Univerzita Karlova

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Dizertační práce

Praha, 2024 **MUDr. Dominik Jenča**

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Srdeční selhání po infarktu myokardu

Heart failure after myocardial infarction

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Key words: heart failure, myocardial infarction, acute coronary syndrome, adverse remodeling, sympathetic system, renin, angiotensin, aldosterone, orexin, iron deficiency, transferin, ferritin, transferrin saturation, ejection fraction

Obsah

Seznam použitých zkratek

ACE	angiotenzin konvertující enzym
AKS	akutní koronární syndrom
BNP	natriuretický peptid typu B
CKD	chronické onemocnění ledvin
CRP	C-reaktivní protein
DM	diabetes mellitus
ECM	extracelulární matrix
EF	ejekční frakce
FAC	fractional area change, frakční změna plochy
FiS	fibrilace síní
GLS	globální longitudinální strain
HF	heart failure, srdeční selhání
HFmrEF	srdeční selhání s mírně sníženou ejekční frakcí
HFpEF	srdeční selhání se zachovalou ejekční frakcí
HFrEF	srdeční selhání se sníženou ejekční frakcí
ICHS	ischemická choroba srdeční
ID	iron deficiency, deficit železa
IL	interleukin
IM	infarkt myokardu
KCCQ	Kansas City Cardiomyopathy Questionnaire
LK	levá komora srdeční
MMP	matrixové metaloproteinázy

NAP	nestabilní angina pectoris
nonSTEMI	infarkt myokardu bez perzistujících elevací ST segmentu
NT-proBNP	N-terminální natriuretický propeptid typu B
PCI	perkutánní koronární intervence
PK	pravá komora srdeční
S-Fe	sérové železo
SGLT2	sodíkovo-glukózový kotransporter 2
STEMI	infarkt myokardu s perzistujícími elevacemi ST segmentu
sTfR	solubilní transferinový receptor
TAPSE	tricuspid annular plain systolic excursion
TEE	transesofageální echokardiografie
TF	tepová frekvence
TTE	transtorakální echokardiografie
WMSI	wall motion score index, index skóre hybnosti stěn

Abstrakt

Ischemická choroba srdeční, nejčastěji ve formě infarktu myokardu (IM), je hlavní příčinou srdečního selhání (HF) ve vyspělých krajinách. Navzdory pokrokům v léčbě IM zůstává reziduální riziko kardiovaskulárních příhod u pacientů po prodělané příhodě vysoké. Nejčastější příčinou morbidity a mortality pacientů po IM je HF. Jeho rozvoj je spojen s trojnásobně vyšším rizikem mortality bez ohledu na ejekční frakci levé komory.

Cílem naší práce bylo zjistit prognostický význam korespondenční diagnostiky symptomů a známek HF jeden měsíc po propuštění z nemocnice. Zjistili jsme, že dotazník Kansas City Cardiomyopathy Questionnaire (KCCQ) dokáže identifikovat osoby ve zvýšeném riziku úmrtí, a to nezávisle na dalších rizikových faktorech, které ovlivňují prognózu po IM. Toto zjištění potvrzuje klinický význam časné diagnostiky HF po IM.

Protože ne všechny komponenty dotazníku KCCQ jsou prognosticky důležité u pacientů po IM, v další práci jsme identifikovali 3 otázky z KCCQ, které nejlépe predikují riziko mortality po IM. Jednalo se o míru omezení při chůzi po rovině, přítomnost otoků dolních končetin a změnu symptomů v posledních 2 týdnech. Ve validační kohortě jsme identifikovali další klinické proměnné ovlivňující mortalitu po IM. Kombinací klinických proměnných a symptomů a známek HF jsme vytvořili nové prognostické skóre – PragueMi skóre. Ve validační kohortě naše PragueMi skóre mělo lepší diskriminační, kalibrační a reklasifikační schopnosti než v současnosti doporučované GRACE (Global Registry of Acute Coronary Events) skóre.

V rámci hledání nových možných terapeutických cílů jsme analyzovali vztah mezi deficitem železa a rizikem celkové mortality po IM. Protože v současné době neexistují kritéria deficitu železa (ID) po IM založené na tvrdých datech, analyzovali jsme prediktivní hodnotu různých parametrů metabolismu železa. Na základě našich analýz jsme vytvořili nové kritérium ID nazvané PragueID kritérium, které vychází z hladiny sérového železa a solubilního transferinového receptoru. PragueID bylo schopné stratifikovat riziko mortality nezávisle na dalších klinických proměnných. V další práci bude nutné objasnit, zdali klinické rozhodování a substituce železa na základě PragueID dokáže zlepšit prognózu po IM.

V další práci jsme poukázali na asociaci mezi aktivitou orexinového systému a rizikem mortality po IM. Homozygoti pro minoritní alelu T v lokusu rs7767652, která se nachází v regulační oblasti pro orexinový receptor 2 a snižuje transkripci tohoto receptoru, jako i pacienti s nižší koncentrací orexinu A měli vyšší riziko mortality.
V naší práci jsme dále prokázali, že i v současné době je prevalence systolické dysfunkce u pacientů po IM vysoká. Ti pacienti, u kterých došlo ke zlepšení ejekční frakce levé komory, měli lepší prognózu v porovnání s těmi, u kterých ejekční frakce levé komory zůstala pod 40 %. Zánětlivá reakce na IM, ale i závažnost koronárního nálezu a vznik fibrilace síní byly negativně asociovány se zlepšením systolické funkce po IM.

Moje dizertační práce poukazuje na klinický význam časné diagnostiky symptomů a známek HF korespondenční cestou jeden měsíc po propuštění z nemocnice. Námi vytvořený dotazník PragueMi dokáže selektovat vysoce rizikové pacienty, kteří by mohli profitovat z časnější ambulantní kontroly a titrace doporučené farmakoterapie. Dále moje práce poukazuje na substituci železa a zvýšení aktivity orexinového systému jako na možné nové terapeutické intervence pacientů s IM. K potvrzení klinického významu těchto intervencí ale budou nutné randomizované intervenční studie.

Abstract

Ischemic heart disease, most commonly in the form of myocardial infarction (MI), is the leading cause of heart failure (HF) in developed countries. Despite advances in the treatment of MI, the residual risk of cardiovascular events remains high after MI. HF is the most common cause of morbidity and mortality in patients after MI. Its development is associated with a threefold higher risk of mortality regardless of left ventricular ejection fraction.

The aim of our work was to determine the prognostic significance of the remote diagnosis of symptoms and signs of HF one month after discharge from the hospital. We found that the Kansas City Cardiomyopathy Questionnaire (KCCQ) can identify individuals at increased risk of death independently of other risk factors that influence prognosis after MI. This finding confirms the clinical importance of early diagnosis of HF after MI.

Because not all components of the KCCQ questionnaire are prognostically important in patients after MI, in further work we identified 3 questions from the KCCQ that best predict the risk of mortality after MI. These included the level of limitation in walking, the presence of lower extremity swelling, and the change in symptoms over the past 2 weeks. In the validation cohort, we identified additional clinical variables influencing mortality after MI. By combining clinical variables and symptoms and signs of HF, we created a new prognostic score – the PragueMi score. In the validation cohort, our PragueMi score had better discrimination, calibration and reclassification capabilities than the currently recommended GRACE (Global Registry of Acute Coronary Events) score.

As part of the search for new possible therapeutic targets, we analysed the relationship between iron deficiency and the risk of total mortality after MI. As there are currently no hard data-based criteria for iron deficiency (ID) after MI, we analysed the predictive value of various parameters of iron metabolism. Based on our analyses, we created a new ID criterion called PragueID criterion, which is based on serum iron level and soluble transferrin receptor concentration. PragueID was able to stratify mortality risk independently of other clinical variables. In further work, it will be necessary to clarify whether clinical decision-making and iron substitution based on the PragueID can improve the prognosis after MI.

In another work, we pointed out the association between the activity of the orexin system and the risk of mortality after MI. Homozygotes for the minor T allele in the rs7767652 locus, located in the regulatory region for orexin receptor 2 and reduces the transcription of this receptor, as well as patients with lower orexin A concentrations, had a higher risk of mortality.

In our work, we further demonstrated that the prevalence of systolic dysfunction in post-MI patients is high even today. Those patients whose left ventricular ejection fraction improved had a better prognosis compared with those whose left ventricular ejection fraction remained below 40%. Inflammatory response to MI, but also the severity of the coronary atherosclerosis and the development of atrial fibrillation were negatively associated with the improvement of systolic function after MI.

My dissertation points to the clinical importance of early remote diagnosis of symptoms and signs of heart failure after discharge from the hospital for MI. The PragueMi questionnaire created by us can select high-risk patients who could benefit from an earlier outpatient check-up and titration of the recommended pharmacotherapy. Furthermore, my work points to iron substitution and increasing the activity of the orexin system as possible new therapeutic interventions for patients with MI. However, randomized intervention studies will be necessary to confirm the clinical significance of these interventions.

1.Úvod

Srdeční selhání (heart failure, HF) je klinický syndrom, který je charakterizovaný přítomností typických symptomů a klinických známek, jakožto důsledku strukturální/funkční abnormality myokardu. Diagnóza HF je podpořena elevací natriuretických peptidů a/nebo objektivní evidencí o městnání ve velkém či malém oběhu.[1] Mezi typické symptomy HF patří námahová dušnost, únava a intolerance zátěže. Klinické známky jako zvýšená náplň krčních žil, hepatomegalie, hepatojugulární reflux, ascites, fluidothorax, symetrické otoky dolních končetin jsou projevem kongesce ve velkém oběhu. Městnání v plicním řečišti je charakterizováno přítomnosti chrůpků, případně pískotů. Méně často se vyskytující známky jako oligurie a chladná akra končetin jsou projevem nízkého srdečního výdeje. Klinické projevy nebývají přítomné v časné/kompenzované fázi HF, což komplikuje jeho diagnostiku, zejména v případě zachovalé ejekční frakce levé komory (EF LK). Podle posledních doporučených postupů Evropské kardiologické společnosti (ESC) pro diagnostiku a léčbu srdečního selhání je možné HF dle EF LK rozdělit do 3 skupin, které se vzájemně odlišují prognózou, hlavní vyvolávající příčinou a evidencí o léčbě: [2]

1) Srdeční selhání se sníženou EF LK (heart failure with reduced ejection fraction, HFrEF), definováno poklesem EF LK ≤ 40 %

2) Srdeční selhání s mírně sníženou EF LK (heart failure with mildly reduced ejection fraction, HFmrEF), charakterizovaného rozpětím EF LK mezi 41-49 %

3) Srdeční selhání se zachovalou EF LK (heart failure with preserved ejection, HFpEF) s EF LK ≥ 50 %).

HFrEF je podskupinou s největší mírou důkazů o léčbě. Typickými představiteli jsou mladší pacienti dominantně mužského pohlaví s anamnézou prodělaného infarktu myokardu (IM). Pacienti s HFmrEF mají podobné rizikové faktory jako HFrEF, i v této skupině je dominantní příčinou HF ischemická choroba srdeční (ICHS).[3] Nemocní s HFpEF jsou obvykle vyššího věku, ženského pohlaví, s vyšším podílem komorbidit a fibrilace síní. V případě léčby pacientů s HFmrEF a HFpEF byl dosud prokázán prognostický benefit jedině u gliflozinů (empagliflozin a dapagliflozin).[4, 5] U obézních pacientů s HFpEF se velmi slibně jeví semaglutid, agonista receptorů pro glucagon-like peptid, který ve studii STEP-HFpEF zlepšoval funkční výkonnost i kvalitu života.[6]

Data o prognostickém benefitu obézních pacientů s HFpEF z léčby tímto preparátem zatím chybí.

HF je konečným fenotypem většiny kardiovaskulárních onemocnění. Mezi hlavní příčiny HF patří ICHS, arteriální hypertenze, kardiomyopatie, chlopenní vady, arytmie, vrozené srdeční vady, kardiometabolické nemoci (obezita a diabetes mellitus 2.typu) a infekční onemocnění (např. Chagasova nemoc). Prognóza HF je nepříznivá a je porovnatelná s maligními onemocněními. Za 5 let od diagnózy HF totiž zemře až 50 % nemocných a deseti let se dožívá jen 10 % z nich.[7] HF je hlavní příčinou pozdní mortality pacientů po IM. Rozvoj HF po IM je spojen s téměř trojnásobným nárůstem mortality.[8] Zvýšená mortalita u pacientů s HF po IM je nezávislá na EF LK.[9] HF je obvykle diagnostikováno pozdě, až ve fázi, kdy jeho léčba vyžaduje hospitalizaci. Takto diagnostikovaní pacienti mají vysokou míru rehospitalizací (za 1 měsíc je znovu přijato přibližně 25 % nemocných) a nepříznivou prognózu.[10, 11]

Vzhledem k závažným společenským a ekonomickým dopadům HF je důležitá prevence a časná léčba. Je známo, že časná diagnostika HF u ambulantních pacientů je spojená s lepší prognózou v porovnání s nemocnými s diagnostikovaným HF až během hospitalizace.[12] Protože ICHS je nadále nejčastější příčinou vzniku HF, moje práce se zaměřuje na problematiku rozvoje HF po infarktu myokardu, včetně možností časné diagnostiky a terapeutické intervence. Tyto poznatky mohou zlepšit prognózu pacientů po infarktu myokardu.

2. Přehled problematiky

2.1 Epidemiologie srdečního selhání

HF je pandemií 21.století. V roce 2017 jím celosvětově trpělo 64 milionů pacientů.[13] V České republice tímto onemocněním trpí téměř 300 000 pacientů.[14] Počet nemocných s HF bude nadále stoupat, a to důsledkem stárnutí populace, zlepšením léčby HF i IM a vzrůstající prevalenci obezity a diabetu mellitu 2.typu. Dle predikcí Ústavu zdravotnických informací a statistiky se do roku 2040 očekává trojnásobný nárůst počtu pacientů se HF.

Z Framinghamské populační studie vyplývá, že každý pátý čtyřicátník onemocní HF.[15] HF je nejčastější příčinou hospitalizací na interních odděleních osob nad 65 let.[7] ICHS, zejména ve formě prodělaného IM, je nejčastější příčinou HF ve vyspělých zemích.[16] Riziko vzniku HF se neliší mezi pacienty s IM s perzistujícími elevacemi ST segmentů (STEMI) a IM bez perzistujících ST elevací (nonSTEMI).[17, 18]

V rámci studií existují významné rozdíly v incidenci HF po IM. Meta-analýza 33 studií zkoumajících HF po IM (celkem téměř 307 000 pacientů) prokázala rozpětí incidence HF mezi 3-53 % pacientů s IM.[8] Jednou z mnoha příčin diskrepance v incidenci je použití rozdílné metodologie stanovení HF (Killipova klasifikace, NYHA třída, Bostonská, Framinghamská, ESC kritéria), u kterého až do nedávné doby (na rozdíl od IM) neexistovala univerzální definice.[7] V řadě studií nebylo rozlišováno mezi časným (při přijetí do nemocnice anebo během hospitalizace) a pozdním vznikem HF. Zlepšení přednemocniční léčby IM a pokroky v reperfuzní terapii vedly ke zvýšenému přežívání pacientů s rozsáhlým IM, u kterých je vysoké riziko rozvoje HF. Na druhé straně, rozvoj nových, citlivějších biochemických metod stanovení IM (vysoce senzitivní troponin) klinikům umožnil diagnostiku rozsahem menších IM, které dřív nebylo možné detekovat konvenčními metodami (aminotransferázy, kreatin kináza, CK-MB, myoglobin) a které mají nižší riziko rozvoje HF. Dalším důvodem významné heterogenity incidence HF po IM je různá rizikovost sledovaných pacientů (pacienti v klinických studiích jsou obvykle mladší a mají méně komorbidit než nemocní v epidemiologických studiích), rozdílná délka jejich sledování a období, ve kterém byly studie prováděny.

2.1.1 Srdeční selhání během hospitalizace pro infarkt myokardu

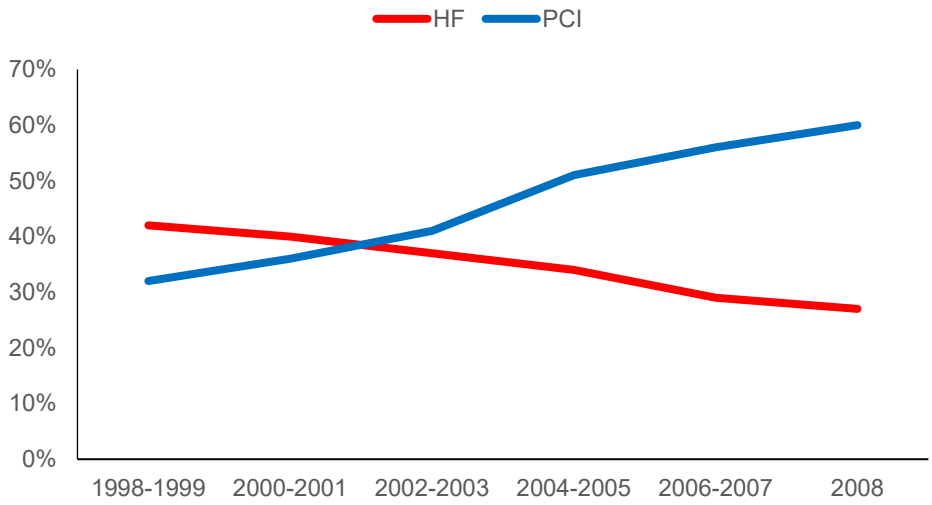
Práce od Killipa a Kimballa v roce 1967 byla jednou z prvních, která analyzovala incidenci a nepříznivý prognostický efekt HF během hospitalizace. V souboru 250 pacientů s konzervativně léčeným IM až 2/3 z nich mělo HF (Killipova klasifikace II-IV). Zatímco hospitalizační mortalita pacientů bez HF byla 6 %, úmrtnost nemocných se známkami srdeční insuficience byla od 17 % (Killip II) do 81 % (Killip IV).[19] Killipova klasifikace je dosud běžně používaná při hodnocení známek HF během hospitalizace pro IM (Killip I – bez známek srdeční insuficience, Killip II: chrůpky nad bázemi plic; Killip III: plicní edém a Killip IV: kardiogenní šok). Vysoký výskyt HF při konzervativní léčbě IM byl prokázán i v populační studii Worcester Heart Attack Study, kdy až 40 % pacientů s IM mezi léty 1975-1978 vykazovalo známky HF během pobytu v nemocnici. Nemocniční mortalita byla také vysoká, činila 19,9 %.[20] Zajímavým aspektem této studie je fakt, že i o 25 let později byla popisována stejná incidence HF během hospitalizace (39,9 %), nicméně mortalita poklesla na 12 %. Jedním z vysvětlení je o 8 let vyšší věk pacientů v kohortě z roku 2001 oproti letem 1975-1978; starší pacienti měli vyšší podíl komorbidit (např. diabetes mellitus 2.typu).

Zavedení trombolýzy jako hlavní metody léčby IM vedlo k poklesu nových případů HF během hospitalizace. V klinických studiích analyzujících různá trombolytická agens byla incidence HF během hospitalizace pro IM mezi 19-23 %.[21-23] Podobný výskyt HF během hospitalizace (27 %) byl prokázán i v meta-analýze 4 studií s přibližně 61 000 pacienty s IM léčených trombolýzou.[24]

Zavedení intervenční léčby IM pomocí perkutánní koronární intervence (PCI) vedlo k další redukci incidence HF během hospitalizace. V klinické studii Global Registry of Acute Coronary Events (GRACE) s 13 707 pacienty s akutním koronárním syndromem (STEMI, nonSTEMI, nestabilní angina pectoris) bez dosud známého HF jen 6 % z nich rozvinulo známky HF během hospitalizace.[25] V této studii bylo 59 % pacientů léčených PCI. Naproti tomu, v jiné studii s přibližně 2000 pacienty se STEMI, kteří byli všichni léčeni pomocí PCI, byla incidence HF během hospitalizace jen 1 %.[26]

Tento příznivý trend poklesu nových případů HF po IM byl prokázán i v různých populačních studiích, kde incidence HF po IM byla uváděna v rozmezí 4-12 %.[9] [27] Inverzní vztah mezi podílem pacientů s IM léčených reperfuzní terapií (trombolýza, PCI)

a incidencí HF během hospitalizace dokumentoval také švédský registr SWEDEHEART s téměř 200 000 pacienty. Mezi léty 1996-2008 došlo k poklesu incidence HF během hospitalizace pro IM ze 46 na 28 % (Obr.1).[28]



Obr. 1 Vztah mezi podílem pacientů s IM léčených pomocí PCI a incidencí HF během hospitalizace (Adaptováno z Desta a kol., 2015) [28]

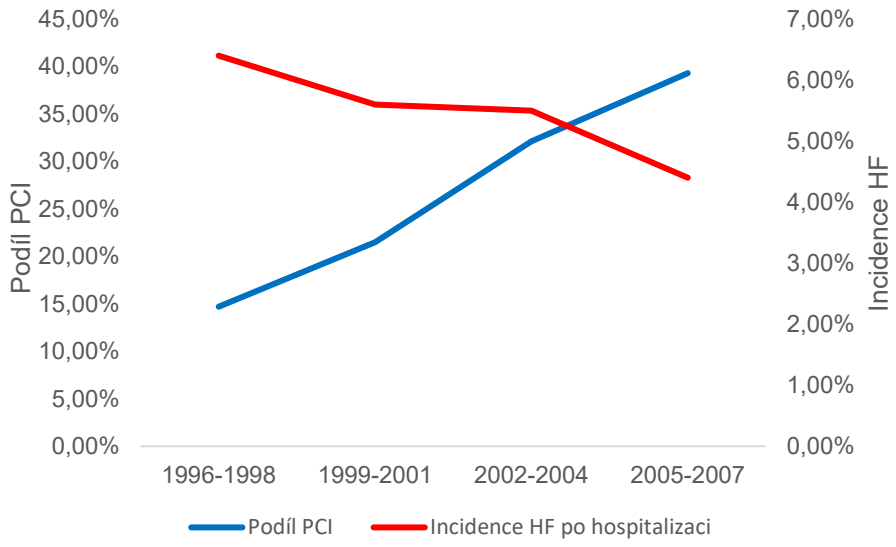
Opačný trend je patrný v případě výskytu HF při přijetí pro IM. Příčinou tohoto zdánlivě paradoxního faktu je zlepšení přednemocniční léčby pacientů s IM, kdy se do nemocnic dostávají pacienti, kteří by dříve přednemocniční fázi IM nepřežili. Zatímco mezi léty 1992-1996 mělo známky HF při přijetí jen 4 % pacientů s IM (60 % z nich léčeno trombolýzou), v již zmíněné studii GRACE z přelomu tisíciletí byla incidence HF při přijetí 13 %. [25, 29] Podobný výskyt (12 %) HF při přijetí pro IM byl popsán v registru ACTION analyzující téměř 270 000 pacientů přijatých pro STEMI i nonSTEMI mezi léty 2007-2011. [30]

2.1.2 Srdeční selhání po hospitalizaci pro infarkt myokardu

Výskyt nových případů HF po hospitalizaci je nejvyšší v časném období po propuštění (první měsíc), následně incidence klesá.[27, 31, 32] Podobně jako v případě HF během hospitalizace, i v případě jeho pozdního rozvoje lze ve většině studií pozorovat postupně klesající incidenci HF, a to díky zlepšení léčby IM. Ve studii Lichsteina a kol. 51 % pacientů s prodělaným IM (před rutinním používáním trombolytické terapie) rozvinulo známky HF během 30-měsíčního sledování.[33] V této studii byl mimo jiné

prokázán pozitivní efekt beta blokátorů na redukci mortality (o 39-55 %) a výskytu HF (o 25-45 %) ve všech 3 skupinách EF LK (<30 %, 30-39 %, ≥40 %). Naproti tomu v éře PCI byla v norské populační studii CVDNOR incidence HF 13 % při podobné délce sledování.[31] V souladu s předchozí evidencí v analýze pacientů s IM ze Západní Austrálie došlo mezi léty 1996-2007 k poklesu incidence HF v prvním roce po IM z 6,4 % na 4,4 % (Obr. 2). V této studii až 85 % z případů HF vzniklo v průběhu prvního měsíce po propuštění. [27]

Na druhé straně v analýze 676 pacientů s IM z Framinghamské studie byla popsána vzrůstající incidence HF po hospitalizaci pro IM. V této studii byli nemocní rozděleni do 3 dekád podle vzniku IM: 1970-1979, 1980-1989 a 1990-1999. Zatímco po adjustaci na více proměnných byla 30-denní incidence HF po IM v první dekádě 10 %, v druhé 14 %, v poslední dekádě činila až 23 %. Podobný trend byl pozorován i v pětileté incidenci HF: 20 %, 22 % a 34 %. Současně došlo k poklesu 30-denní mortality z 12 na 4 % a pětileté mortality z 29 % na 13 %. Tato vyšší incidence HF byla vysvětlována zvýšeným přežíváním pacientů díky zlepšené léčbě IM, zdokonalováním diagnostiky HF (pokrok v zobrazovacích metodách) a vyšším povědomím o HF.[32]



Obr. 2 Vztah mezi proporcí pacientů s IM léčených PCI a incidencí pozdního HF (Adaptováno z Hunga a kol., 2013)

2.2 Vývoj léčby infarktu myokardu

Léčba IM prodělala za posledních 100 let významnou evoluci. V roce 1912 Herrick v časopisu JAMA publikoval článek o tom, že trombóza věnčitých tepen je příčinou vzniku IM.[34] Herrick také navrhnul klid na lůžku jako prevenci ruptury myokardu. Tento postup zůstal hlavní léčebnou modalitou nemocných s IM po dobu následujících 50 let. V té době byla srdeční zástava na podkladě maligní arytmie častou příčinou úmrtí pacientů; nemocniční mortalita tehdy činila až 30 %.[35] Jinou významnou komplikací dlouhodobé imobilizace pacientů byla plicní embolie. Od padesátých let minulého století byla proto terapie IM rozšířena o antikoagulační terapii z důvodu prevence tromboembolické nemoci. Zřizování koronárních jednotek s kontinuální monitorací EKG vedlo ke snížení mortality na polovinu díky časné detekci a léčbě komorových arytmií a AV blokád pomocí defibrilace/kardiostimulace. V 60.letech 20.století se také postupně rozvíjela kardiochirurgická léčba ICHS pomocí bypassů, nicméně se dominantně jednalo o léčbu stabilní anginy pectoris. Postupně se také zlepšovala přednemocniční péče; důraz byl kladen na rychlé vyšetření pacientů s bolestmi na hrudi k potvrzení či vyloučení diagnózy akutního koronárního syndromu (AKS). Od sedmdesátých let byla zkoumána trombolytická léčba IM. Léčba IM pomocí intrakoronární aplikace streptokinázy byla poprvé publikována v r.1976.[36] Tato metoda léčby IM se ale globálně nerozšířila. Široké využití trombolytické léčby nastalo až po publikaci studií GISSI a ISIS-2, ve kterých bylo trombolytikum podáváno intravenózně.[37]

Nejvýznamnějším mezníkem v léčbě IM bylo zavedení PCI.[38, 39] PCI má oproti trombolýze řadu výhod: nižší riziko krvácení, vyšší úspěšnost rekanalizace a menší procento reziduální stenózy postižené tepny. Využití PCI vedlo k redukci mortality o přibližně 2/3 v porovnání s trombolýzou.[40, 41] Revaskularizace byla prováděna iniciálně pomocí implantace metalických stentů, které byly následně nahrazeny lékovými stenty, které mají nižší riziko rozvoje in-stent restenózy. Postupně se také zdokonalovala farmakoterapie ve formě antiagregační terapie – zpočátku byla používaná pouze monoterapie kyselinou acetylsalicylovou,[42] později došlo k implementaci clopidogrelu a následně i dalších, potentnějších inhibitorů P_2Y_{12} receptorů (tikagrelor a prasugrel). Zavedení blokády osy renin-angiotenzin-aldosteron pomocí inhibitorů angiotenzin

konvertujícího enzymu (ACEi) či inhibitorů AT_1 receptorů pro angiotenzin II (sartanů) a antagonistů mineralokortikoidních receptorů, ale také sympatoadrenálního systému pomocí beta blokátorů vedlo k redukci rizika mortality a rozvoje HF u pacientů s poinfarktovou dysfunkcí díky ovlivnění nepříznivé remodelace myokardu.[43-47] Inhibitory sodíko-glukózového kotransportéru 2 (SGLT2i) jsou poslední skupinou léků s pleiotropním efektem, u kterých byl mimo jiné prokázán příznivý efekt na redukci mortality a rozvoje HF u pacientů s anamnézou diabetu a vysokým kardiovaskulárním rizikem (kde byli i pacienti s anamnézou IM). [48, 49] Na druhé straně, v recentních studiích DAPA-MI a EMPACT-MI nebyl prokázán pozitivní vliv dapagliflozinu nebo empagliflozinu na redukci HF v případě jejich nasazení v akutní fáze IM rezultujícího v systolickou dysfunkci LK.[50, 51]

2.3 Rizikové faktory rozvoje srdečního selhání po infarktu myokardu

2.3.1 Věk

Vyšší věk je jedním z nejsilnějších prediktorů vzniku HF po IM.[28, 31, 52] Incidence HF při přijetí se zvyšuje o 50 % a po propuštění o 30-40 % na každých 10 let věku.[18, 25, 52] Jedním z důvodů většího rizika vzniku HF je nižší utilizace revaskularizace, optimální farmakoterapie u starších nemocných a větší počet komorbidit, které samotné poškozují myokard (diabetes mellitus, renální insuficience).[53] Starší pacienti mají sníženou funkční rezervu, kdy již rozsahem menší nekróza myokardu vede k rozvoji symptomatologie HF.

2.3.2 Ženské pohlaví

Navzdory protektivní roli ženských pohlavních hormonů (konkrétně estrogenu) na indukci nepříznivé remodelace myokardu,[54] řada studií popsala vyšší riziko rozvoje HF u žen.[18, 28, 52] Vysvětlením může být vyšší věk žen v době manifestace IM, vyšší prevalence komorbidit (diabetes mellitus, chronická renální insuficience, chronická obstrukční plicní nemoc) a častější výskyt atypické klinické prezentace IM.[55] Dalším predisponujícím faktorem vyšší incidence HF u žen je i vyšší podíl IM přední stěny, nižší využívání doporučené farmakoterapie a revaskularizačních metod ve srovnání s pacienty mužského pohlaví.[56, 57] Ženy jsou víc ohroženy i rozvojem časného HF během

hospitalizace a reinfarktem (poměr rizik 1.28).[57] Na druhé straně, v této práci po adjustaci na rizikové faktory se riziko rozvoje HF mezi muži a ženami nelišilo.[57]

2.3.3 Anamnéza předchozího infarktu myokardu

ICHS může vést k rozvoji asymptomatické dysfunkce myokardu. Tzv. „druhý úder“ v podobě recidivy IM může vést k nepříznivé remodelaci myokardu, která vede k rozvoji pozdního HF. Pacienti s anamnézou ICHS jsou náchylnější také k rozvoji HF během hospitalizace. Na základě dosud publikovaných studií je patrné, že anamnéza IM vede k 21-89% nárůstu rizika HF komplikujícího IM.[25, 28, 52, 58-60]

2.3.4 Chronické onemocnění ledvin

Chronické onemocnění ledvin (CKD) je charakterizováno chronickým systémovým zánětem, který přispívá ke zvýšené kardiovaskulární morbiditě a mortalitě. Důsledkem akcelerované aterosklerózy u pacientů s CKD a IM je prognosticky závažnější koronární nález s vyšším podílem nemoci 3 tepen a častějším postižení kmene levé věnčité tepny. Důsledkem nižšího využívání revaskularizačních metod u pacientů s CKD je větší rozsah infarktového ložiska rezultující ve významnější systolickou dysfunkci LK.[61, 62] V neposlední řadě existuje inverzní vztah mezi využíváním doporučené farmakoterapie po IM (ACEi, BB, antiagregace, statiny) a glomerulární filtrací.[63] Dalšími patofyziologickými mechanismy vysvětlujícími vyšší riziko HF po IM u pacientů s CKD je zvýšená aktivita sympatiku a systému renin-angiotenzin-aldosteron (RAAS), retence tekutin, anémie a sekundární hypertenze.

2.3.5 Diabetes mellitus

Diabetes mellitus (DM) 2.typu je častou komorbiditou pacientů s IM s prevalencí 13-43 %.[28, 31, 52, 59, 64] V různých studiích bylo dokumentováno zvýšené riziko jak časného (o 27-33 %), tak pozdního rozvoje HF (o 42-71 %).[25, 28, 52, 59, 64] Důsledkem diabetické neuropatie je častější atypická prezentace IM s absencí stenokardií vedoucí k prodloužení doby ischemie.[64, 65] DM je asociován se zvýšeným výskytem extenzivnějších aterosklerotických lézí včetně nemocí 3 tepen.[64] Pacienti s DM mají větší rozsah infarktového ložiska.[66] I při úspěšné rekanalizaci a plném obnovení průtoku v epikardiálních koronárních tepnách, byla u diabetiků častěji pozorována mikrovaskulární obstrukce se sníženým průtokem v mikrocirkulaci.[67] Zvýšená

incidence HF po IM u diabetiků je z části výsledkem i koincidencí dalších komorbidit jako jsou arteriální hypertenze, CKD, ale i přímým působením diabetu. Jedním z patofyziologických mechanismů rozvoje HF u DM je inzulinová rezistence, která vede k hyperinzulinémii, nadměrné fibróze myokardu a hypertrofii kardiomyocytů. Druhým mechanizmem je lipotoxicita způsobená nadměrnou koncentrací volných mastných kyselin, které vedou k indukci oxidačního stresu a k ektopickému ukládaní tuků. Výše uvedené změny vedou k rozvoji diastolické dysfunkce, která je u nemocných s IM a diabetem častěji pozorovaná.[68] U diabetiků navíc můžeme pozorovat zvýšenou aktivitu sympatoadrenálního systému a RAAS.

2.3.6 Tepová frekvence

Vyšší tepová frekvence je odrazem zvýšené sympatické aktivity jako kompenzačního mechanismu k zachování srdečního výdeje při rozsáhlejším IM. Každé zvýšení tepové frekvence o 10/min při příjmu je spojeno s 7-23% nárůstem incidence HF.[25, 59]

2.3.7 Fibrilace síní

Primomanifestace fibrilace síní (FiS) během hospitalizace je prediktorem rozvoje jak časného, tak pozdního HF. Jednou z příčin vzniku FiS během IM je objemové přetížení levé síně způsobené selhávající LK a/nebo mitrální regurgitací. Dalším indukujícím faktorem FiS je zánětlivá reakce vznikající po IM.[69] Pacienti s IM a nově diagnostikovanou FiS jsou starší, mají vyšší zastoupení komorbidit a závažnější projevy HF během hospitalizace.[70] Kromě vyššího rizika rozvoje HF mají tito pacienti vyšší riziko náhlé srdeční smrti a cévní mozkové příhody.[70] Primozáchyt FiS je asociován s 20-51 % zvýšením incidence HF po IM.[52, 71]

2.3.8 Rozsah postižení koronárních tepen a lokalizace infarktu

IM přední stěny je významným prediktorem rozvoje časného i pozdního HF.[26, 58] Souvisí to s rozsahem infarktového ložiska, které je největší v povodí ramus interventricularis anterior.[72] IM přední stěny je spojen s vyšším rizikem nepříznivé remodelace LK.[73] Nemoc 3 tepen je odrazem pokročilosti aterosklerotického postižení. Je častější u starších lidí, nemocných s DM a CHRI. Přítomnost nemocí 3 tepen je spojena

s přítomnosti Killipovy třídy >1, větší mortalitou, nižší EF LK a vyšším rizikem nepříznivé remodelace LK.[74, 75]

2.3.9 Predikce rizika po infarktu myokardu

Existuje několik stratifikačních nástrojů pro predikci rizika komplikací pacientů po IM, které vycházejí z klinických proměnných. Pro predikci rizika celkové mortality po IM, recentní doporučení ESC doporučují GRACE skóre pro nejlepší diskriminační schopnost.[76]

2.4 Patofyziologie srdečního selhání po infarktu myokardu

Z hlediska časového vztahu HF a IM rozlišujeme: a) HF vzniklé při rozvoji IM a přijetí do nemocnice, b) HF komplikující hospitalizaci pro IM a c) HF rozvinuté po propuštění z nemocnice.[16] Pozdní rozvoj srdečního selhání má odlišnou patogenezi a horší prognózu v porovnání s prvními 2 skupinami.[9, 16]

2.4.1 Časný rozvoj srdečního selhání

U HF vzniklého při rozvoji IM hraje roli preexistující dysfunkce myokardu (předchozí IM, již přítomné HF/kardiomyopatie, případně postižení myokardu způsobeno působením komorbidit – DM, arteriální hypertenze, obezity) v kombinaci s nekrózou a omráčením myokardu.[16] Již po 30 minutách od rozvoje ischemie dochází k strukturálním změnám kardiomyocytů, rozvíjí se jejich otok. Nastává také posun metabolismu myokardu z dominující beta-oxidace mastných kyselin na anaerobní glykolýzu s produkcí laktátu, která je výrazně méně energeticky efektivní. Při protrahované ischemii nastává kumulace laktátu, což rezultuje v další pokles pH a zvýšení koncentrace intracelulárního kalcia.[77] Nejdříve dochází k diastolické dysfunkci srdečního svalu, a posléze i k poruše kontraktility. Po určité délce trvání ischemie, obvykle v řádu několika hodin, dochází k rozvoji ireverzibilního stavu, a to buněčné smrti ve formě nekrózy a apoptózy. Rychlost ireverzibilního poškození buněk závisí na lokalizaci a dynamice uzávěru/významné stenózy věnčité tepny, ale také na přítomnosti kolaterál.

Stejné faktory vedou i k rozvoji HF během hospitalizace, kde sehrávají roli i mechanické komplikace IM (akutní mitrální regurgitace na podkladě ruptury papilárního svalu, defekt interventrikulárního septa či volné stěny LK), arytmie (FiS, komorové tachykardie, atrioventrikulární blokády), objemové přetížení (krystaloidy, kontrastní látka) či renální selhání (kontrastem indukovaná nefropatie a kardiorenální syndrom typu 1). Obnova průtoku v infarktové tepně (v současnosti zejména pomocí PCI) vede k indukci reperfuzního poškození myokardu. Jeho podkladem je poškození mikrocirkulace, které vede k tzv. „no-reflow“ fenoménu jakožto důsledku mikrovaskulární obstrukce. Po obnovení perfuze také dochází k oxidačnímu stresu s formací volných radikálů, které společně se zvýšenou koncentrací kalciových kationtů pronikají přes otevřené póry a vedou k poškození mitochondrií. [35] Reperfuzní postižení může tvořit až 50 % celkového rozsahu nekrózy kardiomyocytů.[78] Riziko časného HF zvyšují i komplikace PCI jako disekce intervenované tepny, akutní trombóza a malpozice stentu, uzávěr odstupující boční větve či distální embolizace fragmentů aterosklerotických plátů.[79]

2.4.2 Pozdní rozvoj srdečního selhání

Rozvoj HF po hospitalizaci je konsekvencí ztráty kardiomyocytů protrahovanou ischemií, hibernací a nepříznivou remodelací myokardu (NRM).[80] Hibernace myokardu je způsobena jeho protrahovanou hypoperfuzí, případně opakovanými atakami omráčení. Hibernující myokard je charakterizován porušenou kontraktilní schopností, která je protektivním mechanismem vedoucím k omezení spotřeby energie. Dalším ochranným mechanismem je změna hlavního energetického substrátu z mastných kyselin na glukózu, kterou jsou buňky schopny metabolizovat i za hypoxických podmínek. Po úspěšné reperfuzi dochází v tomto případě k obnově kontraktility myokardu. Na druhé straně, prohloubení ischemie hibernujících kardiomyocytů (progrese stenózy věnčité tepny, větší energetické nároky například při zvýšeném napětí ve stěně myokardu) vede k jejich nekróze.[77]

Nejdůležitějším faktorem, který vede k pozdnímu rozvoji HF, je NRM. Tento proces je charakterizován změnami srdečního svalu na makroskopické a mikroskopické úrovni, které vedou k dilataci a změně geometrie LK, posléze k poruše její kontraktility. NRM je důsledkem komplexní interakce mezi buněčnými elementy, extracelulární

matrix, signálními molekulami a neurohumorálními systémy.[81] Význam mají i genetické faktory a pohlaví – ženy jsou postižené méně vlivem estrogenu, který snižuje míru zánětu, apoptózy a změn v extracelulární matrix (ECM).[54]

Proces NRM můžeme rozdělit na časnou a pozdní fázi. Časná remodelace začíná již několik hodin po okluzi věnčité tepny a trvá přibližně týden.[77] Ischemická nekróza kardiomyocytů indukuje zánětlivou reakci s migrací různých buněčných elementů do infarktového ložiska. Prvními zde pronikajícími buňkami jsou neutrofily, které odstraňují nekrotické buňky. Jejich produktem jsou matrixové metaloproteinázy (MMP), které jsou důležitými regulátory v procesu NRM. MMP jsou rodinou 25 proteolytických enzymů, které jsou produkovány řadou buněk, kromě neutrofilů i makrofágy, endoteliálními buňkami, kardiomyocyty a fibroblasty.[82] MMP narušují extracelulární matrix, která je za fyziologických podmínek oporou kardiomyocytů. Aktivita MMP společně s nadměrným mechanickým natažením způsobuje ztenčení stěny myokardu a expanzi infarktového ložiska. Kolem třetího dne do infarktového ložiska migrují i makrofágy. Fibroblasty, které jsou rekrutovány lokálně i z cirkulace, jsou účinkem makrofágů aktivovány na myofibroblasty. Ve stejnou dobu dochází k aktivaci tkáňových inhibitorů matrixových metaloproteináz, které jsou protiváhou MMP. Myofibroblasty jsou nesmírně důležité pro redukci expanze infarktu, jelikož mají kontraktilní schopnosti a produkují bílkoviny ECM.[83, 84] Takto vzniká časná jizva, která je bohatá na buněčné elementy. K maturaci jizvy dochází v řádu dvou týdnů, kdy nastává redukce počtu leukocytů a myofibroblastů mechanismem apoptózy.

Proces pozdní remodelace začíná v průběhu týdnů-měsíců po IM a postihuje vzdálený, viabilní myokard.[85] Vyskytuje se predominantně u IM s větším rozsahem nekrózy, typicky u transmurálního IM přední stěny. Dochází k hypertrofii kardiomyocytů, čímž dle Laplaceova zákona klesá napětí ve stěně myokardu. Kromě hypertrofie kardiomyocytů ale dochází také k jejich elongaci, čímž vzniká excentrická hypertrofie myokardu. Zpočátku se kontraktilita při zvětšování komory díky Frank-Starlingově mechanismu (zmnožení interakcí mezi aktinem a myozinem) zvyšuje, ale po překročení optimální délky sarkomery naopak síla kontrakce myokardu klesá. Dalším negativním jevem je progrese mitrální regurgitace. Postupně se zvětšuje i endsystolický objem a dochází k poklesu systolické funkce LK.

Velký význam v procesu NRM hraje zvýšená aktivita sympatiku a RAAS. Jejich krátkodobá aktivace je prospěšná, protože pomáhá udržet srdeční kontraktilitu a

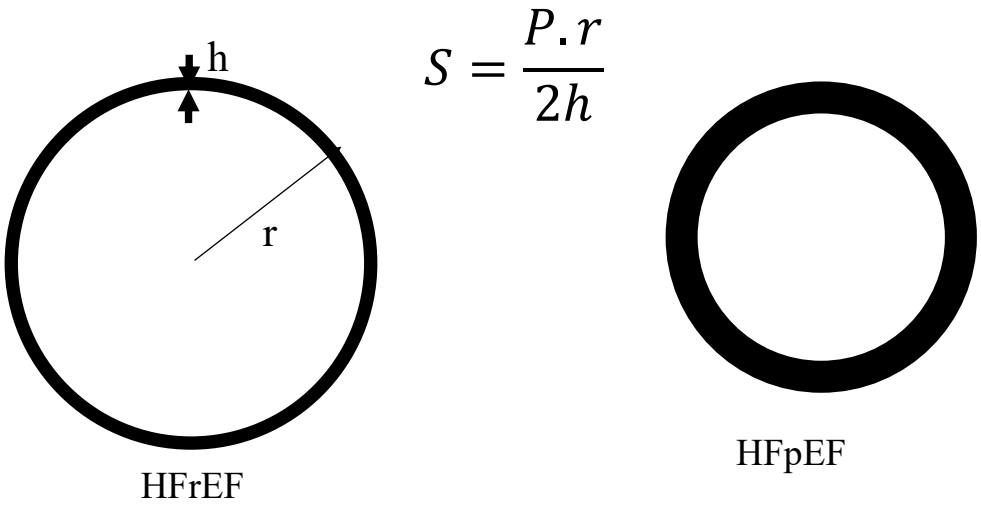
adekvátní perfusi tkání. Sympatikus účinkem na β-adrenergní receptory vede k tachykardii a zvýšení kontraktility viabilního myokardu, kompenzující ischemickou ztrátu kardiomyocytů. Těmito mechanismy se udržuje adekvátní srdeční výdej. Negativním akutním efektem adrenergní hyperstimulace je vyšší riziko tachyarytmií. Aktivace RAAS vede k vazokonstrikci. Dlouhodobá hyperaktivita těchto fylogeneticky starých mechanismů vede k progresi a akceleraci NRM. Zvýšená aktivita sympatiku způsobuje desenzitizaci β-receptorů jak snížením jejich počtu, tak snížením citlivosti. Dochází tím k odpojení excitace od kontrakce kardiomyocytů. Negativním účinkem dlouhodobé adrenergní stimulace je akcelerace apoptózy kardiomyocytů a fibrózy. Dalším důsledkem je zvýšená sekrece reninu, čímž dochází k vystupňování aktivity RAAS. Hlavním mediátorem nepříznivého účinku systému RAAS je angiotenzin II a jeho působení na AT1 receptory. Podílí se na hypertrofii kardiomyocytů, nadměrné fibróze, má proapoptotický efekt a narušuje homeostázu ECM. Indukuje také produkci aldosteronu, který má podobné nepříznivé účinky na myokard.

2.5 Biochemické parametry

2.5.1 Biomarkery nekrózy myokardu a natriuretické peptidy

Srdeční troponin je klíčovým regulačním proteinem kontrakce a relaxace kardiomyocytů. Vysoce senzitivní srdeční troponin (hsTn) je v současnosti doporučeným biomarkerem v rámci diagnostiky IM.[79] Hladiny hsTnT a hsTnI se prudce zvyšují již do 1 hodiny po vzniku symptomů IM, maximálních hodnot dosahují přibližně po 12 hodinách a jejich zvýšení trvá několik dní.[86, 87] U hsTnT byl popsán druhý vrchol po 77 hodinách.[87] Hodnoty hsTnT měřené 48-72 hodin (ve fázi plateau) korelují s velikostí IM stanovené pomocí magnetické rezonance a negativně s EF LK.[88] Maximální hodnoty troponinu T jsou prediktory mortality a HF po IM.[89]

Natriuretické peptidy jsou produkovány kardiomyocyty jako odpověď na zvýšené napětí v cévní stěně. Dle Laplaceova zákonu je napětí ve stěně přímo úměrné poloměru srdeční dutiny a intrakavitálnímu tlaku a nepřímo úměrné tloušťce stěny komory (**Obr.3**). Biologickým efektem natriuretických peptidů je zvýšená diuréza, natriuréza, vazodilatace, mají také antifibrotický efekt. Jsou protipólem RAAS a sympatodrenálního systému.



Obr.3 Laplaceův zákon: napětí ve stěně myokardu je větší u pacientů s HFrEF vzhledem k většímu poloměru komory a menší tloušťce stěn v porovnání s HFpEF

Dalším stimulem k sekreci natriuretických peptidů je ischemie myokardu. Natriuretický peptid typu B (BNP) i jeho biologicky neaktivní N-terminálního fragment (NT-proBNP) korelují s velikostí infarktového ložiska a negativně s EF LK.[90, 91] Hladiny BNP dosahují vrchol za 16-18 h po vzniku IM a následně klesají, ale přibližně u poloviny pacientů s IM dosahují druhé maximum za 5 dní.[92] Tito pacienti s bifázickou dynamikou BNP mají vysoké riziko NRM.[92] Zvýšené hladiny BNP i NT-proBNP po IM jsou asociovány s horší prognózou a vyšší incidencí HF.[93, 94]

2.5.1 Zánětlivé parametry

IM je asociován s rozvojem zánětlivé reakce, jejíž cílem je odstranění nekrotických buněk a detritu s následnou formací jizvy k zachování integrity stěny komory. Protrahovaný zánět vede k expanzi infarktového ložiska a rozvoji NRM.[95] Při rozvoji IM můžeme pozorovat i zvýšený počet bílých krvinek se zvýšeným podílem neutrofilních granulocytů. V meta-analýze 14 studií s 10 000 pacientů po STEMI byl zvýšený poměr neutrofilů ke lymfocytům významným prediktorem nejen mortality, ale i rozvoje HF.[96]

C-reaktivní protein (CRP) je protein akutní fáze, který je senzitivním, ale málo specifickým ukazatelem zánětu. Jeho syntéza v játrech je ovlivňena hladinou interleukinů 1, 6 a tumor necrosis faktorem. Hladina CRP se zvyšuje po 4-6 hodinách od vzniku IM, maximální hladiny dosahuje po 2-4 dnech a následně klesá k bazálním hodnotám po 7-

10 dnech.[97] Stanovení vysoce senzitivního CRP (hsCRP) se ukazuje jako vhodný parametr rizikové stratifikace pacientů s AKS nad rámec standardních biochemických a echokardiografických parametrů.[98, 99] Hodnoty hsCRP při přijetí pozitivně korelují s Killipovou třídou a negativně s EF LK stanovenou 1 rok po IM.[100] Pacienti s IM a hsCRP při přijetí nad 10 mg/L měli 2,4 krát větší riziko rozvoje HF po IM v porovnání s nemocnými s nízkou hladinou hsCRP.[100] Ve studii CANTOS byly vyšší počáteční koncentrace hsCRP u pacientů s prodělaným IM asociovány s větším rizikem hospitalizace pro HF.[101] Významná je i prediktivní hodnota maximální hladiny hsCRP u pacientů s IM, která je asociována s vyšší pravděpodobností NRM, hospitalizací pro HF, nemocniční i dlouhodobou mortalitou. [102, 103]

Vznik IM vede ke zvýšené tvorbě cytokinů v srdci i cirkulujícími buňkami imunitního systému.[104] Cytokiny hrají klíčovou roli v indukci a regulaci zánětlivé odpovědi po IM. Interleukin 1 (IL-1) je nejdůležitějším prozánětlivým cytokinem, který má negativně inotropní efekt.[105] U pacientů po STEMI vedlo podávání anakinry, inhibitoru IL-1, k redukci zánětlivé reakce měřené pomocí hsCRP a snížení incidence HF.[105] IL-1 ovlivňuje syntézu IL-6, který je zástupcem cytokinů s jak prozánětlivým, tak protizánětlivým efektem. [106] Účinek IL-6 je zprostředkován vazbou na membránový receptor (klasická signalizace) nebo solubilní formu receptoru. Jeho hladiny dosahují maxima mezi 1.-2.dnem po přijetí pro IM.[107] IL-6 hraje důležitou roli nejen v procesu NRM, ale i při reperfuzním poškození myokardu.[108] Hladiny IL-6 korelují s rozsahem infarktového ložiska.[109] Existuje evidence o pozitivní asociaci hladin IL-6 se zvýšenou mortalitou a incidencí HF u pacientů po IM, i po adjustaci na hladiny troponinu či natriuretických peptidů.[110] Představitelem protizánětlivého cytokinu je IL-10, který je produkován makrofágy a aktivovanými T lymfocyty v infarktovém ložisku. IL-10 brání rozvoji přehnané zánětlivé reakce po IM.[111] U myší s experimentálně indukovaným IM vedla administrace IL-10 k redukci zánětu a NRM.[112]

2.5.3 Parametry metabolismu železa

Železo je esenciálním prvkem, který je důležitý pro syntézu bílkovin, nukleových kyselin, funkci imunitního systému, erytropoézu, transport kyslíku a v neposlední řadě je kofaktorem enzymů Krebsova cyklu a součástí dýchacího řetězce.[113] Železo má tedy významnou roli pro tvorbu energie ve formě adenozintrifosfátu. Srdeční sval patří mezi

orgány nejvíce zasažené sideropenií. Deficit železa (iron deficiency, ID) je obvykle diagnostikován na podkladě hladin feritinu (zásobní protein obsahující železo) a saturace transferinu (transportní bílkovina přenášející železo ke tkáním). Podstatou absolutního ID je nízká hladina feritinu, což odráží malé zásoby železa v organismu. V případě relativní sideropenie, která je charakterizovaná nízkou saturací transferinu, je dominantní snížená dostupnost železa. Solubilní transferinový receptor je parametr ID, který ukazuje na zvýšenou tkáňovou poptávku po železe. Na rozdíl od předchozích parametrů, není ovlivněn zánětlivou reakcí.[114] ID u pacientů s HF je častou komorbiditou, která je asociována s horší tolerancí zátěže, horší kvalitou života, zvýšenou mortalitou a mírou hospitalizací.[115, 116] ID je častý i u pacientů po IM – v meta-analýze 7 studií s 2821 pacienty činila prevalence ID u pacientů s AKS 43 %.[117] Na rozdíl od HF, vliv ID na prognózu pacientů s IM je nedostatečně analyzován a výsledky studií se liší zejména v důsledku absence uniformní definice ID a malého počtu pacientů.[118-121]

2.5.4 Orexin

Orexin (hypokretin) je hormonem, který je produkován neurony hypotalamu. Existuje ve 2 izoformách (orexin A, orexin B), které působí přes orexinový receptor 1 a 2. Oba orexinové receptory jsou přítomné i v srdečním svalu. Tyto receptory patří do superrodiny receptorů spřažených s G-proteinem, proto jsou schopny aktivovat celou řadu signálních drah. [122] Afinita orexinu A k oběma receptorům je podobná, zatímco orexinu B se preferenčně váže na orexinový receptor 2.[123] Mezi známé účinky orexinu patří regulace spánkového cyklu, apetitu i energetické homeostázy. Nedávno byla popsána funkce orexinu v regulaci kardiorespiračního systému spočívající v interakci se sympatikem.[124] U spontánně hypertenzních myší vedlo podávání antagonisty obou orexinových receptorů k poklesu krevního tlaku a tepové frekvence.[125] U myší s IM indukovaným ligací ramus interventricularis anterior měla aplikace orexinu B kardioprotektivní efekt, protože vedla k redukci infarktového ložiska.[122] Ve vzorku srdečního svalu u lidí s HF podstupujících CABG exprese receptoru 2 pro orexin negativně korelovala s NYHA třídou.[122] Význam orexinového systému u pacientů s IM zatím nebyl popsán.

2.6 Echokardiografie

Echokardiografické vyšetření je základní zobrazovací metodou myokardu na principu ultrazvuku, která hraje fundamentální roli v predikci krátkodobé a dlouhodobé prognózy pacientů po IM.[126] V akutní fázi umožňuje posoudit celkovou systolickou funkci LK, lokální poruchy kinetiky, přítomnost intrakavitálních trombů (k vizualizaci ouška levé síně je nutné transezofageální vyšetření) či mechanických komplikací IM (akutní mitrální regurgitace při ruptuře papilárního svalu, defekt septa komor, ruptura volné stěny komory či pseudoaneurysma). Nevýhodou echokardiografie je velká intra- i interindividuální variabilita.[127] Ejekční frakce je nejčastěji používaným parametrem systolické funkce LK. Šestiměsíční mortalita je výrazně vyšší u pacientů s IM a EF LK pod 40 % před propuštěním v porovnání s pacienty s EF nad 40 %.[128] Úmrtnost pacientů po IM je zvýšená i v případě EF LK v rozmezí 41-49 %.[129] Každé snížení EF LK o 5 % je spojené se 7% nárůstem rizika HF u pacientů po IM.[52] Nesmíme opomenout úlohu echokardiografie v hodnocení funkce pravé komory (PK), která může být postižena infarktem při současném IM spodní stěny. Vzhledem k tvaru PK připomínajícím pyramidu je komplexní posouzení její funkce složité. Tricuspid annular plain systolic excursion (TAPSE) je ukazatelem longitudinální kontraktility PK. Dysfunkce PK hodnocena pomocí TAPSE ≤ 14 mm byla nezávislým prediktorem mortality u 192 pacientů se STEMI komplikovaným kardiogenním šokem.[130] Frakční změna plochy (fractional area change, FAC) je lepším ukazatelem systolické funkce PK než TAPSE, protože hodnotí i radiální kontraktilitu. Ve studii analyzující pacienty s IM byla FAC <32 %, na rozdíl od TAPSE, prediktorem mortality, HF hospitalizací a reinfarktu.[131]

Trojrozměrná echokardiografie je přesnější metodou k posouzení objemů LK či PK v porovnání s konvenční 2D metodou, [132] nicméně její prediktivní hodnota u pacientů s IM dosud nebyla analyzována v žádné klinické studii.

Utilizace levostranné echokontrastní látky zlepšuje viditelnost endokardu v případě špatné vyšetřitelnosti pacientů, a tím přesnější posouzení lokálních poruch kinetiky či EF LK. Dalším benefitem kontrastní echokardiografie je zlepšená detekce trombů a jejich odlišení od artefaktů. Mezi méně využívanými vlastnostmi této metody je detekce neperfundovaných segmentů LK (absence opacifikace po podání echokontrastní látky), a tedy odlišení infarktového ložiska od omráčeného

myokardu.[126] Absence opacifikace myokardu po podání echokontrastu při normálním průtoku v epikardiální koronární tepně po PCI (důsledkem mikrovaskulárního postižení) je prediktorem pozdní NRM.[75]

Index hybnosti stěn (wall motion score index, WMSI) je vypočítáván jako podíl součtu bodů za hybnost jednotlivých segmentů LK (1 bod: normální kinetika, 2 body: hypokinéza, 3 body: akinéza a 4 body: dyskinéza) a počtu segmentů. V akutní fázi WMSI lépe reflektuje závažnost IM, protože na rozdíl od EF LK není ovlivněn kompenzatorní hyperkinézou ischemií nepostižených segmentů myokardu.[126] Různé studie prokázali superioritu WMSI vůči EF LK v predikci mortality či rozvoje HF u pacientů po IM.[133, 134]

Speckle tracking je zástupcem deformační analýzy myokardu. Nejčastěji hodnoceným parametrem pomocí této metody je globální longitudinální strain (GLS) umožňující detekci subklinické systolické dysfunkce LK. Oproti hodnocení EF LK má GLS nižší interindividuální variabilitu.[135] V různých studiích byl GLS nezávislým prediktorem mortality a rozvoje časného a pozdního HF i při EF LK nad 40 %.[136, 137] GLS větší než -12,46 % byl také prediktorem NRM. [138] GLS může být proto vhodným parametrem k identifikaci pacientů potenciálně profitujících z farmakologické neurohumorální blokády i při absenci snížené EF LK.

Echokardiografie umožňuje i hodnocení diastolické funkce LK. Diastolická dysfunkce 3.stupně (restriktivní plnění LK), charakterizovaná poměrem vln E:A > 2 a deceleračním časem vlny E pod 140 ms, byla prediktorem mortality pacientů po IM nezávisle na EF LK.[139] Pomocí dopplerovské echokardiografie lze odhadovat plnící tlaky LK na základě poměru vlny E (časné plnění komory na transmitrálním průtoku) a e‘ (tkáňová dopplerovská analýza). Zvýšené plnící tlaky definované poměrem E/e‘ nad 15 byly asociovány se zvýšenou mortalitou pacientů po IM a výskytem HF bez ohledu na EF LK.[140]

3. Hypotéza

Navzdory značným pokrokům ve farmakologické i intervenční léčbě je reziduální riziko pacientů s IM vysoké. Proto je důležitá včasná identifikace a intervence rizikových pacientů, jako i hledání nových patofyziologických cest, které ovlivňují prognózu pacientů po IM.

Srdeční selhání po IM je spojeno se zvýšeným rizikem morbidity a mortality. Časná identifikace a terapie HF proto nabízí příležitost, jak zlepšit prognózu po IM. V současné době ale chybí jednoduché nástroje pro časnou identifikaci pacientů s HF po IM. Naší první hypotézou proto bylo, že použitím dotazníku zaměřeného na symptomy a známky srdečního selhání dokážeme identifikovat osoby ve zvýšeném riziku vzniku komplikací po IM. Pro tento účel jsme použili dotazník Kansas City Cardiomyopathy Questionnaire (KCCQ), který se používá k hodnocení kvality života pacientů se srdečním selháním. Význam použití KCCQ po IM je nejasný. Dále jsme předpokládali, že kombinací symptomů a známek srdečního selhání s klinickými proměnnými dokážeme vytvořit stratifikační nástroj, který bude lépe identifikovat rizikové osoby než v současné době doporučené GRACE skóre.

Deficit železa u pacientů s HF je spojen s horší prognózou a symptomatologií. U pacientů po IM je efekt sideropenie méně prozkoumán. Naší druhou hypotézou je, že deficit železa má nepříznivý efekt na prognózu pacientů s IM. Očekáváme, že u pacientů s IM bude potřeba stanovit jinou definici deficitu železa než v případě HF, jelikož jsou tyto parametry ovlivněné zánětlivou reakcí. Dalším problémem je, že současné definice ID nejsou založené na morbi-mortalitních datech. Pro budoucí intervenční studie proto bude důležité porovnat prediktivní hodnotu různých definicí ID na prognózu pacientů po IM.

Existuje evidence o vlivu orexinového systému na HF. Zvýšená aktivita orexinového systému měla kardioprotektivní efekt u HF. Zatím ale žádná studie nezkoumala efekt orexinového systému u pacientů po IM. Naši třetí testovanou hypotézou je, že orexinový systém ovlivňuje prognózu pacientů po IM.

4. Cíl práce

1. Posoudit prediktivní hodnotu dotazníku KCCQ (a jeho jednotlivých komponent) u pacientů po IM.

2. Navrhnout nové stratifikační skóre pro predikci rizika mortality po IM kombinující symptomy a známky srdečního selhání a klinické proměnné.

3. Porovnat asociaci různých definicí deficitu železa s rizikem celkové mortality u pacientů s IM.

4. Popsat současný výskyt systolické dysfunkce levé komory u pacientů po prvním infarktu myokardu a zjistit faktory asociované se zlepšením ejekční frakce.

5. Analyzovat vztah mezi aktivitou orexinového systému a přežíváním pacientů po infarktu myokardu.

5. Metodika

5.1 Populace

Analyzovali jsme konsekutivní pacienty, kteří byli přijati na Kliniku kardiologie IKEM s diagnózou IM od června 2017 do roku 2023 a podepsali informovaný souhlas se zařazením do registru AMBITION. Tento prospektivní registr slouží ke shromažďování klinických dat a krevních vzorků pacientů po IM.

5.2 Studijní procedury

Během hospitalizace byla od pacientů odebrána podrobná anamnéza, první den po přijetí do nemocnice byl pacientům proveden odběr biologického materiálu k analýze a alikvoty byly zmraženy na teplotu mínus 80 °C. 1 měsíc po hospitalizaci pacienti korespondenčně vyplnili dotazník KCCQ. Po 1 roce od hospitalizace pro IM byli pacienti se systolickou dysfunkcí a EF pod 40 % v době hospitalizace pozváni ke klinické kontrole k posouzení symptomů a známek HF. Součástí této kontroly bylo provedení biochemické analýzy, opětovné vyplnění pacientského dotazníku KCCQ, analýza záznamu EKG, vyhodnocení klinických pacientských událostí od propuštění z nemocnice a echokardiografické vyšetření k posouzení vývoje EF.

5.3 Statistická analýza

K provedení statistické analýzy dat jsme použili programy R (R Foundation for Statistical Computing, Vídeň, Rakousko), JMP 17, SPSS verze 25.0 (IBM Corporation, Armonk, NY) a STATA verze 17. Podrobná charakteristika použitých statistických metod je uvedena v konkrétních publikacích.

6. Výsledky výzkumné práce

6.1 Prediktivní hodnota dotazníku KCCQ po infarktu myokardu

Pacienti po prodělaném IM jsou ve vysokém riziku nepříznivých kardiovaskulárních událostí, včetně HF. Riziko vzniku HF po IM je nejvyšší v prvních měsících po IM.[27, 31] Časná kontrola pacientů po prodělaném IM nebo s HF zlepšuje jejich adherenci k léčbě a snižuje riziko kardiovaskulárních hospitalizací.[141, 142] Kapacita zdravotnictví ale neumožňuje, aby byli všichni pacienti kardiologicky vyšetřeni časně po hospitalizaci pro IM.

KCCQ představuje vhodný nástroj k posouzení tíže a frekvence symptomů, kvality života a sociálních limitací u pacientů s HF.[143] Je vyplňován samotnými pacienty, čímž odpadá závislost na konkrétním lékaři. KCCQ má vyšší citlivost a spolehlivost k posuzování symptomatologie nemocných než stanovení NYHA třídy. Pozůstává z 23 otázek, maximální možný počet získaných bodů je 100; víc bodů znamená lepší kvalitu života. Existuje dobrá evidence o asociaci KCCQ s prognózou (mortalita, hospitalizace pro HF) pacientů jak s akutním, tak chronickým HF.[144-146] Užitečnost KCCQ dotazníku v predikci prognózy v neselektované populaci pacientů s IM dosud nebyla zkoumána. Cílem naší práce bylo analyzovat asociaci dotazníku KCCQ (celkové souhrnné skóre) a jeho individuálních komponent s rizikem celkové mortality pacientů po IM.

Metodika

Do studie jsme zařadili 1721 pacientů, kteří byli hospitalizováni na Klinice kardiologie IKEM pro IM v období od června 2017 do září 2022. Hodnotili jsme nemocné, kteří vyplnili dotazník KCCQ 1 měsíc po propuštění (papírová forma zaslaná poštou nebo elektronická forma přes aplikaci). Data o mortalitě k 30.červnu 2023 byla získána z ÚZIS. Využili jsme Coxův model proporcionálních rizik k analýze asociace celkového souhrnného skóre KCCQ s rizikem mortality – neadjustovaný a následně adjustované na jednotlivé komponenty GRACE skóre. Následně jsme pomocí dopředné krokové regrese identifikovali komponenty KCCQ dotazníku s nejvyšší asociací s rizikem mortality.

Výsledky

Celkem 1135 pacientů (66 % oprávněných) vyplnilo dotazník KCCQ. Průměrný věk pacientů byl 64 ±12 let, 26,7 % tvořily ženy. Během mediánu sledování 46 měsíců (mezikvartilové rozpětí 29-61) zemřelo 146 pacientů (12,9 %). Pacienti, kteří KCCQ nevyplnili, byli starší, měli vyšší zastoupení Killipovy třídy >1, systolické dysfunkce LK s EF <40 %, ale jejich přežívání se signifikantně nelišilo od pacientů, kteří tento dotazník zodpověděli.

Z vyšetřených pacientů mělo 30 (2,6 %) celkové souhrnné skóre pod 25 bodů odpovídající velmi těžkému až těžkému postižení, 114 (10 %) získalo 25-49 bodů odpovídající těžkému postižení, 274 (24,1 %) mělo 50-74 bodů odpovídající střednímu až lehkému postižení a 717 (63,2 %) nemocných po IM mělo skóre 75-100 bodů odpovídající lehkému až žádnému postižení. V adjustovaném modelu bylo KCCQ skóre 0-24 (HR 6.05, 95% CI 3,43-10,68, p <0.001) a 25-49 (HR 2.66, 95% CI 1.7-4.17, p <0.001) nezávisle asociováno se zvýšeným rizikem úmrtí ve srovnání s KCCQ skóre ≥50. Z dotazníku KCCQ, otoky dolních končetin, změna symptomů v posledních 2 týdnech a omezení chůze nejlépe predikovaly zvýšené riziko mortality pacientů po IM.

Závěr

Objektivizace symptomů a známek srdečního selhání korespondenční cestou 1 měsíc po propuštění z nemocnice pomocí dotazníku KCCQ dokáže identifikovat pacienty ve zvýšeném riziku celkové mortality po IM.

Publikace

Wohlfahrt P, Jenča D, Melenovský V, et al.
Remote Heart Failure Symptoms Assessment After Myocardial Infarction Identifies Patients at Risk for Death. J Am Heart Assoc. 2024;13(2):e032505. doi:10.1161/JAHA.123.032505

Kompletní znění článku v anglickém jazyce je přiloženo na konci práce.

6.2 Prediktivní skóre kombinující klinické proměnné a symptomy srdečního selhání po infarktu myokardu

GRACE skóre je doporučeným nástrojem k určení rizika úmrtí u pacientů s AKS.[86] Rozvoj HF po IM je hlavním determinantem prognózy pacientů.[16] Ke zhodnocení známek HF během hospitalizace pro IM používáme Killipovu klasifikaci, která hodnotí dominantně plicní kongesci. Pozdní rozvoj HF je spojen s horší prognózou v porovnání s HF během hospitalizace, přičemž riziko jeho vzniku je nejvyšší v prvních měsících od propuštění.[9, 27] Pátrání po známkách a symptomech HF musí být nezbytnou součástí ambulantních kontrol u pacientů po IM. V předešlé práci jsme prokázali, že vzdálené hodnocení symptomů HF pomocí dotazníku KCCQ 1 měsíc po hospitalizaci umožňuje určit pacienty po IM s vyšším rizikem úmrtí.

Cílem této práce bylo vytvořit a validovat prognostické skóre k predikci mortality pacientů po IM, které by kombinovalo vzdáleně posuzované symptomy a známky HF a klinické rizikové faktory zjištěné během hospitalizace a porovnat ho s GRACE skóre.

Metodika

Do analýzy jsme zařadili konsekutivní pacienty, kteří byli hospitalizováni na Klinice kardiologie IKEM pro IM v období mezi červnem 2017 a září 2022. Celkem 1135 pacientů bylo náhodně rozděleno mezi derivační (70 %) a validační (30 %) kohortu. Pomocí Coxovy regrese jsme identifikovali jednotlivé komponenty dotazníku KCCQ zasílaného 1 měsíc po hospitalizaci a klinické parametry, které byly prediktory mortality v derivační kohortě. Podkladem námi vytvořeného PragueMI skóre byly regresní koeficienty jednotlivých prediktorů.

Výsledky

Průměrný věk pacientů byl 64 ± 12 let, 26.7 % tvořily ženy. Model s nejlepší prediktivní hodnotou zahrnoval tyto klinické parametry: věk, anamnéza HF, kreatinin, tepová frekvence při přijetí, EF LK před propuštěním a následující symptomy HF: omezení chůze, otoky dolních končetin a změna symptomů v posledních 2 týdnech.

PragueMi skóre bylo schopné stratifikovat riziko celkové mortality. Všichni pacienti s pacienti PragueMi skóre pod 13 bodů (n=196, 17,3 %) se dožili 2 let. Naproti tomu pacienti s PragueMi skóre nad 21 (n=115, 10,1 %) měli 22,2% roční mortalitu.

Ve validační kohortě námi vytvořené PragueMi skóre lépe diskriminovalo riziko mortality než GRACE skóre, a to jak v 6-měsíčním sledování (plocha pod ROC křivkou 90,1; 95% CI 81,8-98,4 pro PragueMI vs. 77,4; 95% CI 62,2-92,5 pro GRACE, p=0,004), tak i v ročním sledování (plocha pod ROC křivkou 89,7; 95% CI 83,5-96,0 vs. 76,2, 95%CI 64,7-87,7; p=0,004).

Závěr

PragueMI skóre kombinující symptomy HF a klinické parametry má u pacientů po IM větší prediktivní hodnotu než v současnosti doporučené GRACE skóre.

Publikace

Wohlfahrt P, Jenča D, Melenovský V, et al.
Development and validation of a prognostic score integrating remote heart failure symptoms and clinical variables in mortality risk prediction after myocardial infarction. The PragueMi score. Eur J Prev Cardiol. Published online March 18, 2024. doi:10.1093/eurjpc/zwae114
Kompletní znění článku v anglickém jazyce je přiloženo na konci práce.

6.3 Analýza parametrů deficitu železa a jejich vlivu na prognózu pacientů po infarktu myokardu

Deficit železa (ID) je častou komorbiditou u pacientů s kardiovaskulárními onemocněním, HF či ICHS nevyjímaje. Podle doporučení ESC jsou k diagnostice ID u pacientů s HF standardně používány hladiny feritinu a saturace transferinu, kdy absolutní ID je stanovena na základě hodnot feritinu pod 100 μmol/L a relativní (funkční) ID je definována hladinou feritinu od 100 do 299 μmol/L a saturací transferinu pod 20 %.[2] Vyšetření samotné hladiny sérového železa (S-Fe) k určení diagnózy ID není dostačující. V případě IM dosud nebyla přijata jednotná diagnostická kritéria ID, která by byla určena na základě „tvrdých" endpointů. Nejčastěji byly ve studiích s pacienty po IM použity stejné referenční meze pro diagnózu ID jako u HF. S-Fe, feritin i transferin jsou ovlivněny zánětlivou reakcí doprovázející IM. Feritin je navíc při IM uvolňován z nekrotických buněk.[147] Vhodnějším parametrem ID v případě IM může být solubilní transferinový receptor (sTfR), který není proteinem akutní fáze. Cílem této práce bylo analyzovat rozdílné definice ID a určit, které jsou nejvhodnějšími ukazateli mortality pacientů po IM.

Metodika

Analyzovali jsme 1156 konsekutivních pacientů přijatých mezi červnem 2017 a únorem 2023 s diagnózou IM 1.typu dle 4.univerzální definice IM [79]. Vyloučili jsme pacienty s anamnézou ICHS a hemolytickém sérem, které znemožnilo analýzu parametrů metabolismu železa. Odběr krve pro stanovení parametrů metabolismu železa jsme prováděli 1. den po přijetí do nemocnice. Stanovení parametrů proběhlo v lokální laboratoři. Pomocí modelu model „omezených kubických splajnů" (z angl. „restricted cubic splines") s adjustací na věk jsme analyzovali nelineární asociaci mezi parametry metabolismu železa a mortalitou. K určení ideálních mezí ID jsme použili metodu rozhodovacích stromů. Coxův model proporcionálních rizik jsme použili k analýze asociace rozdílných definic ID s mortalitou pacientů po IM. Údaje o mortalitě byly získány z Ústavu zdravotnických informací a statistiky (ÚZIS) k 1.prosinci 2023.

Výsledky

Průměrný věk nemocných s IM byl 64±12 let, muži tvořili 75 % populace. Medián sledování byl 3,4 let, během kterého zemřelo 194 (16,8 %) pacientů. Hladina S-Fe ≤13 μmol/L (HR 1.67, 95 % CI 1.19–2.34) a zejména kombinace S-Fe ≤12.8 μmol/L a sTfR ≥3 mg/L (HR 2.56, 95 % CI 1.64–3.99) byly nejvíce asociovány se zvýšeným rizikem mortality i po multivariantní adjustaci (věk, pohlaví, EF <35 %, anamnéza HF, glomerulární filtrace, systolický krevní tlak a tepová frekvence při přijetí, absence PCI, Killipova třída). Vytvořili jsme PragueID kritéria se 4 skupinami pacientů: první skupina měla S-Fe >12,8 μmol/L a sTfR <3 mg/L, další měla S-Fe ≤ 12,8 μmol/L a sTfR ≥3 mg/L, třetí S-Fe >12,8 μmol/L a sTfR ≥3 mg/L, poslední skupina měla S-Fe ≤ 12,8 a sTfR ≥3 mg/L. Nejrizikovější skupinou byli pacienti s nízkou hladinou sérového železa a vysokou hladinou sTfR, kteří měli po multivariantní adjustaci téměř trojnásobně zvýšené riziko úmrtí v porovnání s nemocnými bez ID. Do středně rizikové skupiny patřili nemocní, kteří měli normální hladinu sTfR a nízkou hladinu sérového železa a ti, kteří měli zvýšenou hladinu sTfR a normální hladinu železa v séru.

Celkem 51,6 % pacientů mělo nízké hladiny sérového železa (≤13 μmol/L) a 57,6 % mělo ID podle Prague kritérií (2.-4.skupina). Našli jsme jen slabou korelaci mezi feritinem, sérovým železem, saturací transferinu a velikostí IM (hodnocené maximální hladinou troponinu). Hladiny sTfR na rozsahu IM nezávisely.

Závěr

ID postihovala nadpoloviční většinu pacientů s prodělaným IM 1.typu. Kombinace sTfR a hladiny sérového železa byla nejsilnějším prediktorem mortality.

Publikace

Jenča D, Melenovský V, Mrázková J, et al.
Iron deficiency and all-cause mortality after myocardial infarction.
Eur J Intern Med. Published online May 1, 2024. doi:10.1016/j.ejim.2024.04.020
Kompletní znění článku v anglickém jazyce je přiloženo na konci práce.

6.4 Vývoj ejekční frakce levé komory a jeho determinanty u pacientů s poinfarktovou systolickou dysfunkcí

Stanovení EF je doporučeno u všech pacientů po prodělaném IM.[86] Systolická dysfunkce LK je spojena se zhoršeným přežíváním pacientů po IM, vyšším rizikem HF a náhlé smrti.[52, 148, 149] Časně po IM je EF ovlivněná nejen velikostí infarktového ložiska, ale i reverzibilním omráčením myokardu a na druhé straně hyperkontraktilitou nepostižených segmentů myokardu. U pacientů s EF LK ≤40 % je indikováno kontrolní zobrazovací vyšetření za 6-12 týdnů k posouzení jejího vývoje. Zlepšení EF LK je spojeno s nižším rizikem kardiovaskulárních příhod a menším výskytem nepříznivé remodelace myokardu.[150-152] Existuje poměrně málo dat o evoluci EF LK u pacientů po IM léčených pomocí PCI. Cílem naší práce bylo posoudit vývoj EF LK a určit její determinanty u pacientů po IM

Metodika

Z celkem 1593 konsekutivních pacientů hospitalizovaných pro AKS na Klinice kardiologie IKEM mezi červnem 2017 a listopadem 2021 jsme do studie zařadili celkem 1065 pacientů s diagnózou IM 1.typu. Vyřadili jsme pacienty s anamnézou ICHS (n=268) a HF či kardiomyopatie (n=14), jakožto možných příčin preexistující dysfunkce LK. EF LK byla stanovená transtorakální echokardiografií (TTE) během hospitalizace. V případě opakovaného TTE během hospitalizace jsme k analýze využili výsledky posledního vyšetření. U pacientů s EF LK <40 % bylo s odstupem provedeno kontrolní ambulantní TTE. K porovnání rozdílů mezi skupinami jsme použili ANOVA, Kruskal-Wallisův nebo chi-kvadrát test. Multivariantní logistická regrese byla využita k určení prediktorů systolické dysfunkce LK během hospitalizace a zlepšení EF LK při kontrolním vyšetření. Pomocí Coxova modelu proporcionálních rizik jsme analyzovali vliv zlepšení systolické funkce LK na mortalitu pacientů.

Výsledky

Průměrný věk pacientů byl 64±12 let, 74,6 % tvořili muži. STEMI tvořilo 65,4 % případů. Celkem 93,5 % nemocných podstoupilo invazivní léčbu IM: 901 (84,6 %) z nich bylo léčeno pomocí PCI, 89 (9,4 %) pomocí srdečního bypassu a 6 pacientů (0,6 %) bylo vyžadovalo léčbu oběma metodami. TTE bylo provedeno u všech pacientů během mediánu 1 dne od přijetí (mezikvartilové rozpětí 0-2 dny). Systolickou dysfunkcí s EF

LK <40 % trpělo 238 nemocných (22,3 %), lehce omezenou funkci (EF LK 40-50 %) mělo 326 (30,6 %) a zachovalá EF LK nad 50 % byla přítomná u 501 (47,0 %) pacientů. Pacienti se systolickou dysfunkcí (EF LK <40 %) měli častěji subakutní IM, STEMI přední stěny, známky HF vyžadující podávání intravenózních diuretik, perikarditidu a vyšší maximální troponin i TF při přijetí. Kontrolní TTE bylo dostupné u 169 pacientů, medián odstupu od IM byl 109 dní (mezikvartilové rozpětí 75-281). Normalizace EF LK (nad 50 %) nastala u 39 nemocných (23,1 %), mírné zlepšení EF LK na 40-50 % bylo u 44 z nich (26,0 %) a u 86 pacientů (50,9 %) perzistovala systolická dysfunkce LK. Při použití multivariantní analýzy mezi prediktory zlepšení EF LK patřila menší závažnost koronární aterosklerózy (definované pomocí Gensiniho skóre), vyšší EF LK při hospitalizaci, nižší počet leukocytů a absence rozvoje FiS během hospitalizace. Zlepšení EF LK vedlo ke snížení mortality pacientů.

Závěr

I v současné éře léčby IM pomocí perkutánních koronárních intervencí zůstává incidence systolické dysfunkce vysoká – 22,3 % pacientů po 1. IM mělo EF LK <40 %. U přibližně ¼ z těchto pacientů jsme dokumentovali normalizaci systolické funkce LK. Mezi faktory asociované se změnou EF LK patřily míra zánětu, závažnost koronárního nálezu a primomanifestace FiS.

Publikace

Wohlfahrt P., Jenča D., Melenovský V.et al

Trajectories and determinants of left ventricular ejection fraction after the first myocardial infarction in the current era of primary coronary interventions

Front Cardiovasc Med. Published online November 14, 2022. doi: 10.3389/fcvm.2022.1051995

Kompletní znění článku v anglickém jazyce je přiloženo na konci práce.

6.5 Vliv polymorfizmů orexinu na prognózu pacientů po IM

Orexin je hormon s pleiotropními vlastnostmi. Mezi jeho účinky patří ovlivňování spánkového cyklu, příjmu potravy, energetické bilance organizmu, ale i glukózové tolerance a systému odměny (a tím vliv na riziko vzniku drogových závislostí). [153, 154] Význam orexinového systému byl recentně zjištěn i u HF. Perez a kol. identifikovali u pacientů s HFrEF polymorfizmus lokusu rs7767652 v regulační oblasti pro orexinový receptor 2 jako nejsilnější prediktor zlepšení EF LK po farmakoterapii či resynchronizační léčbě. Ve funkční validační studii vedla minoritní alela T k narušení vazebního místa pro transkripční faktor 4, čímž došlo ke snížení exprese genu pro orexinový receptor 2.[155] U myší infuze orexinu A snižovala míru NRM po podání angiotenzinu II a izoprotenerolu. [155] Význam orexinového systému u pacientů s IM dosud nebyl prozkoumán. Cílem naší práce bylo posoudit vztah aktivitou orexinového systému, hodnocenou na základě polymorfizmu v lokusu rs7767652 i cirkulující hladiny orexinu A, a mortalitou pacientů po IM.

Metodika

Pro analýzu jsme použili data konsekutivních pacientů hospitalizovaných v terciárním kardiocentru od června 2017 do listopadu 2021 pro IM 1.typu. Pacienti, kteří měli anamnézu ICHS a HF, byli z analýzy vyloučeni. DNA byla izolována z periferní krve. Lokus rs7767652 v regulační oblasti byl vyšetřován pomocí analýzy TaqMan SNP (single nucleotide polymorphism). Zastoupení alel u našich pacientů jsme porovnali s jejím zastoupením v náhodně vybraném vzorku obecné populace (n=1953) ze studie Czech post-MONICA (Monitoring of Trends and Determinants in Cardiovascular Disease) pomocí chi-kvadrát testu. Základní charakteristiky jednotlivých genotypů (TT, CT, CC) byly porovnány pomocí chi-kvadrát, ANOVA nebo Kruskal-Wallisova testu. V podskupině pacientů s EF LK <40 % (n=245) jsme stanovili hladinu orexinu A. Mortalitní data byla zjištěná k 1.lednu 2022.

Výsledky

Z celkem 1065 pacientů s IM 1.typu jsme analyzovali data 1009 subjektů s dostupnou analýzou polymorfizmu rs7767652. 62 pacientů (6,1 %) byli homozygotními nosiči minoritní alely T (TT), 398 (39,4 %) byli heterozygoti (CT) a 549 nemocných (54,5 %) byli homozygoti pro majoritní alelu C (CC). Tyto skupiny se podobaly věkem, zastoupením pohlaví, prevalencí komorbidit (arteriální hypertenze, DM, CKD), lokalizací, velikostí IM a hodnotou EF LK před propuštěním. Zastoupení alelických variant rs7767652 u pacientů s IM nebylo odlišné od vzorku z běžné populace.

Během mediánu sledování 27 měsíců (mezikvartilové rozpětí 13-41) zemřelo 8,4 % pacientů. Homozygoti pro minoritní alelu (TT) měli vyšší riziko mortality než heterozygoti (CT) či homozygoti pro majoritní alelu CC (HR 2.83 [95% CI, 1,55−5,19], p= 0,001). Úmrtnost nosičů genotypu CT a CC se nelišila.

U podskupiny pacientů se systolickou dysfunkcí LK se hladiny orexinu A mezi jednotlivými genotypy nelišily. Pacienti s hladinou orexinu A ≥1.0 ng/mL měli o 59 % nižší riziko mortality v porovnání nemocnými s hladinou orexinu pod 1 ng/mL.

Závěr

Snížená orexinová signalizace je spojena se zvýšenou mortalitou pacientů po IM. Mezi přispívající faktory patří zvýšené arytmické riziko a nižší míra zlepšení systolické funkce LK. Ovlivnění orexinového systému se nabízí jako možný nový terapeutický cíl pacientů s IM.

Publikace

Wohlfahrt P, Jenča D, Melenovský V, et al.

Attenuation of Hypocretin/Orexin Signaling Is Associated With Increased Mortality After Myocardial Infarction

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Kompletní znění článku v anglickém jazyce je přiloženo na konci práce.

7. Diskuze

V mojí dizertační práci jsem se zabýval přínosem vzdáleného hodnocení symptomů a známek srdečního selhání pro stratifikaci rizika pacientů po infarktu myokardu, jako i hledáním nových terapeutických cílů u těchto pacientů.

V první práci jsme prokázali, že vzdálené hodnocení symptomů a známek HF pomocí dotazníku KCCQ jeden měsíc po propuštění z nemocnice představuje užitečný nástroj pro stratifikaci rizika pacientů po IM. Pacienti s hodnotou KCCQ <25 a KCCQ 25-49 měli 6,6-násobně a 2,8-násobně vyšší riziko celkové mortality než osoby s KCCQ>75 v plně adjustované analýze. Přitom 2/3 pacientů s KCCQ pod 50 nemělo žádné známky HF během hospitalizace pro IM (Killip třída I). Naše pozorování poukazuje na prognostickou důležitost hodnocení symptomů a známek HF po propuštění z nemocnice pro IM. V předchozí práci až 85 % případů HF vzniklo v průběhu 1. měsíce po propuštění. [27] Přitom HF vznikající po propuštění je spojeno s vyšším rizikem komplikací než HF vznikající během hospitalizace.[9] První měsíc po propuštění proto představuje unikátní příležitost pro časný záchyt HF. Časný záchyt HF následovaný adekvátní terapeutickou intervencí může zlepšit prognózu pacientů a snížit náklady za léčbu a hospitalizace. Korespondenční hodnocení HF umožňuje standardizované hodnocení symptomů a známek HF, a to bez výrazného zvýšení zátěže na ambulantní kardiology.

Dotazník KCCQ byl ale vytvořen pro hodnocení pacientů s HF. Proto ne všechny otázky jsou relevantní a mají prognostickou hodnotu u pacientů po IM. Redukce počtu dotazovaných otázek může snížit zátěž a frustraci pacientů při vyplňování. Ve druhé navazující práci jsme proto testovali hypotézu, že kombinace symptomů a známek srdečního selhání a klinických proměnných dokáže lépe predikovat riziko komplikací než model používající pouze klinické proměnné. Námi vytvořené PragueMi skóre mělo lepší diskriminační, kalibrační a reklasifikační schopnosti než v současnosti doporučované GRACE skóre. Výkonnost PragueMi skóre byla konzistentní napříč různými podskupinami pacientů (pohlaví, věk, EF LK, přítomnost DM a CKD).

PragueMi představuje první dotazník pro pacienty s IM, který kombinuje rizikové faktory a symptomy HF hodnocené po propuštění z nemocnice. Je nenáročný, protože pozůstává z 8 bodů, z kterých pacient hodnotí pouze 3 otázky týkající se symptomů HF. Pomocí tohoto dotazníku jsme byli schopni identifikovat rizikové pacienty (10 %

z hodnoceného vzorku) s 18% a 22% mortalitou během 6, respektive 12 měsíců. V dalších studiích bude nutné zjistit, zda klinické rozhodování a včasná intervence založená na použití PragueMi dokáže zlepšit prognózu po IM.

V rámci hledání nových terapeutických cílů u pacientů s IM jsme se zabývali vlivem deficitu železa na prognózu pacientů po IM. Protože současné definice ID po IM nejsou založené na tvrdých datech, v prvním kroku bylo nutné porovnat asociaci různých kritérií ID s rizikem mortality po IM. Zjistili jsme, že feritin, který se nejčastěji používá pro definici ID, není asociován s rizikem mortality po IM. Toto pozorování lze vysvětlit faktem, že feritin je reaktantem akutní fáze, proto je jeho hodnota ovlivněna zánětlivou reakcí po IM a neodráží tíži ID. Toto pozorování je v souladu s prací Gonzalez-D'Gregorio a kol., ve které pouze saturace transferinu pod 20 % byla asociována s rizikem mortality po IM, nikoliv feritin. [119]. V naší práci kombinace hladiny sérového železa a sTfR nejlépe predikovaly riziko celkové mortality po IM. Hladina sTfR odráží zvýšenou tkáňovou poptávku po železe, a není ovlivněna zánětlivou reakcí a velikostí IM. Zvýšené hodnoty sTfR byly ve studii Weidmanna a kol. nezávislým prediktorem kardiovaskulárního úmrtí a/nebo recidivy IM u pacientů s ICHS.[114] Na základě hladiny sérového železa a sTfR jsme vytvořili nové kritéria pro hodnocení ID u pacientů po IM – PragueID kritéria, které odráží riziko mortality.

Substituce železa u pacientů s ID po IM se může stát novou terapeutickou intervencí ke snížení rizika komplikací. V malé studii Floriana a kol. s 39 pacienty se STEMI vedla jednorázová aplikace ultra malé molekuly superparamagnetického oxidu železa 4 dny po IM k redukci infarktového ložiska a k pozitivní remodelaci myokardu hodnocené magnetickou rezonancí v odstupu 3 měsíců.[156] Naopak, dieta s omezením železa u myší vedla ke snížení aktivity kardioprotektivního systému endoteliální NO syntázy/solubilní guanylát cyklázy a proteinkinázy G. V práci Dziegaly a kol. byl u myší v hypoxických podmínkách pozorován nepříznivý vliv ID na přežívání kardiomyocytů způsobený nadměrnou aktivitou apoptotických drah.[157] V další práci bude nutné objasnit, zdali použití našich PragueID kritérií k rozhodnutí o substituci železe u pacientů po IM povede ke zlepšení prognózy.

Ve čtvrtém článku jsme navzdory očekáváním ukázali, že i v moderní éře léčby IM zůstává incidence systolické dysfunkce LK po IM vysoká. Přibližně čtvrtina pacientů s IM měla EF LK <40 % i při vysoké utilizaci revaskularizačních metod, dominantně PCI. Výskyt systolické dysfunkce v námi studované populaci byl porovnatelný se

staršími studiemi z přelomu 20. a 21.století.[158, 159] Tento fakt lze vysvětlit zlepšením přednemocniční péče, zavedením PCI i použitím mechanických srdečních podpor u rozsáhlých IM s kardiogenním šokem. Proto přežívají i vysoce rizikoví pacienti, kteří by dříve umřeli. Další možnou příčinou vysokého zastoupení systolické dysfunkce po IM je vysoká prevalence komorbidit, zejména diabetu, který je asociován s větším rozsahem infarktového ložiska, zvýšeným rizikem mikrovaskulární obstrukce a NRM. Až 5/6 analyzovaných pacientů se systolickou dysfunkcí mělo IM přední stěny, ¼ vykazovala známky HF (Killip >1) při přijetí, což odráží vysokou rizikovost nemocných.

U přibližně 1/2 pacientů s EF LK <40 % nedošlo při následné echokardiografické kontrole k úpravě EF LK ad integrum i přes fakt, že byli adekvátně léčeni pomocí farmakoterapie blokující RAAS a sympatoadrenální systém - 72,4 % z nich užívalo ACEi/sartan, 83,1 % beta blokátor a 69,8 % mělo zavedenou terapii spironolactonem. Podíl pacientů s plným obnovením systolické funkce je přitom nižší než v recentní studii Wu a kol., která studovala dynamiku vývoje EF LK u mladších pacientů s IM do 50 let. V této studii byla incidence snížené EF LK (pod 50 %) 29 %, ale až u 42 % nemocných došlo k její normalizaci. I v této práci mezi prediktory rozvoje systolické dysfunkce LK patřil rozsah IM charakterizovaný maximální hodnotou troponinu, STEMI, vyšší Gensiniho skóre a diabetes. [151] I když jsme v naší analýze nepozorovali přímý vliv věku na zlepšení EF LK, starší pacienti měli víc komorbidit, které přispěly k nižší odpovědi EF LK na zavedenou terapii. Na druhé straně, 51% zastoupení pacientů se zlepšením EF LK ≥40 % je dvojnásobné v porovnání se studií Ottervangera a kol., která analyzovala dynamiku změn EF LK u pacientů léčených PCI koncem 90.let.[159] V této studii bylo jen 44 % pacientů při propuštění léčeno ACEi.

Mezi faktory ovlivňující zlepšení EF LK v naší studii patřila míra zánětlivé reakce kvantifikovaná pomocí počtu leukocytů. Protrahovaný zánět vede k expanzi infarktového ložiska a k rozvoji NRM, které predisponují k rozvoji HF. Cytokiny, hrající důležitou roli v regulaci zánětu po IM, představují možný cíl farmakoterapeutického ovlivnění. Kanakinumab, monoklonální protilátka proti IL-1b, vedl ve studii CANTOS u pacientů po IM k redukci kardiovaskulárních příhod. [160]V prespecifikované exploratorní analýze této studie byl prokázán na dávce závislý efekt kanakinumabu na redukci HF hospitalizací. [101] Administrace inhibitoru IL-6, tocilizumabu, vedla k redukci ischemicko-reperfuzního poškození myokardu (měřeného pomocí troponinu) a mikrovaskulární obstrukce.[106, 161]. Potenciál monoklonálních protilátek v supresi

nadměrné zánětlivé reakce po prodělaném IM s cílem zachování systolické funkce LK u pacientů po IM je nutné ověřit v randomizovaných klinických studiích. Dalším negativním prediktivním faktorem byl primozáchyt FiS během hospitalizace, který byl asociován s téměř trojnásobně nižší pravděpodobností zlepšení EF LK. Tato arytmie je indukována zánětlivou reakcí po IM, objemovým přetížením, ischemií síní a perikarditidou, tudíž jí lze považovat za důsledek rizikových faktorů spojených s rozvojem HF. Rozvoj FiS negativně ovlivňuje hemodynamiku ztrátou síňové kontrakce, vyšší tepovou frekvencí a nepravidelnou komorovou odpovědí, která má dopad na její plnění.[162]

Třetím činitelem ovlivňujícím zlepšení systolické funkce byla závažnost koronární aterosklerózy, která byla stanovena s využitím Gensiniho skóre. Toto skóre charakterizuje závažnost koronární aterosklerózy přesněji než prostá kvantifikace počtu postižených věnčitých tepen, protože zohledňuje nejen lokalizaci a závažnost stenózy, ale i přítomnost kolaterál.[163]

Jako možný další terapeutický cíl u pacientů po IM jsme analyzovali orexinový systém. Jako první jsme prokázali vztah mezi polymorfizmem lokusu rs7767652 v regulační oblasti pro orexinový receptor 2 s rizikem úmrtí pacientů po IM. Tento efekt byl nezávislý na tradičních rizikových faktorech a komorbiditách. To naznačuje nový patofyziologický mechanizmus, který ovlivňuje prognózu po IM. Pacienti s variantou TT měli vyšší riziko vzniku fibrilace komor během hospitalizace a zvýšené hladiny triglyceridů. To může odrážet vyšší katecholaminergní zátěž rezultující ve zvýšenou lipolýzu. Již dlouho je známá asociace zvýšených koncentrací volných mastných kyselin a rizika náhlé srdeční smrti u pacientů po IM. [164] Dalším faktorem vysvětlujícím horší prognózu homozygotních nosičů minoritní alely je menší vzestup EF LK při kontrolním TTE v porovnání s nosiči alel CT a CC. Snížená EF LK po IM a absence jejího zlepšení jsou významnými prediktory nepříznivých kardiovaskulárních událostí u pacientů s IM. [128, 151, 165] Dalším naším pozorováním, které potvrzuje vliv orexinového systému na prognózu pacientů po IM bylo zjištění, že hladina orexinu A ≥1.0 ng/mL je spojena s nižším rizikem mortality. Tento nález je ve shodě se studií analyzující 113 pacientů s HFrEF, u kterých byly hladiny orexinu A nad 1,04 ng/mL prediktorem reverzní remodelace LK na farmakoterapii nezávisle na tradičních biomarkerech poškození

(troponin) a přetížení kardiomyocytů (NT-proBNP) i fibrózy myokardu (galektin, soluble suppression of tumorigenesis-2 [sST2]).[166]

Příznivý efekt zvýšené orexinové signalizace u pacientů s IM či HF je způsoben aktivací různých signálních drah s příznivým působením na myokard. Jednou z nich je dráha PI3K/Akt (fosfatidylinositol-3-kináza), která má pozitivní vliv na redukci ischemicko-reperfuzního poškození. [122] Aktivátor této dráhy, glucagon-like peptide 1, vedl u pacientů po IM ke zlepšení systolické funkce LK. [167] Stimulace orexinového receptoru 2 vede také k aktivaci dráhy ERK1/2 (extracellular signal-regulated kinase), regulující kontraktilitu pomocí přímé fosforylace Ca^{2+}/kalmodulin-dependentní kinázy. [168] Modulace orexinového systému k ovlivnění reverzní remodelace LK a prognózy u pacientů po IM může být vhodným cílem klinických studií.

8. Závěry

1. Dotazník KCCQ zasílaný 1 měsíc po hospitalizaci pro IM představuje vhodný nástroj k rizikové stratifikaci pacientů po IM. Pacienti, kteří trpí výraznými symptomy HF (celkové sumární skóre pod 50), mají zvýšenou mortalitu v porovnání s pacienty s menší limitací. Otoky dolních končetin, změna symptomů v posledních 2 týdnech a omezení chůze jsou parametry predikující prognózu pacientů po IM.

2. PragueMi představuje jednoduchý nástroj integrující klinické rizikové faktory a symptomy HF k identifikaci nejvíc ohrožených pacientů s IM. Toto skóre má lepší diskriminační vlastnosti než dosud doporučené GRACE skóre.

3. Nedostatek železa je u pacientů po prodělaném IM asociován se zhoršenou prognózou. Kombinace hladiny sérového železa a solubilního transferinového receptoru je nejvhodnějším prediktorem mortality pacientů v této skupině.

4. 53 % pacientů po prodělaném IM má určitý stupeň systolické dysfunkce LK. U přibližně ¼ pacientů s iniciální EF LK pod 40 % dochází k normalizaci její hodnoty. Mezi prediktory zlepšení EF LK nad 40 % patří FiS, míra zánětu a závažnost koronární ateroskleróz.

5. Orexinová signalizace ovlivňuje prognózu pacientů po IM. Homozygotní nosiči minoritní alely T v regulační oblasti pro orexinový receptor 2 (lokus rs7767652) mají přibližně trojnásobnou mortalitu v porovnání s ostatními pacienty. Pacienti s nižší hladinou orexinu A mají zvýšené riziko úmrtí.

9. Conclusions

1. KCCQ questionnaire administered one month after hospitalisation due to myocardial infarction represents an appropriate tool for risk stratification of patients. The patients with low KCCQ overall summary score < 50 points have higher mortality risk compared to those with less symptoms. Leg swelling, change in symptoms during the past 2 weeks and walking impairment are the items that predict prognosis of patients after myocardial infarction.

2. PragueMi is a simple tool integrating clinical risk factors and HF symptoms to identify MI patients at highest risk of mortality. This score has better discriminatory properties than the currently recommended GRACE score.

3. Iron deficiency is associated with worse prognosis in the patients with MI. The combination of serum iron and soluble transferrin receptor is the best predictor of all-cause mortality of these patients.

4. 53 % of patients suffer from systolic dysfunction after MI. Approximately ¼ of patients with initial EF LV below 40 % achieve full recovery of left ventricular systolic function. Atrial fibrillation, severity of inflammatory response and coronary atherosclerosis are the predictors of improvement of EF LV above 40 %.

5. Orexin signalling affects the prognosis of patients with MI. Homozygous carriers of minor allele T in the regulating domain for orexin receptor-2 have almost threefold increase in all-cause mortality compared to others. The patients with a lower concentration of orexin A have a higher mortality risk.

10. Literatura

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REVIEW

Heart failure after myocardial infarction: incidence and predictors

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Abstract

Aims The aim of the present paper was to provide an up-to-date view on epidemiology and risk factors of heart failure (HF) development after myocardial infarction.
Methods and results Based on literature review, several clinical risk factors and biochemical, genetic, and imaging biomarkers were identified to predict the risk of HF development after myocardial infarction.
Conclusions Heart failure is still a frequent complication of myocardial infarction. Timely identification of subjects at risk for HF development using a multimodality approach, and early initiation of guideline-directed HF therapy in these patients, can decrease the HF burden.

Keywords Heart failure; Clinical risk factors; Biomarkers; Genetics; Adverse remodelling

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Introduction

Despite the remarkable advances in the treatment of coronary artery disease and acute myocardial infarction (MI) over the past two decades, MI remains the most common cause of heart failure (HF).[1] According to the time sequence of MI occurrence and HF development, three clinical presentations differing in pathophysiology, clinical characteristics, and outcomes can be identified: (i) HF onset at the time of MI presentation, (ii) HF developing during hospitalization for MI, and (iii) HF onset after discharge from the index hospitalization.

Heart failure developing at the time of myocardial infarction hospitalization

The factors that contribute to the pathogenesis of HF development at the time of the MI hospitalization include myocardial compromise due to myocardial necrosis, myocardial stunning, and mechanical complications such as papillary muscle rupture, ventricular septal defect, and ventricular free wall rupture. Within 30 min of ischaemia, cardiomyocyte structural changes and oedema develop, leading to progressive myocyte death after 3 h of ischaemia. Reperfusion itself causes a second wave of injury through the production of reactive oxygen species. Despite successful epicardial reperfusion, the embolization of thrombotic debris leads to ongoing microvascular dysfunction and myocardial ischaemia.[2] The inflammatory response to myocyte death also contributes to HF development. Furthermore, HF at this stage can be also triggered by exacerbation of pre-existing HF and comorbidities, for example, anaemia, chronic kidney disease (CKD), or chronic obstructive pulmonary disease.

Opposing trajectories of HF incidence presenting at MI admission and during a hospital stay have been observed in the last decades. While the proportion of HF cases at MI admission has increased (from 4% in 1992–1996[3] to 12–13% in 2001–2011[4,5]), the proportion of HF cases developing during the hospital stay has decreased (from 39%[3] to 4–28%[4–6]). The increase in HF at MI presentation may be explained by

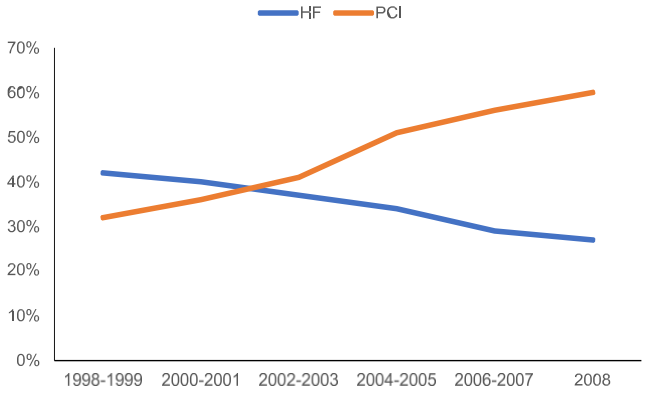
recent improvements in pre-hospital care, which led to a decrease in out of hospital mortality.[7,8] On the other hand, the decrease in in-hospital HF may be caused by the introduction of percutaneous coronary intervention (PCI), which leads to more substantial myocardial salvage as compared with thrombolysis. In the nationwide SWEDEHEART registry,[6] the incidence of in-hospital HF complicating MI has fallen from 46% in the thrombolytic era (the year 1996) to 28% in PCI era (the year 2008) (*Figure 1*). Higher myocardial salvage by PCI can also explain the increase in the proportion of patients with HF with preserved ejection fraction, which increased from 18% in 1998 to 30% in 2008. The second explanation for the in-hospital HF decrease may be the change in MI diagnosis, which is currently based on troponin level and allows the detection of less severe MI cases with a lower risk of HF development.

Heart failure developing after myocardial infarction hospitalization

Heart failure developing after MI hospitalization is a consequence of cardiomyocyte death and scar formation, which triggers chronic neurohumoral activation (renin–angiotensin–aldosterone and sympathetic nervous system up-regulation) and ventricular remodelling. Left ventricular (LV) remodelling is more pronounced in men, patients with larger infarct size, and late or unsuccessful reperfusion of epicardial or microvascular bed.[9] Ventricular remodelling changes ventricular geometry and leads to wall thinning, ischaemic mitral regurgitation, and further cardiomyocyte loss.

Heart failure development after hospital discharge is very prevalent. It is diagnosed in approximately 13% of patients at 30 days and 20–30% at 1 year after discharge for MI.[10,11] The incidence of HF after MI discharge is highest in the first months, and then it drops and remains stable at a rate of 1.3–2.2% per year afterwards.[11]

Figure 1 Percentage of patients with index myocardial infarction undergoing percutaneous coronary intervention (PCI) (orange line) and with in-hospital heart failure (HF) (blue line)—adapted from SWEDEHEART study.[6]



Clinical impact of heart failure after myocardial infarction

The development of HF after MI has a significant impact on outcomes, regardless of the HF type.[12] Among patients with a history of MI, HF development increases total mortality risk three-fold and cardiovascular mortality four-fold. The timing of HF development also has an impact on adverse events. HF developing more than 3 days after MI is associated with a 43% higher mortality risk as compared with patients with HF developing in the first 3 days after MI.[12] This may be explained by different risk factors and mechanisms leading to HF at different time points.

The need for heart failure screening and prevention

As recognized by both the European Society of Cardiology[13] and the American Heart Association,[14] HF prevention is an urgent public health need. The population of patients after MI represent a high-risk group for HF development, in which HF screening and prevention is of particular importance. Missed or delayed diagnosis of HF compromises patient prognosis and increases therapy costs. This underscores the need for close follow-up of MI patients at risk for HF development, which has been shown to result in improved patient adherence, higher prescription of recommended therapy, and lower cardiovascular hospitalizations.[15–17]

The present paper reviews risk factors and biomarkers associated with HF development after MI and suggests a multimodality approach for screening (*Figure 2*). This information is intended to assist clinicians in identifying patients at particular risk of HF development after MI and early initiation of guideline-directed HF therapy in these patients at high risk of adverse clinical events.

Clinical risk factors

The impact of different clinical risk factors on the HF risk after MI is shown in *Table 1*.

Age

The incidence of in-hospital HF is three times higher in patients 75–85 years old as compared with those 25–54 years old. After hospital discharge, HF incidence is six times higher in the older age group.[11] After multivariate adjustment, the

Figure 2 Multimodal approach for prediction of heart failure after myocardial infarction (MI).

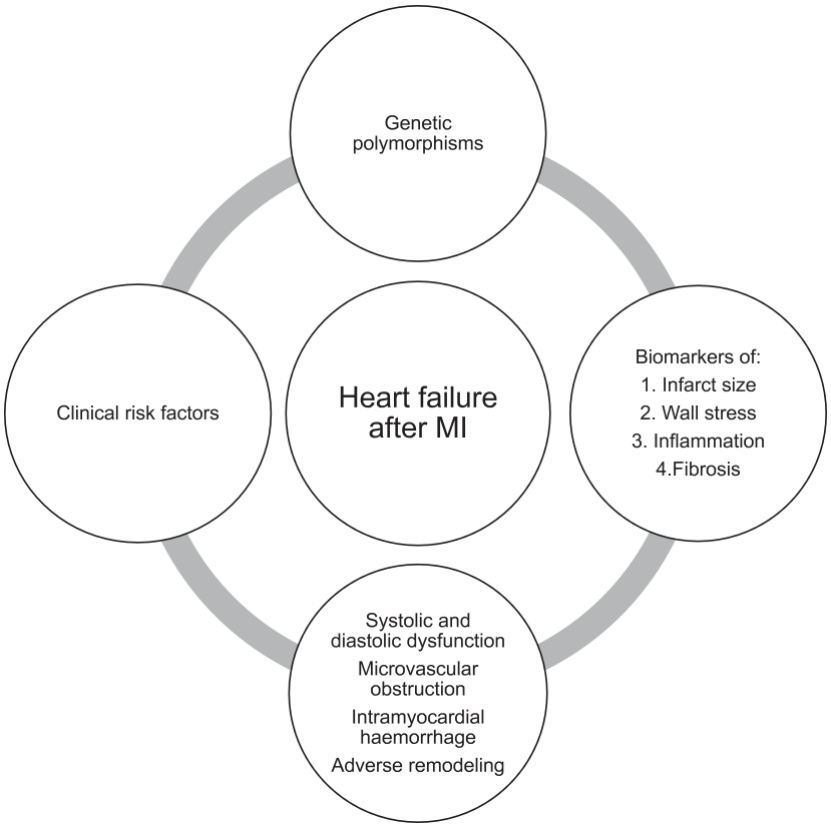


Table 1 Clinical risk factors for HF

Clinical risk factors	Increase in risk of post-MI HF
Age, increase by 10 years	20–50%
Female sex	15–34%
History of previous MI	21–89%
Hypertension	7–70%
Diabetes	30–42%
Glomerular filtration, decrease by 10 mL/min/1.73 m^2	10%
Heart rate, increase by 10 b.p.m.	7–23%
Atrial fibrillation	20–51%

HF, heart failure; MI, myocardial infarction.

in-hospital HF risk increases by approximately 50%[5] and post-discharge HF by 20–50%[18–20] for every 10 years of age.

Gender

Female sex was found to be independently associated with increased HF risk after MI in some studies, but not in others.[18,19,21–23] In the studies that reported higher risk associated with female sex, the excess HF risk ranged from 15% to 34%.[6,20,24]

Several reasons may explain higher HF risk in women. Compared with men, female patients presenting with MI are older and have a higher prevalence of co-morbidities and worse functional status.[25] The impact of co-morbidities such as diabetes, hypertriglyceridemia, and metabolic syndrome on cardiovascular risk appears to be higher in women than men. Furthermore, gender disparities in MI presentation[26,27] and less aggressive hospital care of female patients,[27] including the underuse of revascularization, may further contribute to the higher HF risk in women.[28]

Number and location of infarct-related artery

Multi-vessel disease (MVD) reflects the high atherosclerotic burden with more prominent endothelial dysfunction and systemic inflammation.[29] Patients with MVD are generally older and have diabetes and renal impairment as common co-morbidities. MVD is associated with lower ejection fraction[22,29] and increased risk of major adverse cardiovascular events (MACE), including HF, by 80%.[29] Anterior MI is associated with a higher risk of adverse remodelling[30] and HF.[31] The higher risk of HF associated with anterior MI is caused by the greater magnitude of irreversible LV damage, as compared with other MI locations.[32]

Prior myocardial infarction

A history of MI increases the risk of HF by 21–89%.[5,6,18,21,24,33,34] Excess risk may be explained by pre-existing systolic and/or diastolic dysfunction.

Arterial hypertension

Many studies reported that arterial hypertension increases the risk of HF. The excess risk associated with arterial hypertension ranged from 7% to 70%.[6,18,20,21] More common microvascular injury and myocardial haemorrhage contribute to the excess HF risk in patients with arterial hypertension.[35] Furthermore, higher neurohormonal activation and more common LV remodelling was described in hypertensive patients after MI.[36]

Higher heart rate

A higher heart rate at admission was a risk factor for HF after acute MI in several studies.[5,18,21,22,33] The risk rises by 7–23% for every 10 beats.[5,21,22] Tachycardia may reflect MI severity and imminent cardiac dysfunction.

Atrial fibrillation

New-onset atrial fibrillation complicates 2–21% cases of MI and may reflect left atrial pressure increase and atrial fluid overload during MI.[37] Atrial fibrillation increases the risk of HF after MI by 20–51%.[18,33]

Diabetes

After MI, the incidence of HF among diabetic patients is 60–70% higher than in patients without diabetes.[38] After accounting for other co-morbidities associated with diabetes, its presence still results in 30–42% higher risk of HF after MI.[5,6,39,40] Compared with non-diabetic patients with similar infarct size,[41] similar systolic function, and infarct-related coronary artery patency rate,[42] diabetic patients develop more often adverse LV remodelling and HF.[43] This may be explained by a more common microvascular obstruction[42] and diastolic dysfunction in those with diabetes.[44] The excess risk seems to be similar in patients with pre-existing diabetes and diabetes diagnosed at the time of MI.[41,45]

Chronic kidney disease

Chronic kidney disease increases the risk of HF development after MI approximately two-fold.[20] Excess HF risk in CKD can be explained by accelerated atherosclerosis, more common MVD, atypical MI presentation, and lower odds of revascularization, which results in larger infarct size and more severe ventricular dysfunction. Moreover, CKD leads to fluid overload, secondary hypertension, anaemia, chronic inflammation, and alterations of the renin–angiotensin–aldosterone system.[46,47] Lower prescription of evidence-based medications in CKD patients has also been reported.[48]

Ischaemic preconditioning and heart failure after myocardial infarction

Preconditioning is the process by which brief, repetitive episodes of ischaemia reduce the size of a subsequent MI. Compared with those without antecedent angina, patients with angina have a decreased risk of HF development during MI, lower risk of mortality or adverse LV remodelling after MI, and enhanced recovery of cardiac contractile function after MI.[49,50] The protective effect of angina has been described up to 3 months prior to MI.[51] The difference in outcomes in patients with and without angina preceding MI may be explained by ischaemic preconditioning or a larger extent of collateral circulation in patients with antecedent angina.

Whether the ischaemic preconditioning data could be applied to clinical care to improve outcomes remains to be seen. Remote ischaemic conditioning with transient ischaemia and reperfusion of the arm or leg has been shown in several small randomized controlled trials to reduce myocardial infarct size and increase myocardial salvage in patients with ST-segment elevation MI (STEMI).[52,53] However, in the recent large CONDI-2 trail among 5401 STEMI patients, remote ischaemic conditioning by intermittent ischaemia and reperfusion applied to the arm did not decrease the risk of death or hospitalization for HF.[54]

Coronavirus disease 2019

Coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 likely affects the risk of HF development after MI. However, hard clinical data are still lacking. There are several mechanisms by which COVID-19 pandemic may influence the risk of HF development after MI.

First, the incidence of acute coronary syndrome (ACS) increases in the setting of viral infection, likely due to inflammation-mediated plaque destabilization. The risk in the setting of COVID-19 infection is unknown, but other viruses are associated with a 3-fold to 10-fold increased risk.[55] However, a decrease in MI hospitalizations was observed in several countries,[56–58] with a parallel increase in fatality and complication rates. Also, both patient-related and system-related delays were noted, with a 40% increase in

symptom onset to coronary angiography time during the COVID-19 pandemic. Thus, the absence or delay in coronary revascularization during MI may increase the proportion of patients with HF.

Second, there is growing evidence that COVID-19 leads to direct myocardial injury. Within 24 h from admission for COVID-19, troponin elevation is present in 36% of patients.[59] Among recovering patients evaluated a mean of 71 days after confirmed COVID-19 diagnosis, 78% of patients have demonstrable cardiac involvement via cardiac magnetic resonance imaging (MRI), 76% have detectable high-sensitivity troponin, and 60% have evidence of active myocardial inflammation.[60] The mechanisms responsible for myocardial injury during COVID-19 infection may include inflammation, cytokine storm, hypercoagulable state with formation of microthrombi and macrothrombi, direct viral invasion of the myocardium, and myocardial supply/demand imbalance.[59] MI in the setting of COVID-19 infection likely increases not only the mortality risk[56] but also the risk of subsequent HF development.

Biochemical markers

Biomarkers of infarct size

Cardiac troponin, a biomarker of choice in MI diagnostics, measured at plateau phase (48–72 h after MI symptom onset) is associated with MRI determined infarct size.[61] Similarly, peak levels of creatine kinase (CK) and CK-MB are associated with infarct size on single-photon emission computed tomography.[62] Several studies have shown the association of troponin or CK-MB level with MACE, including HF.[19,63,64] Yet the association of peak troponin or CK-MB with HF has not been seen in all investigations.[65,66]

Natriuretic peptides

Alongside troponin, natriuretic peptides are associated with infarct size and cardiac dysfunction.[67,68] In addition to the magnitude of natriuretic peptides elevation,[66,69] its pattern is also associated with adverse events. While in some patients the brain natriuretic peptide increase after MI has a monophasic pattern with a peak at 16 h after admission, in others, the rise is biphasic with a second peak at 5 days. Patients demonstrating the biphasic pattern have a higher risk of LV remodelling and HF.[70,71] Additionally, premorbid N-terminal prohormone brain natriuretic peptide levels, as well as high-sensitivity troponin T levels measured at a median time of 6 years before MI, have also been associated with adverse events, including HF.[72]

Inflammation markers

There is growing evidence that prolongation or expansion of the post-infarction inflammatory response significantly contributes to LV remodelling and HF development.[73] Numerous methods of inflammatory response quantification have shown promise in HF prediction. C-reactive protein level predicted the risk of adverse events after MI, including HF, in several studies.[74–77] The neutrophil-to-lymphocyte ratio, an indicator of systemic inflammation, predicted MACE and HF in a meta-analysis of 14 studies.[78]

Cytokines are strategic regulators of inflammation. In a study of 4939 patients with ACS, pro-inflammatory cytokine interleukin 6 (IL-6) was an independent predictor of MACE and HF.[79] IL-32 is a relatively novel pro-inflammatory cytokine that induces the release of other inflammatory cytokines such as tumour necrosis factor-α, IL-1β, IL-6, IL-8, and IL-18. Xuan *et al*. showed that IL-32 is an independent predictor of cardiac death and HF among patients after MI.[80]

Renal biomarkers

The estimated glomerular filtration rate (eGFR) is independently associated with HF risk after MI. Fox *et al*. used a creatinine-based MDRD equation for eGFR calculation to show that, after multivariate adjustments, the excess risk of HF attributable to renal dysfunction ranged from 30% to 90% depending on CKD stage.[81] Similar results were reported from the VALIANT study where the risk of HF rose by 10% for each 10 mL/min/1.73 m^2 decrease in eGFR.[18]

Cystatin C is a sensitive marker of renal impairment that, unlike creatinine, is not affected by age, sex, and muscle mass. In the SOLID-TIMI 52 study among patients with ACS, cystatin C provided incremental information for risk stratification, including HF hospitalization, independent of other biomarkers including eGFR.[82]

Biomarkers of fibrosis

Suppressor of tumourigenesis (ST2) is a member of the IL-1 receptor family that is involved in the process of myocardial remodelling and fibrosis.,[8384] It has two isoforms: transmembrane ligand and soluble form. Binding of the soluble form (sST2) to IL-33 prevents the beneficial effect of this IL on the reduction of cell death and fibrosis. While several studies demonstrated the prognostic utility of sST2 testing in HF, there is less evidence for the predictive value of sST2 after MI. Among consecutive MI patients from the Mayo Clinic, sST2 elevation was independently associated with excess risk of death and HF. Patients in the upper tertial of sST2 had three-fold the risk of HF as compared with the lowest tertial.[85]

Galectin-3, a β-galactoside-binding lectin mainly secreted by activated macrophages, is also reflective of fibrosis and cardiac remodelling in response to myocardial injury.[86] The American College of Cardiology/American Heart Association guidelines recommend measurement of both sST2 and galectin-3 for risk prediction in patients with HF.[87] A recent study suggested an independent predictive value of galectin-3 also among unselected MI patients. In a prospectively enrolled incident MI cohort, galectin-3 was associated with increased risk of death and HF even after adjustment for MI severity, co-morbidities, and sST2.[88]

Other biomarkers

Matrix metalloproteinases (MMPs) are proteolytic enzymes that degrade collagen and other proteins of the extracellular matrix. After MI, MMPs regulate the remodelling process by facilitating extracellular matrix turnover and inflammatory signalling. MMP-8 and MMP-9 were shown to predict LV remodelling[89,90] and adverse outcomes, including HF development.[91]

Clusterin is a protein that regulates complement activity, apoptosis, and lipid transport. Proteomic analysis of plasma from patients after the first anterior MI identified increased plasma levels of clusterin to be associated with LV remodelling.[92] Whether clusterin is also associated with the risk HF after MI needs to be determined.

The prognostic utility of serial biomarker measurement and multi-marker approach after MI was evaluated by Reinstadler *et al.*,[93] who measured several biomarkers as aspartate and alanine aminotransferases, high-sensitivity troponin T, N-terminal prohormone brain natriuretic peptide, lactate dehydrogenase, and high-sensitivity C-reactive protein daily for 4 days after admission for an MI. They reported that the peak level of the biomarkers studied was associated with LV remodelling, while the admission value was not. Furthermore, combined biomarker analysis was superior to any of the individual biomarkers.[93] Thus, not only the selection of a biochemical biomarker but also timing of the measurement after MI may be of importance in HF risk prediction.

Genetic aspects

There is a paucity of data on genetic predictors of HF development after MI.

A recent study using weighted gene co-expression network analysis identified genes BCL3, HCK, PPIF, S100A9, SERPINA1, and TBC1D9B to be involved in the inflammatory response, apoptosis, and HF development after MI.[94]

MicroRNAs are products of non-coding DNA transcription consisting of approximately 22 nucleotides that act as significant regulators of mRNA translation. In the heart, they control various processes including cardiac cell death, cardiomyocyte regeneration, and cardiac fibroblast transformation into cardiomyocytes.[95] A study by Niu *et al.* recognized miR-142-3p as a contributor to HF after MI.[94] Shah *et al.* identified lower concentrations of miR-17-5p, miR-20a-5p, and miR-106b-5p to be associated with a higher incidence of HF after MI.[96] In a study by Lakhani *et al.*, miRNA-24 and 29a levels were reduced in patients with acute MI and low ejection fraction, whereas miRNA-34a, miRNA-208b, and miRNA-126 were increased in these patients.[97]

Imaging

Echocardiography

Echocardiography is a commonly used imaging method after MI. In regard to HF prediction, optimal timing of echocardiography is not well defined, as the early post-MI examination may underestimate systolic function due to myocardial stunning. Therefore, repeated echocardiographic examinations after MI are recommended.[98]

Systolic function

Reduced LV ejection fraction (LVEF) is associated with the risk of HF development.[18,21,24] A 5% decrease in LVEF determined by ventriculography performed during the MI hospitalization increases the risk of HF development after the hospital discharge by 12–18%.[22,24] Similarly, a 5% decrease in LVEF evaluated by echocardiography 5–20 months after MI increases the risk of HF by 20%.[18]

The wall motion score index (WMSI) reflects wall motion abnormalities better than LVEF because compensatory hyperkinesia of non-affected regions may compensate for the impaired systolic function.[98,99] In a study of 144 patients with MI, WMSI ≥ 1.5 identified people at increased risk of cardiac death, unstable angina, and HF, independent of LVEF.[100] In a study by Møller *et al.*, each 0.2 increase in WMSI was associated with hazard ratio of 1.21 (95% confidence interval 1.07–1.37, $P = 0.002$) for HF development and hazard ratio of 1.15 (95% confidence interval 1.10–1.21, $P < 0.0001$) for mortality.[99] A study by Jurado-Román *et al.* deemed WMS a more powerful predictor of mortality and HF than LVEF.[101]

Right ventricular (RV) dysfunction significantly contributes to HF development after MI. The tricuspid annular plane systolic excursion (TAPSE) is the most commonly used parameter to evaluate RV systolic function. In patients after MI, RV dysfunction defined by TAPSE ≤ 14 mm was able to predict early cardiac events, including cardiogenic shock.[102] However, TAPSE assesses only longitudinal contraction of RV and as such provides only partial information on RV function. Fractional area change reflects RV function better than TAPSE. In several studies among patients after MI, decreased

fractional area change was associated with an increased risk of adverse events, including HF.[103,104]

Diastolic function

Standard Doppler examination of transmitral flow provides valuable information in patients after MI. A meta-analysis of 12 studies by Møller *et al*. found that restrictive filling pattern is associated with an increased risk of all-cause mortality and HF.[105] Tissue Doppler-derived parameter of E/e′ over 15 is also a strong predictor of mortality and HF development after MI.[106]

Left ventricular remodelling

Left ventricular remodelling is commonly defined as a 20% increase in LV end-diastolic volume.[9] Post-MI remodelling is exacerbated by a larger infarct size, transmural MI, microvascular obstruction, myocardial haemorrhage, and advanced age. In the contemporary era, almost half of patients after MI demonstrate LV remodelling on echocardiography within 1 year from MI. Among patients with LV remodelling, the risk of hospitalization for HF is 2.7 times higher than in those without LV remodelling.[107]

Speckle tracking echocardiography

Speckle tracking echocardiography (STE) measures regional and global myocardial deformation. Global longitudinal (apico-basal) strain is the most used and is superior to LVEF measurement, especially in the early phases of systolic dysfunction. In a study by Ersbøll *et al*. among MI patients with LVEF > 40%, global longitudinal (apico-basal) strain higher than —14 was associated with a five times higher risk of HF and 12 times higher risk of cardiac death.[108] 3D STE is a novel method offering more realistic and accurate models of LV than 2D STE.[109] Global area strain, one of the 3D STE parameters, combines both longitudinal and circumferential strains. Among patients after MI, global area strain is an independent predictor of MACE and HF hospitalization, superior to conventional 2D echocardiography parameters.[110,111]

Myocardial contrast echocardiography

Myocardial contrast echocardiography (MCE) visualizes myocardial perfusion by intravenous or intracoronary infusion of microbubbles. MCE can distinguish reversible and irreversible ischaemia, thus detecting myocardial viability.[98] Lack of perfusion signals caused by microvascular obstruction on MCE is consistent with the results of cardiac magnetic resonance.[98] To detect no-reflow, MCE should be ideally performed 24–48 h after coronary intervention for MI. In several studies, no-reflow after MI was an independent predictor of LV recovery and adverse outcomes including HF.[112,113]

Stress echocardiography

Dobutamine stress echo-derived parameters such as infarction zone non-viability and ischaemia/infarction at a distance were identified as independent predictors of adverse outcomes, including HF, in patients 2 to 7 days after MI.[114]

Cardiac magnetic resonance

Infarct size

Magnetic resonance imaging is currently the gold standard imaging modality for quantifying infarct size using late gadolinium enhancement. According to a meta-analysis of studies measuring infarct size by MRI or single-photon emission computed tomography in patients after STEMI, for every 5% increase in MI size, the risk of hospitalization for HF increases by 20%.[115]

On the other hand, a recent prospective study showed no additional long-term prognostic value of infarct size measured by MRI over LVEF in patients after non-STEMI.[116] The difference in prognostic value in STEMI and non-STEMI may be explained by a different magnitude of myocardial damage.

Microvascular obstruction

Microvascular obstruction refers to the lack of perfusion in the coronary microcirculation, despite revascularization of the epicardial vessels. Microvascular obstruction can be identified as a hypointense core within the area of hyperenhancement on either early (referred to as early microvascular obstruction) or late gadolinium enhancement (late microvascular obstruction). Microvascular obstruction is associated with larger MI size and adverse remodelling. In a recent individual patient data meta-analysis, microvascular obstruction increase by 10% elevated the risk of hospitalization for HF by 80% and all-cause mortality by 114%.[117]

Intramyocardial haemorrhage

If the microvascular injury after MI is severe and the integrity of microcirculation is compromised, extravasation of red blood cells into the myocardium can occur. Red blood cell extravasation is referred to as intramyocardial haemorrhage and can be detected by MRI as a hypointense zone within the MI core on T2* imaging or mapping. Several studies suggest that iron deposits from red blood cells trigger pro-inflammatory response and lead to adverse LV remodelling.[118,119] Smaller studies in patients after STEMI suggested that myocardial haemorrhage was more closely associated with adverse outcomes, including HF, than microvascular obstruction.[120,121]

Multiple scars

A MRI substudy of the third Danish Study of Optimal Acute Treatment of Patients with ST-segment Elevation Myocardial Infarction (DANAMI 3) proved that multiple scars (characterized by late gadolinium enhancement in more than one myocardial areas remote from acute infarction area) were associated with almost three-fold risk of all-cause mortality and HF hospitalization after adjustment for clinical risk factors and MI size.[122]

Molecular imaging

Molecular imaging is an emerging method studying different phases of the post-MI period at a molecular level. The principle is based on the existence of specific tracers that bind to molecules of interest. Various methods of nuclear medicine have shown potential to predict adverse LV remodelling [e.g. tracers binding to MMP-2 or MMP-9 within the infarct zone, angiotensin-converting enzyme inhibitor (ACEi) and angiotensin receptor antagonist-based tracers, growth factor receptors, and $\alpha_v\beta_3$ integrin tracers].[123] Currently, data showing predictive value of these methods for HF prediction after MI are lacking.

Remote monitoring

Among patients with established HF, various remote monitoring strategies have been tested to detect worsening of HF and reduce the risk of HF readmission. Several implantable[124] (using data from cardioverter defibrillators and cardiac resynchronization therapy) and wearable[125] devices have shown the capability to detect HF exacerbation.

However, most of the studies with implantable devices could not detect the mortality benefit of telemonitoring.[126–128] The exception was IN-TIME trial (Biotronik Home Monitoring technology), which documented improvement of a composite clinical score and particularly all-cause mortality in remote monitoring group of patients.[129] Pooled analysis of the three trials with the same monitoring system with daily transmissions (TRUST, ECOST, and IN-TIME) confirmed 38% and 36% reduction of all-cause mortality and the composite endpoint of all-cause mortality or hospitalization for HF worsening, respectively. The benefit of this form of monitoring appears to be driven by the prevention of HF exacerbation, mainly due to early detection of arrhythmias and/or loss of biventricular pacing.[130] Another technology that was capable to reduce HF hospitalizations was the CardioMEMS device—an implantable pulmonary artery pressure monitor.[131] Yet no remote monitoring study has so far targeted at-risk population after MI.

Guideline-recommended therapies

Pharmacotherapy

Beta-blockers

Beta-blockers interfere with the harmful effects of sustained activation of the sympathetic nervous system, particularly by blocking the β_1-adrenergic receptors. Together with ACEi, angiotensin receptor blockers, and statins, beta-blockers indirectly inhibit MMPs.[132]

The evidence for the favourable effect of beta-blockers on post-MI outcomes comes mainly from the pre-thrombolytic era. In a meta-analysis of 31 randomized studies, long-term beta-blocker use reduced all-cause mortality after MI by 23%.[133] However, none of the studies specifically involved patients with systolic dysfunction and HF during MI hospitalization.[134]

In the SAVE and AIRE studies, which originally analysed the effect of ACEi in MI patients with LV systolic dysfunction, beta-blocker use reduced the risk of progression to severe HF by 21% and 42%, respectively.[135,136] In the CAPRICORN study, carvedilol administered in MI patients with systolic dysfunction (LVEF < 40%) reduced all-cause mortality by 23% and HF hospitalization by 14% compared with placebo.[134] This effect was additional to ACEi.[134]

Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers

Activation of the renin–angiotensin–aldosterone system actively participates in the process of LV remodelling, myocardial fibrosis, and HF development after MI. ACEi by blocking conversion of angiotensin I into angiotensin II supresses vasoconstriction and aldosterone secretion mediated by angiotensin II. Angiotensin receptor blockers block this action of angiotensin II by interfering with the binding of angiotensin II to its receptor.

Early initiation of ACEi within 0–36 h from MI symptom onset reduces 30 day mortality and HF by 7% and 4%, respectively.[137] The absolute benefit is greater in high-risk groups (such as Killip Class II/III, heart rate >100 b.p.m. at entry) and anterior MI. Importantly, 40% of the survival benefit occurred on the first day of treatment, underscoring the value of initiating ACEIs early, as long as patients have adequate blood pressure.[137] The positive effect of ACEi post-MI was proved also in long-term studies.[138–140] ACEIs started between 3 and 16 days post-MI reduce the relative risk of mortality by 26% and readmission for HF by 27%.[141]

Angiotensin receptor blockers are used in patients with intolerance of ACEi. Various studies have shown favourable effect of losartan or valsartan on mortality and HF hospitalization.[39,142]

Mineralocorticoid receptor antagonist

Aldosterone by its action on distal nephron increases sodium and water reabsorption leading to an expansion of the extracellular fluid. In the heart, mineralocorticoid receptor activation triggers inflammation, hypertrophy, and fibrosis. Mineralocorticoid receptor antagonist eplerenone was tested in the EPHESUS study, in which patients after MI with LVEF < 40% and HF or diabetes were enrolled. As compared with placebo, eplerenone reduced all-cause mortality and HF hospitalization by 15% and death from cardiovascular causes by 17%.[143] This effect was present only if eplerenone was administered in the first 7 days after MI.[144]

Statins

Statins are lipid-lowering drugs with pleiotropic effects. Besides inhibition of 3-hydroxy-3-methylglutarylcoenzyme A reductase, the key enzyme in cholesterol synthesis, statins exert endothelium-stabilizing, anti-inflammatory, and anti-proliferative effects on cells involved in atherosclerosis.[145] In the IDEAL and PROVE IT-TIMI 22 studies, high doses of statin (atorvastatin 80 mg daily) decreased HF risk by 26% and 45% as compared with low to moderate statin dose, respectively.[146,147] Early administration of statins (within 24 h of hospitalization) is associated with a 2.5-fold risk reduction of HF hospitalization and a three-fold reduction in in-hospital mortality.[148]

Percutaneous coronary intervention

A decrease in HF after MI since the adoption of PCI has been well documented.[10,149–151] In population-based studies from Sweden, Western Australia, Denmark, and Olmsted County in the USA, increase in PCI rates led to 20–41% reduction in HF after MI.[10,149–151]

Conclusions

Development of HF after MI is associated with adverse events, impaired quality of life, and lower survival. As reviewed in this paper, a wide range of clinical, laboratory, and diagnostic findings are associated with HF development after MI. However, precise, cost-effective, and accurate scoring system integrating clinical risk factors, genetics, biomarkers, and imaging methods for HF prediction and prognostication after MI is lacking. Better identification of patients at risk of HF development after MI is needed because timely initiation of guideline-directed HF therapy can reduce the risk of further LV remodelling, morbidity, and mortality.

Conflict of interest

None declared.

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Author contributions

D.J. performed the literature search and wrote the original draft. P.W. performed the literature search and critically revised the work. J.S., J. Kautzner, V.S., V.A., V.M., and J. Kettner critically revised the work.

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ORIGINAL RESEARCH

Remote Heart Failure Symptoms Assessment After Myocardial Infarction Identifies Patients at Risk for Death

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BACKGROUND: Heart failure is a common complication after myocardial infarction (MI) and is associated with increased mortality. Whether remote heart failure symptoms assessment after MI can improve risk stratification is unknown. The authors evaluated the association of the 23-item Kansas City Cardiomyopathy Questionnaire (KCCQ) with all-cause mortality after MI.

METHODS AND RESULTS: Prospectively collected data from consecutive patients hospitalized for MI at a large tertiary heart center between June 2017 and September 2022 were used. Patients remotely completed the KCCQ 1 month after discharge. A total of 1135 (aged 64±12 years, 26.7% women) of 1721 eligible patients completed the KCCQ. Ranges of KCCQ scores revealed that 30 (2.6%), 114 (10.0%), 274 (24.1%), and 717 (63.2%) had scores <25, 25 to 49, 50 to 74, and ≥75, respectively. During a mean follow-up of 46 months (interquartile range, 29–61), 146 (12.9%) died. In a fully adjusted analysis, KCCQ scores <50 were independently associated with mortality (hazard ratio [HR], 6.05 for KCCQ <25, HR, 2.66 for KCCQ 25–49 versus KCCQ ≥50; both P<0.001). Adding the 30-day KCCQ to clinical risk factors improved risk stratification: change in area under the curve of 2.6 (95% CI, 0.3–5.0), Brier score of −0.6 (95% CI, −1.0 to −0.2), and net reclassification improvement of 0.71 (95% CI, 0.45–1.04). KCCQ items most strongly associated with mortality were walking impairment, leg swelling, and change in symptoms.

CONCLUSIONS: Remote evaluation of heart failure symptoms using the KCCQ among patients recently discharged for MI identifies patients at risk for mortality. Whether closer follow-up and targeted therapy can reduce mortality in high-risk patients warrants further study.

Key Words: heart failure ■ KCCQ ■ mortality ■ myocardial infarction ■ prognosis ■ symptoms

Traditional, unstructured patient questioning on disease symptoms is time demanding and influenced by provider skills and subjective interpretation.[1] Accordingly, it has been shown to be inaccurate as physicians may fail to recognize patients' functional disabilities.[2] Patient-reported outcomes (PROs) provide a standardized, valid, reproducible, and sensitive way to capture patient symptoms, function, and quality of life.[3] Importantly, PROs can also predict the risk of adverse clinical events.[4–6] In connection with modern telemedicine options, PROs may provide the opportunity to remotely identify patients who are more symptomatic and at increased risk for complications who could benefit from targeted and timely therapy.

The Kansas City Cardiomyopathy Questionnaire (KCCQ) is a heart failure (HF)–specific PRO that predicts adverse events in patients with acute[7] and chronic HF.[4,8] After myocardial infarction (MI), KCCQ has only been used in a substudy of EPHESUS (Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy

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CLINICAL PERSPECTIVE

What Is New?

- Heart failure is a common complication of myocardial infarction associated with increased mortality risk.
- Whether remote evaluation of heart failure symptoms using the Kansas City Cardiomyopathy Questionnaire (KCCQ) can identify patients at increased mortality risk is unknown.
- In the present study, we show that remote evaluation of HF symptoms using the KCCQ score among patients recently discharged for myocardial infarction identifies patients at risk for mortality.

What Are the Clinical Implications?

- The KCCQ can be part of a toolkit for risk stratification after myocardial infarction.
- Whether closer follow-up and targted therapy can decrease mortality risk in patients with KCCQ score <50 after myocardial infarction warrants further investigation.

Nonstandard Abbreviations and Acronyms

EPHESUS	Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study
GRACE	Global Registry of Acute Coronary Events
KCCQ	Kansas City Cardiomyopathy Questionnaire
NRI	net reclassification improvement
PRO	patient-reported outcome

and Survival Study) among patients with manifest HF and reduced ejection fraction.[9] Yet, it is unknown whether the KCCQ can be used in the general population of patients with MI to identify those at increased mortality risk.

Several prognostic models that aim to estimate the risk of all-cause mortality, or the combined risk of all-cause mortality or MI in patients after MI, have been developed. Among them, the Global Registry of Acute Coronary Events (GRACE) risk score has been recommended in the latest European Society of Cardiology guidelines,[10] as it offers the best discriminative performance.[11,12] The GRACE 2.0 score uses 8 clinical variables (age, systolic blood pressure, heart rate, Killip class, creatinine, ST elevation, elevated troponin level, and cardiac arrest at admission) to predict the risk of in-hospital, 6-month, 1- and 3-year mortality, or death or MI at 1 year.[13] Yet, it is unknown whether the evaluation of HF symptoms has an additional predictive value to variables used in the GRACE score. HF is common after MI, developing in up to 40% of patients,[14] and significantly increases mortality.[15] However, HF is often diagnosed late, at a stage requiring hospital admission, which may increase mortality risk and elevate costs. We hypothesized that early HF symptoms, evaluated with the KCCQ 1 month after hospital discharge for MI, could identify patients at increased mortality risk and improve risk stratification beyond risk factors used in the GRACE score.

The aim of this study was to examine the association of the KCCQ Overall Summary score with total mortality risk in a consecutive group of patients hospitalized for MI at a large tertiary heart center.

METHODS

Data Availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Population

This study used data from the prospective Institute for Clinical and Experimental Medicine Acute Myocardial Infarction Registry (AMBITION).[16] The registry collects clinical data and biospecimens from consecutive patients hospitalized for acute coronary syndrome since June 2017 at the Institute for Clinical and Experimental Medicine, Prague, Czech Republic, a tertiary heart center with around-the-clock coronary intervention service. The Fourth Universal Definition of Myocardial Infarction has been used.[17] Patients underwent a detailed interview during their hospital stay, and additional information was obtained from medical record abstraction and laboratory studies. We included consecutive patients enrolled between June 2017 and September 2022 with death ascertainment through June 2023. Data from consecutive patients hospitalized for MI were used in this analysis. Only patients with missing KCCQ score or patients who died within 1 month of hospital discharge were excluded. The study complies with the Declaration of Helsinki. The institutional review board approved the study, and all participants signed informed consent.

Kansas City Cardiomyopathy Questionnaire

One month after discharge, patients were asked to complete the 23-item KCCQ. Because the majority of patients did not have HF, in the questionnaire we replaced heart failure with heart disease. The patients

had a choice of completing the KCCQ through an online application or on a paper form returned by regular mail. For the present analysis we used the KCCQ Overall Summary score, which we refer to as the KCCQ score. The KCCQ score ranges from 0 to 100, where higher scores indicate better function, fewer symptoms, and higher quality of life. Using published recommendations,[18] scores were categories into ranges of very poor to poor (<25), poor to fair (25–49), fair to good (50–74), and good to excellent (≥75) health status.

Outcomes

The primary outcome of this study was all-cause mortality. Mortality data were provided by the Institute of Health Information and Statistics of the Czech Republic, which keeps a list of all deceased persons in the Czech Republic by law. Deaths in this study were through June 30, 2023.

Statistical Analysis

Descriptive statistics are reported as mean±SD, median (interquartile range), or frequency (percentage). The primary outcome was all-cause mortality, and Cox proportional hazard models were used to assess the association of KCCQ score categories with total mortality in an unadjusted model followed by adjustment for components of the validated GRACE score[13] (age, heart rate, and systolic blood pressure at hospital admission, creatinine, maximal troponin level, double log-transformed value, ST-segment–elevation MI, cardiac arrest at admission and Killip class). Rather than adjusting for the GRACE score, we used adjustment for covariates used in the model. This had 2 reasons. First, the follow-up varied in the registry, thus trimming to the prespecified time point used in the score would decrease the sample size and statistical power. Second, the GRACE score would need recalibration to our population before net reclassification improvement (NRI) could be calculated.

To account for nonlinearity, we tested restricted cubic splines adjusted for the continuous variables of age and 30-day KCCQ scores with total mortality risk. To identify the most predictive items of the KCCQ, we used backward selection adjusted for age.

The proportional hazard assumption fulfilled the Schoenfeld residuals test. The modifying effect of age, sex, and ejection fraction on the association between KCCQ score and mortality risk was tested using interactions.

To examine the added prognostic value of KCCQ to established risk factors used from the GRACE score, we used the C index, Brier score, and NRI. The continuous NRI was calculated using the R survNRI package. All statistical tests and CIs were 2-sided with a significance level of 0.05. Statistical analyses were conducted with R statistical software version 4.2.2 (R Foundation for Statistical Computing), SPSS version 25.0 (IBM), and STATA version 17 (StataCorp).

RESULTS

Between June 2017 and September 2022, 1769 patients were hospitalized for MI. Of these, 69 (3.9%) had missing KCCQ scores due to death within 1 month of hospital discharge. In total, 1135 (66.8% of eligible patients) patients completed the KCCQ 1 month after hospital discharge. Comparison of patients with available and missing KCCQ is shown in Table S1. Patients with missing KCCQ scores were slightly older and more often required cardiopulmonary resuscitation before hospital admission, while maximal troponin and mortality was similar in patients with and without KCCQ.

The mean age of the studied population was 64±12 years, with 26.7% being women, 60% having an ST-segment–elevation MI, and 82% with Killip class I. At 30 days, 30 (2.6%) participants had a KCCQ <25, 114 (10.0%) had scores of KCCQ 25 to 49, 274 (24.1%) had scores of KCCQ 50 to 74, and 717 (63.2%) had KCCQ scores ≥75. Table 1 describes demographic and clinical characteristics by KCCQ categories.

Outcome and KCCQ Predictive Value

During a median follow-up of 46 months (IQR, 29–61), 146 (12.9%) patients died. In the nonlinear analysis adjusted for age (Figure 1), the mortality risk increased with decreasing KCCQ score. Kaplan–Meier survival curves for KCCQ categories are shown in Figure 2. After adjusting for clinical variables included in the GRACE score, KCCQ score<50 was independently associated with mortality risk (Table 2). There were no significant interactions between the KCCQ score categories and age (*P* for interaction 0.86), sex (*P* for interaction 0.72), or systolic dysfunction with ejection fraction <40% (*P* for interaction 0.53).

Improvement in Discrimination, Calibration, and Stratification

In assessing mortality risk at 2 years after MI, the AUC for the 3 KCCQ score categories (KCCQ <25, 25–49, and ≥50) was 67.9 (95% CI, 61.9–73.9). The addition of 3 KCCQ categories to components of the GRACE score associated with the outcome (age, Killip class, ST-segment–elevation MI, heart rate, creatinine level) significantly improved the C index (from AUC, 82.6 [95% CI, 78.0–87.3] to AUC, 85.3 [95% CI, 80.5–90.0]; delta AUC, 2.6 [95% CI, 0.3–5.0], *P*=0.03); and Brier score by −0.6 [95% CI, −1.0 to −0.2, *P*=0.01]). KCCQ score categories improved the continuous NRI by 0.71

Table 1. Population Demographics by KCCQ Score Categories

	KCCQ score <25 (n=30)	KCCQ score 25 to 49 (n=114)	KCCQ score 50–74 (n=274)	KCCQ score ≥75 (n=717)	Total (N=1135)	*P* for linear trend
Age, y	70.5±11.4	63.3±12.6	67.2±11.9	63.2±11.6	64.4±11.9	0.001
Female sex, n (%)	14 (46.7)	36 (31.6)	89 (32.5)	164 (22.9)	303 (26.7)	0.001
BMI, kg/m^2	28.2±4.9	28.9±4.7	28.6±5.3	28.9±4.8	28.8±4.9	0.373
CPR, n(%)	0 (0)	4 (3.5)	8 (2.9)	22 (3.1)	34 (3.0)	0.699
Admission SBP, mm Hg	148±28	142±29	147±29	145±24	145±27	0.904
Admission DBP, mm Hg	78±17	79±14	79±14	80±13	79±13	0.407
Admission HR, beats/min	87±15	80±19	76±19	75±18	76±18	0.001
Maximal troponin, log (ng/L)	6.68±1.82	6.87±1.49	6.85±1.63	6.87±1.51	6.86±1.55	0.690
Creatinine, umol/L	108.8±75.7	106.9±105.6	100.7±69.4	87.8±35.2	93.4±57.1	0.001
HbA_{1c}, mmol/mol	50.93±18.56	46.60±16.09	44.85±11.46	44.91±12.64	45.21±12.96	0.042
STEMI, n (%)	12 (40.0)	65 (57.0)	143 (52.2)	462 (64.4)	682 (60.1)	0.001
Killip class I, n (%)	14 (46.7)	81 (71.1)	217 (79.2)	619 (86.3)	931 (82.0)	0.001
EF, %	41±11	43±11	46±10	46±10	46±10	0.001
EF <40%, n (%)	12 (40.0)	36 (31.6)	65 (23.7)	141 (19.7)	254 (22.4)	0.001
Discharge medication						
ACEI/ARB, n (%)	20 (66.7)	77 (67.5)	213 (77.7)	563 (78.5)	873 (76.9)	0.011
β-Blocker, n (%)	27 (90.0)	88 (77.2)	217 (79.2)	585 (80.8)	917 (80.8)	0.679
Statin, n (%)	24 (80.0)	105 (92.1)	264 (96.4)	690 (96.2)	1083 (95.4)	0.001
Furosemide, n (%)	20 (66.7)	37 (32.5)	74 (27.0)	120 (16.7)	251 (22.1)	0.001
Verospirone, n (%)	10 (33.3)	35 (30.7)	60 (21.9)	135 (18.8)	240 (21.1)	0.001

Data are presented as mean±SD unless otherwise indicated. ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; CPR, cardiopulmonary resuscitation; DBP, diastolic blood pressure; EF, ejection fraction; HbA_{1c}, glycated hemoglobin; HR, heart rate; KCCQ, Kansas City Cardiomyopathy Questionnaire; SBP, systolic blood pressure; and STEMI, ST-segment–elevation myocardial infarction.

(95% CI, 0.45–1.04), with a significant improvement in nonevent NRI of 0.79 (95% CI, 0.50–1.00), but without change in event NRI of −0.10 (95% CI, −0.35 to 0.18). Calibration plots for both models are shown in Figure S1. In a sensitivity analysis, the 12-item KCCQ predictive value was similar to the 23-item KCCQ.

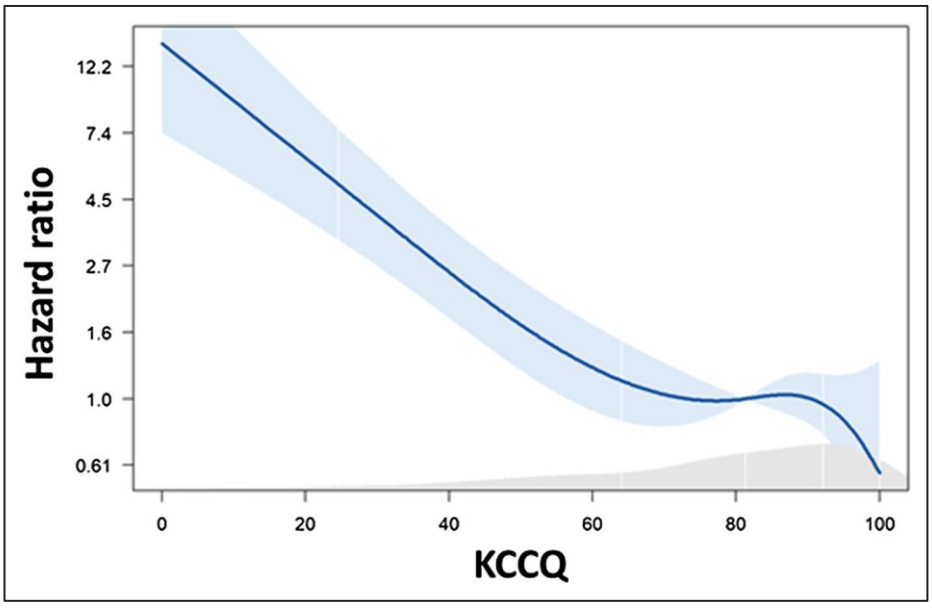

Figure 1. The association of Kansas City Cardiomyopathy Questionnaire (KCCQ) score with mortality risk after myocardial infarction.
Data are adjusted for age. Gray shaded area represents KCCQ histogram in the population. Light blue area is the 95% CI. The reference value is the KCCQ median of 81.

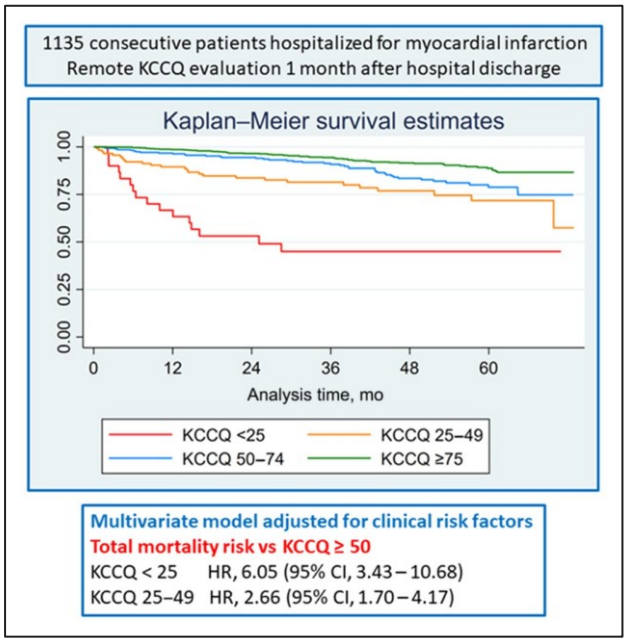

Figure 2. Kaplan–Meier survival curves for Kansas City Cardiomyopathy Questionnaire (KCCQ) score categories. HR indicates hazard ratio.

KCCQ Items and Mortality

To identify KCCQ items most strongly associated with mortality after MI, we used forward stepwise Cox regression adjusted for age. We found that responses to 3 questions were independently associated with mortality. These items included walking limitations, change in symptoms during the past 2 weeks, and leg swelling.

DISCUSSION

Optimally managing patients recovering from MI warrants building a longitudinal infrastructure to assess patients' risk over time so that proactive interventions can be offered to optimize patients' symptoms, function, and survival. To advance current strategies, we examined the prognostic significance of assessing patients' health status with the KCCQ 1 month after hospital discharge in a large, prospective cohort of consecutive patients recovering from an MI. We found that lower KCCQ scores, particularly <50, were independently associated with mortality risk, above and beyond clinical risk factors alone.

This study extends the field of risk stratification after hospital discharge for an MI, as we are unaware of other studies using health status measures after discharge to assess patients' long-term prognosis. Two prior publications from the EPHESUS trial did show the KCCQ to be independently prognostic of cardiovascular death and hospitalizations, but this was in a select group of patients with diabetes or HF during their MI hospitalization.[9,19] Similarly, Dunlay et al examined the prognostic significance of the KCCQ after an admission for HF and, like the current study, found it was independently associated with survival and hospitalization.[20] Thus, these findings of the prognostic significance of postdischarge KCCQ assessment in all-comers with MI further supports the routine use of PROs in designing holistic, patient-centered strategies to optimize patients' outcomes.

HF-related quality-of-life impairment is common in patients after MI.[21] In the present study, KCCQ scores <50 were present in ≈13% of patients 30 days after their MI. Interestingly, 66% of these patients were Killip class I during the hospital stay, suggesting that a large proportion of patients either developed HF symptoms after hospital discharge, or that the Killip class is insufficiently sensitive to HF symptoms. Furthermore, the KCCQ's predictive value was independent of age, sex, and left ventricular ejection fraction at hospital discharge, suggesting that the KCCQ may be a useful patient-centered tool for identifying patients at increased mortality risk following MI.

We identified that the 3 most predictive items of the KCCQ were walking impairment, leg swelling, and change in symptoms. These symptoms are not novel and have been used by clinicians for decades; however, unstructured questioning of HF symptoms is time-consuming, is influenced by physician subjective interpretation, and may not be consistently performed in all patients, and, as such, limits actionability. Therefore, a structured application of the KCCQ score after MI may be helpful in consistent symptom assessment and in subsequent decision-making.

Currently, the guidelines recommend evaluation of HF symptoms during hospital stay using Killip class. The Killip classification describes lung congestion or cardiogenic shock presence, with a Killip class >I being a marker of increased risk of future events.[22]

Table 2. Risk of Mortality by KCCQ Score Categories

Model	Variable	HR (95% CI)
Unadjusted	KCCQ score	
	KCCQ <25	10.52 (6.05–18.27)
	KCCQ 25–49	3.24 (2.05–5.12)
	KCCQ 50–74	1.89 (1.28–2.80)
	KCCQ ≥75	1 (reference)
Adjusted*	KCCQ score	
	KCCQ <25	6.64 (3.67–12.01)
	KCCQ 25–49	2.78 (1.72–4.49)
	KCCQ 50–74	1.18 (0.78–1.77)
	KCCQ ≥75	1 (reference)

*Adjusted for age, sex, ejection fraction, heart rate and systolic blood pressure at hospital admission, creatinine, maximal troponin level (double log-transformed value), ST-segment–elevation myocardial infarction, cardiac arrest at admission, and Killip class. KCCQ indicates Kansas City Cardiomyopathy Questionnaire.

However, evaluation of HF symptoms early after hospital discharge is not routinely or systematically performed, even though MI is a common cause of HF, with HF developing in 13% of patients 1 month after hospital discharge.[23] A large proportion of patients with newly developed HF may therefore be missed if the infrastructure is not in place to consistently assess it, something that remote monitoring with the KCCQ can accomplish. Interestingly, the risk of death associated with HF after MI is independent of ejection fraction and greater for delayed- versus early-onset HF.[15] Thus, not identifying HF symptoms early after hospital discharge represents a missed opportunity to identify patients at increased risk in which guideline-directed medical therapy could be proactively initiated.

Finally, we also demonstrate the feasibility of remotely assessing patients' health status, which may decrease the burden on patients and medical staff and increase the consistency of HF symptom assessment in the post-MI period. Implementation work is needed to test that early identification of patients who develop HF symptoms after MI and are at increased risk for mortality will lead to clinical action, including additional diagnostics and targeted interventions and a subsequent favorable effect on mortality.

Study Limitations

The primary objective of the present study was total mortality rather than cardiovascular mortality since the cause of death could not be reliably ascertained. Nevertheless, early after acute coronary syndrome, cardiovascular deaths are the major cause of mortality,[24] and we therefore believe most deaths were related to patients' cardiovascular disease. Due to the observational nature of the analysis, we cannot exclude an effect of unmeasured confounding. However, when adjusting for the most common clinical variables used to risk stratify patients with an MI, the 30-day KCCQ scores carried independent prognostic significance. The registry enrolled consecutive patients with MI, but ≈34% of patients did not complete KCCQ within 30 days of discharge. While most clinical variables were similar in both groups, we cannot exclude an influence of a selection bias. Finally, as a single-center study, validation of these findings is warranted to support their generalizability.

CONCLUSION

PROs provide a practical and inexpensive means to identify HF symptoms. We show that remote evaluation of HF symptoms using the KCCQ score among patients recently discharged for MI identifies patients at risk for mortality. Whether closer follow-up and targeted therapy can reduce mortality in these at-risk patients warrants further investigation.

ARTICLE INFORMATION

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Supplemental Material

Table S1
Figure S1

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FULL RESEARCH PAPER
Coronary artery disease

Development and validation of a prognostic score integrating remote heart failure symptoms and clinical variables in mortality risk prediction after myocardial infarction: the PragueMi score

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Aims While heart failure (HF) symptoms are associated with adverse prognosis after myocardial infarction (MI), they are not routinely used for patients' stratification. The primary objective of this study was to develop and validate a score to predict mortality risk after MI, combining remotely recorded HF symptoms and clinical risk factors, and to compare it against the guideline-recommended Global Registry of Acute Coronary Events (GRACE) score.

Methods and results A cohort study design using prospectively collected data from consecutive patients hospitalized for MI at a large tertiary heart centre between June 2017 and September 2022 was used. Data from 1135 patients (aged 64 ± 12 years, 26.7% women), were split into derivation (70%) and validation cohort (30%). Components of the 23-item Kansas City Cardiomyopathy Questionnaire and clinical variables were used as possible predictors. The best model included the following variables: age, HF history, admission creatinine and heart rate, ejection fraction at hospital discharge, and HF symptoms 1 month after discharge including walking impairment, leg swelling, and change in HF symptoms. Based on these variables, the PragueMi score was developed. In the validation cohort, the PragueMi score showed superior discrimination to the GRACE score for 6 months [the area under the receiver operating curve (AUC) 90.1, 95% confidence interval (CI) 81.8–98.4 vs. 77.4, 95% CI 62.2–92.5, $P = 0.04$) and 1-year risk prediction (AUC 89.7, 95% CI 83.5–96.0 vs. 76.2, 95% CI 64.7–87.7, $P = 0.004$).

Conclusion The PragueMi score combining HF symptoms and clinical variables performs better than the currently recommended GRACE score.

Lay summary

- The prognosis of patients after myocardial infarction is heterogeneous. Thus, risk stratification is needed to identify and intervene patients at increased risk. While heart failure (HF) symptoms are associated with adverse prognosis, they are not used for patients' stratification.
- We have developed and internally validated the PragueMi score, which integrates clinical risk factors at the time of hospitalization and HF symptoms determined remotely by a questionnaire 1 month after hospital discharge.
- PragueMi score was able to better stratify patients' risk as compared with the currently recommended Global Registry of Acute Coronary Events score.

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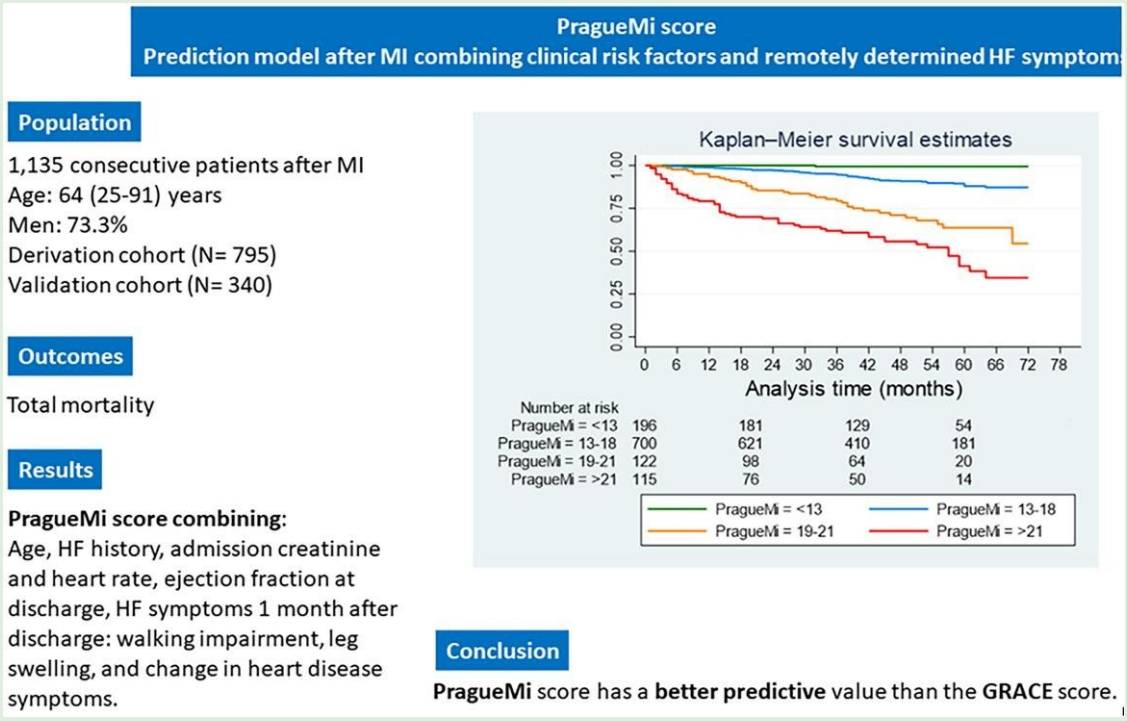
Graphical Abstract



Keywords Myocardial infarction • Heart failure • Symptoms • Risk prediction • Questionnaire • Mortality

Introduction

For optimal management of patients recovering from a myocardial infarction (MI), identification of individuals at increased risk of adverse outcomes is essential. This allows targeted proactive interventions in at-risk patients to improve their symptoms, function, and survival. The Global Registry of Acute Coronary Events (GRACE) score has been recommended by the guidelines to stratify patients' risk after MI.[1] However, discrimination of the GRACE model for 1-year mortality evaluated by the area under the receiver operating curve (AUC) is within the 0.82–0.89 range.[2] Thus, a better performing model is of clinical need.

Heart failure (HF) is a common complication of MI, developing in up to 40% of patients and increasing total mortality risk by three-fold.[3] The GRACE score evaluates HF using the Killip class. However, the Killip classification evaluates only pulmonary congestion, neglecting other HF symptoms. Furthermore, many patients develop HF symptoms early after hospital discharge. Interestingly, HF developing later after MI is associated with higher mortality risk as compared with HF developing at MI presentation.[4] Thus, evaluation of HF symptoms and signs is an important goal of post-discharge visits.

For decades, clinicians have been using unstructured questions on HF symptoms. Nevertheless, unstructured questioning is time-consuming, influenced by the physician's subjective interpretation, and may not be consistently done in all patients, and as such limits actionability. Our previous research showed that structured HF symptom evaluation using the Kansas City Cardiomyopathy Questionnaire (KCCQ) identifies HF symptoms in two out of five patients after MI[5] and identifies patients at increased mortality risk.[6] We hypothesized that the integration of HF symptoms with clinical risk factors may provide superior risk prediction after MI beyond the GRACE score. This may better define a high-risk group that may benefit from a more proactive approach and pharmacological and non-pharmacological therapy of HF.

The objectives of this study were as follows: (i) to select KCCQ items and clinical factors associated with total mortality risk after MI, (ii) to create a prognostic score (PragueMI score) based on identified variables in the derivation cohort, and (iii) to compare the predictive value of the PragueMi score against the GRACE score in the validation cohort.

Methods

Population

In this cohort design study, we have used data from the prospective Institute for Clinical and Experimental Medicine Acute Myocardial Infarction Registry (AMBITION registry).[7] The registry collects clinical data and biospecimens from consecutive patients hospitalized for acute coronary syndrome since June 2017 at the Institute for Clinical and Experimental Medicine, Prague, Czech Republic, a tertiary heart centre with around-the-clock coronary intervention service. The Fourth Universal Definition of Myocardial Infarction has been used.[8] Patients underwent a detailed interview during their hospital stay, and additional information was obtained from medical record abstraction and laboratory studies. One month after discharge, patients were asked to complete the 23-item KCCQ. Because most patients did not have HF, in the questionnaire, we have replaced 'heart failure' with 'heart disease'. The patients had a choice of completing the KCCQ through an online application or on a paper form returned by regular mail.

The inclusion criterion was hospitalization for MI between June 2017 and September 2022. Patients with missing KCCQ were excluded from this analysis. Death was ascertained through June 2023. Mortality data were provided by the Institute of Health Information and Statistics of the

Czech Republic (UZIS), which keeps a list of all deceased persons and dates of death in the Czech Republic by law. This study was approved by a local ethics committee and complies with the Declaration of Helsinki.

Primary outcome

The primary outcome of the analysis was all-cause mortality.

Global Registry of Acute Coronary Events score

The Eagle model estimates for death within 6 months after discharge was used.[9] Variables included in the model were age, heart rate, systolic blood pressure, creatinine level, troponin elevation, ST segment depression on initial electrocardiogram (ECG), previous history of MI and HF, and percutaneous coronary intervention (PCI).

Statistical methods

Continuous variables are presented as mean and SDs or medians and interquartile range (IQR). Nominal variables are shown as counts and percentages. All consecutive patients hospitalized for MI between June 2017 and September 2022 were included in this analysis. No formal power calculation was performed.

To identify factors associated with mortality risk after MI, we have used restricted cubic splines adjusted for age. This allowed us to detect non-linear associations and to categorize continuous variables. We have used Cox regression with both forward and backward selection to identify factors independently associated with the mortality risk. Potential variables selection was based on a literature search and included the following factors: age, admission heart rate, systolic blood pressure, creatinine level, fasting glycaemia, glycated haemoglobin, haemoglobin, maximal troponin level, ST segment depression on initial ECG, ST-elevation myocardial infarction (STEMI), previous history of MI, HF or PCI, ejection fraction at hospital discharge, and KCCQ items. Variables independently associated with the mortality risk in the derivation cohort were used for the PragueMi score creation. We have used regression coefficients to create relative weights for each category. To compare the performance of the PragueMi score as compared with the GRACE score, we have used the following methods: (i) assessment of the difference in the area under the receiver operating characteristic curve (AUC), (ii) the Brier score, and (iii) the continuous net reclassification improvement (NRI).

The AUC is an overall measure of model discrimination. It measures the model's ability to distinguish between patients with and without events. The AUC ranges from 0 to 1, where 0.5 indicates a random classification and 1 signifies a perfect classifier. To compare differences in AUC, we have used the Delong–Delong test using the R riskRegression package.[10]

The Brier score is a measure of model calibration. It is calculated as the mean squared difference between the predicted probability and the actual outcome. The Brier score for a perfectly calibrated model is 0.[11] The riskRegression package was also used to calculate the Brier score at different time points.[10]

The NRI quantifies how well a new model reclassifies subjects—either appropriately or inappropriately—as compared with an old model.[12] We have used the R nricens package for continuous NRI calculation.

Statistical analyses were conducted with R statistical software version 4.2.2 (R Foundation for Statistical Computing, Vienna, Austria), SPSS version 25.0 (IBM Corporation, Armonk, NY, USA), and STATA version 17 (StataCorp, College Station, TX, USA). All statistical tests and confidence intervals were two sided with a significance level of 0.05.

Results

Population

Between June 2017 and September 2022, 1769 patients were hospitalized for MI. Of these, 69 (3.9%) had missing KCCQ due to death within 1 month after hospital discharge. In total, 1135 (66.8% of eligible) patients had available both clinical data and KCCQ that patients filled 1 month after hospital discharge. A comparison of patients with available and missing KCCQ is shown in Supplementary material online, *Table S1*.

Table 1 Characteristics of the derivation and validation cohort

	Derivation cohort	Validation cohort
Total, No	795	340
Age, years	64.7 ± 11.5	63.7 ± 12.8
Female sex, *n* (%)	208 (26.2)	95 (27.9)
Risk factors		
Current smoking, *n* (%)	331 (41.6)	126 (37.1)
Arterial hypertension, *n* (%)	507 (63.8)	208 (61.2)
Diabetes, *n* (%)	153 (19.2)	72 (21.2)
CVD history		
Previous MI, *n* (%)	96 (12.1)	36 (10.6)
Heart failure history, *n* (%)	31 (3.9)	13 (3.8)
Previous PCI, *n* (%)	112 (14.1)	41 (12.1)
Previous CABG, *n* (%)	34 (4.3)	11 (3.2)
Previous stroke, *n* (%)	49 (6.2)	23 (6.8)
Clinical characteristics at MI presentation		
STEMI, *n* (%)	471 (59.2)	211 (62.2)
Heart rate, b.p.m.	76 ± 18	77 ± 19
Systolic BP, mmHg	144 ± 26	146 ± 25
Cardiac arrest, *n* (%)	23 (2.9)	11 (3.2)
Killip class		
I, *n* (%)	650 (81.8)	287 (84.4)
II, *n* (%)	115 (14.5)	42 (12.4)
III, *n* (%)	21 (2.6)	9 (2.6)
IV, *n* (%)	9 (1.1)	2 (0.6)
Creatinine, mmol/L	83.8 (71.5–100.5)	83.1 (70.5–100.6)
ST depression, *n* (%)	125 (15.7)	40 (11.8)
EF below 35%, *n* (%)	112 (14.1)	44 (12.9)
Outcomes		
Primary composite outcome, *n* (%)	105 (13.2)	43 (12.6)
Death, *n* (%)	103 (13.0)	43 (12.6)

CABG, Coronary artery bypass grafting; STEMI, ST-elevation myocardial infarction; BP, blood pressure; EF, ejection fraction.

Patients not included in this analysis due to missing KCCQ were slightly older and required more often cardiopulmonary resuscitation before hospital admission, while maximal troponin and mortality were similar in those included and not included in this analysis. The study CONSORT diagram is shown in Supplementary material online, *Figure S1*.

During a median follow-up of 46 months (IQR 29–61), 146 (12.9%) patients died. The study population was randomly split into derivation (70%, *n* = 795) and validation cohort (30%, *n* = 340).

Model development

Demographic characteristics of the 795 patients in the derivation cohort are shown in *Table 1*. Restricted cubic splines for age and age-adjusted continuous variables are shown in *Figure 1*. Based on cubic splines, categories of continuous variables were created and used in the multivariate Cox model. Forward and backward variable selection was used to create the final model. The final model included the following variables: age, HF history, admission creatinine and heart rate, ejection

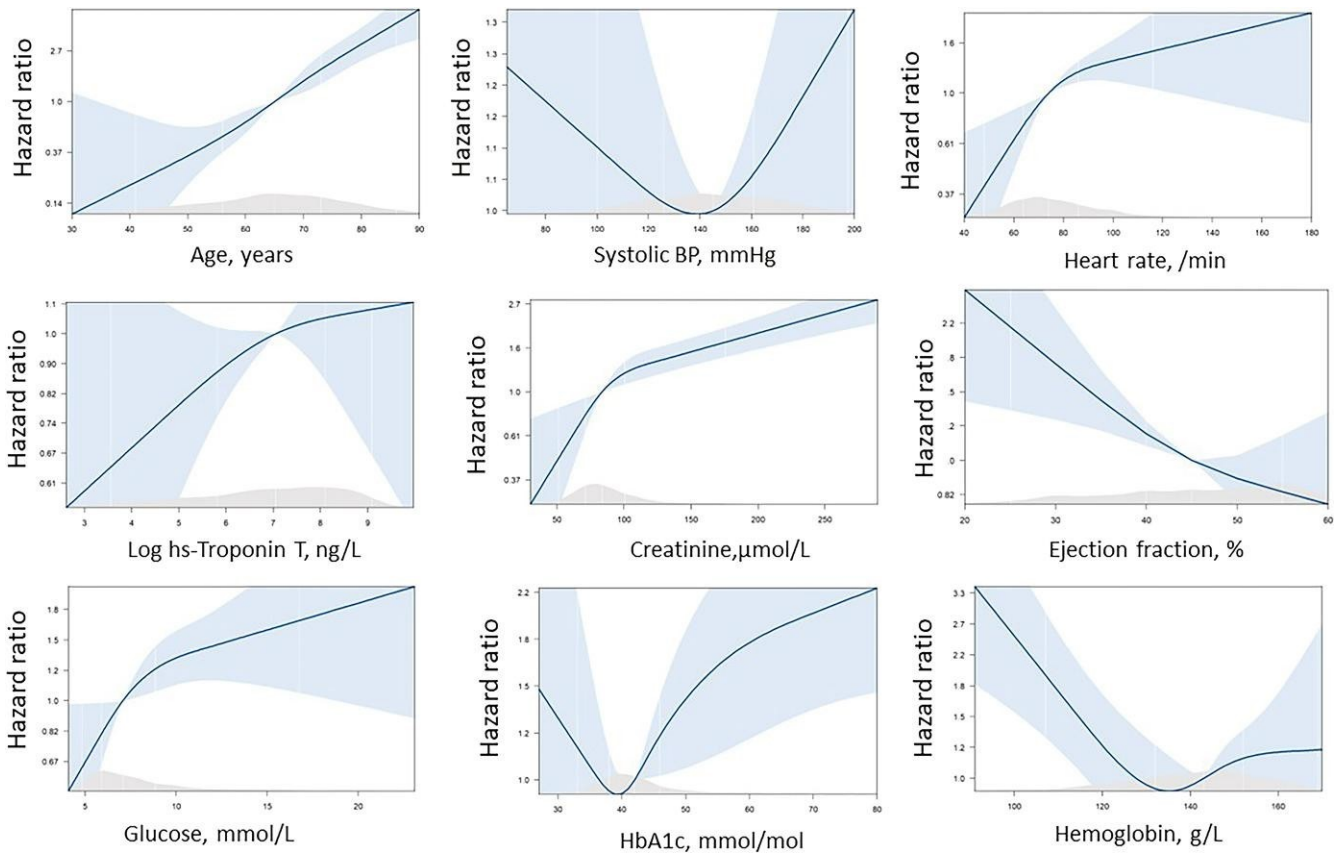


Figure 1 Restricted cubic splines of continuous variables association with all cause death.

Table 2 PragueMi score

No.	Variables	Levels	Score
1.	**Age, years**	≤45	1
		46–49	2
		50–69	4
		70–79	6
		≥80	10
2.	**Creatinine, μmol/L**	<100	1
		100–119	3
		120–159	4
		≥160	7
3.	**Heart rate, /min**	< 50	1
		50–69	3
		70–99	4
		≥100	7
4.	**Discharge EF, %**	≤35	3
		>35	1
5.	**Heart failure history**	No	1
		Yes	3
6.	**Walking 1 block on ground level**		
		Extremely limited	4
		Quite a bit limited	2
		Moderately limited	2
		Slightly limited	1
		Not at all limited	1
		Limited for other reasons	4
7.	**Compared with 2 weeks ago, have your symptoms of heart disease (shortness of breath, fatigue, or ankle swelling) changed? My symptoms have become**		
		Much worse	3
		Slightly worse	3
		Not changed	2
		Slightly better	2
		Much better	1
		I've had no symptoms	1
8.	**Over the past 2 weeks, how much has swelling in your feet, ankles, or legs bothered you? It has been**		
		Extremely bothersome	3
		Quite a bit bothersome	3
		Moderately bothersome	1
		Slightly bothersome	1
		Not at all bothersome	1
		I've had no swelling	1

Creatinine level and heart rate at hospital admission.
Walking impairment, change in symptoms, and leg oedema evaluated at 1 month after hospital discharge.

Table 3 Grace and PragueMi scores comparison in the derivation (Table A) and validation cohort (Panel B)

	Model discrimination			Model calibration		Reclassification		
Time (months)	Grace score AUC (95% CI)	PragueMi score AUC (95% CI)	*P*	Delta Brier score	*P*	NRI	NRI+	NRI−
Table A								
6	75.1 (64.7–85.4)	95.0 (91.5–98.4)	<0.0001	−0.4 (−0.7 to −0.1)	0.01	2.00 (1.98–2.00)	1.00 (1.00–1.00)	1.00 (0.98–1.00)
12	74.7 (66.7–82.7)	90.1 (84.5–95.7)	<0.0001	−0.8 (−1.3 to −0.2)	0.004	2.05 (1.97–2.23)	1.11 (1.00–1.27)	0.94 (0.93–1.00)
18	73.4 (66.0–80.8)	87.0 (81.1–92.9)	<0.0001	−1.3 (−2.0 to −0.6)	<0.001	2.47 (2.26–3.11)	1.60 (1.40–2.20)	0.87 (0.83–0.92)
24	72.2 (65.1–79.3)	86.4 (80.9–91.9)	<0.0001	−1.3 (−2.0 to −0.6)	<0.001	2.39 (2.08–2.54)	1.57 (1.28–1.71)	0.82 (0.80–0.85)
36	67.9 (61.4–74.4)	82.3 (76.4–88.1)	<0.0001	−1.7 (−2.6 to −0.8)	<0.001	1.85 (1.66–2.83)	1.45 (1.28–2.30)	0.39 (0.39–0.52)
Table B								
6	77.4 (62.2–92.5)	90.1 (81.8–98.4)	0.04	−0.5 (−1.1 to 0.1)	0.099	1.13 (0.42–1.34)	0.54 (0.16–0.80)	0.59 (0.25–0.72)
12	76.2 (64.7–87.7)	89.7 (83.5–96.0)	0.004	−0.7 (−1.4 to 0.0)	0.068	1.15 (0.85–1.72)	0.56 (0.20–1.00)	0.59 (0.51–0.78)
18	71.8 (60.7–82.8)	85.6 (76.5–94.6)	0.002	−1.4 (−2.3 to −0.4)	0.005	1.14 (0.88–1.40)	0.54 (0.30–0.88)	0.60 (0.38–0.65)
24	73.3 (64.0–82.5)	84.3 (76.5–92.1)	0.003	−1.4 (−2.4 to −0.4)	0.007	0.97 (0.64–1.38)	0.39 (0.08–0.74)	0.58 (0.54–0.65)
36	69.0 (59.7–78.2)	80.1 (72.1–88.2)	0.0009	−1.6 (−2.8 to −0.3)	0.016	0.85 (0.55–1.05)	0.27 (−0.02–0.49)	0.58 (0.52–0.68)

fraction at hospital discharge, and HF symptoms evaluated by the KCCQ 1 month after discharge, which included walking impairment, leg swelling, and the change in heart disease symptoms over the last 2 weeks. Based on the regression coefficients in the final model, the PragueMi score was developed (*Table 2*). In the derivation cohort, the PragueMi score showed superior discrimination and calibration as compared with the GRACE score (*Table 3*).

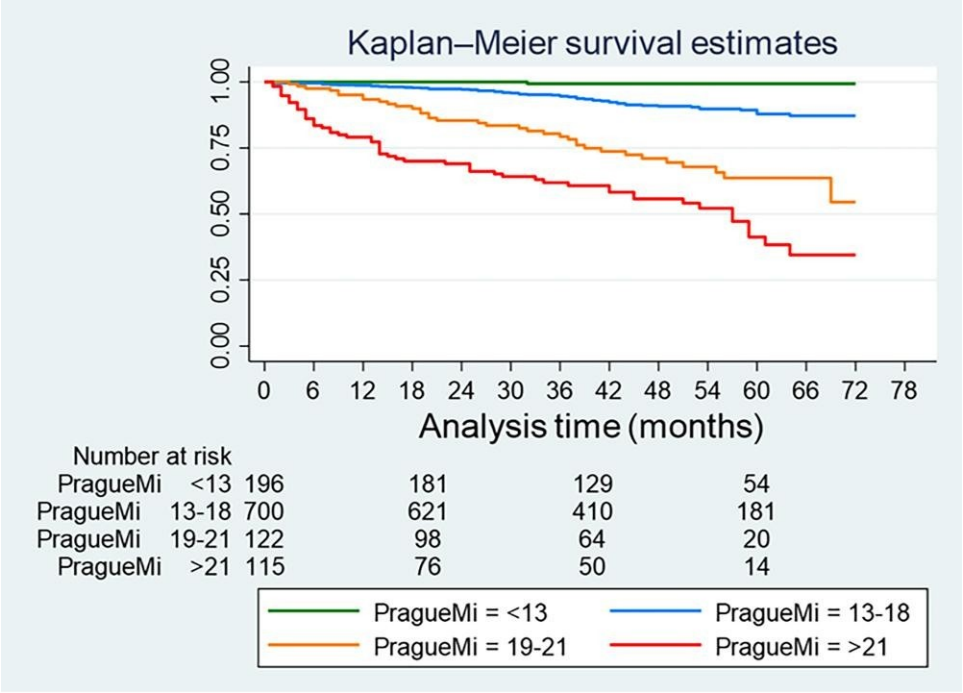


Figure 2 Kaplan–Meier survival curves by PragueMi categories.

Table 4 PragueMi score performance in different subgroups

Variables	AUC (95% CI)	P
Sex		
Male	0.87 (0.85–0.89)	0.41
Female	0.91 (0.87–0.94)	
Age, years		
≤60	0.94 (0.91–0.96)	0.19
>60	0.84 (0.81–0.87)	
eGFR, mL/min/1.73 m^2		
<60	0.83 (0.78–0.87)	0.87
≥60	0.84 (0.82–0.87)	
Diabetes		
No	0.89 (0.87–0.91)	0.63
Yes	0.86 (0.81–0.90)	
Ejection fraction, %		
>40	0.87 (0.84–0.89)	0.58
<40	0.89 (0.85–0.93)	
MI type		
Non-STEMI	0.86 (0.83–0.89)	0.41
STEMI	0.90 (0.88–0.92)	

eGFR, estimated glomerular filtration rate; STEMI, ST-elevation myocardial infarction.

Model validation

The validation cohort included 340 patients. The PragueMi score showed superior discrimination and calibration as compared with the GRACE score (*Table 3*). Over several study time points, PragueMi improved the continuous NRI, significantly improving both event and non-event NRI (*Table 3*). While the AUC and Brier scores were similar in the derivation and validation cohort, NRI was lower in the validation cohort probably due to lower statistical power in a smaller cohort.

Risk categories of the PragueMi score

Due to similar model performance in the derivation and validation cohort, we have combined them and created PragueMi risk categories based on observed risk. The Kaplan–Meier curves by PragueMi score categories are shown in *Figure 2*. The 196 patients (17.3% of the study cohort) with PragueMi score of <13 had excellent prognosis, with 100% event-free survival at 2 years. On the other hand, event-free survival in patients with PragueMi > 21 (10% of the study cohort) was 82.1% at 6 months and 77.8% at 1 year. The PragueMi score performance was consistent in different subgroups (*Table 4*).

Discussion

In this study, we show that HF symptoms evaluated remotely using a questionnaire possess an important prognostic value that adds to clinical risk factors. Our PragueMi score based on five clinical variables and three HF symptoms has superior discrimination, calibration, and risk reclassification properties as compared with the currently guideline-recommended GRACE score based only on clinical risk factors.

The prognosis of patients after MI is very heterogeneous.[13] Thus, the identification of patients at increased mortality risk is of clinical need. This allows a personalized approach to secondary prevention with intervention targeted at individuals that benefit the most.

Until now, the prediction models after MI have been only based on clinical risk factors, neglecting patients' symptoms. However, for

decades, clinicians have been searching for HF symptoms in patients after MI to identify at-risk individuals and to modify treatment accordingly.[14] Yet, this approach is time-consuming, influenced by provider skills and subjective interpretation.[15] Patient-reported outcomes coupled with modern telemedicine options allow the remote collection of patients' symptoms and empower patients to become a valuable source of clinically important data, without increasing the burden on the provider.[15]

Several previous studies have shown the utility of the KCCQ to predict prognosis in patients after MI.[6,16,17] No previous study evaluated the utility of combining patient-reported outcomes with clinical risk factors after MI. As KCCQ was developed for HF patients, not all items are relevant in patients after MI. In this study, we have identified that among the 23 KCCQ items, walking limitation, leg oedema, and change in heart disease symptoms over the last 2 weeks have the greatest predictive value among patients after MI.

In the present study, we have decided to evaluate HF symptoms 1 month after hospital discharge instead of evaluating them during the hospital stay. This decision was based on the fact that in many patients, HF symptoms develop later after discharge due to left ventricular remodelling. Furthermore, functional requirements for everyday living are higher outside of the hospital; thus, the patient may not recognize the newly developed limitations during the hospital stay.

In clinical settings, the PragueMi score may be particularly useful during post-discharge outpatient visits and also for remote monitoring of patients after discharge to identify high-risk patients who may benefit from closer follow-up and advanced therapies. As compared with other prediction scores that are based only on clinical variables, a potential barrier of the PragueMi score is that it also requires patients' symptoms evaluation. However, it includes only three easy-to-answer questions, which may also be answered remotely before the outpatient visit using an online questionnaire or dedicated app, thus decreasing the burden on providers. Furthermore, identifying HF symptoms before the outpatient visit may help to streamline the visit to this important issue.

Among discharged patients, the PragueMi score > 21 identified 10% of the population as very high risk, with 18% 6-month and 22% 12-month mortality rates, respectively. Timely identification of these patients followed by initiation or up-titration of HF pharmacotherapy and referral for advanced HF therapies such as heart transplant and left ventricular assist device has the potential to improve prognosis in these high-risk patients. Based on results of the STRONG-HF[18] study with rapid up-titration of HF pharmacotherapy, a meta-analysis of sodium-glucose transport protein 2 inhibitors use in HF,[19] and sacubitril–valsartan studies results,[20] we estimate that a multifactorial intervention targeted at these high-risk patients may decrease the mortality risk by at least 20–30%. Future randomized studies will be needed to test whether clinical decision-making based on the PragueMi score will lead to an improvement in clinical outcomes.

Study limitations

First, this is a single-centre study; thus, the model performance was only internally validated. Because no previous study systematically collected KCCQ 1 month after hospital discharge, we were unable to externally validate our model. This may limit the generalizability of our findings. However, the characteristics of our cohort are very similar to other recent cohorts of patients after MI.[21] In the future, the performance of our model needs to be tested in other cohorts. Second, due to missing KCCQ in some patients, our results may be the subject of a selection bias. However, while there were some statistically significant differences between patients with and without KCCQ available, clinically these differences are negligible. Thus, we assume that these missing data do not affect the generalizability of our results. Furthermore, in this study, we have identified the three most predictive items of the KCCQ. This reduction in the number of questions may improve the response rate in future studies. Third, data required for the PragueMi score were collected at different time points. Automated data collection of in-hospital data together with remote HF symptoms evaluation online or using an app may help to integrate PragueMi score into everyday practice without additional burden on clinicians.

The strengths of our study include a well-defined systematically collected cohort of consecutive MI patients with multiple clinical factors and remote HF symptoms evaluated as possible predictors of mortality risk.

Conclusion

Heart failure symptoms evaluated remotely using a questionnaire possess an important prognostic value that adds to clinical risk factors. The PragueMi risk score combines these predictors and has superior discrimination, calibration, and risk reclassification properties compared with the guideline-recommended GRACE score. Future studies will have to address whether clinical decision-making based on the PragueMi score can significantly improve the care of patients after MI.

Supplementary material

Supplementary material is available at *European Journal of Preventive Cardiology*.

Author contributions

P.W. conceived and designed the study and analysed the data. J.M., D.J., M.Ž., M.Š., and M.K collected the data. All authors were involved in writing and revising the manuscript and approved the final version. P.W. is the guarantor of this work and as such has full access to all the data and takes responsibility for the integrity of all data and the accuracy of the data analysis.

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Conflict of interest: none declared.

Data availability

The data that support the findings of this study are available from the corresponding author (P.W.) upon reasonable request.

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Original Article

Iron deficiency and all-cause mortality after myocardial infarction

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ABSTRACT

Background: Data on the clinical significance of iron deficiency (ID) in patients with myocardial infarction (MI) are conflicting. This may be related to the use of various ID criteria.
We aimed to compare the association of different ID criteria with all-cause mortality after MI.
Methods: Consecutive patients hospitalized for their first MI at a large tertiary heart center were included. We evaluated the association of different iron metabolism parameters measured on the first day after hospital admission with all-cause mortality.
Results: From the 1,156 patients included (aged 64±12 years, 25 % women), 194 (16.8 %) patients died during the median follow-up of 3.4 years. After multivariate adjustment, iron level ≤13 μmol/L (HR 1.67, 95 % CI 1.19–2.34) and the combination of iron level ≤12.8 μmol/L and soluble transferrin receptor (sTfR) ≥3 mg/L (HR 2.56, 95 % CI 1.64–3.99) termed as PragueID criteria were associated with increased mortality risk and had additional predictive value to the GRACE score. Compared to the model including iron level, the addition of sTfR improved risk stratification (net reclassification improvement 0.61, 95 % CI 0.52–0.69) by reclassifying patients into a higher-risk group. No association between ferritin level and mortality was found. 51 % of patients had low iron levels, and 58 % fulfilled the PragueID criteria.
Conclusion: Iron deficiency is common among patients with the first MI. The PragueID criteria based on iron and soluble transferrin receptor levels provide the best prediction of mortality and should be evaluated in future interventional studies for the identification of patients potentially benefiting from intravenous iron therapy.

1. Introduction

Iron is an essential element required for normal mitochondrial function [1,2] oxygen transport, synthesis of proteins and nucleic acids, and normal immune system function. Although iron is environmentally abundant, iron deficiency (ID) is one of the most common nutritional deficits worldwide affecting approximately two billion people [3].

In cardiovascular disease, the effect of ID has been best described in patients with heart failure (HF) [4]. ID affects approximately 50 % of HF patients and is associated with worse functional capacity, impaired quality of life, increased mortality, and hospitalization rate, irrespective of anemia presence [5]. Treatment with intravenous ferric carboxymaltose in patients with HF and ID improves symptoms, functional capacity, and quality of life, and reduces the risk of hospital admissions for HF and cardiovascular causes [6,7] Despite that, there is no consensus on ID definition in HF [8,9] The most commonly used are the guideline-recommended ID criteria based on ferritin and transferrin saturation [8,10] However, other criteria have been used as well [9,11] Much less is known about ID effects in patients with myocardial infarction (MI). A systematic review and meta-analysis of 7 studies including a total of 2821 patients described worse long-term outcomes in the ID population, whereas short-term outcomes were heterogeneous across studies [12]. However, ID did not affect prognosis in MI patients with cardiogenic shock [13]. A small sample size and different criteria

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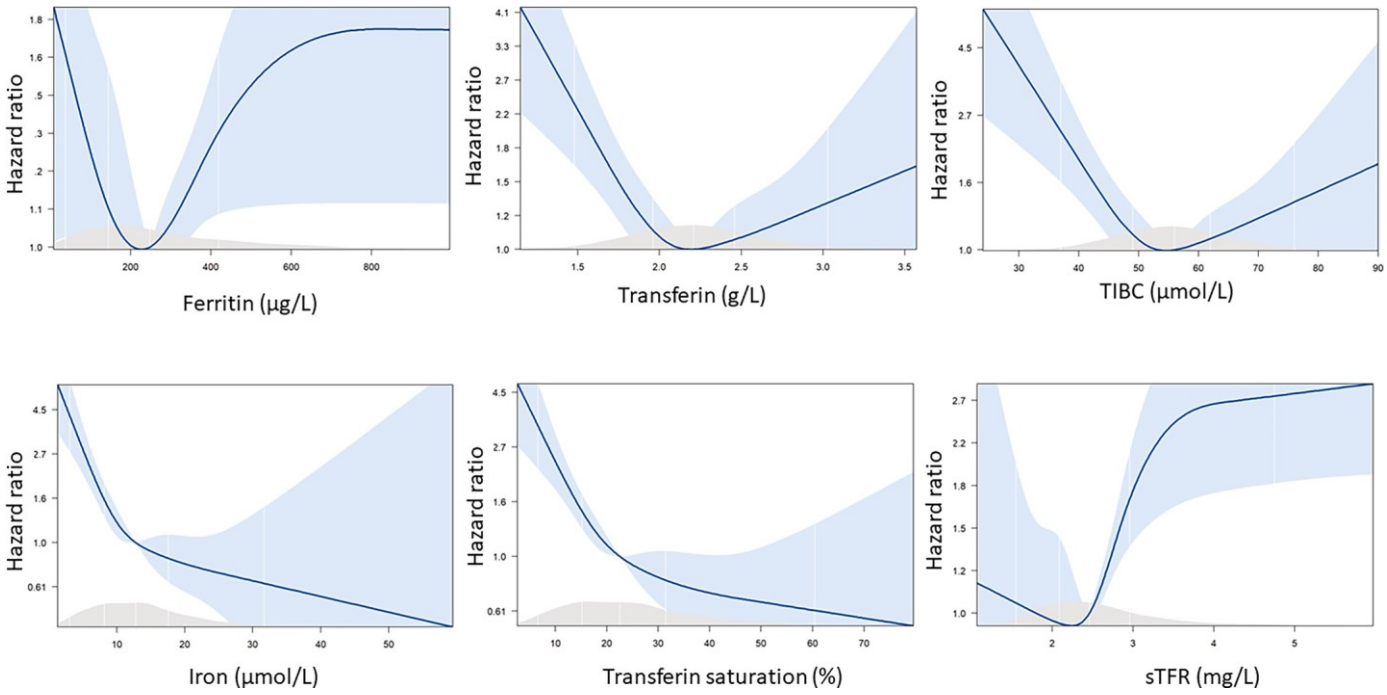

Fig. 1. Restricted cubic splines of different iron metabolism parameters and all-cause mortality after myocardial infarction.

for ID definitions may explain this heterogeneity in study outcomes. Furthermore, several criteria use ferritin to define ID. Nonetheless, ferritin is a positive acute phase reactant, thus the inflammatory reaction to MI may influence it [14]. Besides, ferritin has been suggested as a leakage product from damaged cells [15]. Therefore, ferritin may not be a good marker of ID in patients with MI.

For selecting patients potentially benefiting from intravenous iron therapy, the definition of ID is important. However, ID criteria currently used are based only on a consensus, while ID definition based on hard outcomes is missing. Misclassification of patients may dilute the therapy effect. This issue is further supported by an animal model of MI, which has shown no effect of iron supplementation in normal iron status [16]. Thus, the correct definition of ID is of great clinical importance. Until now, no previous study compared the association of different ID criteria with total mortality after MI.

To address this issue, the present study aimed to compare the prognostic significance of diverse criteria of iron deficiency measured on the first day after hospital admission in a large cohort of consecutive patients hospitalized for their first myocardial infarction at a large tertiary heart center.

2. Methods

2.1. Population

This study used data from the prospective Institute for Clinical and Experimental Medicine Acute Myocardial Infarction Registry (AMBITION registry) [17]. The registry collects clinical data and biospecimens from consecutive patients hospitalized for acute coronary syndrome since June 2017 at the Institute for Clinical and Experimental Medicine, Prague, Czech Republic, a tertiary heart center with around-the-clock coronary intervention service. The Fourth Universal Definition of Myocardial Infarction has been used [18]. Patients underwent a detailed interview during their hospital stay, and additional information was obtained from medical record abstraction and laboratory studies. For this analysis, we included consecutive patients enrolled between June 2017 and February 2023 with type I MI and no previous history of coronary artery disease. Iron metabolism was measured in the central laboratory from blood samples collected on the morning of the first day after hospital admission. Death was ascertained through December 1st, 2023. Mortality data were provided by the Institute of Health Information and Statistics of the Czech Republic (UZIS), which keeps a list of all deceased persons and dates of death in the Czech Republic by law. All patients signed informed consent. This study was approved by a local ethics committee and complies with the Declaration of Helsinki.

2.2. Primary outcome

The primary outcome of the analysis was all-cause mortality.

2.3. GRACE score

The Eagle model estimates for death within 6 months after discharge was used [19]. Variables included in the model were age, heart rate, systolic blood pressure, creatinine level, troponin elevation, ST segment depression on initial ECG, previous history of MI and heart failure, and PCI.

2.4. Statistical methods

Continuous variables are presented as mean and SDs or medians and IQRs. Hazard ratios (HR) are shown with a 95 % confidence interval (CI). Nominal variables are shown as counts and percentages.

We have used restricted cubic splines adjusted for age to detect a nonlinear association between different parameters of iron metabolism and the primary outcome. Furthermore, we have used decision tree analysis to set the cut points for ID definition. The Cox regression model was used to analyze the association of different ID criteria with the outcome.

The Global Registry of Acute Coronary Events (GRACE) score has been recommended by the guidelines to stratify patients' risk after MI [20]. To analyze the additional predictive value of different ID criteria to the GRACE score, we have used the difference in the area under the receiver operating characteristic curve (AUC), the Brier score, and the continuous net reclassification improvement (NRI).

Statistical analyses were conducted with R statistical software

Table 1
Population demographics.

Characteristics	Iron >12.8 & sTfR<3 (*n* = 490)	Iron ≤12.8 & sTfR<3 (*n* = 394)	Iron >12.8 & sTfR≥3(*n* = 83)	Iron ≤12.8 & sTfR≥3 (*n* = 189)	p
Age (years)	62.0 ± 11.9	64.3 ± 12.7*	66 ± 12.7*	67.6 ± 12.2*	< 0.001
Male sex, n (%)	376 (77 %)	292 (74 %)	60 (72 %)	139 (74 %)	0.68
STEMI, n (%)	304 (62 %)	279 (71 %)*	45 (54 %)	125 (66 %)	0.001
Anterior MI, n (%)	195 (40 %)	175 (44 %)	38 (46 %)	97 (51 %)	0.052
Subacute MI, n (%)	33 (7 %)	81 (21 %)*	8 (10 %)	41 (22 %)*	<0.0001
Multi-vessel disease, n (%)	138 (28 %)	121 (31 %)	26 (31 %)	74 (39 %)	0.052
CPR before admission, n (%)	14 (3 %)	31 (8 %)*	1 (1 %)	13 (7 %)	0.001
Admission HR, min^{-1}	74 ± 16	80 ± 20*	77 ± 17	82 ± 18*	<0.0001
Admission SBP, mmHg	145±26	138±29*	149±23	142±24	0.0002
Admission DBP, mmHg	80±13	78±15	82±14	79±14	0.10
Creatinine, $\mu mol.l^{-1}$	81 (70–93)	86 (72–102)*	86 (70–101)	91 (75–118)*	<0.0001
CKD-EPI, $ml/s/1.73m^2$	1.39 ± 0.30	1.28 ± 0.39*	1.26 ± 0.37*	1.16 ± 0.42*	<0.0001
Fasting glucose, mmol/L	7.93 ± 3.42	8.78 ± 3.81*	8.24 ± 3.19	9.72 ± 4.84*	<0.0001
HbA1c, $mmol.mol^{-1}$	41 (38–46)	42 (39–47)	41 (37–49)	44 (40–53)*	<0.0001
Maximal hsTroponin T, ng/L	1047 (314–3088)	2256 (825–5159)*	813 (255–2183)	2011 (685–4045)*	<0.0001
Total cholesterol	4.99 ± 1.16	4.57 ± 1.12*	5.09 ± 1.25	4.60 ± 1.26*	<0.0001
LDL cholesterol	3.34 ± 1.01	2.96 ± 1.03*	3.45 ± 1.23	2.97 ± 1.16*	<0.0001
Leukocyte count, $10^9.l^{-1}$	10.5 (8.4–15.2)	11.7 (9.5–15.0)*	10.0 (7.4–11.8)	11.8 (9.1–14.0)*	<0.0001
Hemoglobin, g/L	145 ± 13	141 ± 15*	144 ± 19	137 ± 21*	<0.0001
Hemoglobin <120, n (%)	12 (3 %)	38 (10 %)*	7 (9 %)*	38 (20 %)*	<0.0001
LV EF (%)	50 (40–55)	40 (35–50)*	50 (40–55)	40 (35–50)*	<0.0001
LV EF ≤ 40%, n (%)	69 (14 %)	125 (32 %)*	16 (19 %)	61 (32 %)*	< 0.0001
PCI or CABG, n(%)	479 (98 %)	355 (90 %)*	76 (92 %)*	165 (87 %)*	< 0.0001
Killip class I, n (%)	427 (87 %)	276 (70 %)*	75 (90 %)	114 (60 %)*	<0.0001
Risk factors					
Arterial hypertension, n (%)	270 (55 %)	228 (58 %)	54 (65 %)	135 (71 %)*	0.001
Diabetes mellitus, n (%)	88 (18 %)	82 (21 %)	19 (23 %)	82 (43 %)*	<0.0001
Current smoking, n (%)	247 (51 %)	184 (47 %)	32 (39 %)	66 (35 %)*	0.002
BMI, kg/m^2	28.6 ± 4.5	28.5 ± 4.8	30.3 ± 6.4*	29.3 ± 5.2	0.006
COPD, n (%)	28 (6 %)	24 (6 %)	5 (6 %)	11 (6 %)	0.996
Atrial fibrillation history, n (%)	17 (4 %)	18 (5 %)	7 (8)*	24 (13 %)*	<0.0001
Medications on admission					
ACE inhibitors or ARB, n (%)	212 (43 %)	168 (43 %)	36 (43 %)	95 (50%)	0.31
Statins, n (%)	85 (17 %)	76 (19 %)	15 (18%)	49 (26 %)	0.08
Antiplatelet therapy, n (%)	47 (10 %)	54 (14 %)	11 (13 %)	45 (24 %)*	0.002
Anticoagulants, n (%)	20 (4 %)	19 (5 %)	11 (13 %)*	21 (11 %)*	0.0002
Discharge medication#					
ACE inhibitors or ARB, n (%)	382 (78 %)	282 (74 %)	70 (84 %)	144 (79 %)	0.16
Beta blocker, n (%)	382 (78 %)	296 (78 %)	68 (82 %)	151 (83 %)	0.43
Statins, n (%)	480 (98 %)	365 (96 %)	79 (95 %)	168 (92 %)*	0.004
Aspirin, n (%)	474 (97 %)	349 (91 %)*	77 (93 %)	158 (86 %)*	<0.0001
Clopidogrel, n (%)	88 (18 %)	136 (36 %)*	34 (41 %)*	73 (40 %)*	<0.0001
Prasugrel, n (%)	19 (4 %)	5 (1 %)	3 (4 %)	2 (1 %)	0.05
Ticagrelor, n (%)	365 (75 %)	226 (59 %)*	44 (53 %)*	88 (48 %)*	<0.0001
Anticoagulation, n (%)	52 (11 %)	85 (22 %)*	15 (18 %)	55 (30 %)*	<0.0001
Tripple therapy, n (%)	33 (7 %)	48 (13 %)*	10 (12 %)	23 (13 %)*	0.02
Iron metabolism					
Iron, μmol/L	19.8 ± 7.0	8.4 ± 2.9*	17.6 ± 4.1*	7.5 ± 2.9*	<0.0001
Ferritin, μg/L	240 (138–391)	292 (180–490)*	189 (97–278)*	230 (103–412)	<0.0001
Transferrin, g/L	2.25 ± 0.35	2.1 ± 0.39*	2.4 ± 0.36*	2.31 ± 0.46*	<0.0001
TIBC, μmol/L	56.6 ± 8.9	53.0 ± 9.8*	60.6 ± 9.2*	58.1 ± 11.6	<0.0001
TSAT,%	35.9 ± 13.7	16.2 ± 5.6*	29.6 ± 7.1*	13.6 ± 5.3*	<0.0001
sTFR, mg/L	2.23 ± 0.40	2.33 ± 0.37	3.60 ± 0.85*	4.0 ± 1.62*	<0.0001
Scores					
GRACE	114 ± 23	122 ± 26*	121 ± 25	129 ± 26*	<0.0001
Outcome					
Death, n (%)	36 (7 %)	74 (19%)*	19 (23 %)*	65 (34 %)*	<0.0001

*$p < 0.05$ vs. Iron >12.8 & sTfR<3 group.
#missing in patients with in-hospital death.

version 4.2.2 (R Foundation for Statistical Computing, Vienna, Austria), JMP 17, SPSS version 25.0 (IBM Corporation, Armonk, NY), and STATA version 17 (StataCorp, College Station, TX). All statistical tests and confidence intervals were 2-sided with a significance level of 0.05.

3. Results

In total, 1156 patients (mean age 64 years, 75 % male) hospitalized for their first type I myocardial infarction between June 2017 and February 2023 were included in this analysis. During the median follow-up of 1224 days (IQR 626–1782), 194 (16.8 %) patients died.

Fig. 1 presents restricted cubic splines of the association between different parameters of iron metabolism and all-cause mortality risk. While there was no association between ferritin level and all-cause mortality, low iron, transferrin, TSAT, total iron binding capacity (TIBC), and high sTfR were associated with increased mortality risk.

3.1. Development of pragueid criteria

In the decision tree model, among the analyzed iron metabolism

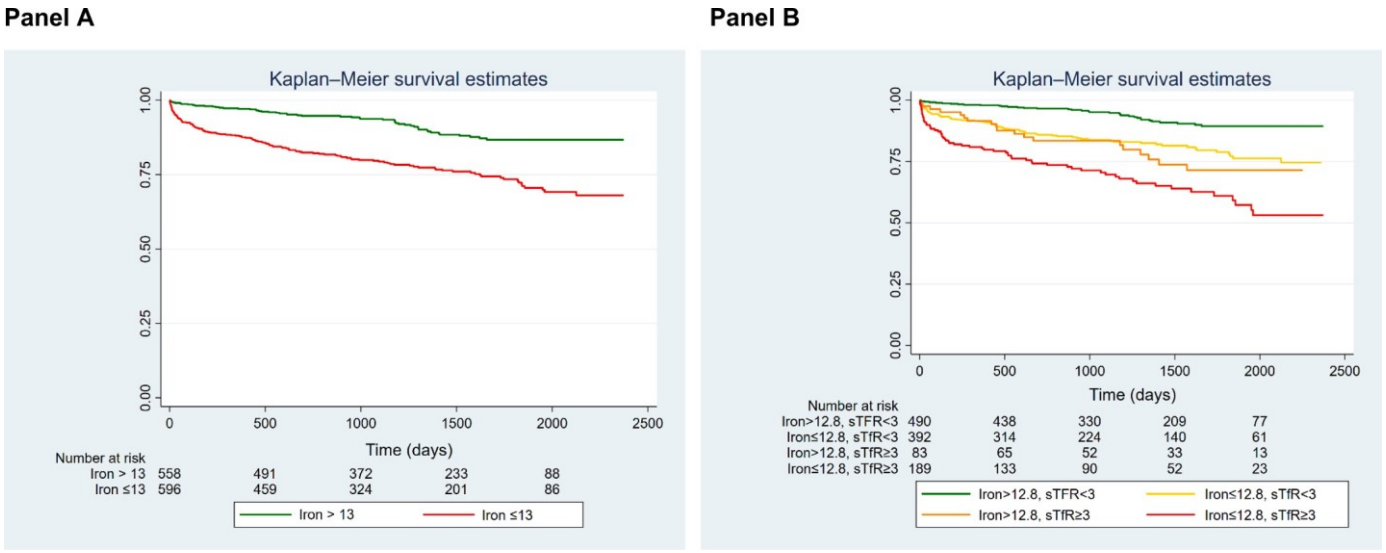

Fig. 2. Kaplan-Meier survival for iron (Panel A) and PragueID (Panel B) categories.

Table 2
Association of different iron deficiency criteria with all-cause mortality.

Iron deficiency criteria	Prevalence n(%)	Unadjusted HR (95 % CI)	Adjusted* HR (95 % CI)	Adjusted** HR (95 % CI)
Iron ≤13 μmol/L	598 (51.7)	2.78 (2.03–3.82)	2.06 (1.50–2.84)	1.67 (1.19–2.34)
TSAT <20 %	468 (40.5)	2.46 (1.85–3.28)	1.89 (1.41–2.53)	1.38 (1.01–1.90)
Ferritin <30 μg/L	20 (1.7)	1.44 (0.59–3.50]	1.58 (0.64–3.84)	1.55 (0.63–3.80)
Ferritin <100 μg/L	157 (13.6)	1.50 (1.05–2.13)	1.37 (0.96–1.95)	1.36 (0.93–1.98)
Guideline ID definition	357 (31.0)	1.69 (1.28–2.24)	1.57 (1.19–2.08)	1.34 (0.99–1.82)
Prague ID criteria				
2. Iron ≤12.8 μmol/L & sTfR<3 mg/L	394 (34.1)	2.79 (1.87–4.15)	2.07 (1.38–3.10)	1.75 (1.16–2.64)
3. Iron >12.8 μmol/L & sTfR≥3 mg/L	83 (7.2)	3.27 (1.88–5.70)	2.64 (1.51–4.61)	2.05 (1.15–3.64)
4. Iron ≤12.8 μmol/L & sTfR≥3 mg/L	189 (16.3)	5.76 (3.83–8.66)	3.72 (2.46–5.63)	2.56 (1.64–3.99)

* Adjusted for GRACE score.

** Adjusted for age, gender, HF history, CKD-EPI, admission systolic blood pressure and heart rate, absence of PCI, Killip class, ejection fraction <35 at discharge

A 95 % confidence interval is shown in bracelets. Guideline ID criteria were ferritin <100 μg/L or TSAT <20 % if ferritin was 100–299 μg/L.

parameters (iron, transferrin, TSAT, TIBC, TfR), the combination of iron ≤12.8 μmol/L and sTfR ≥ 3.0 mg/L showed the best association with total mortality risk. Based on these cut-points, we have created 4 groups – group 1 with normal iron and normal sTfR, group 2 with low iron and normal sTfR, group 3 with normal iron and high sTfR, and group 4 with low iron and high sTfR. We have termed this classification as PragueID criteria. Population demographics by PragueID criteria are shown in Table 1.

As shown in Fig. 2, the addition of sTfR to iron level can reclassify the risk associated with low iron to intermediate and high, while high sTfR in the presence of normal iron is associated with an intermediate risk.

3.2. Comparison of ID criteria

After adjustment for the GRACE score or other variables affecting mortality risk after MI, all ID criteria except for ferritin were independently associated with the total mortality (Table 2). The hazard ratio was highest for the Prague ID criteria and iron level. As assessed by the AUC and Brier score (Table 3), only the iron level and Prague ID criteria had additional prognostic value to the GRACE score. When the additional prognostic value of iron or PragueID was compared, there was no difference in AUC, but there was a borderline difference in the Brier score and an improvement in net reclassification improvement (NRI) in favor of the PragueID criteria. Beyond the iron level, PragueID correctly reclassified cases patients into the higher-risk group (Table 4).

4. Discussion

In the present study, we have analyzed the association of different ID criteria with all-cause mortality in patients hospitalized for their first MI. We show that ID is common among these patients, but the prevalence and prognostic implications differ by the criteria used. Among several criteria evaluated, only iron level and particularly the combination of iron level and soluble transferrin receptor were independently associated with the risk of all-cause mortality and improved risk prediction beyond the guidelines recommended GRACE score.

While ferritin is a guideline-recommended parameter for ID diagnosis in HF, we did not find any association between ferritin level and mortality risk. This finding among MI patients may be explained by the effect of cell necrosis and inflammatory response on ferritin levels. Thus, ferritin should not be used to define ID after MI.

Our observation is in line with previous studies. In patients with chronic HF, TSAT <20 % and serum iron ≤13 mmol/L were independently associated with death, but lower serum ferritin concentrations were paradoxically associated with better survival [9]. In a study of the prognostic value of temporal changes of iron metabolism parameter in patients with acute coronary syndrome, a decrease in TSAT and iron levels, but not changes in ferritin levels were associated with an increased risk of cardiovascular death and nonfatal ACS [21]. Among patients with coronary artery disease, sTfR was independently associated with an increased risk of cardiovascular death or MI [22]. We add to this evidence the observations that among several criteria of ID, the combination of low iron and high sTfR can identify patients at increased mortality risk, which may have the biggest benefit from iron supplementation.

To the best of our knowledge, this is the first large-scale study among consecutive MI patients evaluating the prevalence and prognostic significance of different ID criteria. We found that 51 % of patients after MI

Table 3
Additional predictive value of different iron deficiency criteria to the GRACE score 6 months (**Table A**) and 12 months (**Table B**) after hospital discharge.

Table A

	6 months				
	AUC	Δ AUC	p	Δ Brier	p
Iron ≤13 μmol/L	82.6 (77.1—88.0)	2.5 (1.1—3.9)	0.001	−0.1(−0.2— −0.001)	0.01
TSAT <20 %	81.7 (76.2—87.2)	1.6 (0.1—3.2)	0.04	−0.1 (−0.2— −0.01)	0.047
Ferritin <30 μg/L	79.9 (74.3—85.6)	−0.2 (−0.3—0.001)	0.04	0.01 (−0.001—0.001)	0.74
Ferritin <100 μg/L	80.0 (74.3—85.8)	−0.1 (−0.6—0.5)	0.90	−0.001 (−0.1—0.01)	0.19
Guideline	80.5 (74.7—86.2)	0.4 (−0.7—1.5)	0.5	−0.1 (−0.2—−0.1)	0.02
Prague criteria	82.9 (77.5—88.2)	2.8 (0.9—4.7)	0.004	−0.3 (−0.4 — −0.1)	0.0003

Table B

	12 months				
	AUC	Δ AUC	p	Δ Brier	p
Iron ≤13 μmol/L	81.9 (77.0—86.9)	2.1 (0.7—3.6)	0.004	−0.2 (−0.3—−0.1)	0.005
TSAT <20 %	81.5 (76.6—86.4)	1.7 (0.2—3.2)	0.03	−0.1 (−0.3—0.1)	0.096
Ferritin <30 μg/L	79.8 (74.8—84.8)	−0.01 (−0.4—0.4)	0.96	0.01 (−0.001—0.001)	0.90
Ferritin <100 μg/L	79.8 (74.7—84.9)	0.001(−0.5—0.5)	1.0	−0.001 (−0.1—0.01)	0.19
Guideline	80.2 (75.1—85.3)	0.4 (−0.6—1.4)	0.4	−0.1 (−0.2 — −0.1)	0.044
Prague criteria	82.4 (77.6—87.2)	2.6 (0.7—4.5)	0.007	−0.3 (−0.6— −0.1)	0.001

A 95 % confidence interval is shown in bracelets.

Table 4
Comparison of model discrimination, calibration, and reclassification.

	Discrimination				Calibration		Reclassification		
Time	AUC Iron	AUC PragueID	AUC	p	Brier	p	NRI	NRI+	NRI-
6 months	82.6 (77.1–88.0)	82.9 (77.5–88.2)	0.3 (−1.1–1.7)	0.70	−0.1 (−0.3–0.01)	0.06	0.56 (0.34–0.87)	-10^{-15} (−0.20–0.28)	0.56 (0.52–0.59)
1 year	81.9 (77.0–86.9)	82.4 (77.6–87.2)	0.5 (−1.0–1.9)	0.50	−0.2 (−0.3–0.01)	0.06	0.66 (0.62–0.81)	0.64 (0.55–0.78)	0.01 (−0.004–0.08)
2 years	81.5 (77.3–85.6)	82.2 (78.1–86.3)	0.7 (−0.6–2.1)	0.30	−0.3 (−0.5–0.001)	0.04	0.60 (0.49–0.76)	0.57 (0.44–0.67)	0.03 (−0.01–0.09)
3 years	79.8 (75.6–84.0)	80.3 (76.0–84.6)	0.5 (−0.8–1.9)	0.40	−0.3 (−0.6–0.01)	0.06	0.61 (0.52–0.69)	0.56 (0.50–0.63)	0.04 (−0.009–0.08)

A model with Grace score and Iron class (Iron ≤13 μmol/L vs. Iron >13 μmol/L) was compared with a model including Grace score and PragueID class. A 95 % confidence interval is shown in brackets.
AUC – area under the curve, NRI – net reclassification improvement.

have iron ≤13 μmol/L and 58 % have ID if PragueID criteria are used. Thus, more than 50 % of patients with the first MI are affected by ID. This is similar to the ID prevalence in HF, among which 43 % of men and 54 % of women had iron ≤13 mmol/L [9]. After adjustment for other covariates, the mortality risk associated with low iron level in our study was increased by 67 %, and by 156 % in patients with low iron and high sTfR. Interestingly, this risk in MI patients is higher than the 37 % risk increase associated with iron ≤13 μmol/L among patients with HF [9]. This difference may be partially explained by the addition of antiplatelet therapy in MI patients, which may further worsen the pre-existing ID.

In previous studies, MI was associated with serum iron, TIBC, and TSAT decrease and ferritin increase, with MI severity affecting the magnitude of this change [23,24] Thus, low iron levels may be only a marker of MI severity. However, sTfR as a marker of iron demand is not affected by inflammation [22] and MI severity (**Supplementary Table 1**). This suggests that ID is not only a marker of MI severity but also a risk factor that may be intervened. Previous studies suggest the biological plausibility of this concept. In an animal model, the deleterious effect of ID was at least in part explained by increased oxidative/nitrosative stress and altered antioxidant defense caused by inhibition of the endothelial nitric oxide synthase (eNOS)/ soluble guanylate cyclase/protein kinase G pathway, leading to eNOS degradation via ubiquitin/proteasome system [25]. Altered energy metabolism is another possible explanation of the deleterious effect of ID in CAD [26,27] In a small study among STEMI patients, application of ultrasmall superparamagnetic iron-oxide within 4 days following an acute myocardial infarction led to smaller infarct size [28]. While our observational study is not able to answer the question of whether ID is a risk marker or a risk factor after MI, identifying ID criteria with the best predictive value sets the ground for future interventional studies with iron supplementation.

4.1. Strengths and limitations of the study

We must admit several limitations of our study. First, iron metabolism was measured at a single time point one day after hospital admission. Because iron parameters dynamically evolve after MI, we were unable to determine how measurements at different time points would affect the prognostic value of ID criteria.

Nevertheless, in a previous study using serial measurement in ACS patients, iron status patterns did not differ in those with and without events [21].

Second, we have used all-cause, rather than cardiovascular mortality, as we were unable to ascertain the cause of death. On the other hand, cardiovascular death is the leading cause of mortality in patients in the first four years after MI [29]. Based on previous studies analyzing the association of ID with total and cardiovascular mortality, we believe that changing the primary study objective would not affect our results [12, 30]

Third, due to the observational nature of our study, no causal inferences can be drawn from our results. Future interventional studies will be needed to evaluate the effects of iron supplementation in patients with ID defined by our criteria.

Fourth, we did not measure hepcidin level, which is considered a key regulator of iron homeostasis [31]. However, in a previous study hepcidine level was not independently associated with the outcome of patients with coronary heart disease [32].

Fifth, because we did not have data on iron supplementation during the study follow-up, we were unable to account for this effect.

The strengths of our study include analysis of various iron status parameters including sTfR and the large single-center cohort of consecutive MI patients with a relatively long follow.

5. Conclusion

The present study among consecutive patients hospitalized for their first myocardial infarction shows that iron deficiency is present in over 50 % of patients. Among several iron deficiency criteria, the combination of low iron level and high soluble transfer receptor were independently associated with mortality risk and improved risk stratification. The clinical benefit of iron supplementation decision-making based on our criteria will have to be addressed in future studies.

Declartion of competing interest

Dr. Jenˇca has received consulting fees from Swixx Biopharma. The remaining authors have nothing to disclose.

Data availability

The data that support the findings of this study are available from the corresponding author (PW) upon reasonable request.

Ethical approval information

The study was approved by a local ethics committee. All participants gave their written informed consent prior to data collection.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ejim.2024.04.020.

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Trajectories and determinants of left ventricular ejection fraction after the first myocardial infarction in the current era of primary coronary interventions

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Background: Left ventricular ejection fraction (EF) is an independent predictor of adverse outcomes after myocardial infarction (MI). However, current data on trajectories and determinants of EF are scarce. The present study aimed to describe the epidemiology of EF after MI.

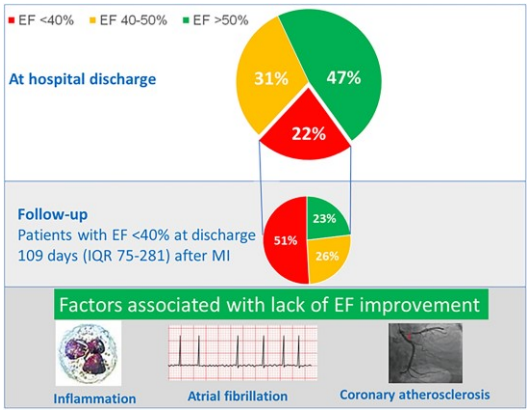
Methods: Data from a single-center prospectively-designed registry of consecutive patients hospitalized at a large tertiary cardiology center were utilized.

Results: Out of 1,593 patients in the registry, 1,065 were hospitalized for MI type I (65.4% STEMI) and had no previous history of heart failure or MI. At discharge, EF < 40% was present in 238 (22.3%), EF 40–50% in 326 (30.6%) and EF >50% in 501 (47.0%). Patients with EF < 40% were often those who suffered subacute and anterior STEMI, had higher heart rate at admission and higher maximal troponin level, and had more often HF signs requiring intravenous diuretics. Among subjects with EF < 40%, the follow-up EF was available in 166 (80% of eligible). Systolic function recovered to EF > 50% in 39 (23.1%), slightly improved to EF 40–50% in 44 (26.0%) and remained below 40% in 86 (50.9%). Systolic function improvement to EF > 40% was predicted by lower severity of coronary atherosclerosis, lower leukocyte count, and the absence of atrial fibrillation.

Conclusions: Despite recent improvements in in-hospital MI care, one in five patients has systolic dysfunction at hospital discharge. Out of these, EF improves in 51%, and full recovery is observed in 23%. The severity of coronary atherosclerosis, inflammatory response to MI, and atrial fibrillation may affect EF recovery.

KEYWORDS

myocardial infarction, ejection fraction (EF%), systolic dysfunction, inflammation, atrial fibrillation, epidemiology



GRAPHICAL ABSTRACT
Trajectories and determinants of EF after the first MI.

Introduction

Left ventricular ejection fraction (EF) is a guideline-recommended tool for risk stratification of patients with acute myocardial infarction (MI) (1). Numerous studies have shown that low EF after MI is associated with an increased risk of cardiovascular and total mortality, heart failure, and sudden cardiac death (2–5). Several studies have also shown that EF may improve after hospital discharge, and such EF recovery is associated with a lower risk of cardiovascular events (6–9) and improved quality of life (10). The phenotype of heart failure with improved ejection fraction has been recently recognized by the guidelines and refers to patients with previous heart failure with reduced ejection fraction who have an LVEF >40% (11, 12).

In the last 20 years, the implementation of evidence-based therapy as primary percutaneous coronary intervention (PCI), dual antiplatelet therapy, and statin therapy have significantly improved MI mortality (13, 14). This may have also influenced systolic dysfunction prevalence and trajectories after MI. However, epidemiologic studies evaluating systolic dysfunction prevalence and trajectories coming from the contemporary era of MI therapy are scarce. Therefore, we sought to evaluate the incidence, trajectories, and determinants of left ventricular ejection fraction among consecutive patients hospitalized for their first MI.

Methods

Population

This study utilized data from the prospective AMBITION registry (Institute for Clinical and Experimental Medicine Acute Myocardial Infarction Registry), which collects clinical data and biospecimens from all consecutive patients hospitalized for acute coronary syndrome at a tertiary heart center since June 2017. During the hospital stay, all patients underwent detailed interviews, and additional information was obtained through manual chart abstraction and laboratory studies. For this analysis, data from individuals without previous history of heart failure and coronary artery disease, hospitalized for type I MI between June 2017 and November 2021 were used. The institutional review board of the Institute for Clinical and Experimental Medicine approved the study, and all participants signed informed consent.

Left ventricular ejection fraction

Left ventricular EF was measured using transthoracic echocardiography. In patients with several in-hospital EF measurements, the last one before hospital discharge was used as the baseline value. According to baseline EF, patients were categorized as having systolic dysfunction (EF < 40%), mid-range EF (EF 40–50%), or preserved systolic function (EF > 50%). In patients with systolic dysfunction at the time of MI hospitalization, optimal medical therapy with angiotensin converting enzyme inhibitor, beta-blocker and spironolactone was initiated. However, in patients with contraindications as hypotension or bradycardia/bradyarrhythmia this was not initiated. The patient was discharged with the recommendation for OMT therapy up-titration by an outpatient cardiologist. In patients with EF <40% at hospital discharge, follow-up EF beyond 6 weeks from the index hospitalization was recorded. By the follow-up EF, patients with systolic dysfunction at hospital discharge were categorized as having full EF recovery (follow-up EF > 50%), slightly improved EF (follow-up EF 40–50%), or persistent systolic dysfunction (follow-up EF < 40%).

Definition of comorbidities

History of diabetes was defined by the use of oral antidiabetic drugs or insulin at the time of hospital admission or by glycated hemoglobin ≥48 mmol/L at the time of hospitalization. Arterial hypertension was defined as self-reported use of antihypertensive drugs at admission. Self-reported history of smoking was used. A person was considered a current smoker if smoking at least one cigarette per day during the last 12 months. Positive family history of CVD was defined by MI or stroke in the first-degree relatives before 55 years in males and before 60 years in females, respectively.

Coronary artery stenosis degree was based on percent diameter stenosis by visual estimation done by an experienced invasive cardiologist. Culprit lesion intervention was performed during the index hospitalization. In patients with multiple vessel disease, additional interventions of non-culprit lesions were done during the index-hospitalization or patients were

invited for additional elective procedure, aiming for complete revascularization. During the follow-up, in none of the studied patient additional intervention was required due to restenosis, in-stent thrombosis or recurrent MI.

Gensini score was used to quantify the overall severity of coronary artery atherosclerosis, while accounting for lesion location, as previously described (15, 16). Mortality data were provided by the Institute of Health Information and Statistics, keeping a list of all deceased by law.

Statistical methods

Data are presented as mean ± standard deviation, median (interquartile range–IQR), or frequency (percent). Analysis of variance (ANOVA), Kruskal-Wallis or chi-square tests were used to compare differences across the three EF groups, as appropriate. Multivariate logistic and linear regression were used to assess factors associated with systolic dysfunction at baseline and EF recovery at follow-up. Factors with a significant association ($p<0.05$) in the univariate analysis (Table 1; Supplementary Table 1) were used as inputs for the multivariate model. Log-rank test was used to compare survival by EF categories. Cox proportional hazard model was used to assess the prognostic value of EF.

Results

Of 1,593 patients in the AMBITION registry, 1,347 had type I MI. Of these, 268 had a previous history of coronary artery disease, and another 14 had chronic heart failure history. Of the 1,065 eligible patients (65.4% STEMI), all had available EF at the time of MI hospitalization.

Systolic dysfunction at the time of MI hospitalization

Baseline echocardiography was performed on the median 1 day (IQR 0–2) after MI. Systolic dysfunction with EF below 40% was present in 238 (22.3%), mid-range systolic function with EF 40–50% in 326 (30.6%) and EF above 50% in 501 (47.0%), respectively. Population demographics by EF categories are shown in Table 1. In the multivariate analysis (Table 2), patients with systolic dysfunction at the time of hospitalization (EF < 40%) were more likely to experience subacute and anterior STEMI, had higher heart rate at admission and higher maximal troponin level, more often clinical signs of heart failure requiring intravenous diuretic therapy and more often pericarditis. After adjustment for age and gender, we found a non-linear association between discharge EF and mortality risk, with increased mortality in subjects with EF < 40% (Figure 1).

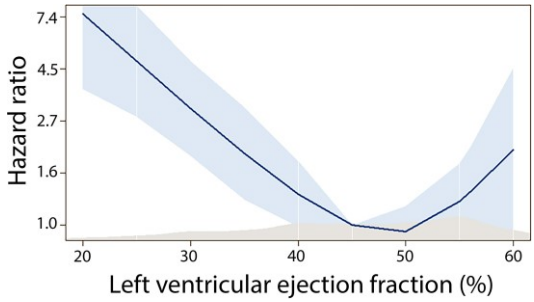


FIGURE 1
Association between discharge ejection fraction and mortality risk.

In the multivariate model, discharge EF was an independent predictor of total mortality risk after MI (Table 3).

Recovery of systolic function

Of the 238 patients with EF < 40% at the time of hospitalization, follow-up EF was not available in 26 due to in-hospital death or death within 6 months since the hospital discharge. Of the 212 eligible patients, follow-up EF was collected in 169 (80% of eligible). The follow-up systolic function evaluation was done on a median of 109 days (IQR 75–281) after MI. During this period, systolic function recovered to EF > 50% in 39 (23.1%), slightly improved to EF 40–50% in 44 (26.0%) and remained below 40% in 86 (50.9%).

Characteristics of patients by EF improvement at follow-up are shown in the Supplementary Table 1. In the multivariate analysis, improvement in systolic function to EF > 40% was predicted by lower severity of coronary artery atherosclerosis (lower GENSINI score), a higher discharge EF, lower leukocyte count and the absence of atrial fibrillation (AF) during MI hospitalization (Table 4). These factors were confirmed in the sensitivity analysis with the absolute change in EF as a dependent variable, with the addition of female gender associated with EF improvement (Supplementary Table 2). Recovery of systolic function was associated with lower mortality risk (log-rank $p = 0.012$) (Figure 2).

Discussion

The present study shows that in the current era of MI therapy, one in five patients after the first MI has reduced EF. In the months following the MI, one in four patients will fully recover EF, with severity of coronary atherosclerosis, inflammatory response, and AF being associated with lack of EF improvement.

TABLE 1 Population demographics by left ventricular ejection fraction at the time of hospitalization.

Variable	EF < 40 N = 238	EF 40–50 N = 326	EF > 50 N = 501	*p* for linear trend
Age, years	66.2 ± 12.6	62.8 ± 12.2	63.4 ± 11.7	0.012
Male gender, *n* (%)	177 (74.4)	249 (76.4)	368 (73.5)	0.654
Risk factors				
Arterial hypertension, *n* (%)	106 (44.7)	145 (44.5)	193 (38.6)	0.074
Diabetes, *n* (%)	65 (27.3)	84 (25.8)	122 (24.4)	0.380
Current smoking, *n* (%)	101 (42.4)	168 (51.5)	218 (43.5)	0.801
Statin use before admission, *n* (%)	35 (14.7)	46 (14.1)	112 (22.4)	0.003
Family history of CVD, *n* (%)	68 (28.6)	75 (23.0)	151 (30.1)	0.371
COPD, *n* (%)	15 (6.3)	22 (6.7)	26 (5.2)	0.457
AF history, *n* (%)	11 (4.6)	15 (4.6)	24 (4.8)	0.905
Index event				
CPR before admission, *n* (%)	19 (8.0)	14 (4.3)	20 (4.0)	0.032
STEMI, *n* (%)	202 (84.9)	252 (77.3)	242 (48.5)	0.0001
Subacute MI, *n* (%)	63 (26.5)	51 (15.6)	35 (7.0)	0.0001
Killip class >1, *n* (%)	114 (47.9)	59 (18.1)	47 (9.4)	0.0001
Selective coronarography, *n* (%)	233 (97.9)	323 (99.1)	500 (99.8)	0.009
PCI, *n* (%)	196 (82.4)	277 (85.0)	434 (86.6)	0.129
CABG, *n* (%)	17 (7.1)	35 (10.7)	43 (8.6)	0.732
In-hospital AF, *n* (%)	44 (18.5)	46 (14.1)	40 (8.0)	0.0001
Pericarditis, *n* (%)	14 (5.9)	7 (2.1)	6 (1.2)	0.0001
Intravenous diuretics, *n* (%)	135 (56.7)	64 (19.6)	53 (10.6)	0.0001
Anterior MI, *n* (%)	186 (78.2)	134 (41.1)	142 (28.3)	0.0001
Admission SBP, mmHg	138.2 ± 25.4	140.4 ± 26.3	147.5 ± 26.8	0.0001
Admission DBP, mmHg	79.9 ± 15.9	78.5 ± 14.1	79.6 ± 12.5	0.958
Admission heart rate, min^{-1}	85.2 ± 20.2	76.8 ± 16.8	73.9 ± 16.4	0.0001
Max Troponin natural log, ng/L	7.58 ± 1.56	7.47 ± 1.30	6.4 ± 1.4	0.0001
CKD EPI, ml/min/1.73 m^2	73.9 ± 23.2	78.5 ± 22.1	78.6 ± 21.3	0.014
BMI, kg/m^2	28.3 ± 4.8	28.6 ± 4.9	28.9 ± 4.9	0.135
HbA1c, mmol/L/mol	45.9 ± 13.3	45.7 ± 13.9	44.5 ± 12.4	0.145
Fasting glycemia, mmol/L	9.4 ± 4.6	8.4 ± 3.9	7.8 ± 3.2	0.0001
Total cholesterol, mmol/L	4.9 ± 1.3	4.9 ± 1.2	4.8 ± 1.2	0.829
Triglycerides, mmol/L	1.7 ± 1.7	1.6 ± 1.0	1.9 ± 1.3	0.048
HDL cholesterol, mmol/L	1.2 ± 0.3	1.2 ± 0.3	1.1 ± 0.3	0.002
LDL cholesterol, mmol/L	3.2 ± 1.1	3.3 ± 1.1	3.2 ± 1.1	0.998
Leukocytes, 10^9/L	12.4 ± 4.3	12.0 ± 4.0	11.3 ± 20.7	0.309
Erythrocytes, 10^{12}/L	4.7 ± 0.6	4.7 ± 0.5	4.6 ± 0.5	0.683
Hemoglobin, g/L	141.9 ± 16.8	142.8 ± 16.7	142.2 ± 14.6	0.939
Discharge medication				
ACEi/ARB, *n* (%)	163 (72.4)	258 (79.4)	377 (75.9)	0.538
Beta-blocker, *n* (%)	187 (83.1)	279 (85.8)	384 (77.3)	0.017
Statin, *n* (%)	209 (92.9)	314 (96.6)	485 (97.6)	0.003
Furosemide, *n* (%)	143 (63.6)	56 (17.2)	30 (6.0)	<0.001
Spironolactone, *n* (%)	157 (69.8)	45 (13.8)	16 (3.2)	<0.001
Acetylsalicylic acid, *n* (%)	208 (92.4)	306 (94.2)	481 (96.8)	0.009
Clopidogrel, *n* (%)	87 (38.7)	83 (25.5)	132 (26.6)	0.004
Prasugrel, *n* (%)	5 (2.2)	5 (1.5)	16 (3.2)	0.285
Ticagrelor, *n* (%)	119 (52.9)	222 (68.3)	335 (67.4)	0.001
Warfarin, *n* (%)	24 (10.7)	29 (8.9)	17 (3.4)	<0.001
Apixaban, *n* (%)	4 (1.8)	3 (0.9)	3 (0.6)	0.147
Dabigatran, *n* (%)	6 (2.7)	6 (1.8)	4 (0.8)	0.049
Rivaroxaban, *n* (%)	5 (2.2)	5 (1.5)	8 (1.6)	0.614
Outcome				
Death, *n* (%)	39 (16.4)	18 (5.5)	32 (6.4)	0.0001

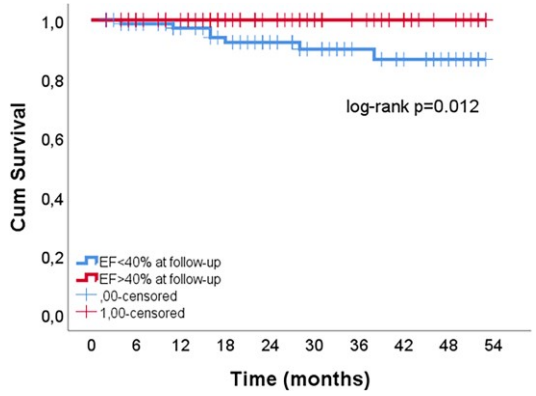


FIGURE 2
The influence of EF improvement on mortality risk in patients with EF<40% at hospital discharge.

TABLE 2 Multivariate logistic regression of factors associated with EF < 40% at the time of hospitalization.

Variable	OR (95% CI)	p
Anterior MI	8.39 (5.57–12.65)	0.001
Admission heart rate	1.01 (1.00–10.2)	0.01
STEMI	2.57 (1.60–4.14)	0.001
Subacute MI	1.95 (1.20–3.20)	0.01
Pericarditis	3.13 (1.12–8.74)	0.029
Intravenous diuretics	3.64 (2.16–6.13)	0.001
Maximal troponin level	1.22 (1.07–1.40)	0.003
Killip class above I	2.00 (1.15–3.45)	0.013

TABLE 3 Cox regression of factors associated with mortality after myocardial infarction.

Variable	HR (95% CI)	p
Age	1.047 (1.021–1.74)	0.001
CKD EPI	0.978 (0.968–0.989)	0.001
Current smoking	1.875 (1.153–3.048)	0.011
LV EF		0.004
EF < 40% vs. EF > 50%	1.841 (1.065–3.184)	0.029
EF 40–50% vs. EF > 50%	0.669 (0.357–1.251)	0.208
AF during hospitalization	1.688 (1.024–2.785)	0.040
Glycemia	1.063 (1.019–1.110)	0.005
Killip class >I	2.339 (1.402–3.900)	0.001
STEMI	0.510 (0.322–0.809)	0.004

TABLE 4 Multivariate logistic regression of factors associated with systolic function improvement to EF to >40% during follow-up.

Variable	OR (95% CI)	p
Coronary atherosclerosis severity (GENSINI score)	0.983 (0.969–0.997)	0.017
Leukocyte count	0.827 (0.735–0.931)	0.002
AF during hospitalization	0.359 (0.130–0.995)	0.049
Left ventricular ejection fraction	1.212 (1.100–1.337)	0.001

There is a lack of historical data on left ventricular systolic function after MI, because EF was not routinely measured in the past. In the Euro Heart Survey analyzing MI management in the year 2000 in 25 European countries, only 73% of STEMI and 61% of non-STEMI patients had EF measured (17). Thus, reported data may be a subject of a selection bias. This may bias direct comparison of historical data coming from the thrombolysis era with data observed in our study.

In the present study, 53% of patients at hospital discharge had EF < 50%. This is very similar to the 46–60% prevalence observed in the thrombolysis era (18–20). Similarly, the 22% prevalence of EF < 40% in our study is close to the 27–36% range observed at the turn of the century (21–24). Thus, despite significant improvements in MI management, systolic dysfunction immediately after MI is still common, with a prevalence similar to that observed in the thrombolysis era. There are several explanations for this finding. First, recent improvements in pre-hospital care led to a decrease in out of hospital mortality (25, 26). Second, introduction of PCI has decreased in-hospital mortality (27, 28). Thus, more patients that would previous die pre- or in-hospital are discharged with systolic dysfunction. Third, the landscape of MI patients is changing, (29) with risk factors as obesity and obesity-related comorbidities increasing especially in young patients with MI (30). Therefore, the higher burden of metabolic risk factors may have influenced systolic dysfunction prevalence.

Among patients with EF < 40% at the hospital discharge, we have observed full EF recovery in 23%. This is much lower than the 42% EF recovery rate observed in a retrospective cohort study of consecutive young patients aged ≤50 hospitalized for their first MI (9). While we did not find any direct effect of age on EF recovery in the present study, the different burden of comorbidities affecting EF recovery in younger subjects may explain this difference. On the other hand, the observed 51% proportion of patients with systolic function improvement to EF ≥ 40 in the present study is higher than the 24% proportion observed at the turn of the century (24). In other recent studies, the proportion of patients with systolic function improvement varies around 50% (8, 31, 32). This suggests that implementation of evidence-based therapy may have increased the proportion of patients with EF recovery. Recent recommendation to use Sodium-glucose

Cotransporter-2 (SGLT2) inhibitors and angiotensin receptor-neprilysin inhibitor (ARNI) in patients with heart failure with reduced ejection fraction may further increase the proportion of patients with EF improvement after MI (11). However, the PARADISE-MI study in patients with acute MI did not show superiority of ARNI on cardiovascular mortality and incident heart failure as compared to ramipril (33).

In the present study, we have identified several factors that may influence the course of EF recovery. Increased leukocytes count as a proxy of excess innate immunity activation was associated with a lower likelihood of EF improvement at follow-up. Lately, the importance of inflammation in patients after MI has been increasingly recognized (34). Due to excessive and prolonged inflammatory response to MI leukocytes infiltrate viable border zone of the infarction, thereby extending ischemic injury beyond the original MI zone (35). Prolonged inflammation also triggers adverse left ventricular remodeling. In the CANTOS study among patients after MI, monoclonal antibody targeting IL-1β significantly reduced recurrent major adverse cardiovascular events (36). Similarly, a low-dose colchicine, a potent anti-inflammatory drug affecting inflammasome, has decreased risk of ischemic cardiovascular events in patients after recent MI (37). Our results suggest that targeting of the inflammatory resolution pathways may influence EF recovery in patients with systolic dysfunction and increased inflammatory response to MI.

Another factor identified in the present study, that increased mortality risk by 69% and decreased EF improvement odds by 64%, was the new onset of AF during the MI hospitalization. On the other hand, pre-existing AF was not associated with mortality risk or EF recovery. This is in line with a previous study, in which mortality risk associated with a new onset AF during MI was 87% higher as compared to pre-existing AF (38). Several mechanisms such as atrial ischemia, volume overload, inflammation, and pericarditis have been described to trigger AF during MI (39). Thus new onset AF may be a marker of risk factors, which are known to affect EF recovery and increase heart failure risk. However direct hemodynamic effects of AF caused by the loss of atrial contraction, heart rate irregularity and increased heart rate may negatively influence EF recovery (40). Whether targeting patients with new onset AF can decrease mortality risk and improve EF after MI needs to be further evaluated.

In our sensitivity analysis, female gender was associated with a higher increase in EF during follow-up. This is in line with a meta-analysis of 18 studies, in which females had a higher odds of EF recovery (41). The gender difference may be explained by a higher level of signaling molecules with anti-inflammatory effects and more reparative immune cells in females (42).

Our study evaluating EF trajectories after MI is limited by the echocardiographic method of EF measurement. A large intra- and inter-individual variability in echocardiographic EF measurement has been reported (43). Despite this limitation, our and other studies have shown the prognostic value of this parameter. Because follow-up EF was available in 80% of eligible patients, our results may be influenced by the selection bias. The major strength of our study is the use of prospective registry which collects data of all consecutive patients hospitalized for MI at a high-volume center. This precludes several sources of bias. Furthermore, all patient records were adjudicated by the study physicians, which is more accurate that data derived from billing codes.

In summary, systolic dysfunction after the first MI is still common, with 1 in 5 patients having EF < 40%. Severity of coronary atherosclerosis, inflammatory response to MI, and AF may all affect EF recovery. These observations provide novel therapeutic targets for EF recovery.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, upon reasonable request.

Ethics statement

The studies involving human participants were reviewed and approved by IKEM Ethics Committee. The patients/participants provided their written informed consent to participate in this study.

Author contributions

All authors have contributed in full extent to the conception and design of the work, to the acquisition of data and/or their analysis, interpretation, have participated in drafting the manuscript, revising it critically for its intellectual content, and have given their approval of the final version to be published.

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Conflict of interest

PW has received consulting fees or honoraria from Servier. JK reports grants and personal fees from Biosense Webster, Biotronik, Boston Scientific, Medtronic, grants and personal fees

from Abbott (SJM), personal fees from Merit Medical, Daiichi Sankyo, Boehringer Ingelheim, BMS, Bayer, Merck, MSD, Pfizer, all outside the submitted work.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2022.1051995/full#supplementary-material

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Journal of the American Heart Association

ORIGINAL RESEARCH

Attenuation of Hypocretin/Orexin Signaling Is Associated With Increased Mortality After Myocardial Infarction

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BACKGROUND: The hypocretin/orexin system has been shown to play a role in heart failure. Whether it also influences myocardial infarction (MI) outcomes is unknown. We evaluated the effect of the rs7767652 minor allele T associated with decreased transcription of the hypocretin/orexin receptor-2 and circulating orexin A concentrations on mortality risk after MI.

METHODS AND RESULTS: Data from a single-center, prospectively designed registry of consecutive patients hospitalized for MI at a large tertiary cardiology center were analyzed. Patients without previous history of MI or heart failure were included. A random population sample was used to compare allele frequencies in the general population. Out of 1009 patients (aged 64±12 years, 74.6% men) after MI, 6.1% were homozygotes (TT) and 39.4% heterozygotes (CT) for minor allele. Allele frequencies in the MI group did not differ from 1953 subjects from general population (χ^2 P=0.62). At index hospitalization, MI size was the same, but ventricular fibrillation and the need for cardiopulmonary resuscitation were more prevalent in the TT allele variant. Among patients with ejection fraction ≤40% at discharge, the TT variant was associated with a lower increase in left ventricular ejection fraction during follow-up (P=0.03). During the 27-month follow-up, there was a statistically significant association of the TT variant with increased mortality risk (hazard ratio [HR], 2.83; P=0.001). Higher circulating orexin A was associated with a lower mortality risk (HR, 0.41; P<0.05).

CONCLUSIONS: Attenuation of hypocretin/orexin signaling is associated with increased mortality risk after MI. This effect may be partially explained by the increased arrhythmic risk and the effect on the left ventricular systolic function recovery.

Key Words: hypocretin/orexin receptor-2 ■ hypocretin/orexin system ■ inflammation ■ mortality ■ myocardial infarction ■ outcomes ■ recovery

In the central nervous system, the hypocretin/orexin (H/O) system regulates sleep–wake cycles and metabolism. The loss of orexin-producing neurons in the hypothalamus causes narcolepsy with cataplexy (narcolepsy type I).[1] On the other hand, orexin receptor antagonists have been used for insomnia treatment.[2] Other studies suggested the role of the brain's H/O system in feeding behavior and propensity for weight gain, with orexin signaling acting through a net increase in energy expenditure.[3]

Outside of the central nervous system, the impact of the H/O system has been recently recognized in patients with heart failure (HF). In an unbiased systems-biology search, Perez et al identified the rs7767652 locus in the regulating domain of HCRTR-2 (hypocretin receptor-2) as the strongest predictor of left ventricular ejection fraction (EF) improvement in response to HF pharmacotherapy.[4] In the functional validation study, the rs7767652 minor allele T was associated with disruption of a transcription factor

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CLINICAL PERSPECTIVE

What Is New?

- In patients after myocardial infarction, attenuation of hypocretin/orexin signaling is associated with increased mortality risk.

What Are the Clinical Implications?

- Orexin receptor agonists may improve outcomes after myocardial infarction, but further research is needed.

Nonstandard Abbreviations and Acronyms

AMBITION	Institute for Clinical and Experimental Medicine Acute Myocardial Infarction Registry
HCRTR-2	hypocretin orexin receptor-2
H/O	hypocretin/orexin

4 binding site, leading to decreased transcription of HCRTR-2. Impact of the H/O system on HF was further confirmed in an animal model of HF, in which orexin administration improved left ventricular EF. In a human HF study, subjects with a higher circulating orexin A concentration (≥1.04 ng/mL) had more significant reduction in left ventricular end-diastolic and end-systolic volume and a trend toward greater improvement in left ventricular EF in response to HF therapy.[5]

Myocardial infarction (MI) is one of the most common causes of HF development and is associated with increased mortality risk.[6] Until now, no study has evaluated the effect of the H/O system on MI outcomes. The aim of the present prospective study was to describe the effect of the H/O system on total mortality among consecutive patients hospitalized for their first MI. To overcome typical biases associated with biochemical biomarker measurements that may impact results validity, we have used a genetic variant in the regulating domain of the HCRTR-2 gene, which is associated with attenuated HCRTR-2 signaling. Because of Mendelian inheritance laws, genetic variants are randomly distributed in the population. Unlike biochemical variables, genetic variants are not confounded by environmental and other factors. As a sensitivity analysis to further confirm the impact of the H/O system on survival, we have also measured circulating orexin A levels in a high-risk subgroup of patients with systolic dysfunction after MI.

METHODS

Data Availability Statement

The data that support the findings of this study are available from the corresponding author, upon reasonable request.

Population

This study used data from the prospective AMBITION (Institute for Clinical and Experimental Medicine Acute Myocardial Infarction Registry) registry,[7] which has been collecting clinical data and biospecimens from all consecutive patients hospitalized for acute coronary syndrome at a tertiary heart center since June 2017. The methods of this study were previously described.[8] During the hospital stay, all patients underwent detailed interviews, and additional information was obtained through manual chart abstraction and laboratory studies.

For this analysis, data from individuals without a previous history of HF and coronary artery disease hospitalized for type 1 MI (caused by atherosclerotic plaque rupture and thrombosis)[9] between June 2017 and November 2021 were used. The institutional review board of the Institute for Clinical and Experimental Medicine approved the study, and all participants signed informed consent. The investigation conformed to the principles outlined in the Declaration of Helsinki.

To identify the impact of rs7767652 on MI risk, we compared allele frequencies in the general population and patients after MI. As a control group, we used data from the Czech post-MONICA (Monitoring of Trends and Determinants in Cardiovascular Disease) study, which examined a 1% random population sample in 9 districts of the Czech Republic. Methods of the Czech post-MONICA study were previously reported.[10]

Definition of Comorbidities

History of diabetes was defined by oral antidiabetic drugs or insulin use at the time of hospital admission or by glycated hemoglobin ≥48 mmol/mol at the time of hospitalization. Arterial hypertension was defined as self-reported use of antihypertensive drugs at admission. Self-reported history of smoking was used. A person was considered a current smoker if smoking at least 1 cigarette per day during the past 12 months. Positive family history of cardiovascular disease was defined by MI or stroke in first-degree relatives before age 55 years in men and before age 60 years in women, respectively.

rs7767652 Genotyping

DNA was isolated from peripheral blood. The rs7767652 locus in the regulating domain of HCRTR-2 was analyzed using the TaqMan SNP assay

No.C_29161754_20. Genotyping was performed according to the manufacturer's protocol on an ABI 7300 real-time polymerase chain reaction instrument.

Orexin A Concentration Measurement

In 245 patients with systolic dysfunction and EF <40% at hospital discharge, we measured the concentration of orexin A in blood samples drawn on the first day after hospital admission using the ELISA method (Phoenix Pharmaceuticals, Burlingame, CA).

Outcomes

The primary outcome of this study was all-cause mortality. Mortality data were provided by the Institute of Health Information and Statistics, which keeps a record of all deceased individuals by law.

Statistical Analysis

Data are presented as mean±SD, median (interquartile range [IQR]), or frequency (percent). ANOVA, Kruskal-Wallis, or χ^2 tests were used to compare differences across the 3 allele variants, as appropriate. A log-rank test was used to compare survival by allele variants. A Cox proportional hazard model was used to assess factors influencing survival after MI. The proportional hazard assumption was checked and fulfilled. Follow-up was defined as the time from hospital discharge to death ascertained to January 1, 2022, without censoring for any additional events.

Statistical analyses were performed using SPSS version 25.0 (IBM, Armonk, NY), Stata version 17 (StataCorp, College Station, TX), or R software version 3.6.2 (R Foundation for Statistical Computing, Vienna, Austria). Statistical significance was set at $P<0.05$. The same threshold was used for variables to enter the multivariable analyses.

RESULTS

Of the 1593 patients in the AMBITION registry, 1347 had type 1 MI. Of these, 268 had a previous history of coronary artery disease, and another 14 had chronic heart failure and were therefore excluded. Of the 1065 eligible patients, rs7767652 allele variants were available in 1009 patients. The study flowchart is shown in Figure 1. The main study findings are summarized in Figure 2.

rs7767652 Allele Variants in MI and the General Population

In 1009 patients from the MI population, 6.1% patients were homozygotes (TT) and 39.4% heterozygotes (CT) for the hypofunctional rs7767652 minor T allele. Similarly, in 1953 subjects from the general population of the Czech post-MONICA study, 6.6% were homozygotes and 37.8% were heterozygotes for the rs7767652 minor allele. Allele frequencies in the MI and general population were not statistically different (χ^2 $P=0.62$), suggesting that rs7767652 does no increase MI risk.

Traditional Risk Factors and MI Complications by rs7767652 Allele Variants

Demographic characteristics by allele variants are shown in Table 1. There were no statistically significant differences in traditional risk factors such as diabetes, body mass index, glycemia or low-density lipoprotein cholesterol by the rs7767652 allele variants. Similarly, there was no statistically significant difference in MI size as assessed by maximal troponin level or discharge EF. However, subjects with the TT variant more often experienced ventricular fibrillation (12.9% versus 4.8%, $P=0.01$) and more often required cardiopulmonary resuscitation (16.1% versus 7.0%, $P=0.02$), as compared with the CT and CC variants combined. Among the 243 patients with EF ≤40% at hospital discharge and available follow-up EF measured on a median of 128 days (IQR, 98–395 days) after the baseline EF measurement, minor allele homozygotes had a lower increase in EF during the follow-up (2.5±11.0% versus 8.4±9.4%, $P=0.04$, for TT versus CT and CC combined).

rs7767652 Allele Variants and Total Mortality

During the median follow-up of 27 months (IQR, 13–41 months), the total mortality rate was 8.4% (n=83). Homozygotes for the rs7767652 minor and hypofunctional allele had a higher mortality risk as compared with heterozygotes ($P=0.001$) and homozygotes for the major allele ($P=0.001$), with no statistically significant difference between heterozygotes and major allele homozygotes ($P=0.836$) (Figure 3). After multivariable adjustment, minor allele homozygotes remained at increased mortality risk (hazard ratio, 2.83 [95% CI, 1.55–5.19]) (Table 2).

Orexin A Concentration and Mortality

To further confirm the effect of the H/O system on mortality after MI, we measured orexin A levels in 245 patients with systolic dysfunction and EF ≤40% at hospital discharge. At baseline, patients with the rs7767652 TT allele variant had no statistically significant difference in orexin A concentrations from those with the CT (0.76±0.26 versus 0.80±0.28 ng/mL, $P=0.82$) and CC (0.76±0.26 versus 0.84±0.29 ng/mL, $P=0.48$) variants, respectively. In the analysis adjusted for age, mortality risk was lowest in subjects with orexin concentration ≥1.0 ng/mL (Figure 4). After multivariable adjustment,

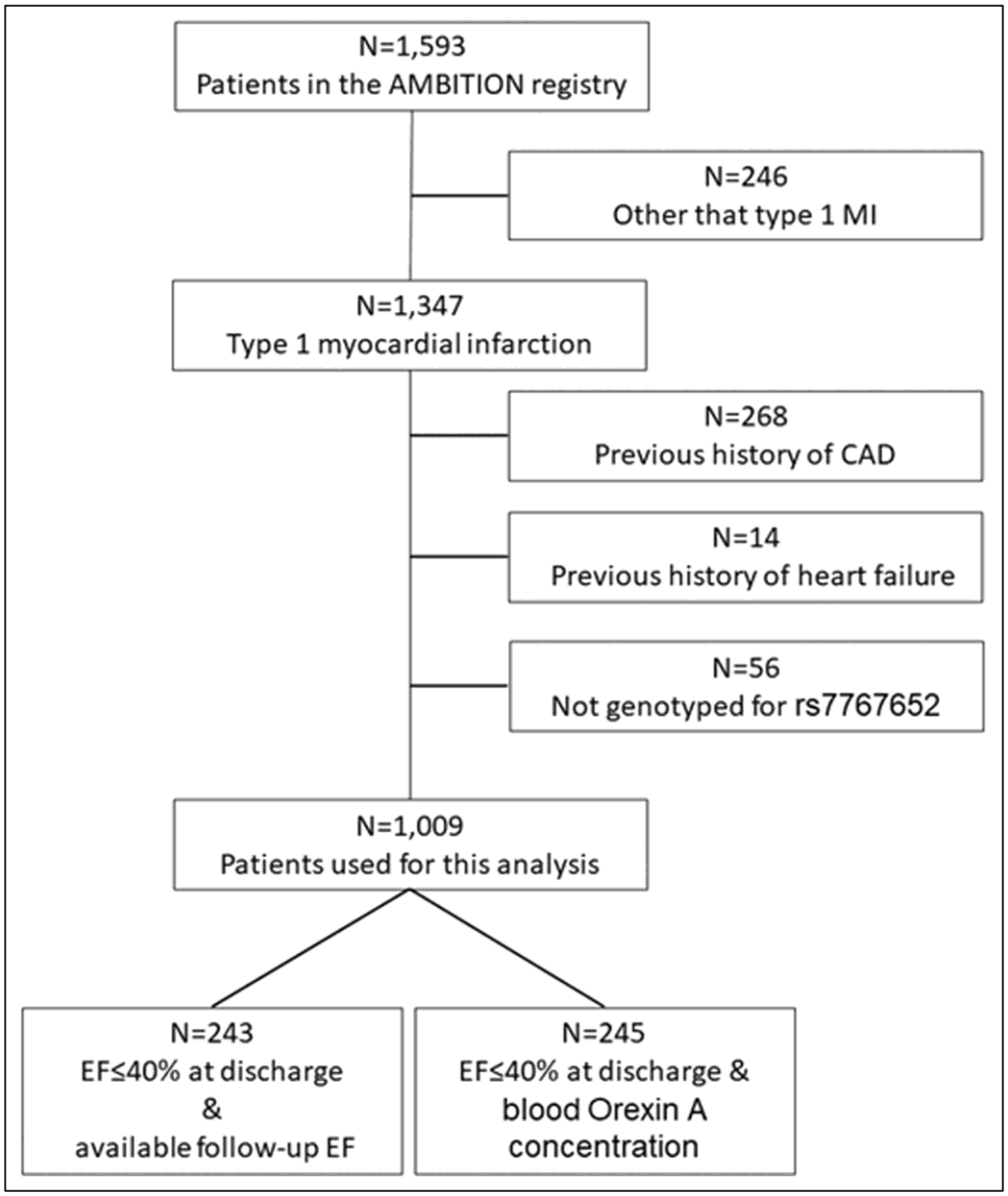

Figure 1. Study flowchart.
AMBITION indicates Institute for Clinical and Experimental Medicine Acute Myocardial Infarction Registry; CAD, coronary artery disease; EF, ejection fraction; and MI, myocardial infarction.

the mortality risk among patients with orexin A concentration ≥1.0 ng/mL was 59% lower than in patients with orexin <1.0 ng/mL (Table 3).

DISCUSSION

This is the first study to describe the influence of the H/O system on the prognosis of patients after the first MI. We have shown that the rs7767652 minor allele, which is associated with attenuated H/O signaling, does not increase MI risk and is not associated with traditional risk factors. Although MI size was similar, the long-term outcome differed by rs7767652 allele variants. Minor allele homozygous, which confers with lower HCRTR-2 transcription,[4] and subjects with lower circulating orexin A level were at increased total mortality risk. This effect of the H/O system on mortality may be partially explained by the increased arrhythmic risk and the impact on the left ventricular systolic function recovery.

The H/O system was first described almost 25 years ago by 2 independent groups searching for a possible treatment for obesity. De Lecea et al named discovered proteins hypocretins because of their location in the hypothalamus and amino acid similarities with a gut hormone secretin.[11] Sakurai et al named peptides

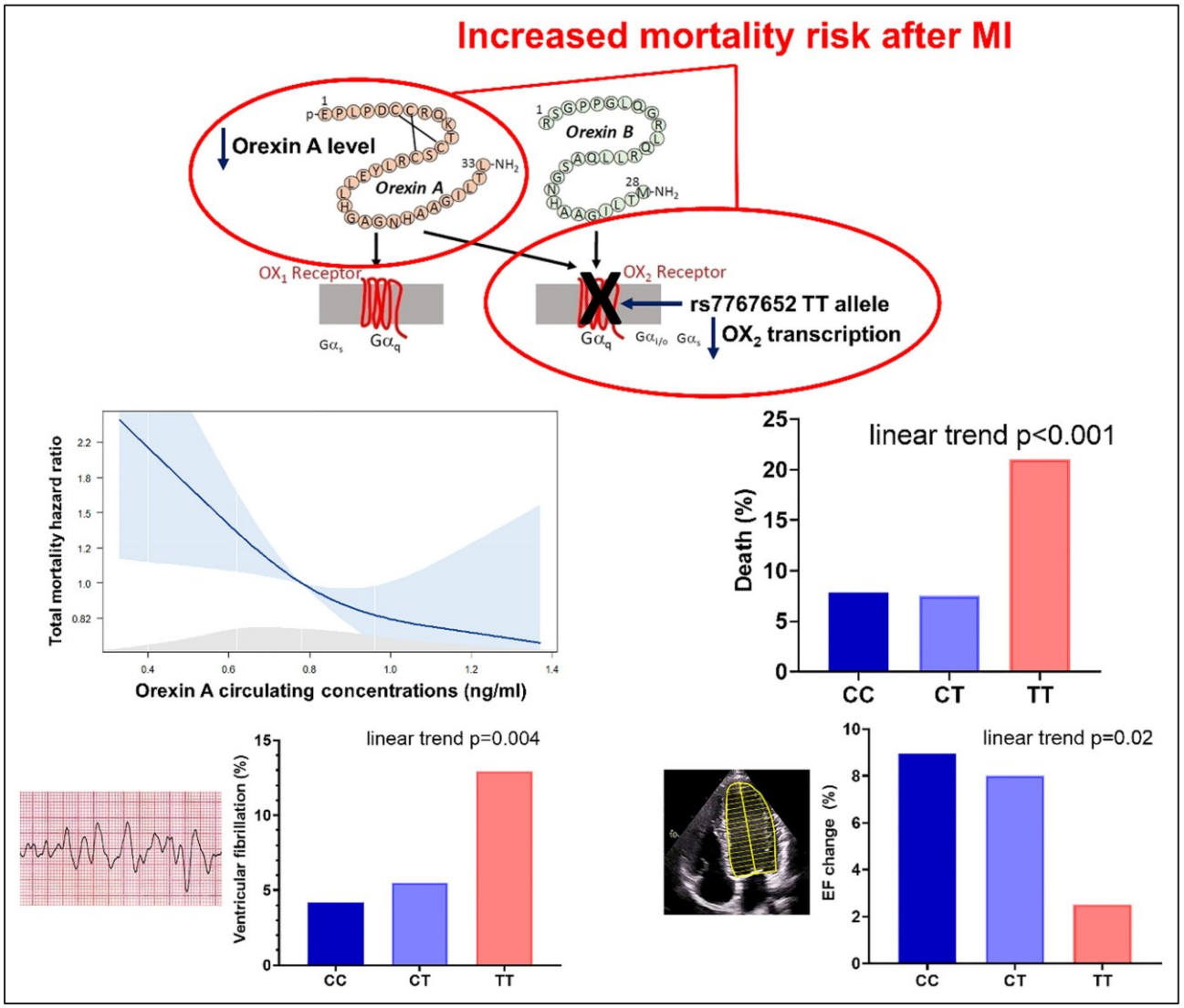

Figure 2. Main study findings.
EF indicates ejection fraction; and MI, myocardial infarction.

orexins after the Greek word for appetite, because their application induced feeding in rats.[12] It was discovered that the proteins identified by these groups were identical.

In the following years, the research on the central nervous system described involvement of the H/O system in maintaining wakefulness,[13] food intake, energy homeostasis, reward-seeking, stress, motivation, and drug addictions.[14] Outside the central nervous system, the H/O system may influence the risk of digestive tract cancer, inflammatory bowel syndrome, and glucose metabolism.[15] In humans, orexin deficiency is associated with glucose intolerance and insulin resistance.[16] In rodents, orexin overexpression protects from diet-induced obesity and improves glucose control.[17] This is related to orexin-induced increase in GLUT4 (glucose transporter type 4) expression in the liver and increased insulin secretion.[18,19]

The involvement of the H/O system in heart disease has been recognized only recently among patients with HF.[4,5,20] We added to this evidence by showing for the first time that the H/O system also influences prognosis after MI.

Several possible mechanisms may mediate the influence of the H/O system on mortality after MI. First, this effect may be caused by long-term exposure to classical risk factors. Association of the H/O system with metabolic syndrome and insulin sensitivity was described in previous studies,[15,16] both of which influence outcomes after MI.[21] However, we did not find any difference in diabetes, glucose, or body mass index by the rs7767652 allele variants in the present study. Although the H/O system influences drug addiction, including smoking,[14] there was no difference in the proportion of smokers by allele

Table 1. Demographic Characteristics by rs7767652 Allele Variants (N=1009)

Variable	CC, N=549	CT, N=398	TT, N=62	*P* for linear trend
Age, y	63.6±12.6	63.5±11.7	66.5±12.0	0.078
Male sex	414 (75.4)	294 (73.9)	46 (74.2)	0.843
Risk factors				
Arterial hypertension, n (%)	309 (56.4)	236 (59.4)	44 (66.1)	0.268
Diabetes, n (%)	131 (23.9)	106 (26.6)	18 (29.0)	0.491
Current smoking, n (%)	248 (45.2)	186 (46.7)	27 (43.5)	0.799
Statin use before admission, n (%)	91 (16.6)	72 (18.1)	14 (22.6)	0.242
Family history of CVD, n (%)	145 (26.4)	117 (29.4)	13 (21.0)	0.348
AF history, n (%)	24 (4.4)	20 (5.0)	4 (6.5)	0.470
Index event				
Cardiopulmonary resuscitation, n (%)	34 (6.2)	32 (8.0)	10 (16.1)	0.005
Ventricular fibrillation, n (%)	23 (4.2)	22 (5.5)	8 (12.9)	0.004
In-hospital AF, n (%)	65 (11.8)	52 (13.1)	7 (11.3)	0.890
STEMI, n (%)	361 (65.8)	262 (65.8)	38 (61.3)	0.481
Subacute MI, n (%)	78 (14.2)	54 (13.6)	10 (16.1)	0.674
Killip class >1, n (%)	108 (19.7)	78 (19.6)	14 (22.6)	0.584
Selective coronarography, n (%)	546 (99.5)	393 (98.7)	61 (98.4)	0.410
PCI, n (%)	460 (83.8)	346 (86.9)	53 (85.5)	0.744
CABG, n (%)	54 (9.8)	31 (7.8)	5 (8.1)	0.659
Pericarditis, n (%)	11 (2.0)	9 (2.3)	5 (8.1)	0.004
Intravenous diuretics, n (%)	130 (23.7)	91 (22.9)	15 (24.2)	0.922
Anterior MI, n (%)	241 (43.4)	173 (43.5)	26 (41.9)	0.769
Admission systolic BP, mm Hg	143.6±26.2	142.4±26.6	142.2±29.8	0.697
Admission diastolic BP, mm Hg	80.0±14.0	78.6±13.5	77.6±14.6	0.193
Admission heart rate, min^{-1}	77.9±19.2	76.9±17.0	77.4±16.2	0.851
Maximum troponin natural log, ng/L	7.00±1.53	7.01±1.54	6.76±1.38	0.242
Discharge EF, %	44.9±10.1	45.3±10.3	46.1±10.9	0.382
CKD EPI, mL/min per 1.73 m^2	77.6±22.2	77.9±22.7	75.8±19.9	0.528
BMI, kg/m^2	28.6±4.7	28.9±5.1	28.3±5.7	0.564
HbA1c, mmol/L per mol	44.5±11.6	45.8±14.5	44.9±11.8	0.852
Fasting glycemia, mmol/L	8.3±3.8	8.4±3.8	8.1±3.2	0.743
Total cholesterol, mmol/L	4.86±1.15	4.89±1.34	4.63±1.08	0.153
Triglycerides, mmol/L	1.7±1.0	1.8±1.4	1.9±1.3	0.031
HDL cholesterol, mmol/L	1.14±0.34	1.12±0.31	1.06±0.27	0.047
LDL cholesterol, mmol/L	3.25±1.11	3.21±1.11	2.99±0.97	0.075
Leukocytes, $10^9/L$	11.37±3.97	11.37±4.04	10.73±3.64	0.234
Hemoglobin, g/L	142.7±15.6	141.4±16.1	142.0±15.9	0.759
Discharge medication				
ACEi/ARB, n (%)	397 (73.7)	309 (78.2)	49 (81.7)	0.177
β-Blocker, n (%)	436 (80.9)	327 (82.8)	49 (81.7)	0.894
Furosemide, n (%)	106 (22.3)	67 (19.3)	13 (23.6)	0.792
Spironolactone, n (%)	100 (21.0)	67 (19.3)	13 (23.6)	0.634
Statin, n (%)	520 (96.5)	377 (95.4)	58 (96.7)	0.929
Echocardiography follow-up*				
EF change, %	9.0±8.7	8.0±9.2	2.5±11.0	0.019

(*Continued*)

Table 1. Continued

Variable	CC, N=549	CT, N=398	TT, N=62	*P* for linear trend
End-diastolic diameter change, mm	2.2±5.6	2.6±5.6	4.8±9.4	0.146
Outcome				
30-d mortality	14 (2.6)	9 (2.3)	3 (4.8)	0.276
Death, n (%)	43 (7.8)	30 (7.5)	13 (21.0)	<0.001

ACEi/ARB indicates angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; AF, atrial fibrillation; BMI, body mass index; BP, blood pressure; CABG, coronary bypass grafting; CKD EPI, Chronic Kidney Disease Epidemiology Collaboration; CVD, cardiovascular disease; EF, ejection fraction; HbA1c, glycated hemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein; MI, myocardial infarction; PCI, percutaneous coronary intervention; and STEMI, ST-segment–elevation myocardial infarction.

*Analyzed in 243 patients with discharge EF ≤40% and available follow-up echocardiography.

variants. Second, infarct size, assessed by EF, troponin release, or medication use, was not affected by the rs7767652 polymorphism, indicating that infarct size per se does not explain the difference in survival. Third, the orexin system effected arrhythmia risk. We found a higher prevalence of ventricular fibrillation in rs7767652 minor allele homozygotes. Minor allele homozygotes had also higher triglyceride levels at the time of MI, which may reflect increased lipolysis in subcutaneous and epicardial adipose with release of nonesterified fatty acids and adipokines that promote arrhythmogenesis.[22] Fourth, on the effect on inflammation, we found that pericarditis was more prevalent in minor allele homozygotes despite a similar MI size, suggesting a higher inflammatory response to MI. This may be explained by an immunomodulatory effect of the orexin system.[23] Several recent studies have described the effect of the inflammatory response on outcomes after MI.[24] Fifth, we found that the H/O system affects EF recovery after MI, which is associated with improved survival.[25] Previously, variation in rs7767652 identified superresponders to pharmacotherapy, who had improved EF because of reverse remodeling.[4] In the present study among patients with EF ≤40% at hospital discharge, rs7767652 minor allele homozygotes had a lower increase in EF during follow-up. This is also supported by the fact that 30-day mortality did not differ by allele variants, whereas

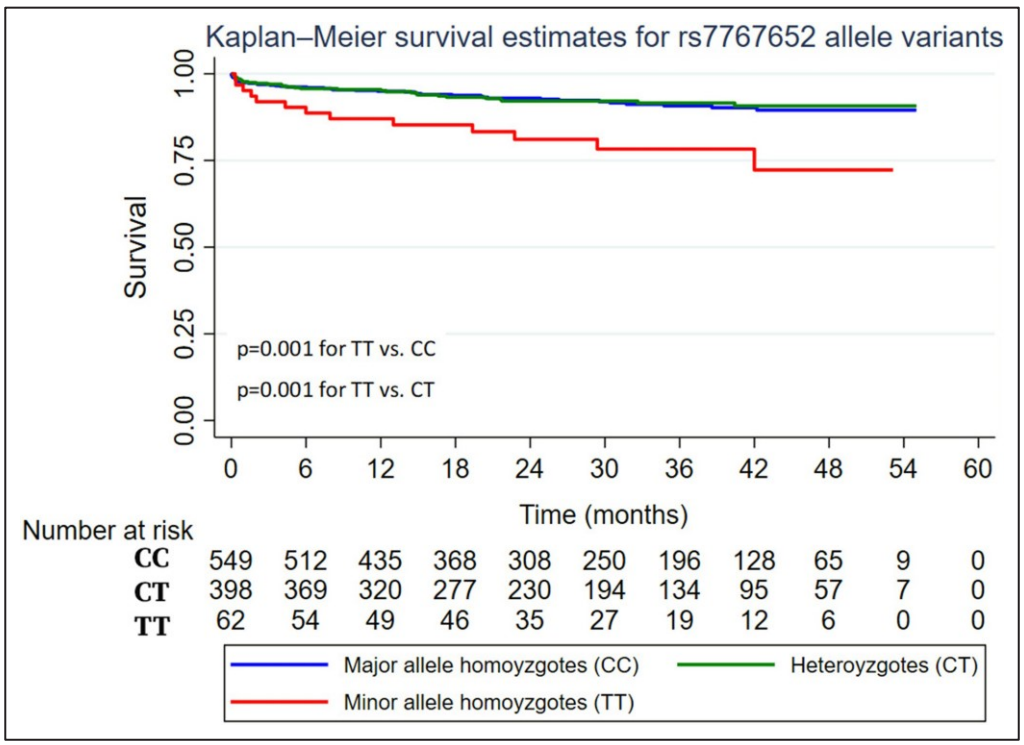

Figure 3. Kaplan-Meier survival estimates for rs7767652 allele variants.
Patients with the rs7767652 TT allele combination (red line) are at higher mortality risk as compared with those with the CC (blue line) and CT (green line) allele combination (both log-rank *P*<0.001).

Table 2. Factors Associated With Mortality Risk After Myocardial Infarction (N=1009)

Variable	HR (95% CI)	*P* value
Age	1.052 (1.027–1.78)	<0.001
CKD EPI	0.973 (0.962–0.984)	<0.001
Smoking	1.741 (1.080–2.807)	0.023
Left ventricular EF		0.016
EF <40% vs EF >50%	1.628 (0.977–2.714)	0.061
EF 40%–50% vs EF >50%	0.699 (0.378–1.294)	0.254
Glycemia	1.061 (1.016–1.108)	0.008
Killip class >I	2.551 (1.562–4.166)	<0.001
rs7767652 minor allele homozygote	2.833 (1.545–5.194)	0.001

CKD EPI indicates Chronic Kidney Disease Epidemiology Collaboration; EF, ejection fraction; and HR, hazard ratio.

Table 3. Factors Associated With Mortality Risk in Patients With Systolic Dysfunction at Hospital Discharge (n=245)

Variable	HR (95% CI)	*P* value
Age	1.029 (1.003–1.055)	0.030
CKD EPI	0.274 (0.140–0.535)	<0.001
Admission heart rate	1.012 (1.003–1.024)	0.013
Killip class >I	2.862 (1.710–4.792)	<0.001
Orexin ≥1.0 ng/mL	0.413 (0.186–0.914)	0.029

CKD EPI indicates Chronic Kidney Disease Epidemiology Collaboration; and HR, hazard ratio.

there was a difference in long-term mortality. The variety of mechanistic links connecting orexin signaling with increased mortality risk in our study may seem tricky at first. However, a multitude of downstream orexin signaling that involves SGK-1 (serum and glucocorticoid-regulated kinase-1)[26]; HIF-1 (hypoxia-inducible factor-1)[26]; phospholipase A2, C, and D; diacylglycerol lipase; Ca2+; and adenylyl cyclase cascades[23] may explain this variety of orexin signaling effects. In a recent study by Patel et al, orexin B but not orexin A had a direct cardioprotective effect in human heart samples that was mediated by the ERK1/2 (extracellular signal-regulated kinase 1 and 2) phosphorylation.[20] ERK1/2 phosphorylation is involved in the activation of contractile responses through direct phosphorylation of the Ca2+/calmodulin-dependent MLC (myosin light chain) kinase.[27]

Our findings have several clinical implications. Orexin receptor antagonists are widely used for insomnia treatment and in patients with MI. Whether their use may influence outcomes after MI needs to be examined. In addition, targeting the H/O system and increasing its activity by oral receptor antagonists, currently developed for treatment of narcolepsy, may be a novel therapeutic pathway to decrease the mortality risk and improve myocardial recovery after MI.

Study Limitations

Although this is an observational study, the use of a genetic instrumental variable with natural randomization of individuals under the Mendel law of segregation and independent assortment excludes the effect of confounding factors on our results. Although our

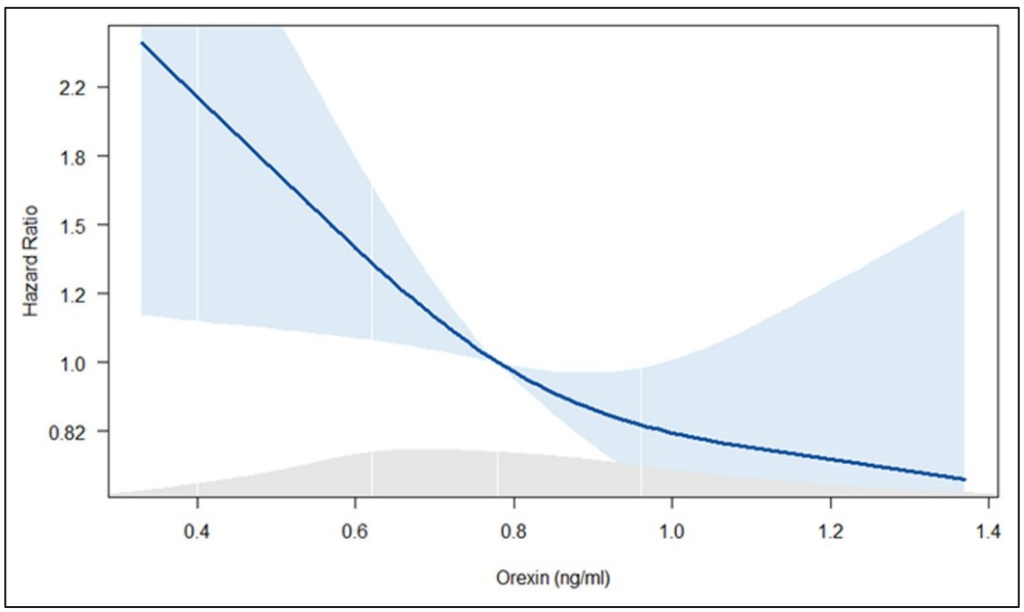

Figure 4. Circulating orexin A concentrations and mortality risk after myocardial infarction.
The relationship between circulating orexin A concentration assessed at the time of myocardial infarction and total mortality hazard ratio. Data are adjusted for age. The gray area represents orexin A histogram, and the light blue area is the 95% CI.

study is relatively small by genetic standards and uses only a single nucleotide polymorphism, the effect of this polymorphism on survival is substantial, thus requiring a lower sample size. As a sensitivity analysis, we have confirmed the impact of the H/O system on survival using circulating orexin A concentrations. Our results are consistent with those observed in patients with HF.

CONCLUSIONS

The present study shows for the first time the effect of the attenuation of H/O signaling on increased mortality risk after myocardial infarction. Several mechanisms may mediate this association, of which the effect on left ventricular systolic function recovery and ventricular fibrillation risk seems promising. Future studies will have to address potential relevance of the H/O axis pharmacomodulation on post-MI remodeling and survival.

ARTICLE INFORMATION

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