testing is not currently recommended in guidelines, our findings, in line with previous research, suggest its potential utility in evaluating acute HF patients.

Elevated serum bilirubin concentration was also associated with the composite endpoint in elderly patients with decompensated HF. Previous studies demonstrated that higher serum bilirubin levels are a prognostic indicator in elderly patients with decompensated HF [37–39]. Congestive hepatopathy is a common symptom of decompensated HF, occurring in ~70% of cases [37]. Among hepatic markers of congestive hepatopathy secondary to decompensated HF, the most sensitive is a slightly elevated serum bilirubin concentration [40]. From a pathophysiological point of view, hyperbilirubinemia in acute HF is mainly due to venous congestion, leading to passive liver congestion and, consequently, impaired hepatocyte function [41,42], compounded by hepatic hypoxia from reduced cardiac output, which further raises bilirubin levels [41,43]. Thus, elevated bilirubin level reflects high central venous pressure and reduced cardiac index, both signs of advanced HF [38].

Another independent factor of the composite endpoint in the analyzed elderly population with decompensated HF was elevated uric acid concentration, whose role as a cardiovascular risk factor has been extensively discussed for decades. Multiple large population-based studies have shown that increased uric acid levels were independent predictors of mortality in decompensated HF [36,44,45]. Uric acid, through the activation of pro-inflammatory pathways, stimulates the proliferation of vascular smooth muscle cells and endothelial fibrosis, and it also contributes to insulin resistance [36,44]. These mechanisms indirectly influence the development and progression of HF [36,42,44].

The last factor associated with rehospitalization for HF or death during the 6-month follow-up was ischemic etiology of HF, which is a well-known risk factor of worse outcomes in HF [46–49]. In European countries, myocardial ischemia is the leading cause of HF. It plays a significant role in myocardial remodeling, which encompasses changes in the heart's shape and size, as well as diminished blood flow to the myocardium and a reduction in ejection fraction [48,49]. In addition, myocardial ischemia can both cause and accelerate HF decompensation [47,48]. However, further studies are needed to elucidate the mechanisms underlying the association of HF etiology with outcomes in HF patients who are admitted to the hospital with acute decompensated HF.

This study has several limitations. Firstly, it was a single-center analysis with a relatively small sample size, which may limit the generalizability of the findings to the entire population. Secondly, copeptin was measured only at admission, and we did not assess serial changes. Probably, dynamic changes in copeptin over time might provide additional prognostic information. Thirdly, our cohort consisted of very elderly patients with advanced HF, so the results may not be fully applicable to younger populations. Importantly, women were significantly underrepresented in the study cohort (approximately 20% of the enrolled population), which limits the applicability of the findings to older female patients and highlights the need for future studies addressing sex-specific differences in biomarker performance and prognosis. Finally, our study was observational in nature; therefore, it cannot establish causality between elevated copeptin levels and adverse outcomes.

5. Conclusions

Our findings highlight the utility of copeptin and other biochemical markers as potential tools for risk stratification in elderly patients with decompensated HF. However, future large multi-center studies are needed to validate these findings and determine whether the routine use of copeptin and other biomarkers can improve clinical outcomes or guide therapy in decompensated HF in the elderly.

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Informed Consent Statement: Informed consent was obtained from all subjects involved in this study.

Data Availability Statement: The data presented in this study are available upon request from the corresponding author. The data are not publicly available due to privacy restrictions related to the rules in our institution.

Conflicts of Interest: The authors declare that they have no conflicts of interest.

References

1. Sunayama, T.; Matsue, Y.; Dotare, T.; Maeda, D.; Iso, T.; Morisawa, T.; Saitoh, M.; Yokoyama, M.; Jujo, K.; Takahashi, T.; et al. Multidomain Frailty as a Therapeutic Target in Elderly Patients with Heart Failure. *Int. Heart J.* **2022**, *63*, 1–7. [CrossRef]
2. Liu, E.; Lampert, B.C. Heart Failure in Older Adults: Medical Management and Advanced Therapies. *Geriatrics* **2022**, *7*, 36. [CrossRef]
3. Nadziakiewicz, P.; Szczurek-Wasilewicz, W.; Szyguła-Jurkiewicz, B. Heart Failure in Elderly Patients: Medical Management, Therapies and Biomarkers. *Pharmaceuticals* **2024**, *18*, 32. [CrossRef] [PubMed]
4. Skrzypek, A.; Mostowik, M.; Szeliga, M.; Wilczyńska-Golonka, M.; Dębicka-Dąbrowska, D.; Nessler, J. Chronic Heart Failure in the Elderly: Still a Current Medical Problem. *Folia Medica Cracoviensia* **2018**, *58*, 47–56. [CrossRef] [PubMed]
5. Clemente, G.; Soldano, J.S.; Tuttolomondo, A. Heart Failure: Is There an Ideal Biomarker? *Rev. Cardiovasc. Med.* **2023**, *24*, 310. [CrossRef]
6. Candeloro, M.; Di Nisio, M.; Balducci, M.; Genova, S.; Valeriani, E.; Pierdomenico, S.D.; Porreca, E. Prognostic Nutritional Index in Elderly Patients Hospitalized for Acute Heart Failure. *ESC Heart Fail.* **2020**, *7*, 2479–2484. [CrossRef]
7. Manzano, L.; Babalis, D.; Roughton, M.; Shibata, M.; Anker, S.D.; Ghio, S.; Van Veldhuisen, D.J.; Cohen-Solal, A.; Coats, A.J.; Poole-Wilson, P.P.A.; et al. Predictors of Clinical Outcomes in Elderly Patients with Heart Failure. *Eur. J. Heart Fail.* **2011**, *13*, 528–536. [CrossRef]
8. Pacho, C.; Domingo, M.; Núñez, R.; Lupón, J.; Núñez, J.; Barallat, J.; Moliner, P.; De Antonio, M.; Santesmases, J.; Cediel, G.; et al. Predictive Biomarkers for Death and Rehospitalization in Comorbid Frail Elderly Heart Failure Patients. *BMC Geriatr.* **2018**, *18*, 109. [CrossRef]
9. Mu, D.; Cheng, J.; Qiu, L.; Cheng, X. Copeptin as a Diagnostic and Prognostic Biomarker in Cardiovascular Diseases. *Front. Cardiovasc. Med.* **2022**, *9*, 901990. [CrossRef] [PubMed]
10. Balling, L.; Goetze, J.P.; Jung, M.H.; Rossing, K.; Boesgaard, S.; Gustafsson, F. Copeptin Levels and Invasive Hemodynamics in Patients with Advanced Heart Failure. *Biomark. Med.* **2018**, *12*, 861–870. [CrossRef]
11. Stoiser, B.; Mörtl, D.; Hülsmann, M.; Berger, R.; Struck, J.; Morgenthaler, N.G.; Bergmann, A.; Pacher, R. Copeptin, a Fragment of the Vasopressin Precursor, as a Novel Predictor of Outcome in Heart Failure. *Eur. J. Clin. Investig.* **2006**, *36*, 771–778. [CrossRef]
12. Yoshikawa, Y.; Shiomi, H.; Kuwahara, K.; Sowa, N.; Yaku, H.; Yamashita, Y.; Tazaki, J.; Imai, M.; Kato, T.; Saito, N.; et al. Utility of Copeptin for Predicting Long-Term Clinical Outcomes in Patients with Heart Failure. *J. Cardiol.* **2019**, *73*, 379–385. [CrossRef]
13. Ianos, R.D.; Iancu, M.; Pop, C.; Lucaciu, R.L.; Hangan, A.C.; Rahaian, R.; Cozma, A.; Negrean, V.; Mercea, D.; Procopciuc, L.M. Predictive Value of NT-proBNP, FGF21, Galectin-3 and Copeptin in Advanced Heart Failure in Patients with Preserved and Mildly Reduced Ejection Fraction and Type 2 Diabetes Mellitus. *Medicina* **2024**, *60*, 1841. [CrossRef]
14. Zimodro, J.M.; Gasecka, A.; Jaguszewski, M.; Amanowicz, S.; Szkiela, M.; Denegri, A.; Pruc, M.; Duchnowski, P.; Peacock, F.W.; Rafique, Z.; et al. Role of Copeptin in Diagnosis and Outcome Prediction in Patients with Heart Failure: A Systematic Review and Meta-Analysis. *Biomarkers* **2022**, *27*, 720–726. [CrossRef] [PubMed]

15. Alehagen, U. Association of Copeptin and N-Terminal proBNP Concentrations With Risk of Cardiovascular Death in Older Patients With Symptoms of Heart Failure. *JAMA* **2011**, *305*, 2088. [CrossRef]
16. Holmström, A.; Sigurjonsdottir, R.; Fu, M.L.X.; Gustafsson, D.; Petzold, M.; Hammarsten, O. Levels of Copeptin among Elderly Patients in Relation to Systolic Heart Failure and Heart Failure with Normal Ejection Fraction. *Eur. Geriatr. Med.* **2013**, *4*, 139–144. [CrossRef]
17. Zhang, P.; Wu, X.; Li, G.; Sun, H.; Shi, J. Prognostic Role of Copeptin with All-Cause Mortality after Heart Failure: A Systematic Review and Meta-Analysis. *TCRM* **2017**, *13*, 49–58. [CrossRef] [PubMed]
18. Dobsa, L.; Cullen Edozien, K. Copeptin and Its Potential Role in Diagnosis and Prognosis of Various Diseases. *Biochem. Medica* **2013**, *23*, 172–192. [CrossRef] [PubMed]
19. Strait, J.B.; Lakatta, E.G. Aging-Associated Cardiovascular Changes and Their Relationship to Heart Failure. *Heart Fail. Clin.* **2012**, *8*, 143–164. [CrossRef]
20. Regan, J.A.; Kitzman, D.W.; Leifer, E.S.; Kraus, W.E.; Fleg, J.L.; Forman, D.E.; Whellan, D.J.; Wojdyla, D.; Parikh, K.; O'Connor, C.M.; et al. Impact of Age on Comorbidities and Outcomes in Heart Failure With Reduced Ejection Fraction. *JACC Heart Fail.* **2019**, *7*, 1056–1065. [CrossRef]
21. Krane, V.; Genser, B.; Kleber, M.E.; Drechsler, C.; März, W.; Delgado, G.; Allolio, B.; Wanner, C.; Fenske, W. Copeptin Associates with Cause-Specific Mortality in Patients with Impaired Renal Function: Results from the LURIC and the 4D Study. *Clin. Chem.* **2017**, *63*, 997–1007. [CrossRef]
22. Fukuzawa, J.; Haneda, T.; Kikuchi, K. Arginine Vasopressin Increases the Rate of Protein Synthesis in Isolated Perfused Adult Rat Heart via the V1 Receptor. *Mol. Cell. Biochem.* **1999**, *195*, 93–98. [CrossRef]
23. Smaradottir, M.I.; Andersen, K.; Gudnason, V.; Näsman, P.; Rydén, L.; Mellbin, L.G. Copeptin Is Associated with Mortality in Elderly People. *Eur. J. Clin. Investig.* **2021**, *51*, e13516. [CrossRef] [PubMed]
24. Morgenthaler, N.G.; Müller, B.; Struck, J.; Bergmann, A.; Redl, H.; Christ-Crain, M. Copeptin, A Stable Peptide Of The Arginine Vasopressin Precursor, Is Elevated In Hemorrhagic And Septic Shock. *Shock* **2007**, *28*, 219–226. [CrossRef]
25. Klein, L.; O'Connor, C.M.; Leimberger, J.D.; Gattis-Stough, W.; Piña, I.L.; Felker, G.M.; Adams, K.F.; Califf, R.M.; Gheorghiade, M. Lower Serum Sodium Is Associated With Increased Short-Term Mortality in Hospitalized Patients With Worsening Heart Failure: Results From the Outcomes of a Prospective Trial of Intravenous Milrinone for Exacerbations of Chronic Heart Failure (OPTIME-CHF) Study. *Circulation* **2005**, *111*, 2454–2460. [CrossRef] [PubMed]
26. Herrero-Puente, P.; Marino-Genicio, R.; Martín-Sánchez, F.J.; Vázquez-Alvarez, J.; Jacob, J.; Bermudez, M.; Llorens, P.; Miró, Ò.; Pérez-Durá, M.J.; Gil, V.; et al. Characteristics of Acute Heart Failure in Very Elderly Patients—EVE Study (EAHFE Very Elderly). *Eur. J. Intern. Med.* **2014**, *25*, 463–470. [CrossRef]
27. Greenberg, B. Managing Hyponatremia in Patients with Heart Failure. *J. Hosp. Med.* **2010**, *5*, S33–S39. [CrossRef]
28. Filippatos, T.D.; Makri, A.; Elisaf, M.S.; Liamis, G. Hyponatremia in the Elderly: Challenges and Solutions. *CIA* **2017**, *12*, 1957–1965. [CrossRef]
29. Clark, B.A.; Shannon, R.P.; Rosa, R.M.; Epstein, F.H. Increased Susceptibility to Thiazide-Induced Hyponatremia in the Elderly. *J. Am. Soc. Nephrol.* **1994**, *5*, 1106–1111. [CrossRef]
30. Gheorghiade, M.; Abraham, W.T.; Albert, N.M.; Gattis Stough, W.; Greenberg, B.H.; O'Connor, C.M.; She, L.; Yancy, C.W.; Young, J.; Fonarow, G.C.; et al. Relationship between admission serum sodium concentration and clinical outcomes in patients hospitalized for heart failure: An analysis from the OPTIMIZE-HF registry. *Eur. Heart J.* **2007**, *28*, 980–988. [CrossRef] [PubMed]
31. Maisel, A.; Xue, Y.; Shah, K.; Mueller, C.; Nowak, R.; Peacock, W.F.; Ponikowski, P.; Mockel, M.; Hogan, C.; Wu, A.H.; et al. Increased 90-day mortality in patients with acute heart failure with elevated copeptin: Secondary results from the Biomarkers in Acute Heart Failure (BACH) study. *Circ. Heart Fail.* **2011**, *4*, 613–620. [CrossRef] [PubMed]
32. Kalogeropoulos, A.P.; Tang, W.H.W.; Hsu, A.; Felker, G.M.; Hernandez, A.F.; Troughton, R.W.; Voors, A.A.; Anker, S.D.; Metra, M.; McMurray, J.J.V.; et al. High-Sensitivity C-Reactive Protein in Acute Heart Failure: Insights From the ASCEND-HF Trial. *J. Card. Fail.* **2014**, *20*, 319–326. [CrossRef]
33. Zhang, L.; He, G.; Huo, X.; Tian, A.; Ji, R.; Pu, B.; Peng, Y. Long-Term Cumulative High-Sensitivity C-Reactive Protein and Mortality Among Patients With Acute Heart Failure. *JAHA* **2023**, *12*, e029386. [CrossRef] [PubMed]
34. Santas, E.; Villar, S.; Palau, P.; Llàcer, P.; De La Espriella, R.; Miñana, G.; Lorenzo, M.; Núñez-Marín, G.; Górriz, J.L.; Carratalá, A.; et al. High-Sensitivity C-Reactive Protein and Risk of Clinical Outcomes in Patients with Acute Heart Failure. *Sci. Rep.* **2024**, *14*, 21672. [CrossRef] [PubMed]
35. Habibi, D.; Daneshpour, M.S.; Asgarian, S.; Kohansal, K.; Hadaegh, F.; Mansourian, M.; Akbarzadeh, M. Effect of C-Reactive Protein on the Risk of Heart Failure: A Mendelian Randomization Study. *BMC Cardiovasc. Disord.* **2023**, *23*, 112. [CrossRef]
36. Huang, G.; Qin, J.; Deng, X.; Luo, G.; Yu, D.; Zhang, M.; Zhou, S.; Wang, L. Prognostic Value of Serum Uric Acid in Patients with Acute Heart Failure: A Meta-Analysis. *Medicine* **2019**, *98*, e14525. [CrossRef]
37. Chintanaboina, J.; Haner, M.S.; Sethi, A.; Patel, N.; Tanyous, W.; Lalos, A.; Pancholy, S. Serum Bilirubin as a Prognostic Marker in Patients with Acute Decompensated Heart Failure. *Korean J. Intern. Med.* **2013**, *28*, 300. [CrossRef]

38. Okada, A.; Sugano, Y.; Nagai, T.; Honda, Y.; Iwakami, N.; Nakano, H.; Takashio, S.; Honda, S.; Asaumi, Y.; Aiba, T.; et al. Usefulness of the Direct and/or Total Bilirubin to Predict Adverse Outcomes in Patients With Acute Decompensated Heart Failure. *Am. J. Cardiol.* **2017**, *119*, 2035–2041. [CrossRef]
39. Shinagawa, H.; Inomata, T.; Koitabashi, T.; Nakano, H.; Takeuchi, I.; Naruke, T.; Ohsaka, T.; Nishii, M.; Takehana, H.; Izumi, T. Prognostic Significance of Increased Serum Bilirubin Levels Coincident With Cardiac Decompensation in Chronic Heart Failure. *Circ. J.* **2008**, *72*, 364–369. [CrossRef]
40. Allen, L.A.; Felker, G.M.; Pocock, S.; McMurray, J.J.V.; Pfeffer, M.A.; Swedberg, K.; Wang, D.; Yusuf, S.; Michelson, E.L.; Granger, C.B.; et al. Liver Function Abnormalities and Outcome in Patients with Chronic Heart Failure: Data from the Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity (CHARM) Program. *Eur. J. Heart Fail.* **2009**, *11*, 170–177. [CrossRef]
41. Nikolaou, M.; Parissis, J.; Yilmaz, M.B.; Seronde, M.-F.; Kivikko, M.; Laribi, S.; Paugam-Burtz, C.; Cai, D.; Pohjanjousi, P.; Laterre, P.-F.; et al. Liver Function Abnormalities, Clinical Profile, and Outcome in Acute Decompensated Heart Failure. *Eur. Heart J.* **2013**, *34*, 742–749. [CrossRef] [PubMed]
42. Samsky, M.D.; Patel, C.B.; DeWald, T.A.; Smith, A.D.; Felker, G.M.; Rogers, J.G.; Hernandez, A.F. Cardiohepatic Interactions in Heart Failure. *J. Am. Coll. Cardiol.* **2013**, *61*, 2397–2405. [CrossRef]
43. Lau, G.T.; Tan, H.C.; Kritharides, L. Type of Liver Dysfunction in Heart Failure and Its Relation to the Severity of Tricuspid Regurgitation. *Am. J. Cardiol.* **2002**, *90*, 1405–1409. [CrossRef]
44. Alimonda, A.L.; Núñez, J.; Núñez, E.; Husser, O.; Sanchis, J.; Bodí, V.; Miñana, G.; Robles, R.; Mainar, L.; Merlos, P.; et al. Hyperuricemia in Acute Heart Failure. More than a Simple Spectator? *Eur. J. Intern. Med.* **2009**, *20*, 74–79. [CrossRef]
45. Kumrić, M.; Borovac, J.A.; Kurir, T.T.; Božić, J. Clinical Implications of Uric Acid in Heart Failure: A Comprehensive Review. *Life* **2021**, *11*, 53. [CrossRef]
46. Remme, W.J. Overview of the Relationship between Ischemia and Congestive Heart Failure. *Clin. Cardiol.* **2000**, *23*, IV-4–IV-8. [CrossRef] [PubMed]
47. Canepa, M.; Anastasia, G.; Ameri, P.; Vergallo, R.; O'Connor, C.M.; Sinagra, G.; Porto, I. Characterization of Ischemic Etiology in Heart Failure with Reduced Ejection Fraction Randomized Clinical Trials: A Systematic Review and Meta-Analysis. *European J. Intern. Med.* **2025**, *134*, 51–58. [CrossRef]
48. Kajimoto, K.; Minami, Y.; Sato, N.; Kasanuki, H. Etiology of Heart Failure and Outcomes in Patients Hospitalized for Acute Decompensated Heart Failure With Preserved or Reduced Ejection Fraction. *Am. J. Cardiol.* **2016**, *118*, 1881–1887. [CrossRef] [PubMed]
49. Flaherty, J.D.; Bax, J.J.; De Luca, L.; Rossi, J.S.; Davidson, C.J.; Filippatos, G.; Liu, P.P.; Konstam, M.A.; Greenberg, B.; Mehra, M.R.; et al. Acute Heart Failure Syndromes in Patients With Coronary Artery Disease. *J. Am. Coll. Cardiol.* **2009**, *53*, 254–263. [CrossRef]

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Załącznik nr 13
do *Zasad i trybu*
postępowania w sprawie nadania stopnia doktora
w Śląskim Uniwersytecie Medycznym w Katowicach

OŚWIADCZENIE WSPÓŁAUTORÓW
o merytorycznym udziale w powstaniu publikacji:
monografii/artykułu naukowego wchodzącego w skład cyklu powiązanych tematycznie artykułów naukowych*

publikacja nr 1

Tytuł: **Heart failure in elderly patients: medical management, therapies and biomarkers. Pharmaceuticals: 2025, (18), (1), 1-13.** Tytuł publikacji, czasopismo lub wydawca, rok wydania, tom, strony

Autorzy: Nadziakiewicz Paulina, Szczurek-Wasilewicz Wioletta, Szyguła-Jurkiewicz Bożena
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2	Wioletta Szczurek-Wasilewicz	Udział w koncepcji pracy, zatwierdzenie wersji ostatecznej do druku	Wioletta Szczurek-Wasilewicz
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publikacja nr 2

Tytuł: **Copeptin, Routine Laboratory Parameters, and Ischemic Etiology of Heart Failure Predict Outcomes in Elderly Patients with Decompensated Heart Failure. Biomedicines. 2025; 13(9):2048.** tytuł publikacji, czasopismo lub wydawca, rok wydania, tom, strony

Autorzy: **Nadziakiewicz Paulina, Szczurek-Wasilewicz Wioletta, Jurkiewicz Michał, Skrzypek Michał, Gorzkowska Agnieszka, Gąsior Mariusz, Szyguła-Jurkiewicz Bożena**
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7	Bożena Szyguła-Jurkiewicz	koncepcja pracy, przygotowanie metodologii, kierowanie projektem, pozyskiwanie funduszy, wsparcie administracyjne, nadzór nad pracą	Bożena Szyguła-Jurkiewicz