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HEART AND BLOOD VESSELS

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Review article

Koronavirus i kardiološke implikacije

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Ovaj pregledni članak je napisan u ime Udruženja kardiologa Srbije povodom pandemije koronavirusom i postavaljen i na sajt UKS.

Koristeći dostupnu literaturu, koja se menja iz sata u sat i publikuje na poseban način, kao i domaće vodiče posvećene ovoj temi, Udruženje kardiologa Srbije posvetilo je posebnu pažnju kardiološkim posledicama infekcije Koronavirusom.

U poslednje dve decenije, koronavirus je po treći put prešao na drugu vrstu da bi zarazio čoveka. Pre sedamnaest godina epidemija virusa čiji RNK nizovi jako liče na virus koji tiho cirkuliše kod slepih miševa - takozvani „SARS-CoV" - izazvao je ozbiljan akutni respiratorni sindrom sa stopom smrtnosti od 9 do 11%. Nekoliko godina kasnije (2012), koronavirus bliskoistočnog respiratornog sindroma - takozvani „MERS-CoV" - imao je smrtnost od 34%. Kod oba virusa, starost i komorbiditeti kao dijabetes ili srčane bolesti, bili su nezavisni prediktori nepovoljnog ishoda.[1] Isto važi i za novi koronavirus, označen kao 2019-nCoV, koji se pojavio u Wuhanu, Kina, krajem 2019.[2,3] Od strane Svetske zdravstvene organizacije (WHO) virus je zvanično nazvan „Teški akutni respiratorni sindrom koronavirus 2 (SARS-CoV-2)".

SARS-CoV-2 inficira ćelije domaćina putem receptora angiotenzin-konvertirajućeg enzima 2 (ACE2), što često dovodi do pneumonije povezane sa ovim virusom (COVID-19). Dakle, isti virus se može nazvati 2019- nCoV, SARS-CoV-2 ili COVID-19.[4] U ovom članku koristimo izraz „COVID-19", jer je to do sada najčešće upotrebljavano. Pretpostavlja se da COVID-19, osim što oštećuje pluća, može da ošteti i **kardiovaskularni sistem.**[4] Iz tih razloga je važno istražiti moguća COVID-19 oštećenja srca, ulogu kardiologa i kardiovaskularnih lekova u trenutnoj epidemiji (ili pandemiji).

Jedino je sigurno da je raširenost COVID-19 ogromna: zahvatila je više od 190 zemalja. Dobra vest je da postoji utisak da je COVID-19 manje patogen od MERS-CoV i SARS-CoV.[1] U Kini, većina obolelih i smrtnih ishoda bila je u provinciji Hubei, gde se nalazi grad Wuhan, sa stopom smrtnosti od 0.5-2%, što je značajno niže nego kod prethodnih infekcija koronavirusom. U drugim delovima sveta stopa smrtnosti je izgleda veća - oko 4–6%, i zavisi od broja zaraženih osoba i širine testiranja na prisustvo virusa.

Intrahospitalno širenje i veća smrtnost omogućuju efektivno sprečavanje širenja virusa preko nadzora simptoma i znakova kliničkog sindroma (temperature) i smanjivanje kontakata. Suprotno tome, nedostatak teških manifestacija bolesti, kao kod COVID-19, smanjuje mogućnost obuzdavanja širenja inekcije. Ako zaražene osobe ostanu asimptomatske ili blago simptomatske, neće završiti u zdravstvenim centrima ili bolnicama. Umesto toga, oni će nastaviti da idu na posao, da se bave sportom i putuju, šireći virus na svoje kontakte, čak i na međunarodnom nivou. To se najverojatnije dogodilo sa COVID-19, kome je pogodovalo globalno međusobno povezivanje u našem svetu od 7,8 milijardi ljudi.

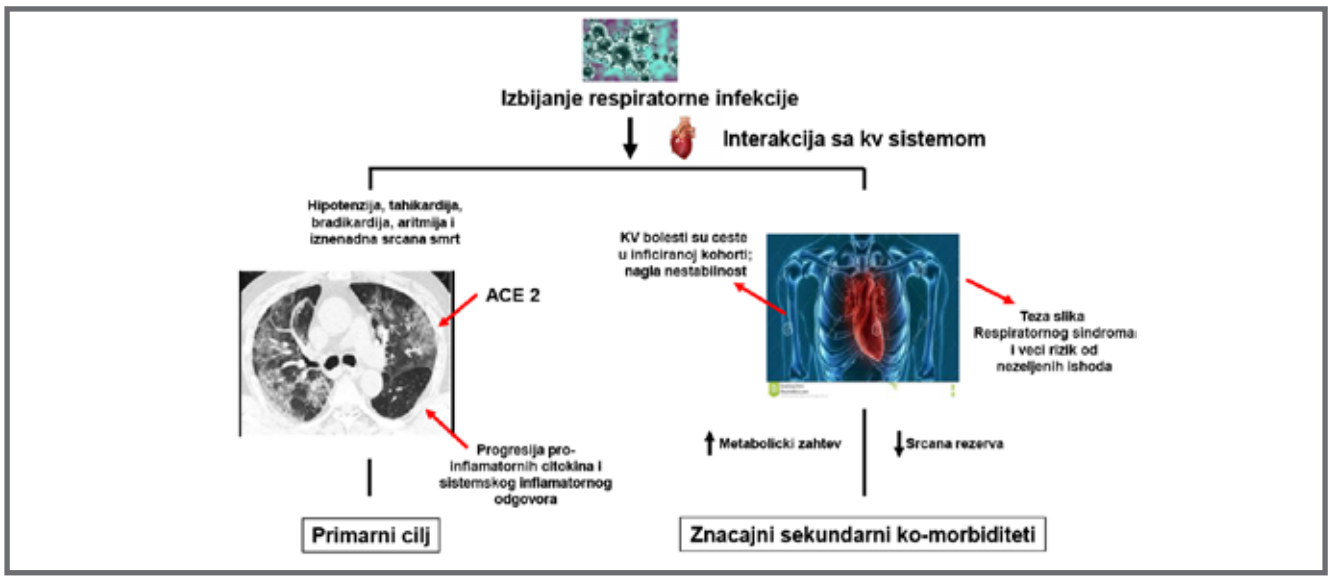
Što je niža patogenost virusa, to je i veća njegova transmisija, naročito u kombinaciji sa događajima super - širenja. Paradoksalno, globalizacija podstiče poboljšanja u komercijalnoj i društvenoj praksi, ali takođe pruža idealno okruženje i mogućnost da zoonotski patogeni inficiraju ljudska bića.

Kakav je odnos COVID-19 s kardiovaskularnim bolestima? Ranije saopštenje o 99 pacijenata hospitaliziranih od 1. do 20. Januara 2020. u bolnici Jinyntan, Wuhan, Kina, zbog pneumonije COVID-19, pokazalo je da je 40% bolesnika imalo prethodnu kardiovaskularnu bolest.[5]

Drugi izveštaj iz istog perioda o 138 pacijenata hospitalizovanih u Univerzitetskoj bolnici Zhongnan u Wuhanu pokazuje da je 26% pacijenata zahtevalo kardiološku intenzivnu negu. Od toga je 16.7% razvilo aritmije a 7.2% je imalo akutni koronarni sindrom.[6] Neki bolesnici sa pneumonijom usled infekcije COVID-19 u Wuhanu takođe su imali povećanje visoko - senzitivnog srčanog troponina I, što je ukazivalo na leziju miokarda.[7] U ostalim testiranim slučajevima koji su bili pozitivni na COVID-19, srčani simptomi (palpitacije i bol u grudima) bili su prve manifestacije.[4] Drugi objavljeni i pojedinačni izveštaji ukazuju na prisustvo miokarditisa, srčanog zastoja i akutne srčane insuficijencije. Nije jasno da li su ova srčana stanja provocirana COVID-19 ili su nespecifične komplikacije, tipične za bilo koju drugu patologiju sa većim kardio-metaboličkim zahtevom.

Odnos COVID-19 sa inhibitorima renin-angiotenzin sistema i anti-inflamatornim činiocima (posrednicima). Infekcija COVID-19. podstaknuta je vezivanjem šiljka proteina virusa na ACE2, što omogućava prodiranje virusa u epitelne ćelije pluća i u manjoj meri srca. ACE2 je homolog ACE1, koji pretvara angiotenzin I u angiotenzin II, **Slika 1**. Povećanje endotelnog i cirkulirajućeg ACE1 ima štetne posledice na kardiovaskularni sistem, kao što su povišen krvni pritisak, progresija koronarne ateroskleroze i srčane insuficijencije.

Redukcija ACE1 primenom ACE1 inhibitorima je jedan od terapijskih ciljeva kod hipertenzije, bolesti koronarnih arterija i srčane insuficijencije. Uloga ACE2 u kardiovaskularnom sistemu nije tako jasna. Smatra se da on ima ulogu antagonista štetnim efektima ACE1 i na taj način ima povoljno dejstvo. U ovom trenutku ne postoji



posebna terapija koja uključuju ACE2. S obzirom na važnost ACE2 za prodiranje COVID-19 u ćeliju, pretpostavljena je negativna veza sa lekovima koji mogu posredno povećati aktivnost ACE2. Ovi lekovi su inhibitori receptora angiotenzina II, koji se obično koriste za lečenje hipertenzije. U korist ove hipoteze postoji činjenica da hipertenzija povećava težinu infekcije COVID-19[8].

Slika 1. **Direktne i indirektne kardiovaskularne posledice resiratorne virusne infekcije**

Ipak, nasuprot ovoj hipotezi, postoje nalazi da je ekspresija ACE2 smanjena u hipertenzivnim modelima i da hipertenzija ne utiče na druge infekcije koronavirusom. Stoga, trenutno svi predlozi koji se odnose na blokatore receptora za angiotenzin i / ili inhibitore ACE u epidemiji COVID-19 nisu podržani podacima zasnovanim na dokazima.[8] Nekoliko anti-inflamatornih lekova predloženo je za lečenje infekcije COVID-19 i nedavno je Nacionalna zdravstvena komisija Narodne Republike Kine dodala peto izdanje smernica koje se odnose na lečenje COVID-19 Tocilizumabom, lekom koji inhibira interleukin 6, a koristi se kod reumatoidnog artritisa.[9]

Koje lekcije pruža COVID-19 kardiolozima? Srčani bolesnici ne bi trebalo da izbegavaju, u slučaju recidiva ili bilo kakvog stvarnog pogoršanja zdravstvenog stanja, upućivanje u kardiološki centar zbog straha da će se otkriti infekcija. U većini, ako ne i u svim bolnicama postavljen je siguran, zaseban put. Treba razviti posebne protokole za upravljanje akutnim infarktom miokarda u kontekstu izbijanja COVID-19, što je u Srbiji i urađeno. Uzimanje pažljive epidemiološke anamneze, obvezno merenje temperature i ispitivanje plućnih promena pre početka primarne angioplastike je praktični deo standardnog protokola. To će uz adekvatnu primenu lične zaštitne opreme osigurati dovoljnu post-proceduralnu sterilizaciju i adekvatno praćenje bolesnika kojima je potrebna izolacija. Slične podatke treba dobiti i telefonom pre prihvatanja pacijenata na eventualne elektivne procedure. Trenutna epidemija koronavirusa mogla bi takođe ponuditi stimulus za sprovođenje programa telemedicine za negu srčanih bolesnika.

Koliko je relevantna vakcina za pacijente i kardiologe u eri COVID-19?

Odsustvo izuzetno potrebne vakcine za COVID-19 daje na značaju i važnosti vakcinacije protiv gripa i / ili pneumokoka, uprkos tome što su vakcine lako dostupne. Pacijenti s kardiovaskularnim bolestima obavezno bi trebali biti u toku sa sa pomenutom vakcinacijom, s obzirom na povećan rizik od sekundarnih bakterijskih infekcija u slučaju COVID-19 infekcije. Prednosti vakcinacije kod bolesnika sa srčanom insuficijencijom i akutnim ishemijskim sindromima dobro su dokumentovane.[10-12] Vakcinacija pacijenata se preporučuje u smernicama za koronarne sindrome i srčanu insuficijenciju. U različitim zemljama stepen vakcinacije protiv gripa kreće se od 30 do 40%, što očito nije dovoljno. Vakcinacija je dužnost kardiologa zbog zaštite pacijenata, jer respiratorne komplikacije kod kardiopatskog pacijenta same po sebi imaju ozbiljne posledice, a posebno u trenutnom kontekstu.

Koliko su bitne čiste ruke? WHO smatra da je jedna od najkorisnijih mera za zadržavanje COVID-19 često i pravilno pranje ruku.[12,13] Jednako je ključna dekontaminacija površina, uključujući stetoskope, sonde i bilo koji uređaj. Naravno, to su opšta pravila koja bi se trebala uvek primenjivati, ali doba COVID-19 snažno nas podseća na to. U ažuriranom biltenu od 6. marta 2020. Američki Koledž kardiologa preporučuje stimulisanje dodatnih, razumnih mera opreza kod svih kardiovaskularnih bolesnika zbog povećanog rizika od infekcije COVID-19.

Ovo su jasna razmatranja, ali postoje i druge, suptilnije posledice sadašnje situacije. Prelazak sa straha na anksioznost u eri COVID-19 jedinstvena je borba sa kojom se suočava više zemalja istovremeno. Ljudska bića nikada nisu doživela takvu globalnu borbu jer nema opipljivog neprijatelja. Neprijatelj je nevidljiv. U osnovi, **ljudi se moraju izolovati**, mada u različitom stepenu, zavisno od toga da li su simptomatski ili ne.

Zaključci

Tabela 1 naglašava efekte pandemije COVID-19 na kardiološku zajednicu. Uopšteno, zdravstvena politika ima za cilj očuvanje bolnica i bolničkih kapaciteta smanjenjem

Tabela 1. Posledice pandemije COVID-19 na kardiološku zajednicu

Organizacioni aspekti	Emocionalni/ psihološki aspekti	Klinički / naučni aspekti
Promena profesionalnih prioriteta	Osećaj nepripremljenosti i neadekvatnosti	Svest od kardioloških komplikacija za vreme i posle infekcije
Reorganizacija kardioloških odeljenja na područja posvećena kritično bolesnim pacijentima	Strah i anksioznost Osećaj"suspendovanog vremena "	Doprinos naučnim istraživanjima novih antivirusnih / protiv-upalnih lekova
Preusmeravanje svakodnevnih aktivnosti na pacijente s COVID-19	Promena personalnih / porodičnih prioriteta	

vrha epidemije, što znači izolovanje ljudi. Ekonomska politika ima za cilj smanjenje zatvaranja fabrika i nedostatka osoblja. Vlade će nastojati uspostaviti ravnotežu. Kardiolozi će morati „oprati ruke i zasukati rukave" kako bi pokušali rešiti ovo teško vreme.

Ključne poruke

COVID-19 Kliničke preporuke za kardiovaskularni tim
Trenutno kliničko stanje COVID-19

- Ukupna stopa smrtnih slučajeva od COVID-19 na osnovu objavljenih izveštaja ostaje niska i iznosi 2,3% u Kini. Dalje od Kine, sadašnji izveštaji pokazuju da se mortalitet kreće od 4-6%.
- Više od 80% zaraženih pacijenata ima blage simptome i oporavlja se bez intenzivnih medicinskih intervencija. Međutim, prema velikim Kineskim izveštajima morbiditet i smrtnost značajno rastu sa godinama života, povećavajući se na 8,0% među pacijentima izmedju 70 i 79 godina, i 14,8% kod bolesnika starijih od 80 godina.
- Stope smrtnosti bolesnika sa **komorbiditetima** značajno su veće od prosečne populacije:
  - Malignitet: 5,6%
  - Hipertenzija: 6,0%
  - Hronična respiratorna bolest: 6,3%
  - Dijabetes: 7,3%
  - Kardiovaskularne bolesti: 10,5%

Akutne kardiološke komplikacije COVID-19

- U nedavnim prikazima slučajeva od 138 hospitalizovanih bolesnika s COVID-19, 16,7% bolesnika razvilo je aritmiju, a 7,2% je imalo akutno srčano oštećenje, pored ostalih komplikacija povezanih sa COVID-19.
- Objavljeni i anegdotalni izveštaji ukazuju na slučajeve akutne srčane insuficijencije, infarkta miokarda, miokarditisa i srčanog zastoja; kao i kod bilo koje akutne bolesti, veći kardiometabolički zahtev može da podstakne srčane komplikacije.
- Srčane komplikacije COVID-19 približno su proporcionalne sa SARS-om, MERS-om i analognim gripom.
- Potrebno je oformiti timove za kritične pacijente i kardiološke timove koji treba da vode brigu o najkompleksnijim pacijentima

COVID-19 implikacije za bolesnike s kardiovaskularnim stanjima

- Pacijenti sa postojećom KV bolešću imaju veći rizik od zaraze COVID-19 i imaju lošiju prognozu.
- Razumno je savetovati sve KV pacijente sa povećanim rizikom da sprovode dodatne, razumne mere opreza u skladu s smernicama udruženja.
- Razumno je tretirati bolesnike sa COVID-19 u skladu s osnovnim KV, endokrinološkim, respiratornim, bubrežnim, onkološkim ili drugim komorbidnim stanjima za prioritetno lečenje.
- Opšte imunološko zdravlje ostaje važno i za medicinsko osoblje i za pacijente, uključujući dobru ishranu, spavanje i upravljanje stresom.

Preporuke za spremnost tokom COVID-19 specifične za srce

- Institut za javno zdravlje Srbije „Dr Milan Jovanović Batut" je izdao **stručno-metodološko uputstvo za kontrolu unošenja i sprečavanje širenja novog korona virusa SARS-CoV-2 u Republici Srbiji** [14]

- Protokoli za dijagnozu, trijažu, izolaciju i upravljanje bolesnicima sa COVID-19 s KV komplikacijama i / ili KV bolesnicima s COVID-19 su detaljno razrađeni i uvežbani i istovremeno evoluiraju shodno promeni situacije;
- Razvijeni su posebni protokoli za lečenje pacijenata sa AKS u kontekstu epidemije COVID-19, kako za pacijente sa dijagnozom COVID-19, tako i bez nje. Poseban naglasak treba staviti na primarnu PCI i CABG, uključujući protokole za primenu lične zaštitne opreme i procenu adekvatne post-proceduralne sterilizacije. U ekstremnim okolnostima, potrebno je proceniti odnos rizika i koristi intervencije kod pacijenata sa AKS (s obzirom na ograničene podatke koristnosti primarne PCI za tip-2-IM kod akutne virusne bolesti) kao i rizik od nozokomijalne infekcije.

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Review article

Coronavirus and cardiovascular complications

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Abstract Patients with cardiovascular risk factors or established cardiovascular disease represent a vulnerable population when suffering from COVID-19 disease. In this paper, we provide a brief overview of current knowledge on the impact of COVID-19 on the cardiovascular system and more importantly on the outcome of cardiovascular patients as well as a review of the contemporary literature.
Key-words: COVID-19, cardiovascular complications

Using the available literature, which is updating from hour by hour and is published in a special way, as well as guidelines dedicated to this topic, the Cardiology Society of Serbia gave special attention to the cardiac consequences of coronavirus infection.

This is the third time in the last 2 decades that coronavirus has led to pandemic levels of infection in humans. In 2003, it was so-called "SARS-CoV" - a severe acute respiratory syndrome with a mortality rate of 9-11%[1]. In 2012, the Middle East respiratory syndrome coronavirus – "MERS-CoV", had a mortality rate of 34%[1]. The current coronavirus-induced pandemic has been officially named "Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2)", or COVID-19, by the World Health Organization (WHO)[2].

The prevalence of COVID-19 is enormous and is currently registered in 185 countries. The mortality rate varies from 1 to 12%, and most often around 4-6%[1,2]. At the moment, the mortality rate in Serbia is 2.1% and depends on the number of infected people and the extent of testing for the presence of the virus.

The largest percentage of patients do not have any clinical symptoms or have very mild flu-like symptoms (about 80% of all infected). In more serious forms, COVID-19 is manifested by an infection of the lower respiratory tract (so-called "virus-induced interstitial pneumonia"). Today, it is evident that COVID-19 can damage and has significant consequences for the cardiovascular system[2].

COVID-19 and cardiovascular disease

Based on scientific reports from China from January 2020, it is estimated that about 40% of patients with COVID-19 have a previous cardiovascular disease[3].

On the other hand, COVID-19 infection itself can cause direct damage to various cardiac structures including causing various forms of arrhythmias (16.7%), acute coronary syndrome 7.2%, or myocarditis, which is manifested by an increase in the concentration of highly sensitive cardiac troponin I[4]. Chest pain, palpitations, acute heart failure or cardiac arrest have been described as isolated cases[3,4].

Relationship of COVID-19 with renin-angiotensin system inhibitors - angiotensin converting enzyme inhibitors (ACE-I) or angiotensin receptor blockers (ARB).

Based on currently available data and demonstrated evidence of efficacy of these drug groups in cardiovascular patients, ACE-I and ARBs therapy should be continued or initiated in patients with heart failure, hypertension or myocardial infarction in accordance with current guidelines, regardless of COVID-19[5-7].

Key messages

COVID-19 Clinical recommendations
Current clinical condition COVID-19

- The overall death rate from COVID-19 based on published reports remains low and currently stands at 2.1% in Serbia. Worldwide, this percentage varies from 1 to 12%.
- More than 80% of infected patients have no or mild symptoms and recover without intensive medical intervention. However, according to large official reports, morbidity and mortality increase significantly with age, increasing to 8.0% in patients between 70 and 79 years of age, and 14.8% in patients older than 80 years.
- Mortality rates of patients with COVID-19 and comorbidities are significantly higher than the average population:
  - Malignancy: 5.6%
  - Hypertension: 6.0%
  - Chronic respiratory disease: 6.3%
  - Diabetes: 7.3%
  - Cardiovascular diseases: 10.5%

Acute cardiac complications COVID-19

- The incidence of heart complications in patients hospitalized for COVID-19 is: 16.7% for arrhythmias, 7.2% for acute coronary syndrome.
- Isolated cases have been reported indicating a rare possibility of acute heart failure, myocarditis and cardiac arrest; as with any acute illness, a higher cardiometabolic requirement may induce cardiac complications.

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COVID-19 implications for patients with cardiovascular disease

- Patients with pre-existing cardiovascular disease have a higher risk of COVID-19 infection and have a poorer prognosis.
- All cardiovascular patients at increased risk should be advised to take additional precautions in accordance with general and specific guidelines at the time of the pandemic. When it comes to the use of certain groups of drugs that are controversial at the time of the COVID-19 pandemic, the views at the moment are as follows:
  - If patients tolerate ACE inhibitors well, there is no scientific evidence or reason to discontinue their recommended therapy.
  - The use of non-steroidal anti-inflammatory drugs (ibuprofen), as a modulator of the prostaglandin response to inflammation, also has insufficient scientific evidence for discontinuation of this type of drug in patients with COVID-19, although most physicians do so based on non-randomized studies and reports.
  - The use of chloroquine or hydroxy-chloroquine for preventive purposes and without a doctor's supervision is absolutely contraindicated; these drugs are prescribed only in hospital conditions under strict medical supervision due to possible side effects (serious cardiac arrhythmias).
  - Treatment of patients with COVID-19 and cardiovascular, endocrinological, respiratory, renal, oncological or other comorbid conditions, which require priority treatment, should be in accordance with current good clinical practice.
- General immune health remains of paramount importance to medical staff and patients, including good nutrition, sleep, and stress avoidance.

Application of standard precautions during the COVID-19 epidemic in the treatment of cardiac patients

- The Institute of Public Health of Serbia "Dr Milan Jovanović Batut" has issued an expert-methodological instruction for controlling the introduction and prevention of the spread of the new coronary virus SARS-CoV-2 in the Republic of Serbia
- Protocols for the treatment of patients with acute coronary syndrome (acute myocardial infarction or unstable angina pectoris) in the context of the COVID-19 epidemic, both for patients diagnosed with COVID-19 and without it, have been specially developed and applied in everyday clinical practice. In each individual case, the risk-benefit ratio of the intervention in patients with acute coronary syndrome as well as the risk of nosocomial infection should be assessed.

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Sažetak

Koronavirus i kardiovaskularne komplikacije

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Pacijenti sa kardiovaskularnim faktorima rizika ili utvrdjenim kardiovaskularnim bolestima predstavljaju ranjivu populaciju kada boluju od COVID-19 oboljenja. U ovom radu dajemo sažet pregled trenutnih saznanja o uticaju COVID 19 na kardovakularni sistem i jos vaznije na ishod lecenja kod kardiovaskularnih bolensika kao i pregled savremene literature.

Ključne reči: COVID 19, kardiovaskularne komplikacije

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Case report

COVID-19: Our story – the beginning

Hadzi Slavica Karamarkovic[1], Zeljko Delic[2], Goran Grujic[1], Ana Dulic[1], Verica Pajic[1], Tatjana Halupa[1], Jelena Jakovljevic[1]

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Abstract **Background.** Cardiovascular diseases are common in patients with coronavirus disease 2019 (COVID-19) and carry the risk of developing a severe clinical presentation varies from a syndrome similar to acute coronary syndrome and acute fulminant myocarditis to cardiogenic shock.
Case reports. This paper presents a patient with a history of cardiovascular and pulmonary diseases admitted to the hospital with COVID-19 and LV dysfunction. Our main findings are that cardiac involvement can occur with COVID-19 with signs of the respiratory tract and symptoms of infection. We diagnosed COVID-19, which triggered the emergency on our department. We have never experienced anything like this before.
Conclusion. Myocardial injury has a significant association with fatal outcomes of COVID-19, while the prognosis of patients with underlying CVD but without myocardial injury appears relatively favorable.

Kew words COVID-19, myocardial injury

"Open your mind for new diagnostic/ therapeutic approach: we are the students again…" Dr Aleksandar Veljkovic, Head of Interventional Pulmonology - San Luigi University Hospital Gonzaga of Orbassano

Introduction

Cardiovascular diseases are common in patients with coronavirus disease 2019 (COVID-19) and carry the risk of developing a severe clinical presentation varies from a syndrome similar to acute coronary syndrome and acute fulminant myocarditis to cardiogenic shock. The first cases of (COVID-19) were reported in the end of December 2019, originating in Wuhan, China, with rapid spread worldwide[1]. The emergence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which causes COVID-19, has rapidly grown into a pandemic, and a large proportion of affected patients have been reported to have underlying cardiovascular diseases (CVD).[2,3]

Do COVID-19 patients have a significantly increased incidence of myocarditis, arrhythmias or acute heart failure? COVID-19 is associated with a high inflammatory burden that can induce vascular inflammation, myocarditis, and cardiac arrhythmias. SARS CoV-2 appears to affect the myocardium and cause myocarditis. Biopsy–proven myocarditis is more common in the young, may occur in the middle age, but is rare in the elderly Cardiac biomarker studies suggest a high prevalence of myocardial injury in hospitalized patients. Myocardial injury defined as increased troponin (Tn) and natriuretic peptides, and it is likely associated with infection-related myocarditis and/or ischemia and is an important prognostic factor in COVID-19. COVID-19 can cause a viral pneumonia with additional extra-pulmonary complications. A many of patients have underlying CVD and/or cardiac risk factors. Negative predictors for death in COVID-19 include older age (>60-70 years), male sex, and comorbidities such as hypertension, diabetes mellitus, CVD and chronic obstructive pulmonary disease (COPD). Acute cardiac injury (elevated high-sensitivity troponin levels) is observed in severe cases and is strongly associated with mortality. Acute respiratory infections are well-recognized triggers for CVD and the underlying CVD is usually associated with comorbidities, which may increase the incidence and severity of infectious diseases[4].

Case presentation

We present an obese 77 years-old woman with previous history of cardiovascular and pulmonary diseases. She arrived at the emergency room 22nd March with shortness of breath, severe dyspnea without fever and cough. On admission to the emergency department, physical examination revealed blood pressure of 140/80 mmHg, heart rate of 100 beats per minute, oxygen saturation of 91 % while breathing ambient air, and body temperature of 36,4°C. The patient was admitted to the intensive care unit with a diagnosis of pulmonary edema?! Capillary gas analysis showed a pH of 7,38 oxygen partial pressure of 8,93mmHg, carbon dioxide partial pressure of 7,52 mmHg. A 12-lead electrocardiogram (ECG) showed the minimal transient ST-segment elevation in the inferior lead and the minimal ST-segment depression in lateral lead, as well as ECG changes during hospitalization and the occurrence of atrial fibrillation with a rapid ventricular response (Figure 1, 2, and 3).

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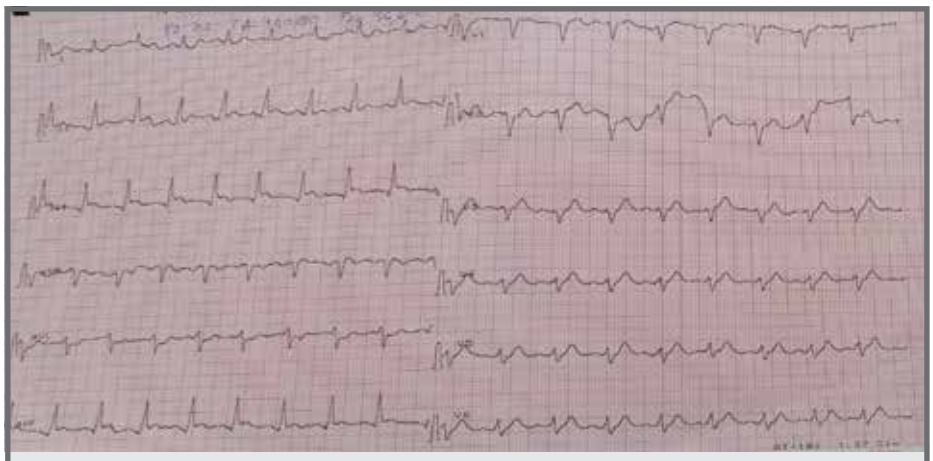

Figure 1. A 12- lead electrocardiogram on admission

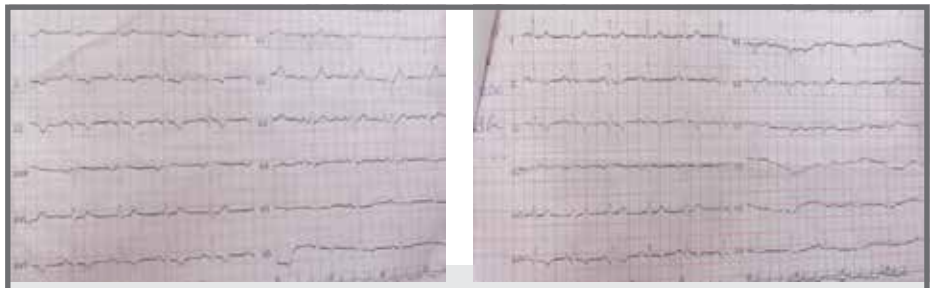

Figure 2. ECG changes during hospitalization

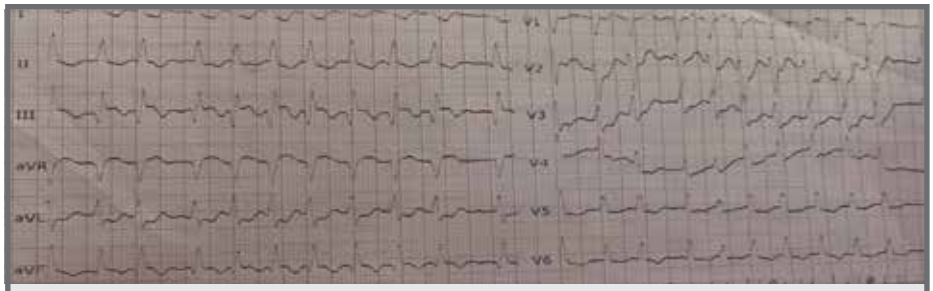

Figure 3. Atrial fibrilation with a rapid ventricular response on 26th March

23.03.dry cough occurs, fever up to 38,5 o C. Blood tests revealed elevated levels of markers of myocyte necrosis TnI 157,0 NG/ML and creatine kinase–MB level of 110 IU/L elevated LDI level of 728 IU/L, increase in C-reactive protein levels of 42,64 mg/L and blood cells WBC 19,8 x 10^9/L Ly 2,45 x 10^9/L, ferritin 167 ng/ml Blood sample tests also revealed hypokalemia, hypochloremia and hyperglycemia. Transthoracic echocardiography revealed normal left ventricular (LV) dimensions with an estimated LV ejection fraction (LVEF) of 50%. There was no evidence of severe heart valve disease. Left ventricular diastolic function was mildly impaired with mitral inflow patterns. Given the echocardiography changes, regional wall motion abnormalities (hypo-kinesis posterior, lateral wall, akinesias to hypo-kinesis inferior wall) and elevated markers of myocardial necrosis, urgent coronary angiography was indicated, but was not performed. Findings on chest radiography:23.03. pronounced hypostasis changes, hilus trimmed. On 24.03. pulmonary changes in the lungs In the lower lung field, blotchy shading that corresponds to pulmonary consolidation.

Based on the clinical history and the COVID-19 outbreak, COVID-19 was deemed as likely. Lung ultrasound – Comet sing and highly suspected interstitial pneumonia. MSCT thorax in the lungs mutually discrete changes in the form of ground glass (Figure 4). We suspected (courtesy Dr G. Grujic) a coronavirus infection and immediately called to request a nasopharyngeal swab. The patient did not meet the national criteria for coronavirus testing, but we decided to do it anyway. Even before we received the test result, our decision was to isolate the patient because the risk of not doing so was too high.

A nasopharyngeal swab was performed with a positive result for SARS-CoV. Further treatment was continued in a tertiary institution.

Here in, we describe a patient with a history of cardiovascular and pulmonary diseases admitted to the hospital with COVID-19 and LV dysfunction. Our main findings are that cardiac involvement can occur with COVID-19 with signs of the respiratory tract and symptoms of infection. We diagnosed COVID-19, which triggered the emergency on our department. We have never experienced anything like this before.

Discussion

COVID-19 is the clinical manifestation of infection with SARS-CoV2 and most frequently presents with respiratory symptoms that can progress to pneumonia and, in severe cases, acute respiratory distress syndrome (ARDS) and shock. We are dealing with a severe emergency. There is increasing awareness of the cardiovascular manifestations of COVID-19 disease and the adverse impact that cardiovascular involvement has on prognosis[5]. Some parameters of poorer disease outcome: high values of D dimer (microthrombosis), lymphopenia, increased values of LDH, ferritin, cardio-tropic enzymes, IL 6.[6]

Putative mechanisms of myocardial injury in COVID-19 patients are ACE2 mediated direct damage, hypoxia-induced myocardial injury, cardiac microvascular damage and systemic inflammatory response syndrome. Myocardial injury has a significant association with fatal outcomes of COVID-19, while the prognosis of patients with underlying CVD but without myocardial injury appears relatively favorable.

Myocardial injury is associated with impairment of cardiac function and ventricular tachy-arrhythmias. Arrhythmia is not common feature of COVID-19. Inflammation may be associated with myocardial injury. Aggressive treatment may be considered for the patients with myocardial injury.[7]

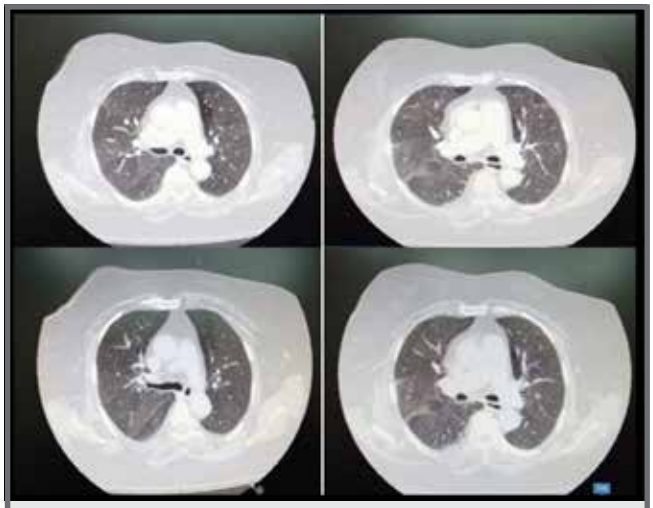

Figure 4. MSCT thorax "Ground glass"

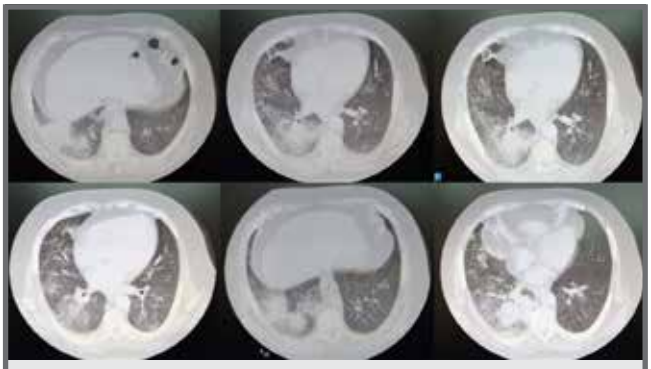

Figure 5. MSCT thorax bilateral pulmonary infiltration

Clinical information about COVID-19 symptoms: Fever 83-88%, Cough 68-82%, Dyspnea 22-31% 2. Severity: Mild-Moderate 60-80% Severe 15-25% Critical 5-15% 3.Mortality risk : older age, comorbidities, respiratory failure 4.Laboratory : Lymphopenia 50%, CRP elevation, IL-6 high. PCT low. (8,9) Diagnosis of COVID 19 is based among other things on RT-PCR (sensitivity ≈ 60-95%).
Up to approximately 50% of patients with COVID-19 infection may have normal CT scans 0–2 days after onset of flu-like symptoms from COVID-19. COVID-19 RT-PCR sensitivity may be as low as 60-70%; therefore, patients with pneumonia due to COVID-19 may have lung abnormalities on chest CT but an initially negative RT-PCR Lung abnormalities during the early course of COVID-19 infection usually are peripheral focal or multifocal ground-glass opacities affecting both lungs in approximately 50%–75% of patients. As the disease progresses, paving and consolidation become the dominant CT findings, peaking around 9–13 days followed by slow clearing at approximately 1 month and beyond (10).

Conclusion

The global pandemic caused by COVID-19 has affected **4 088 848** worldwide, in Serbia **10 438**, mortality **2,16%***
Discriminating between a cardiac or respiratory etiology of symptoms can be challenging since each may present predominantly with dyspnea. It is also critical to recognize when cardiac and pulmonary involvement coexist.
A 2020 report by the China Medical Treatment Expert Group for COVID-19 showed the spectrum of clinical and diagnostic features associated with SARS-CoV-2 infection among. (11) This case provides records of cardiac involvement as a possible early onset of the viral respiratory infection and the simultaneous presence of coronary disease. The predominant presenting symptoms of this patient were cardiac in nature without symptoms suggestive of infection.

* data taken from covid.rs source Institute of Public Health of Serbia updated for the world on 12.05. and for Serbia 15.05.2020)

"Before I came to this lecture, I was confused. After hearing it I am still confused, but on a higher level"
Enrico Fermi

Dilemma: this patient was COVID 19 negative?

The swab is the best we have. Even without test results, if a patient has a fever, cough, shortness of breath, and an X-ray showing lung infiltrates, it should be considered positive.

This case presentation is dedicated to all health professionals who managed Covid 19 patients during pandemia, with some of them get sick and even died during the course of the infection

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Original article

The use of non-vitamin K antagonists in the treatment of pulmonary thromboembolism: nationwide experience from Serbia 2011-2019

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Abstract

Introduction. Pulmonary embolism (PE) is one of the major cause of hospitalization and morbidity. All studies that compared efficacy and safety of novel oral anticoagulants (NOACs) to vitamin K antagonists (VKAs) in the treatment of PE, have showed that all NOACs were equally effective as VKAs, but superior in safety.

Materials and Methods. This retrospective study included 1095 of patients from the Serbian Academic Pulmonary Embolism Registry (SAPERE) with a confirmed diagnosis of PTE treated in Military Medical Academy Belgrade, Institute for Pulmonary Diseases and Institute for Cardiovascular Diseases Vojvodina, Clinical Center Niš, Kragujevac, Banja Luka, General Hospital Pančevo, Clinical Hospital Center Zemun and Zvezdara.

Results. Of the 863 total patients, NOACs were therapeutic choice in 452 (52.4%) of patients.The most preferred NOAC in Military Medical Academy was Rivaroxaban, which was therapeutic choice in 117 (33.8%) of patients in this institution. On the other hand, VKAs were administered in 103 (88.0%) of patients treated in University Clinical Center Kragujevac. The use of different type of OACs was greatly influenced by the year of PE diagnosis. From 2018, VKAs are drastically less used for the treatment of PE, while the use of Rivaroxaban and Apixaban is slowly rising. The use of OACs was also influenced by the initial treatment with/without thrombolysis, value of Creatinin Clearence (CrCl) on admission, history of previous major or non-major bleeding, presence of active malignancy and HAS-BLAD score value.

Conclusion. In Serbia, VKAs are still predominantly used in the treatment of PE, however, decision of the type of OAC (VKAs or NOACs) used in the treatment of this patient population greatly varies between health institutions from Serbia.

Kew words pulmonary embolism, NOACs, bleeding, malignancies

Introduction

Venous thromboembolism (VTE) holds third place in the spectrum of cardiovascular diseases, with an increasing incidence with aging[1,2]. The most common form of VTE, pulmonary embolism (PTE) is a major cause of hospitalization and morbidity, with a presentation ranging from sudden death to an incidental finding[3]. Recurrence of PTE is also one of the major problems with the highest risk in the first 12 months after the initial event and the rate of recurrence ranging from 8.6-10.1% in the first 6 months[4]. Therefore anticoagulation therapy represents one of the corner stones of the treatment of PTE[5].

In the last decade, non-vitamin K antagonists (NOACs), such as Dabigatran, Rivaroxaban and Apixaban have found their place in the treatment of patients with VTE. Between 2009 and 2013, 6 different studies examined NOACs (Dabigatran, Rivaroxaban, Apixaban and Edoxaban) in a total of 27,023 patients[6]. All studies which compared efficacy and safety of NOACs to VKAs in the treatment of PTE (RE-COVER and RE-COVER II investigated Dabigatran, EINSTEIN-DVT and EINSTEIN-PE, investigated Rivaroxaban and AMPLIFY apixaban) have shown that all of the abovementioned NOACs were equally effective as VKAs, but superior in safety with a lower occurrence of the clinically significant and major bleedings[7-12]. Furthermore, a lot of other beneficial features of NOACs have been demonstrated, indicating a clear advantage of their use over VKAs, such as the rapid onset of action, no need for routine monitoring of coagulation parameters, administration in fixed doses, etc.[13]

With the introduction of NOACs, their use in the treatment of PTE is rapidly increasing, however important

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data from low income countries are still missing. Therefore the aim of this study was to assess the use of NOACs and VKAs in patients with PTE who were treated at various institutions from Serbia from 2011 until 2019.

Methods

Study design

This retrospective study included patients from the Serbian Academic Pulmonary Embolism Registry (SAPERE) with a confirmed diagnosis of PTE treated in Military Medical Academy Belgrade, Institute for Pulmonary Diseases Sremska Kamenica, Clinical Center Niš, Clinical Center Kragujevac, Clinical Center Banja Luka, General Hospital Pančevo, Clinical Hospital Center Zemun and Cardiology Clinic Zvezdara. SAPERE registry was formed in 2011, and for the next several years has been managed by the Military Medical Academy Belgrade. In 2015, Institute for Pulmonary Diseases Sremska Kamenica has started contributing, in 2018 Clinical Center Zemun, Clinical Center Niš, Clinical Center Banja Luka, Clinical Center Kragujevac and finally General Hospital Pančevo in 2019. In the previous period, Clinical Center Zvezdara also contributed to the development of the registry, but currently they are not participating in data collection.

Patient population

This study included 1095 consecutive patients with pulmonary thromboembolism, confirmed using multidetector CT pulmonary angiography (MDCT-PA) enrolled during the period from January 2011 – November 2019. However, the data regarding anticoagulation therapy is missing for 232 patients and therefore these patients were not included in the analysis and the total number of patients was 863. The study was approved by each facility's Institutional Review Board and the permission for conducting the study was obtained. All patients gave written consent and the study was conducted according to the Helsinki Declaration.

Treatment

Risk stratification to low, intermediate and high risk PTE was done according to the latest available ESC guidelines[5]. All patients received standard anticoagulant therapy: intravenous unfractionated heparin (UFH) or a subcutaneous weight-adjusted dose of low-molecular-weight heparin (LMWH), followed by an oral anticoagulant (such as Warfarin or Acenocoumarin) or novel, direct oral anticoagulants: Dabigatran, Rivaroxaban or Apixaban. Edoxaban is not a registered drug in Serbia and therefore it was not used. Patients with high and intermediate-high risk PTE were treated with thrombolytic therapy. The initial use of thrombolytic therapy in intermediate-high risk PTE group was not in accordance with ESC guidelines but was used as a standard practice in included hospitals[14]. The protocol for lytic therapy which was used was in accordance with the ESC guidelines, or protocol for the recombinant tissue plasminogen activator (rTPA) as previously described[14,15]. So called slow-protocol for lytic therapy was used predominantly in intermediate-high risk group of patients. Bleeding events were assessed by using the International Society of Thrombosis and Haemostasis criteria[16,17].

Variables

The following parameters were recorded when the PTE was diagnosed: sex, age, body weight, presence of active cancer (defined as newly diagnosed malignancy or malignancy already treated by surgery, chemotherapy, radiation therapy, hormones, separately or in combination), previous major or non-major bleeding, major bleeding in the first 90 days and creatinine clearance (CrCl) by using Cockcroft-Gault formula[18]. HAS-BLED scor was used for the stratification of bleeding risk[19].
The primary end-points were overall hospital death and PE related death rates. Secondary end-points were the rate of major and fatal bleeding events.

Statistical analysis

Mean ± standard deviations (SD) were used for expression of the continuous variables. We presented categorical variables as numbers and frequency percentages. Continuous variables was compared by using the unpaired t-test or the Mann-Whitney U test. Comparison of categorical variables was done by the $\chi 2$-test or one-way ANOVA test. P value less than 0.05 was considered as statistically significant.

Results

From the total number of 863 patients included in our analysis, 40.1% (346) of patients were enrolled at Military Medical Academy in Belgrade, 13.6%[117] were from University Clinical Center Kragujevac, 11.5%[) were from Institute of Pulmonary Diseases Vojvodina and Clinical Center Novi Sad, 10.3% (89) were from University Clinical Center Niš, 7.2% (62) were from University Clinical Center Banja Luka, 7% (61) patients from Cardiology Clinic Zvezdara in Belgrade, 5.7% (49) patients were enrolled from Clinical Hospital Center Zemun and 4.6% (40) patients from General Hospital Pančevo (Figure 1.). Figure 1. also shows the use of anticoagulants (VKAs and different NOACs) in various health care institutions in Serbia. A large number of patients were treated in Military Medical Academy, where NOACs, as a treatment of choice for PTE, were used more than VKAs. Out of the total number of 863 patients, NOACs were the therapeutic choice in 452 (52.4%) of patients.The most preferred NOAC in Military Medical Academy was Rivaroxaban, which was a therapeutic choice in 117 (33.8%) of patients in this institution. On the other hand, VKAs were administered in 103 (88.0%) of patients treated in the University Clinical Center Kragujevac.

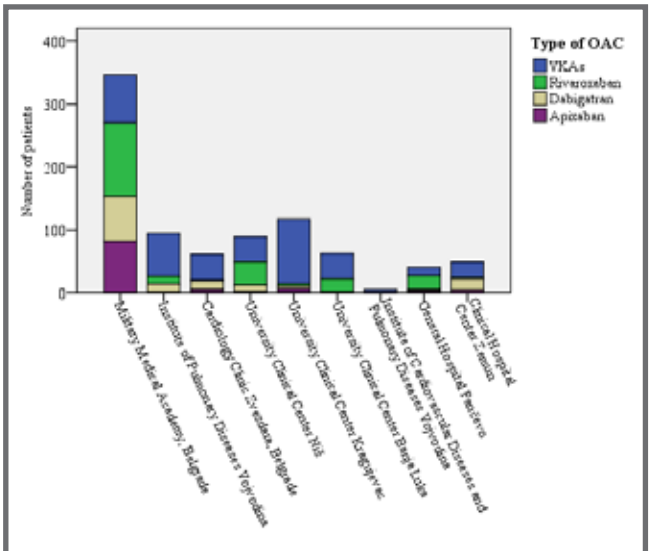

Figure 1. The use of NOACs vs. VKAs in different health institutions in our country

The baseline characteristics of patients are shown in Table 1. Out of the total number of 863 patients, 448 (51,9%) were female. When it comes to relation to gender, there was no significant difference between the use of NOACs and VKAs (p=0.154). The mean age of patients was 62.54 ± 15.44 years, while patients receiving VKAs were significantly older than patients treated with Rivaroxaban (p=0.004). In all groups due to choice of anticoagulation, mean BMI was above the normal range.
Out of the total number of 863 patients (Our study showed that), NOACs were therapeutic choice in 452 (52.4%) of patients, while VKAs were used in 411 patients. Out of NOACs, Rivaroxaban was most frequently used NOAC with 19.7%, followed by Dabigatran with 133 patients and Apixaban was used in 103 patients (9.4%).

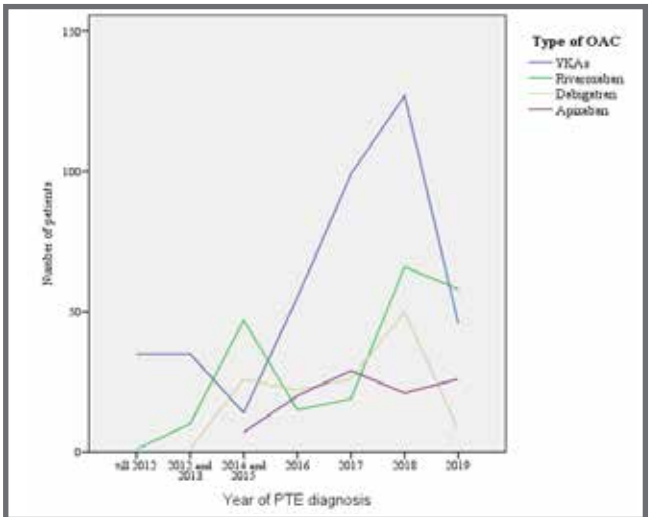

Figure 2. The use of different OACs in relation to the year of PTE diagnosis

The use of a different type of OACs was greatly influenced by the year of PTE diagnosis, with higher use of VKAs until 2013 and a peak in the use of VKAs in 2018, while Rivaroxaban was used more than VKAs in 2014 and 2015 (p<0.000, χ2 test) . From 2018, VKAs have been drastically less used for the treatment of PTE, while the use Rivaroxaban and Apixaban is slowly rising (Figure 2.).

Table 1. Characteristics of the patients at the baseline

			VKAs	Rivaroxaban	Dabigatran	Apixaban	p-value (among 4 groups)
Age (mean±SD)			64.2±15.0#	59.85±15.6	60.63±15.4	63.89±16.2	p=0.002[b]
Sex (male no. %)			190 (45.8)	102 (24.6)	76 (18.3)	47 (11.3)	p=0.154[a]
BMI (mean±SD)			27±4#	28.5±5.4	27.7±5	28±6	p=0.021[b]
Malignancy (yes: numb.%)			40 (48.8)	18 (22)	9 (11.0)	15 (18.3)	p=0.207[a]
Thrombolysis (yes; numb.%)			73 (30.4)	87 (36.3)	40 (16.7)	40 (16.7)	p<0.001[a]
CrCl < 60mL/min/1.73m^2 (yes:numb.%)			137 (56.9)	36 (15.7)	30 (13.0)	27 (11.7)	p<0.001[a]
CrCl < 30mL/min/1.73m^2 (yes; numb.%)			23 (63.9)	5 (13.9)	5 (13.9)	3 (8.3)	p=0.173[a]
Risk of early mortality	High (no.%)		46 (54.8)	23 (27.4)	7 (8.3)	8 (9.5)	p=0.185[a]
	Intermediate-high (no.%)		105 (43.2)	61 (25.1)	43 (17.7)	34 (14.0)	
	Intermediate-low (no.%)		84 (44.0)	54 (28.3)	35 (18.3)	18 (9.4)	
	Low (no.%)		176 (51.0)	78 (22.6)	48 (13.9)	43 (12.5)	
HASBLED score (no.%)		0	100 (11.6)	69 (8.0)	36 (4.2)	25 (2.9)	p=0.018[a]
		1	150 (17.4)	90 (10.4)	51 (5.9)	30 (3.5)	
		2	96 (11.1)	44 (5.1)	37 (4.3)	31 (3.6)	
		3	53 (6.1)	12 (1.4)	7 (0.8)	15 (1.7)	
		4	9 (1.0)	1 (0.1)	2 (0.2)	1 (0.1)	
		5	3 (0.4)	0 (0)	0 (0)	1 (0.1)	
Previous bleeding (yes; numb. %)			15 (28.3)	13 (24.5)	11 (20.8)	14 (26.4)	p=0.001[a]
ASA or other drugs associated with bleeding (yes/numb.%)			94 (43.1)	45 (20.6)	38 (17.4)	41 (18.8)	p=0.001[a]

Statistical test used: [a]-χ2 test; [b]-One-way ANOVA (post hoc Bonferonni); For statistical significance was considered p<0.05; #Statistical significance in relation to Rivaroxaban; ¶ Statistical significance in relation to Dabigatran; ‡ Statistical significance in relation to Apixaban;

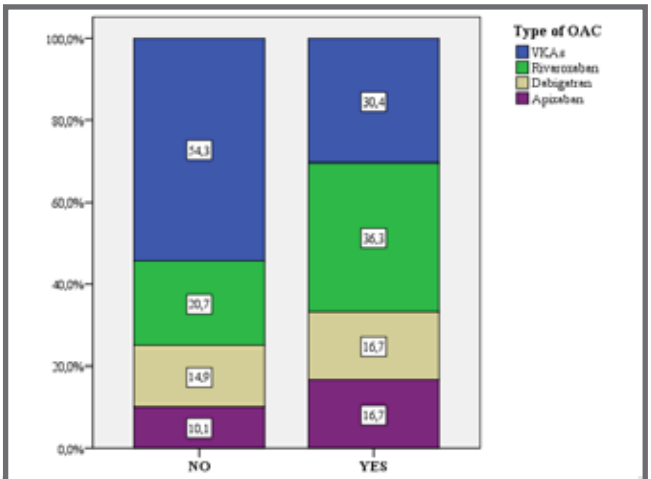

Figure 3. Use of NOACs vs. VKAs in patients initially treated with/without throbolysis

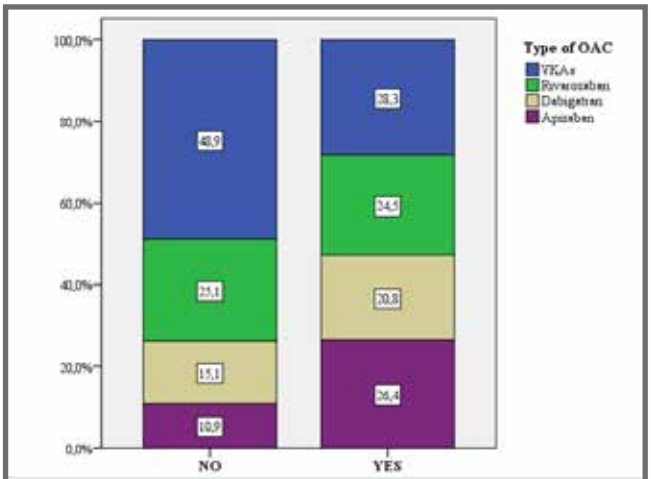

Figure 5. Use of NOACs vs. VKAs in regard to previous major or non-major bleeding

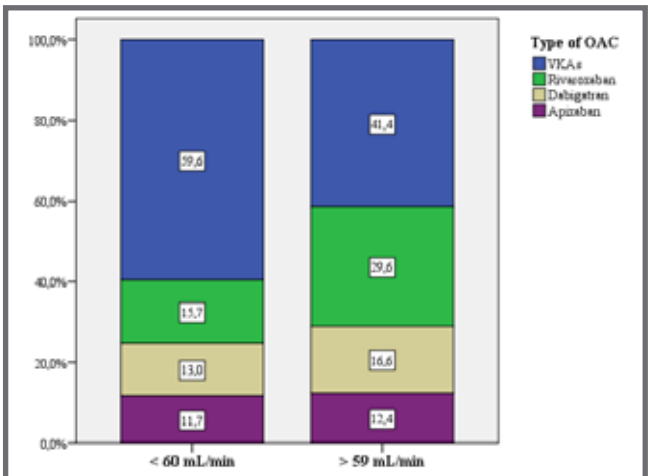

Figure 4. Use of NOACs vs. VKAs in patients with CrCl more or less than 60mL/min/1.73m^2

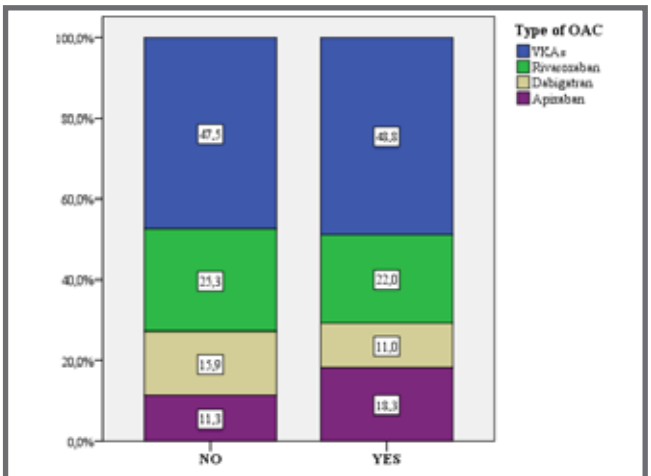

Figure 6. Use of NOACs vs. VKAs in regard to presence of active malignancy

When we classified patients according to the risk of early mortality due to PTE, the frequency of administration of NOAC and VKAs was statistically independent of the early mortality risk categories (p=0.185). In high-risk patients, VKAs was administered in 46 patients, Rivaroxaban in 23 patients, Dabigatran in 7, and Apixaban in 8 patients (Table 1.)

According to the data from our registry, thrombolytic therapy was administered to 240 (27.8%) patients. Statistical analysis revealed that the initial treatment with thrombolytic therapy and the choice of oral anticoagulant treatment were dependent characteristics with more NOACs used in patients that received thrombolytic therapy (p<0.001) (Figure 3).

Out of the total number of 863 patients included in this analysis, CrCl was evaluated on admission in 827 patients. In patients with CrCl <60mL/min/1.73m^2 VKAs were used significantly more than NOACs. Rivaroxaban was the second option for the treatment of those patients with 15.7%, Dabigatran with 13% and Apixaban with 11.7%. In a group of patients with CrCl <30mL/min/1.73m^2 (n=36) VKAs were also the treatment of choice, but without significant difference among gropus. Patients with PTE and CrCl >59 mL/min/1.73m^2 were also more often treated with VKAs, but with much lesser proportion (41.4%), while 29.6% of patients received Rivaroxaban (Figure 4. and Table 1.).

Out of the total number of 863 patients, 218 was using acetil-salicil acid (ASA) or some other drug associated with bleeding risk. In those patients the use of any NOAC drug was significantly higher than VKAs (p=0.001). However, VKAs were still predominant when compared to specific NOAC drug (Rivaroxaban, Apixaban and Dabigatran).

History of previous bleeding was obtained in 859 patients, out of which 53 (6.2%) patients had previous bleeding. In patients with previous major or non-major bleeding, there was an equal distribution of the use of different OACs (Figure 5.).

In 82 patients (9.5%) there was active malignancy present. Among these patients, VKAs were predominantly used in 40 patients, Rivaroxaban in 18 patients, Dabigatran in 9 and Apixaban in 15 patients. In these patients there was no significant difference in the frequency of use of NOACs or VKAs (p=0.207) (Figure 6.).

When we calculated HAS-BLED score for patients in our registry, VKAs were significantly more used among all clusters of patients followed by Rivaroxaban and Dabigatran, while Apixaban was least used in all clusters of patients (Figure 7.).

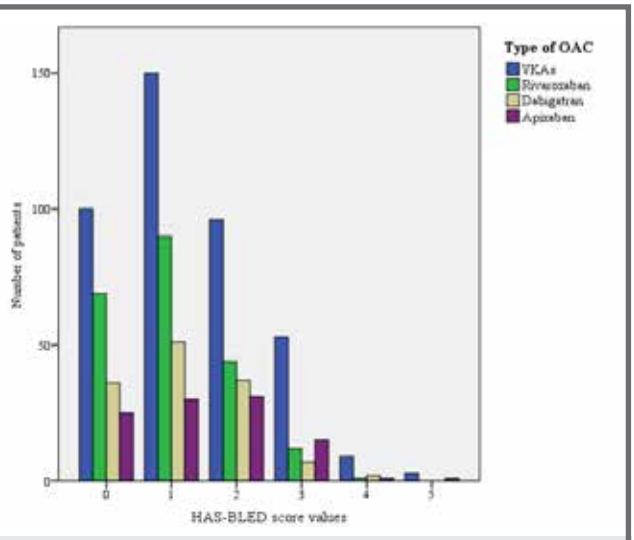

Figure 7. The use of NOACs vs. VKAs in correlation with value of HAS-BLED score

Discussion

The observational studies have a great ability for the assessment of implementing a new therapeutic approaches in an appropriate patient population, such as our, SAPERE registry. In this analysis, we have shown that VKAs are still predominantly used in the treatment of PTE, in low income country, such as Serbia. However, the decision of the type of OAC used (VKAs or NOACs) in the treatment of this patient population greatly varies between institutions, with Rivaroxaban predominantly used in Military Medical Academy and VKAs in Clinical Center Kragujevac. Also, the use of OACs in the treatment of PTE was largely influenced by the year of PTE diagnosis, with the greatest proportion of patients treated with VKAs in the year when SAPERE registry started, but when Rivaroxaban and Dabigatran were registered for PTE treatment in Serbia in 2012, NOACs soon became the treatment of choice and the use of VKAs drastically fell. When other institutions from Serbia started enrolling patients, we realized that their choice for OAC was predominantly VKAs as we can see, with the peak of their use in 2018, alongside Rivaroxaban and Dabigatran.

The real incidence of PTE is hard to estimate, although it has been shown a rising patterne from 24 to 65 cases per 100 000 persons in 25 years (from 1985 to 2009)[3,20-21]. There is an equal distribution of the incidence of PTE between male and female sex, however with a trend towards higher incidence in females, such as in our registry[22]. This higher incidence in females correlates with higher mortality of females after PTE, as shown in the large World Health Organization Mortality Database for Europe[23]. One of the possible explanations lies in the higher risk of thromboembolic events in females, even after full adjustment, as described in the Swedish nationwide study[24]. However, the data regarding influence of female sex on the risk of thromboembolic is not consistent, the data from Danish registries showed that females did not confer a higher risk for thromboembolic risk[25]. However, in a meta-analysis, it has been shown that there were small differences in NOACs efficacy and safety between male and female patients[26].

The choice of initial treatment of patients with PTE is greatly influenced by the risk of early PTE-related mortality, since it correlates with the choice of initial treatment regimen[27]. Based on the presence of early PTE-related mortality risk indicators (hemodynamic instability, PESI/sPESI score, values of cardiospecific enzymes, signs of right ventricular dysfunction), patients with PTE are classified into 1 of 4 categories: high, intermediate-high, intermediate-low and low risk of early mortality[27]. Thus the data from available RCTs and observational studies showed that NOACs are effective and safe as VKAs in treating patients with PTE and at some point even superior, however the data from our registry showed that in our health care institutions the use of VKAs is still dominant among patients with PTE, independently of the early PTE-related mortality risk stratification[28].

The presence of renal dysfunction and chronic kidney disease (CKD) significantly increase the risk of recurrence of VTE and the rate of glomerular filtration has a predictive role in intrahospital all-cause and PTE-related mortality rates, as shown in the previous report from this registry[29,30]. Although the use of NOACs is associated with a less major bleeding events in patients with atrial fibrillation (AF) and CKD, the data from our registry shows that VKAs are still predominantly used in the population of patients with eGFR lower than 60 mL/min/m^2.[31]

The use of thrombolysis and NOACs in the treatment of PTE has been proven safe and effective in moderate and severe PTE[32]. Previously published results also suggest that NOACs can result in shorter hospitalization and favorable first 3-month outcomes[33]. Results from our registry show that after thrombolysis the preferable choice of OAC was NOACs with 69.7% vs VKAs with 30.4%, while the most frequently used NOAC was Rivaroxaban, while Dabigatran and Apixaban were equally distributed in the population of patients with PTE treated with thrombolysis. On the other hand, the data from our registry shows that in patients that were not treated with thrombolysis after PTE, VKAs still hold the majority of OAC choice.

The data on previous bleeding events before PTE also influenced the choice of OAC, with a higher proportion of patients treated with NOACs in whom there was previous bleeding with higher use of Apixaban in this patient population. This coincides with a different meta-analysis that shown that NOACs are safer than VKAs in patients with AF and VTE[34]. Also, higher use of Apixaban in this patient population correlates with lower major and non-major bleeding rates associated with Apixaban use in patients with VTE[35]. In one meta-analysis, Dabigatran and Edoxaban in lower doses, did not show efficacy as other NOACs[36]. Also, concomitant use of other agents associated with bleeding resulted in higher use of NOACs in our registry, however VKAs are still predominantly used in patients receiving drugs that is associated with bleeding. Despite that fact, it is interesting that the use of Apixaban was doubled when we com-

pared presence of other agents that could lead to bleeding vs. without those agents, while the use of Rivaroxaban fell from 26.5% in patients that were not using bleeding agents to 20.6% in patients treated with concomitant bleeding agents. One meta-analysis has suggested that NOACs may be better choice compared to VKAs, when there is an inevitable need for concomitant use of anticoagulant and antithrombotic drug. (37). Even though we are witnessing a higher focus of research on cancer and thromboembolic risk, there is a huge gap in this area. The data from our registry shows that after PTE in cancer patients, VKAs still hold the majority of anticoagulant treatment, followed by Rivaroxaban and Apixaban. The meta-analysis that included key phase III clinical trials showed that by applying NOACs in this population that there recurrent VTE and bleeding events were reduced[38]. Also, it has been shown that NOACs are as effective as low-molecular weight heparin at preventing recurrent VTE, as suggested by Al-Samkari et al.[39]
The data from our registry shows that VKAs are still predominantly used among patients with higher HAS-BLED score, even though previous researches have shown that use of VKAs in these patients is associated with grater risk of major bleeding events[40]. Nevertheless, VKAs are also the treatment of choice in patients with HAS-BLED score less than 3, as we have shown in our registry. These results may be a result of lower income from Serbia, because as we have previously discussed NOACs have far better safety than VKAs, especially in patients that are in at high risk of bleeding.

Conclusions

VKAs are still predominantly used in the treatment of PTE, in low income country, such as Serbia. However, the decision of the type of OAC used (VKAs or NOACs) in the treatment of this patient population greatly varies between institutions from Serbia. The data from our registry shows that NOACs are only predominantly used in the subpopulation of patients that were treated with thrombolysis, patients with the previous history of bleeding, eGFR higher than 59 mL/min/1.73m^2 and in patients that were receiving other drugs that are associated with bleeding. However, in patients that were in higher bleeding risk, assessed by HAS-BLED score, VKAs are still predominantly used.

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Sažetak

Upotreba novih oralnih antagonista u lečenju plućne tromboembolije: iskustva iz Srbije 2011-2019

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Uvod. *Plućna embolija (PE) jedna je od glavnih uzroka hospitalizacije i morbiditeta. Sve studije koje su poredile efikasnost i bezbednost novih oralnih antikoagulanasa (NOAK) u odnosu na vitamin K antagoniste (VKA) u lečenju PE, pokazale su da su svi NOAK podjednako efikasni, ali i bezbedniji u odnosu na VKA.*

Materijal i metode. *Ovo retrospektivno istraživanje obuhvatilo je 1095 pacijenata iz Srpskog Akademskog PE Registra (SAPERE) sa potvrđenom dijagnozom plućne embolije, lečenih u Vojno-medicinskoj Akademiji (Beograd), Institutu za plućne bolesti Vojvodina, Institutu za kardiovaskularne bolesti Vojvodina, Kliničkom centru Niš, Kliničkom centru Kragujevac, Kliničkom centru Banja Luka, Opštoj bolnici Pančevo, Kliničko-bolničkom centru Zemun i Kliničko bolničkom centru Zvezdara.*

Rezultati. *Od ukupno 863 pacijenata, NOAK su bili terapijski izbor kod 452 (52.4%) pacijenata. Rivaroksaban je najviše primenjivan u Vojno-medicinskoj Akademiji i to kod 117 (33.8%) pacijenata. Sa druge strane, VKA su primenjivani kod 103 (88.0%) pacijenata lečenih u Kliničkom centru Kragujevac. Odabir različitih antikoagulanasa veoma je zavisio od godine u kojoj je postavljena dijagnoza plućne embolije. Od 2018.-te godine, VKA su drastično manje primenjivani za lečenje plućne embolije, dok upotreba Rivaroksabana i Apiksabana polako raste. Odabir antikoagulansa zavisio je i od inicijalne primene trombolize, vrednosti klirensa kreatinina na prijemu, podataka o postojanju prethodnog krvarenja, prisustva aktivnog maligniteta i vrednosti HAS-BLED skora.*

Zaključak. *U Srbiji, VKA se još uvek dominantno koriste za lečenje plućne embolije. međutim odluka o odabiru vrste antikoagulantne terapije (NOAK ili VKA) za lečenje ove populacije pacijenata veoma varira među zdravstvenim institucijama u našoj zemlji.*

Ključne reči: plućna embolija, ne-vitamin K antagonisti, krvarenje, maligniteti

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Case report

Hypertrophic cardiomyopathy: from accidental diagnosis to sudden cardiac death prevention

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Abstract Hypertrophic cardiomyopathy is defined by the presence of increased thickness of the left ventricular wall, which cannot be explained only by abnormal loading conditions. This definition applies to children and adults and makes no „a priori „assumptions about etiology or myocardial pathology. Cellular architecture disorders, interstitial fibrosis, microvascular infarctions, play a role in the emergence of electrical instability, malignant ventricular arrhythmias that cause Sudden Cardiac Death in patients with HCM. Although most cases have a benign prognosis, identifying patients at a risk for Sudden Cardiac Death, requiring prophylactic therapy with ICD ,is crucial and prioritized. With increasing awareness of the disease, lower-risk patients are now more frequently diagnosed, and more recent studies show that the annual Sudden Cardiac Death rate 0.5-1%, was not negligible,unfortunately among young and asymptomatic individuals. This paper presents a case of HCM, accidentally detected in a young adult, completed with ICD implantation in primary Sudden Cardiac Death prevention .

Kew words hypertrophic cardiomyopathy, sudden cardiac death

Introduction

Cardiomyopathies have been defined as structural and functional abnormalities of the ventricular myocardium that cannot be explained by disease due to limited flow in the coronary arteries or pathological loading conditions[1]. Historically, this group of disorders has been divided into primary diseases, in which the heart is the only nvolved organ , and secondary forms where cardiomyopathy is the manifestation of a systemic disorder. The guidelines of the European Society of Cardiology (ESC) define cardiomyopathies by specific morphological and functional criteria, and then group them into family / genetic and non-familial / non-genetic subtypes, regardless of the presence of some other heart diseases.

Hypertrophic cardiomyopathy (HCM) is defined by the presence of increased left ventricular (LV) wall thickness that cannot be explained by abnormal loading conditions alone. This definition applies to children and adults and makes no "a priori" assumptions about the etiology or myocardial pathology.[1]

Cellular architecture disorder, interstitial fibrosis, microvascular infarctions play a role in the onset of electrical instability, ie malignant ventricular arrhythmias that cause sudden cardiac death / SCD / in patients with HCM.[2]

In up to 60% of adolescents and adults with HCM, the disease is an autosomal dominant genetic trait caused by mutations in the heart sarcomer protein genes.[3,4,5,6] Five to 10 percent of adults with HCM are caused by other genetic disorders, including hereditary metabolic and neuromuscular diseases and chromosome abnormalities.

In adults, HCM is defined by a wall thickness of ≥15mm in one or more LV segments - measured by any imaging technique (echocardiography, cardiac magnetic resonance imaging (CMR) or computed tomography (CT)), which cannot be explained exclusively loading conditions. Genetic and non-genetic disorders can be represented by a lesser degree of wall thickening (13-14mm) - in these cases, the diagnosis of HCM requires evaluation of other elements, including family history, non-cardiac symptoms and signs, pathologic electrocardiogram (ECG), laboratory tests, and multiple cardiac modalities of imaging.

Age are one of the most important factors to consider a possible cause of HCM. For example, hereditary metabolic disorders and congenital dysmorphic syndromes are much more common in infants than in older children or adults. Creating a family history of three to four generations helps to confirm the genetic origin of the disease and identify other family members who are at risk of developing the disease. Specificities to be noted in family history include: SCD, unexplained cardiac arrest, heart transplantation, implanted pacemaker and defibrillator and evidence of systemic disease (young age, skeletal muscle weakness, kidney dysfunction, diabetes, deafness, etc.). crucial for the diagnosis and monitoring of HCM. In most patients, hypertrophy primarily involves the interventricular septum in the basal segments of the LV, but often extends to the lateral wall, posterior septum, and apex.[7]

CMR should be considered in patients with HCM in their baseline assessment if local resources and expertise allow. In patients with good echocardiographic imaging, CMR provides similar information on ventricular function and morphologies and[8,9], but is useful in establishing a

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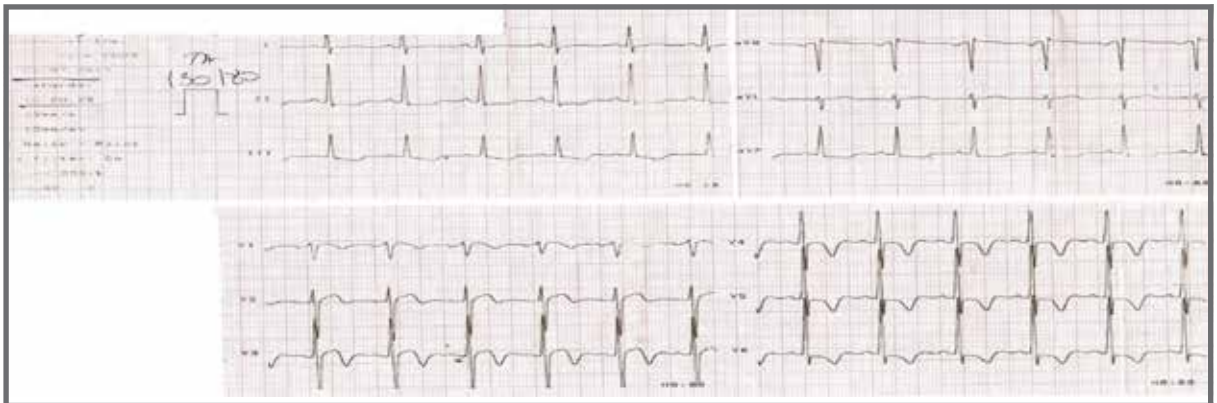


Figure 1. ECG on admission

diagnosis of HCM in patients with poor acoustic window or when some LV regions are poorly visible - such as the anterolateral wall , top of LV and right ventricle.[10,11]
Most people with HCM are asymptomatic and have a normal lifespan, but some develop symptoms, often many years after the onset of ECGs or echocardiographic signs of HCM. SCC, heart failure, and thromboembolism are major causes of death[12] The most commonly reported fatal arrhythmic event is spontaneous ventricular fibrillation (VF), but asystole, AV block, and electromechanical dissociation have also been reported. [13,14,15,16,17] The disease is mostly asymptomatic and is discovered by accident.

Case presentation

Patient aged 31, hospitalized in our institution in July 2019 after seeing ECG changes in the type of negative T waves, predominantly precordial with frequent palpitations, rapid fatigue. Symptoms were presented since November 2018 when his brother, a born aunt, an athlete, died in sleep at the age of 29. Autopsy finding: "HCM and most likely arrhythmic event as cause of death. Heart muscle thickened to about 23 mm".
The patient has no risk factor for ischemic heart disease, denies any chronic diseases and regular medication. ECHOcardiographically revealed concentric hypertrophy of the left ventricular wall, with 17 mm thick IVS, pseudoSAM movement of the anterior mitral leaf, with no significant gradient in the left ventricular outflow tract / LVOT /. and smaller, mild MR with preserved global left ventricula systolic function. EF 65%.

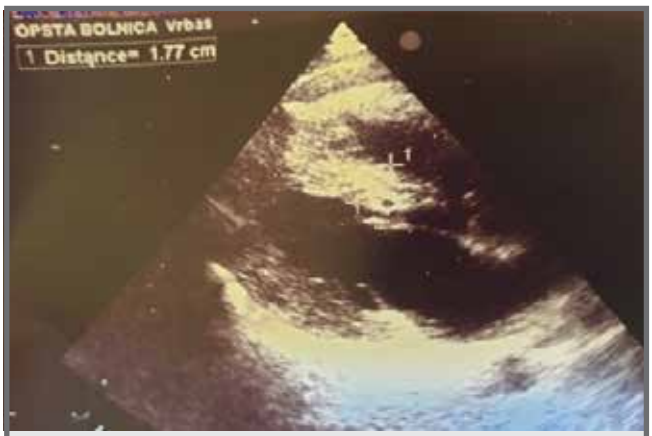
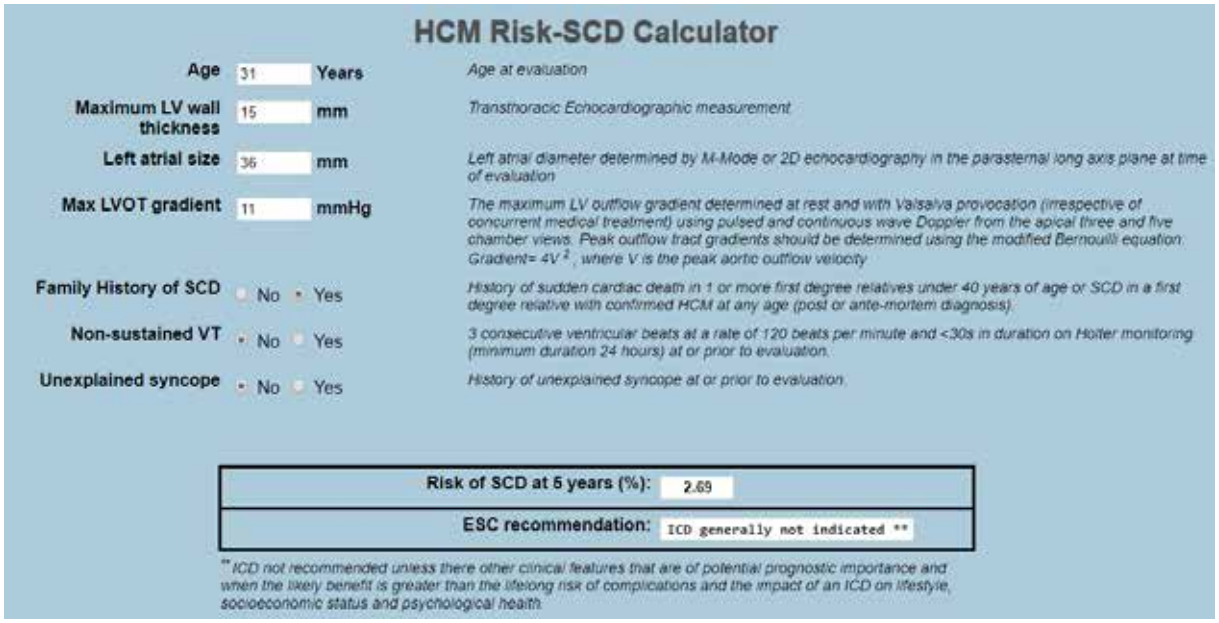


Figure 2. ECHOcardiography PLAX position in maximal diastole

Clinical diagnosis of HCM in the first degree of relatives of patients with clear disease (HCM ≥15 mm) is based on the presence of an unexplained increase in LV wall thickness ≥13 mm in one or more LV myocardial segments as measured by any cardiac imaging technique. Holter monitoring doesn t show heart rhythm disorders. The patient's medical records were presented to the Cardiology council in a tertiary institution,which indicating an expert Echocardiographic examination and MSCT coronarography. Cardiopulmonary compensated, rhythmically stable, with low dose / 2.5 mg / of cardioselective Beta blocker,patient was released for further home treatment from our hospital. Expert heart ultrasound done for better visualization of the endocardium, using transpulmonary contrast with a registered IVS thickness of 15 mm. MSCT coronarography with neat finding.CMR scan detected moderately pronounced myocardial hypertrophy, without focal zones of pathological signal. Stress echocardiography (SEHO) finding with neat finding. CFR for RCA preserved 2.87 CFR flow reserve for LAD preserved 2.81

Should we suggest this patient to incorporate ICD in primary SCD prevention?
Patients who have previously had abortion SCC and malignant ventricular arrhythmias are at greater risk for further arrhythmic events, and in such patients implantation of ICD is not disputed. However, the choice of patients to receive ICD for primary prevention of ISS is more difficult.
There are very few randomized, controlled, clinical studies in patients with HCM, and therefore most current ESC recommendations are based on the findings of observational retrospective cohort studies and consensus of expert opinions. In one study conducted by Spirito et al., which included 668 patients with HCM without conventional risk factors, assymptomatic or with mild symptoms, the risk of SCD was not negligible - a rate of 0.6% per year. (**18**)
This finding therefore underscores the importance of stratifying the risk of SCC in patients with proven HLV. Since 2014, the ESC has recommended the use of a new quantitative risk score / HCM Risk-SCD /, composed of seven disease-related characteristics, to predict ISS over a five year period. Based on the results, patients were stratified into three subgroups for recommendation to install ICDs in primary prevention of SCC. Scor <4% indi-



cated as low and in which the implantation of ICD is not indicated, Scor 4-6% indicated as median , may consider implantation of ICD ,while group with a score of ≥6% indicates implantation of ICD.

HCM Risk-SCD Score 2.69 classified our patient to a Low risk group for SCD, and the installation of ICD should not be considered, but continued subjective status monitoring with more frequent Holter monitoring. However, it was decided to seek the opinion of an eminent arrhythmologist , after the searches had been carried out. Opinion was stated in one sentence: **„ICD, without delay".**

Conclusion

Although most cases of HCM have a benign prognosis, identifying patients at risk for SCD requiring prophylactic therapy with ICD, is crucial and prioritized. With increasing awareness of the disease, lower-risk patients are now more frequently diagnosed, and more recent studies show that the annual rate of SCD is 0.5-1% , unfortunately among young and asymptomatic individuals.

There are very few randomized, controlled, clinical studies in patients with HCM, and therefore most current ESC recommendations are based on the findings of observational retrospective cohort studies and the consensus of expert opinions.

In this case, the expert opinion of an Eminent arrhythmologist was sought and the patient was implanted with an ICD device in primary prevention of SCD . The patient is enrolled in one of the clinical studies ,that will allow additional genetic testing through participation.

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Sažetak

Hipertrofična kardiomiopatija: od slučajne dijagnoze do prevencije iznenadne srčane smrti

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Hipertrofična kardiomiopatija je definisana prisutnošću povećane debljine zida leve komore, što se ne može objasniti samo nenormalnim uslovima opterećenja. Ova se definicija odnosi na decu i odrasle i ne daje „a priori" pretpostavke o etiologiji ili miokardnoj patologiji Poremećaji ćelijske arhitekture, intersticijalna fibroza, mikrovaskularni infarkti igraju ulogu u nastanku električne nestabilnosti tj malignih ventrikularnih aritmija koje uzrokuju iznenadnu srčanu smrt u bolesnika sa Hipertrofičnom kardiomiopatijom. Iako je u većini slučajeva prognoza benigna, prepoznavanje bolesnika s rizikom Iznenadne Srčane Smrti ,koji zahtevaju profilaktičku terapiju ICD-om, presudno je i prioritetno. S povećanjem svesti o bolesti, pacijenti sa nižim rizikom sada se dijagnostikuju više, a novija istraživanja pokazuju da godišnja stopa iznenadne srčane smrti iznosi 0,5-1% što nije zanemarljivo, nažalost među mladim i asimptomatskim pojedincima. U ovom radu prikazan je slučaj HCM-a, slučajno otkriven u mlađe odrasle osobe sa pozitivnom porodičnom anamnezom,završen implantacijom ICD-a u primarnoj prevenciji iznenadne srčane smrti

Ključne reči: hipertrofična kardiomiopatija, iznenadna srčana smrt

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Acute coronary syndromes*

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Preamble

The management of acute coronary syndromes (ACS) has made enormous progress over the last five decades due to the introduction of defibrillation, beta blockers, thrombolytics, aspirin, primary percutaneous transluminal intervention (PCI), P_2Y_{12} inhibitors, statins, radial access, and eventually PCSK9 inhibitors, among others.[1] However, in spite of all these remedies, there is a remaining acute mortality risk, in particular, in those presenting in cardiogenic shock or after resuscitation and an accruing number of major cardiovascular events (MACE) over the following years.[2] Thus, there is an unmet need in the management of ACS. In 2019, there were a number of important papers published in the *European Heart Journal* and other journals that deepened our knowledge about the spectrum of ACS and their management. Today patients presenting with acute chest pain and changes in the electrocardiogram (ECG) or biomarkers may have ST-segment elevation myocardial infarction (STEMI) or non-STEMI (NSTEMI) caused by atheroma, coronary dissection,[3] takotsubo syndrome,[4,5] MINOCA (Myocardial infarction with Non-Obstructed Coronary Arteries[6]), or myocarditis.[7]

Genetics

Whole-genome sequencing and early acute myocardial infarction

The relative prevalence and importance of monogenic mutations related to familial hyper-cholesterolaemia (FH) and of high polygenic score (cumulative impact of many common variants) pathways for early-onset myocardial infarction (MI) remain uncertain. Whole-genome sequencing enables simultaneous ascertainment of both monogenic mutations and polygenic score for each individual. Khera *et al.*[8] performed whole-genome sequencing in 2081 patients hospitalized for early-onset AMI to assess the prevalence and clinical importance of FH mutations and a high polygenic score. They observed an FH mutation in 1.7% of patients and a high polygenic score in 17% of patients, each of which was associated with a greater than three-fold increased odds of early-onset AMI. Beyond clinical risk stratification, the polygenic score may additionally foster insights into the mechanistic underpinnings of AMI. Indeed, this risk associated with a high polygenic score is not the result of a discrete underlying mechanism but rather a quantitative blend of numerous risk pathways.

Pathophysiology

Plaque rupture and healing assessed by optical coherence tomography

The mechanisms and the pathologic substrate of plaque erosion and plaque fissure are different. Indeed, plaques complicated by erosion tend to be matrix-rich, lipid-poor, and usually lack prominent macrophage collections, unlike plaques that rupture, which characteristically have thin fibrous caps, large lipid pools, and abundant foam cells.[9] In a prospective study in 211 patients with STEMI who underwent pre-intervention optical coherence tomography (OCT) examination for the culprit lesion, Tan *et al.*[10] found that trimethylamine N-oxide (TMAO) levels, a gut microbiota-dependent metabolite derived from dietary phosphatidylcholine and choline, were significantly and independently higher in patients with plaque fissure than in those with plaque erosion. The area under the receiver operating characteristic curve for distinguishing plaque rupture from plaque erosion was 0.89. Thus, plasma TMAO has the potential to serve as a novel biomarker for plaque rupture in patients with STEMI and indeed is a prognostic marker in these patients (see below). This might be relevant because risk stratification and management are probably different for plaque fissure and erosion.

Healed plaque ruptures or erosions may be considered as a signature of an aborted ACS. However, the role of plaque healing in the natural history of ischaemic heart disease (IHD) is largely unknown. OCT has been validated for the detection of healed coronary plaques against histology and therefore, offers the opportunity of assessing their clinical relevance. Vergallo *et al.*[11] assessed plaque healing in two groups of patients at the extremes of the clinical presentations of IHD: (a) patients with recurring ACS, defined as history of at least three AMIs or at least four ACS with at least one AMI; (b) patients with long-standing chronic coronary syndromes, defined as a minimum 3-year history of stable angina in the absence of previous ACS. In the first group, non-culprit plaques only were assessed. They found that patients with recurrent ACS had a distinct atherosclerotic phenotype compared with those with chronic coronary syndrome and longstanding angina, including a much lower prevalence of healed coronary plaques, suggesting that plaque healing may play a role in leading the natural history of patients with IHD.

*Radovi su dobijeni na objavljivanje u saradnji sa mrežom urednika nacionalnih časopisa iz oblasti kardiologije pod okriljem i uz odobrenje ESC-a.

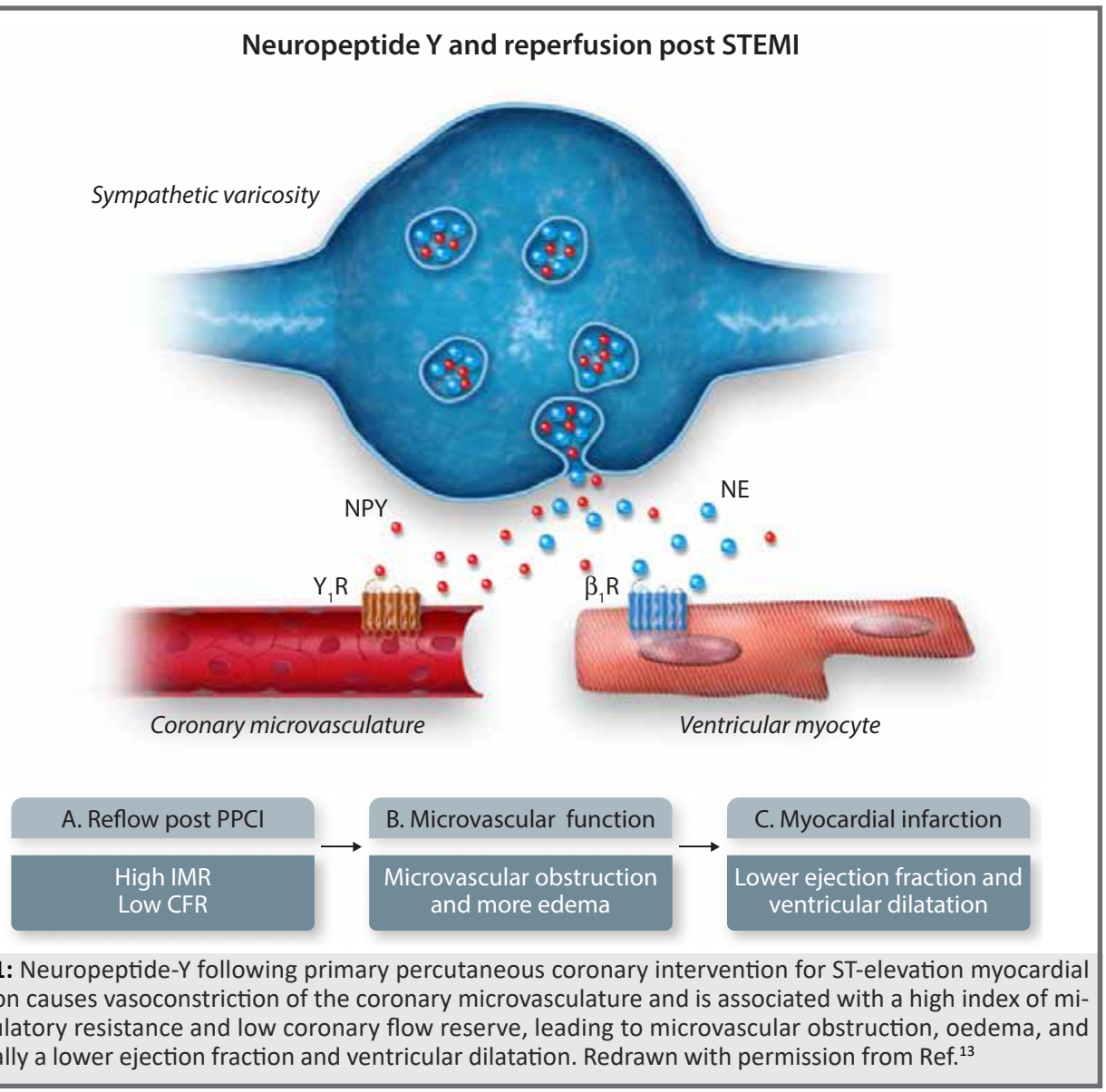


Figure 1: Neuropeptide-Y following primary percutaneous coronary intervention for ST-elevation myocardial infarction causes vasoconstriction of the coronary microvasculature and is associated with a high index of microcirculatory resistance and low coronary flow reserve, leading to microvascular obstruction, oedema, and eventually a lower ejection fraction and ventricular dilatation. Redrawn with permission from Ref.[13]

In another OCT study, Fracassi *et al.*[12] assessed plaque healing in the culprit stenosis, among 376 patients with ACS and found plaque healing in more than one-quarter. Such patients more frequently were diabetic or hyperlipidaemic; furthermore, healed plaques frequently showed OCT features of local and systemic inflammation. This suggests that the combination of risk factors and local in addition to systemic inflammation may outweigh the protective mechanism of plaque healing and predispose those plaques to develop occlusive thrombus. Thus, a better knowledge of the mechanisms promoting plaque healing might provide new therapeutic targets to reduce ACS burden in addition to optimal risk factor control.

Mechanisms of coronary microvascular obstruction

The rapid re-opening and stenting of occluded epicardial coronary arteries via emergency PCI have revolutionized STEMI treatment. Despite technical refinements and the introduction of numerous antiplatelet and anticoagulant drugs, more than one-third of patients demonstrate coronary microvascular obstruction (CMVO) which deny the benefit of an apparently successful PCI. The mechanisms of CMVO are still largely unknown, while its prevention and treatment remain an unmet need.

Herring *et al.*[13] found that STEMI patients with the highest neuropeptide Y levels in the coronary sinus had significantly lower coronary flow reserve, and higher index of microvascular resistance measured with a coronary flow wire, both markers of CMVO. After 2 days, they also had significantly higher levels of myocardial oedema and microvascular obstruction (MVO) on magnetic resonance imaging (MRI), and significantly lower ejection fractions and ventricular dilatation 6 months later. Interestingly, neuropeptide Y (NPY) (100–250 nM) caused significant vasoconstriction of rat microvascular coronary arteries via increasing vascular smooth muscle calcium waves, and increased coronary vascular resistance and infarct size in Langendorff hearts. These effects were blocked by the Y1 receptor antagonist BIBO3304. Immunohistochemistry of the human coronary microvasculature confirmed the presence of vascular smooth muscle Y_1 receptors. Thus, antagonism NPY might be an attractive future therapeutic target in the prevention of CMVO (*Figure 1*).

New insight into post-myocardial infarction remodelling

The immune response to AMI involves two equally important, consecutive phases: the inflammatory phase and the reparatory phase. During the inflammatory phase, neutrophils and inflammatory Ly6C^{hi} monocytes are recruited into the ischaemic myocardium. Subsequently, the Ly6C^{hi} monocytes give rise to reparatory Ly6Clo macrophages, with an important role in cardiac recovery. A balance between the two phases is crucial for recovery of cardiac function and patient prognosis. An excessive inflammatory response to AMI amplifies myocardial injury, leading to larger infarcts and loss of function. However, clinical trials testing anti-inflammatory strategies in AMI have so far led to non-significant or even deleterious effects. Ideally, an efficient therapy should inhibit the damaging effects of excessive inflammation, while leaving the repair mechanisms intact.

Alarmins are a group of heterogeneous molecules released from dying cells and activated leucocytes that signal tissue damage and trigger an innate immune response. S100A9 and its dimerization partner S100A8, also called myeloid-related proteins 8 and 14, are pro-inflammatory alarmins that are readily produced and stored in large amounts in neutrophils and are increased at the site of acute coronary occlusion.[14] Marinković *et al.*[15] studied 524 patients with ACS and found that high plasma S100A8/A9 at the time of ACS was associated with lower left ventricular ejection fraction (LVEF) at 1 year and increased hospitalization for heart failure during follow-up. Moreover, in wild-type C57BL/6 mice with AMI induced by permanent coronary artery ligation, treatment with the S100A9 blocker ABR-238901 during the inflammatory phase of the immune response inhibited haematopoietic stem cell proliferation and myeloid cell egression from the bone marrow. The treatment reduced the numbers of neutrophils and monocytes/macrophages in the myocardium, promoted an anti-inflammatory environment, and significantly improved cardiac function compared with controls. To mimic the clinical scenario, they further confirmed the effects of the treatment in a mouse model of ischaemia and reperfusion. Compared with untreated mice, 3-day ABR-238901 treatment significantly improved LVEF. Thus, S100A9 blockade might represent a feasible strategy to improve prognosis in ACS patients.

Tang *et al.*[16] investigated the effects of gut microbiota on cardiac repair after AMI. C57BL/6J mice were treated with antibiotics 7 days before AMI to deplete mouse gut microbiota. Antibiotic-treated mice displayed drastic, dose-dependent mortality after AMI associated with a reorganization of the gut microbial community such as a reduction in Lactobacillus. The physiological status and survival of mice were significantly improved after faecal reconstitution or dietary supplementation with short-chain fatty acids that are altered after antibiotic treatment; this benefits appeared to be mediated by immunomodulatory effects. In addition, supplementing antibiotic-treated mice with a Lactobacillus probiotic before AMI restored yielded cardioprotective effects. Thus, this study uncovers the adverse effects of antibiotics on survival after MI and addresses a promising therapeutic strategy that involves modulation of gut microbiota composition through probiotic supplementation (*Figure 2*).

Mechanisms of takotsubo syndrome

In 55 patients with takotsubo syndrome, Scally *et al.*[17] found myocardial macrophage inflammatory infiltrates as assessed by MRI as well as changes in the distribution of monocyte subsets and an increase in systemic pro-inflammatory cytokines. Many of these changes persisted for at least 5 months suggesting a low-grade chronic inflammatory state. Obviously, whether inflammation is a cause or a consequence of the acute takotsubo event remains to be shown. Moreover, whether inflammation is maladaptive and implicated in the persistence in the long-term consequences of this condition is uncertain. Nevertheless, inflammation might play a role in the complex pathogenesis of this syndrome.

Most importantly, novel investigations using functional MRI of the brain suggest that an altered limbic and central autonomic signal processing plays a crucial role in takotsubo and may explain the inappropriately excessive reaction of the sympathetic nervous system to stressful triggers. Thus, takotsubo is indeed by a brain disease and the heart may just represent the target organ.[18]

Diagnosis

Troponins

Boeddinghaus *et al.*[19] prospectively enrolled patients presenting with symptoms suggestive of AMI in three large diagnostic studies in order to assess the validity of the 0/h-algorithms according to age (<55 years, ≥55 to <70 years, and ≥70 years). Rule-out safety of the ESC high-sensitivity cardiac troponin T (hs-cTnT) 0/1 h-algorithm was very high with a sensitivity of >99.3% in all age-strata, while triage efficacy decreased with increasing age with sensitivity dropping from 93% to 55%. Slightly higher cut-off concentrations optimized for older patients maintained very high safety of rule-out and increased specificity. Findings were confirmed in two validation cohorts and also for hsTnI. While safety of the ESC 0/1 h-algorithms remained very high, increasing age significantly reduced overall efficacy and the accuracy of rule-in. Thus, alternative slightly higher cut-off concentrations may be considered for older patients, although the problem remains for other confounders like chronic kidney disease, chronic heart failure, atrial fibrillation, and others that also need to be incorporated. Twerenbold *et al.*[20] confirmed the excellent applicability, short time to emergency department discharge, and low rate of 30-day MACE associated with the routine clinical use of the ESC 0/1-h-algorithm for the management of patients presenting with acute chest discomfort to the emergency department in a real-world setting.

Finally, important concepts for institutional transition to hs-cTn methodology providing recommendations useful for education before implementation have been reported in an Expert Panel chaired published by Januzzi *et al*.[21]

Implantable cardiac alert system

Symptoms remain a poor prompt for ACS. In a multicentre, randomized trial of an implantable cardiac monitor

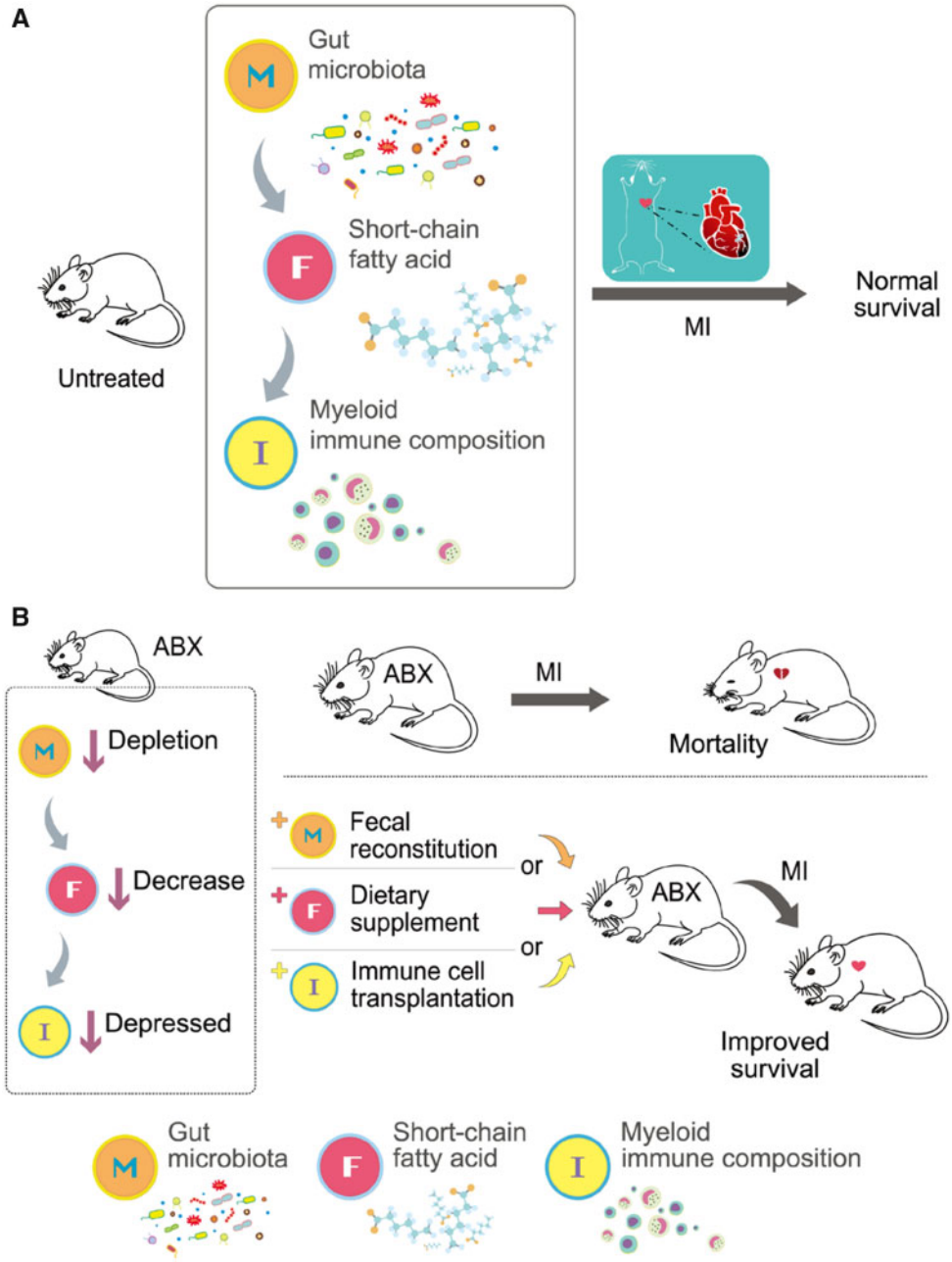


Figure 2: A schematic diagram showing the importance of gut microbiota-derived short-chain fatty acids for maintaining immune composition and repair capacity during homoeostasis. (*A*) In untreated mice, gut microbiota-derived short-chain fatty acids modulate immune composition and repair capacity during homoeostasis. (*B*) On antibiotics-mediated dysbiosis, the depletion of the gut microbiota and the short-chain fatty acid products are associated with changes in immune composition and an abolishment of repair response, leading to exacerbated mortality after myocardial infarction. Restoration of the system across each level through the faecal reconstitution of the gut microbiota, dietary supplementation of short-chain fatty acids, or immune cell transplantation results in improved survival. Reprinted with permission from Ref.[16]

that alerted 907 high-risk ACS patients with rapidly progressive ST-segment deviation randomized to a control (alarms deactivated) or treatment group for 6 months, after which alarms were activated in all subjects.[22] Safety revealed a 96.7% freedom from system-related complications. The primary efficacy endpoint of cardiac or unexplained death, new Q-wave MI, and detection to presentation time >2 h following a confirmed occlusive event within 7 days was numerically, but not statistically reduced among patients with activated alarms group. When the observation window was extended to 50, 70, and 90 days in a prespecified analysis to include the majority of confirmed occlusive events in the control group, and an exploratory dual-baseline ECG analysis was used to reduce noise, a significant reduction in the primary endpoint was observed. Moreover, alarms significantly decreased detection to arrival time at a medical facility. This device may be beneficial among high-risk subjects in potentially identifying asymptomatic events.

Risk stratification

Biomarkers

Among 4257 patients of the VISTA-16 trial, initial and subsequent increases in high-sensitivity C-reactive protein (hsCRP) levels during 16 weeks after ACS were associated with a greater risk of the combined MACE endpoint, cardiovascular (CV) death, and all-cause death despite established background therapies.[23] Further studies will be required to determine whether initial and serial hsCRP measurements can help guide the use of targeted anti-inflammatory therapies after ACS or whether more specific inflammatory markers will be needed to this end.

Four new biomarkers have been investigated in different trials in the setting of ACS: (a) galectin-3, implicated in fibrosis[24]; (b) impaired endogenous fibrinolysis[25]; (c) trimethyllysine and TMAO, gut-microbiota derived metabolite[26]; (d) serum cholesterol efflux capacity.[27] All these biomarkers were found to be independently associated with MACE at follow-up. Again, further studies will be required to establish whether these markers identify patient subsets who need personalized forms of treatment.

Finally, Lindholm *et al.*[28] assessed the association between cystatin-C, growth differentiation factor-15 (GDF-15), hsCRP, hs-TnT and TnI, and N-terminal pro-B-type natriuretic peptide (NT-proBNP) and specific causes of mortality among 17 095 ACS patients of the PLATO trial. They found that NT-proBNP and GDF-15 were strong markers associated with all-cause death based on their associations with death due to heart failure as well as due to arrhythmia and sudden cardiac death. Growth differentiation factor-15 had the strongest associations with death due to other vascular or non-vascular causes and possibly with death due to bleeding. It remains to establish how to these important prognostic information can guide treatment.

Cardiac magnetic resonance and entropy

Entropy is a new late gadolinium-enhanced MRI-derived parameter to evaluate tissue inhomogeneity, independent of signal intensity thresholds. Androulakis *et al.*[29] enrolled 154 consecutive post-AMI patients undergoing late gadolinium-enhanced MRI prior to implantable cardioverter-defibrillator (ICD) implantation. When entropy involved the entire left ventricle (LV), this was associated with mortality. After adjusting for multivessel disease, acute revascularization, and ejection fraction, entropy of the scar was independently associated with the presence of ventricular arrhythmias. The association between LV entropy and mortality may reflect adverse and irreversible, inhomogeneous remodelling of the post-infarct LV and/or possibly fatal arrhythmias. Further studies are warranted to establish whether this new marker can allow a better identification of candidates for ICD after AMI.

Treatment

Ticagrelor compared to prasugrel were studied in the ISAR-REACT 5 study (*Figure 3*).[30] Patients with ACS and a proposed interventional strategy were randomized and the primary composite endpoint was death, MI, or stroke. In these patients with or without STEMI, prasugrel therapy was superior to ticagrelor with no difference in bleeding. These important comparative data are likely to change clinical practice.

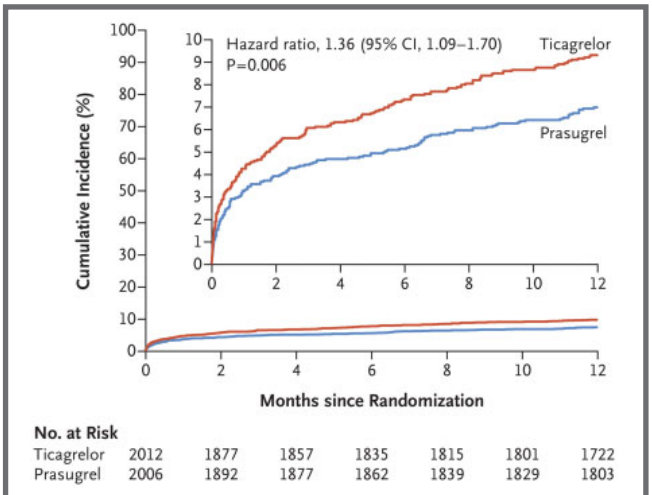


Figure 3: The Kaplan–Meier curves of the ISAR–REACT5 show the cumulative incidence of the primary endpoint, which was a composite of death, myocardial infarction, or stroke at 1 year. The inset shows the same data on an enlarged *y* axis. Reprinted with permission from Ref.[30]

Timing of treatment

The optimal timing of administration of dual antiplatelet therapy (DAPT) in STEMI patients was investigated by the *Swedish Coronary Angiography and Angioplasty Registry*.[31] Patients were stratified between either post- or pre-procedure treatment with P_2Y_{12} receptor antagonists. Of the 44'804 patients 58% had been on clopidogrel, 35% on ticagrelor, and 5% on prasugrel. There was no survival benefit from pre-treatment or any impact on infarct-related artery patency, stent thrombosis, or bleeding. These data are surprising as a potential impact on early stent thrombosis, in particular, might have been anticipated. Existing Guidelines[32] recommend catheter-lab administration of antiplatelet drugs and these data are supportive of that strategy, although Abtan and Steg[33] argue that we should continue to give P_2Y_{12} receptor antagonists as early as possible in probable STEMI patients as there is a strong biological plausibility of likely benefit with no obvious likely detriment. Whether patients with patients with transient ST-elevation (patients who present initially with ST-elevation on the electrocardiogram but, subsequently, show complete normalization of the ST-segment and relief of symptoms before reperfusion therapy) require immediate revascularization was studied in a trial[34] of 142 patients who were randomized to immediate (mean 0.3 h) or delayed angiography (mean 22.7 h). The outcome was infarct size by MRI at Day 4. The observed infarcts were generally small and there was no clear benefit from the immediate strategy, although 4/71 patients required urgent intervention because of further symptoms and ST elevation whilst waiting. Consequent-

ly, these data can probably be interpreted as allowing decisions about timing of revascularization in patients with transient STEMI, to be guided by the availability of angiography and careful clinical assessment.

The management of non-culprit lesions in STEMI patients has been extensively discussed over the last years. Small randomized trials have suggested a probable benefit from complete revascularization. The large COMPLETE trial randomized 4041 STEMI patients (*Figure 4*) to complete or partial revascularization.[35] Complete revascularization was superior to culprit-only as it reduced the risk of CV death or AMI. There was also benefit from complete revascularization in reducing ischaemic endpoints. Timing appeared to be less important and deferring any secondary revascularization procedure was safe. Thus, the advantage of complete revascularization will presumably be reflected in subsequent ESC Guidelines.

Can we tailor treatment in acute coronary syndromes?

There remains a desire to tailor drug therapy to the individual patients and perhaps the individual lesion. This strategy would allow pharmaceutical optimization of protection with minimization of side effects or bleeding risk. The CHAMPION PHOENIX trial[36] has suggested that complex coronary lesions can be characterized and that it is inadequate treatment of these 'high risk' lesions that leads to repeat revascularization or clinical events. Compared with a loading dose of clopidogrel, cangrelor reduced MACE occurring within 48 h after PCI in patients with ACS regardless of baseline lesion complexity. However, the absolute benefit: risk profile for cangrelor was greatest during PCI in complex coronary anatomy. In a substudy of the PROSPECT trial,[37] virtual histology and grey scale intravascular ultrasound (IVUS) was a predictor of a suboptimal final angiographic result reflected as a high residual Syntax Score after intervention. A detailed Expert consensus review has provided detail on characterization of acute coronary lesions using IVUS or OCT and suggested a triaged therapeutic approach.[38]

Unfortunately measuring individuals' responses to antiplatelet drugs has not shown clinical utility. Randomizing patients to measuring platelet function in the TROPICAL trial[39] showed no measurable clinical advantage. Within the trial, those patients with maximal platelet inhibition were predictably most prone to bleeding.

Optimizing treatment in ST-segment elevation myocardial infarction

About one-third of STEMI patients have suboptimal reperfusion after PCI and it is this group of patients that might experience heart failure and premature death. MRI can provide evidence of MVO and myocardial haemorrhage.[40] In the DANAMI-3 trial delayed presentation[41] as evidenced by prolonged *door-to-wire-time* predicted adverse clinical outcome, consistent with previous observations using intracoronary physiology measurements suggesting increased risk in these 'late presenters'.[42] Enhanced and continued public information campaigns are required to optimize outcomes in high-risk STEMI patients along with novel

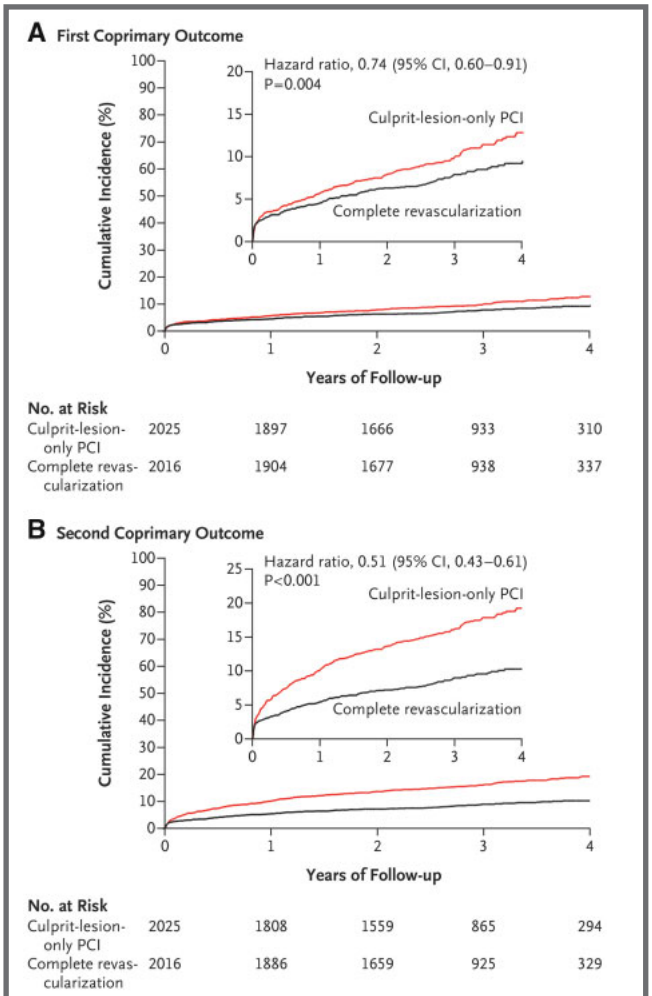


Figure 4: The Kaplan–Meier curves show the cumulative incidence of the primary endpoint, which was a composite of death, myocardial infarction, or stroke at 1 year. The inset shows the same data on an enlarged *y* axis. Reprinted with permission from Ref.[35]

adjunctive therapies. In this context, full dose intracoronary tenectaplase was inferior to abciximab in a small randomized trial[43] and using low dose intracoronary tenecteplase after reperfusion in the T-time trial also failed to reduce MVO measured using cardiac magnetic resonance imaging (CMRI).[44]

Hypothesis generating results were presented by the *Microvascular Reperfusion Utilizing Sonothrombolysis in Acute Myocardial Infarction* (MRUSMI) investigators.[45] They randomized STEMI patients to either standard PCI or diagnostic ultrasound transducer guided, high mechanical index impulses during an ultrasound agent transfusion prior to and following PCI. The ultrasounds high mechanical index impulses create microbubble cavitation that induce shear forces, designed to dissolve intracoronary thrombi. The treatment cohort demonstrated higher recanalization (48% vs. 20%) and TIMI 3 flow rates (32% vs. 14%) within the infarcted vessel ST-segment resolution prior to primary PCI occurred more frequently. Furthermore, infarct size as assessed by MRI and TNT peak values was also reduced by the intervention. Optimizing reperfusion for patients with STEMI when there is lot of thrombus is challenging and these

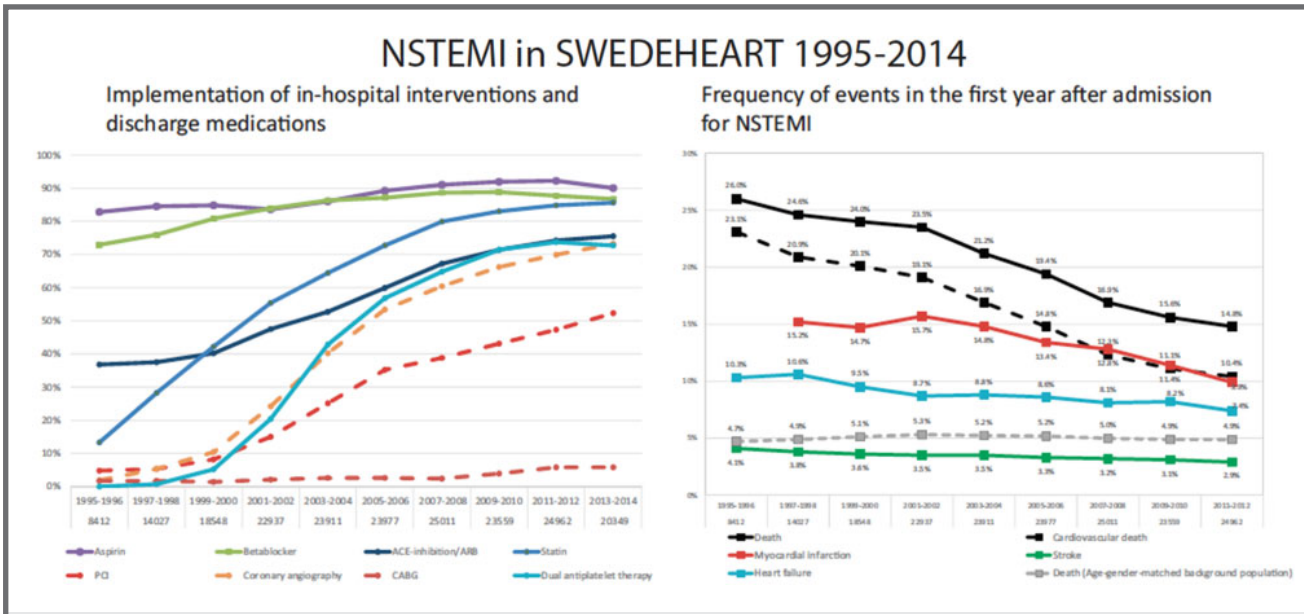


Figure 5: (*A* and *B*) Kaplan–Meier estimates of the cumulative incidence of the first coprimary outcome (death from cardiovascular causes or new myocardial infarction) and the second coprimary outcome (death from cardiovascular causes, new myocardial infarction, or ischaemia-driven revascularization), respectively. Insets show the same data on an enlarged *y* axis. PCI, percutaneous coronary intervention. Reprinted with permission from Ref.[48]

preliminary results hint at a possible alternate approach. Remote preconditioning in STEMI was studied in the CONDI-2/ERIC PPCI trial[46] which randomized 5401 patients to standard treatment (including a sham simulated remote ischaemic conditioning at UK sites) or remote ischaemic conditioning (intermittent ischaemia and reperfusion applied to the arm through four cycles of 5-min inflation and 5-min deflation of an automated cuff device) before primary PCI. Unfortunately, remote ischaemic conditioning did not improve clinical outcomes (cardiac death or hospitalization for heart failure) at 12 months. New approaches and therapies within this area are warranted if this experimentally well-documented concept should ever reach the clinical applicability.

Outcomes

Quality of treatment and outcomes

In a cohort of 389 507 NSTEMI patients, optimal care, defined as the receipt of all eligible treatments, was inversely related to risk status (defined by the GRACE risk score), i.e. 25.6% in low, 18.6% in intermediate, and 11.5% in high-risk patients. At the end of 2.3 years of follow-up, the association between the use of all eligible guideline-indicated treatments and improved survival remained only significant for high-risk NSTEMI.[47] Thus, optimal use of guideline-indicated care for NSTEMI was associated with greater survival gains with increasing GRACE risk, but its use paradoxically decreased with increasing GRACE risk, thus leaving room for improvement.

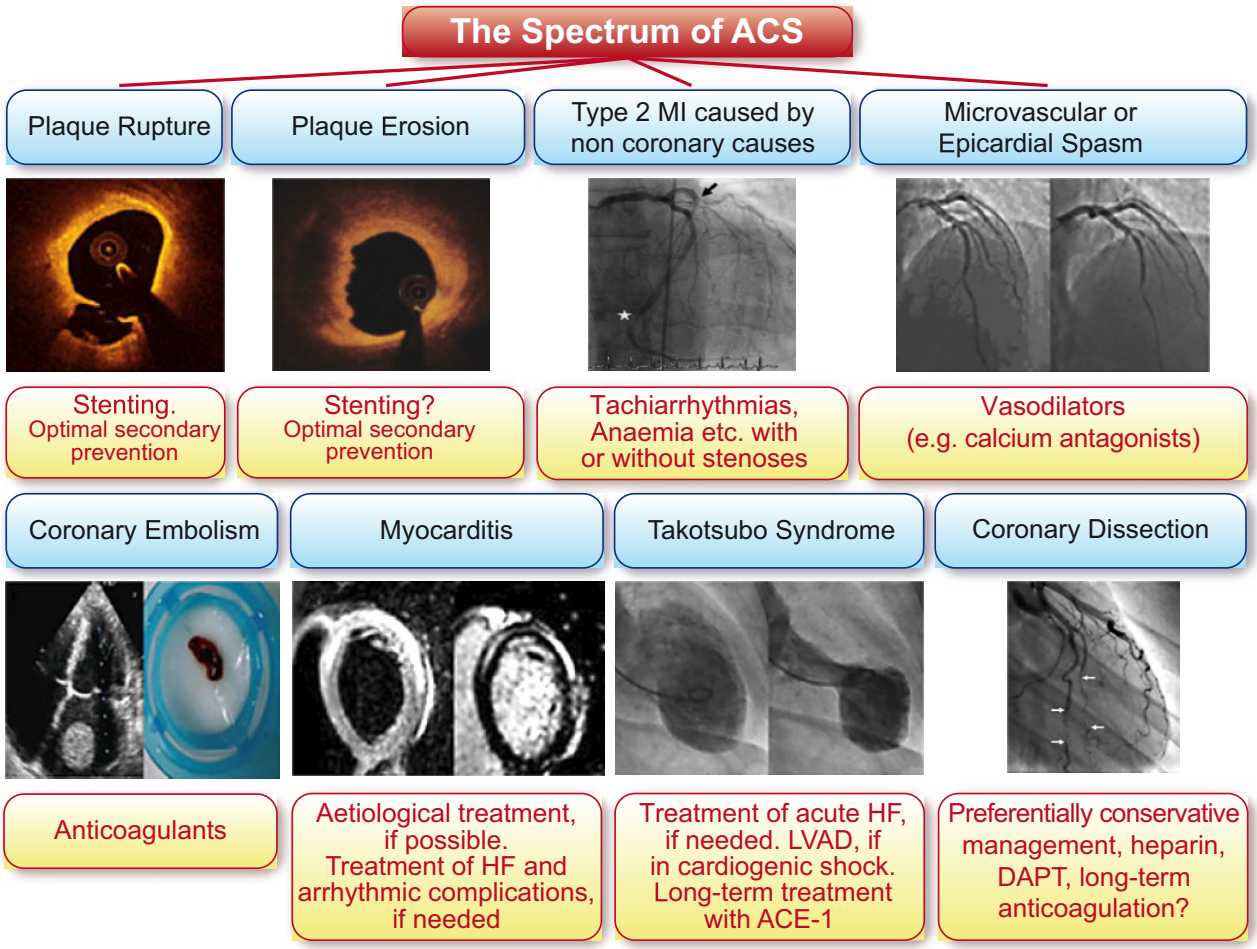
In the SWEDHEART registry, outcomes of patients presenting with NSTEMI followed over 20 years demonstrated a substantial improvement in long-term survival and reduction in the risk of MACE.[48] These improvements were associated with the gradual uptake and widespread use of PCI and long-term use of evidence-based medications, consistent with the anticipated effectiveness of their implementation as proposed in guidelines (*Figure 5*).

The value of a cardiac rehabilitation programme was compared in 839 patients who attended a planned programme at discharge after ACS or surgical revascularization, while 441 patients were discharged without it.[49] At multivariable Cox proportional hazard analysis, the cardiac rehabilitation programme was an independent predictor of lower occurrence of MACE (hazard ratio 0.55), while in a propensity-matched analysis patients attending the cardiac rehabilitation programme also experienced a lower total mortality (10% vs. 19%) and CV mortality (2% vs. 7%) compared to non-rehabilitated ones. Thus, the positive effects of ambulatory of cardiac rehabilitation are also notable in a real-world population.

Finally, in a cohort study of 123 780 consecutive PCIs from the Pan-London PCI Registry the outcomes pre- and post-public reporting in the UK were compared.[50] After public reporting was introduced, patients were older and had more complex medical problems, while in-hospital MACE and MACCE and 30-day mortality rates were significantly lower. These results probably reflect continued improvements in PCI outcomes concomitant with the introduction of public reporting, but the lower reported complication rate could also reflect a change in the documentation of risk factors and a change in operator behaviour. Reassuring, additional data from the UK registry also confirm continued temporal improvement in outcomes in ACS and notably demonstrate no difference in outcome depending on the times of day that treatment occurred. Patients treated as emergencies at night had similar outcomes to those treated within 'office hours'.

Modes of death after non-ST-segment elevation myocardial infarction

In 66 252 patients with NSTEMI enrolled in 14 TIMI trials, baseline characteristics and modes and timing of



Take home Figure: The spectrum of acute coronary syndromes encompasses plaque rupture and erosion (=Type 1 myocardial infarction), Type 2 myocardial infarction, epicardial and microvascular coronary spasm, coronary embolism, acute myocarditis, takotsubo syndrome, and coronary dissection.

death were examined. Of the 2606 patients with known modes of death, 75.1% were related to MACE, 3.0% were related to a bleeding event (including intracranial haemorrhage), and 21.8% were related to a non-CV/non-bleeding event.[51] The most common modes of CV death were sudden death and recurrent AMI (36.4% and 23.4%, respectively). The proportion of CV deaths related to recurrent AMI was higher in the first 30 days than it was after 30 days following NSTEMI (30.6% vs. 18.7%), whereas the proportion of sudden death was lower in the first 30 days than after 30 days (21.6% vs. 46.2%). Thus, sudden death represented the largest proportion of CV deaths after 30 days. Further investigations aimed at defining management approaches to reduce sudden death following NSTEMI may be critical to reducing late mortality.

Outcomes of in-hospital acute coronary syndromes

In a cohort study of 1.3 million patients hospitalized in US Veterans Health Administration facilities, an incidence of in-hospital AMI of 4.27 per 1000 admissions and risk factors associated with in-hospital AMI such as history of IHD, elevated heart rate, low haemoglobin level, and elevated white blood cell count were reported.[52] Compared with matched controls, mortality was significantly higher for in-hospital AMI. Thus, in-hospital AMI is common and associated with common CV risk factors and markers of acute illness and with high mortality approaching 60% at 1 year. Further studies of in-hospital AMI may yield opportunities to reduce in-hospital AMI risk and improve patient outcomes.

Outcomes of atypical acute coronary syndromes

Spontaneous coronary artery dissection

Spontaneous coronary artery dissection (SCAD) is an underdiagnosed and poorly understood condition and an important cause of AMI in young women.[3] In the Canadian multicentre, prospective, observational study of 750 patients, predisposing conditions included fibromuscular dysplasia in 31.1%, systemic inflammatory diseases in 4.7%, peripartum in 4.5%, and connective tissue disorders in 3.6% were noted.[53] Most were treated conservatively, while 14% underwent PCI and a few coronary artery bypass surgery. In-hospital composite MACE was 8.8%, but higher in peripartum SCAD (20.6% vs. 8.2%). Overall 30-day MACE was 8.8% with peripartum SCAD and connective tissue disease being independent predictors of 30-day MACE.

Takotsubo syndrome

Two different studies of the *InterTak Registry* including over 1500 patients with takotsubo syndrome found that both in-hospital cardiac arrest (4.9 of patients)[54] or

the presence of an associated malignancy (16.6% of patients)[55] were associated with worse long-term outcome. Of note, patients with cardiac arrest were more likely to be younger, male, and have apical takotsubo, atrial fibrillation, neurologic comorbidities, physical triggers, longer corrected QT-interval, and lower LVEF, while those with malignancy were older and more likely to have physical triggers, but less likely to have emotional triggers.

Myocardial infarction with non-obstructed coronary arteries

The long-term outcome of MINOCA was investigated in a large US Registry of 286 780 AMI admissions of which 5.9% had MINOCA.[56] Following risk-adjustment, MINOCA patients had a 43% lower risk of MACE over 12 months compared to those with AMI and coronary artery disease. This pattern was similar for adjusted risks of the MACE components. Thus, MINOCA has an unfavourable prognosis in elderly patients with one in five suffering a major adverse event over 12 months.

Women vs. men

The impact of gender was assessed in 13 451 NSTEMI and STEMI patients undergoing PCI in the *Victorian Cardiac Outcomes Registry* in Australia.[57] Women with STEMI had significant delays in presentation and revascularization with a higher 30-day mortality compared with men, while women with NSTEMI had no delay in presentation or revascularization, with mortality comparable to men. Thus, public awareness campaigns might be needed to address women's recognition and early action for STEMI.

In a Swiss population of 4360 patients with STEMI ischaemic time in women remained greater than that in men due to persistently greater patient delays.[58] In contrast to men, clinical signs of ongoing chest discomfort did not predict delays in women, suggesting that female STEMI patients were less likely to attribute symptoms to a condition requiring urgent treatment.

In a Chinese population of 82 196 patients women hospitalized for ACS less frequently received acute treatments and strategies for secondary prevention than men.[59] The observed sex differences in in-hospital mortality were mainly due to worse clinical profiles and fewer evidence-based acute treatments provided to women with ACS.

Finally, Vicent *et al.*[60] in an octogenarian Spanish population of 535 patients with STEMI found that female sex was independently associated with death and hospitalization at 6-month follow-up.

Medicaid beneficiaries vs. privately insured individuals

In 42 645 and 171 545 STEMIs receiving Medicaid or private insurance, respectively,[61] in unadjusted analyses, Medicaid beneficiaries had lower rates of coronary revascularization and higher rates of in-hospital mortality compared with privately insured individuals. Similar results were found in a propensity-matched cohorts. Further studies are needed to identify and understand the causes of the variation in STEMI outcomes by insurance status.

Black vs. White patients

In a US cohort of 6402 patients, self-identified black and white patients differed in several clinical and socioeconomic characteristics.[62] The higher the prevalence of characteristics associated with being black, the higher the 5-year mortality rate, but no differences were observed between black and white patients with similar characteristics. Thus, a greater prevalence of characteristics associated with black race, but not race itself, was associated with higher mortality risk after AMI.

Conclusions

Important data from large randomized trials have augmented the management of patients presenting with ACS. Importantly, recognition of the clinical spectrum of ACS has expanded in recent years and atypical forms, besides the classical STEMI and NSTEMI, such as takotsubo syndrome, coronary dissection, MINOCA, and myocarditis have been increasingly recognized, characterized and their causes and mechanisms defined. The management of these novel forms of ACS is still not evidence-based, but significant progress has been made recently. Furthermore, disparities in the implementation of guideline-based therapies are increasingly addressed to the benefit of the patient population at large. The opinions expressed in this article are not necessarily those of the Editors of the *European Heart Journal* or of the European Society of Cardiology.

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Heart failure*

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Preamble

The past year has brought many new concepts and an abundance of new data on the nature, management, and outcome of heart failure. The pace of change is accelerating. We look forward to an exciting new decade of research. The prognosis of cardiovascular disease is determined to a large extent by the ability to delay or prevent the development and progression of heart failure.[1] Accordingly, attention is shifting to earlier diagnosis of and intervention for heart failure. Patients with type-2 diabetes mellitus (T2DM)[2] or coronary artery disease (CAD)[3] have a relatively good prognosis unless plasma concentrations of natriuretic peptides are increased, indicating important cardiac or renal dysfunction. Adoption of a simple 'Universal Definition' of heart failure based on natriuretic peptides would facilitate early diagnosis and treatment but lead to an enormous increase in its prevalence and demand upon medical services.[4] We need to prepare for the impending shock.

Epidemiology and prevention

In cardiology, the term prevention is often used to mean delaying the onset of disease; in other words, procrastination. Failure to appreciate the difference between prevention and procrastination leads to problems in projecting future healthcare needs and costs. Older people have more co-morbid conditions that complicate management but may also offer more opportunities for intervention; consequently, more time and resources are required to manage older patients well.

A detailed report on heart failure in the UK shows that the median age of onset has risen to about 80 years, consistent with improvements in the treatment of hypertension and other risk factors for atherosclerosis and better management of myocardial infarction.[5] Unfortunately, data on left ventricular ejection fraction (LVEF) were not available for this report. Analyses of the diagnostic pathway in primary care in the UK suggest that key investigations are often not done.[6–8] Similar data from other countries are urgently required. Several large epidemiological surveys[9,10] and analyses of large trials[11,12] have recently been published that allow the demographics, aetiology, and management of heart failure to be compared internationally.

Mineralocorticoid receptor antagonists (MRAs) are effective anti-hypertensive agents that also improve the prognosis of patients with heart failure and a reduced (HFrEF) and possibly preserved (HFpEF) LVEF.[13] Whether MRAs have specific effects on reducing other potential drivers of the progression to heart failure such as inflammation and fibrosis is currently under investigation.[14,15] Genetic propensity to greater body fat was associated with the risk of developing heart failure in an analysis on 367 703 UK Biobank participants.[16] However, the incidence of heart failure was only 1% (4803 patients), the diagnostic criteria were not robust, and the increase in risk was modest (odds ratio 1.22; 95% CI 1.06–1.41). Further analyses on this population showed a strong relationship between cardio-respiratory fitness and grip strength and future incidence of heart failure.[17] A study of 4403 people considered for bariatric surgery in Sweden and followed for 22 years, found that 188 (9%) of the 2003 who had surgery (25–35 kg weight loss; BMI 1 year after surgery 32 kg/m^2) developed heart failure compared with 266 (13%) of 2030 who did not (BMI after 1 year observation 40 kg/m^2).[18] Although these data suggest links between obesity and the risk of developing heart failure, it is possible that obesity just provokes similar symptoms. Once heart failure has developed, obesity is associated with a lower mortality, but this may also reflect earlier diagnosis rather than a protective effect.[19] Randomized controlled trials (RCTs) of effective interventions for obesity are required to demonstrate whether weight loss improves symptoms (likely) and clinical outcomes (less certain).

A report from 'the Atherosclerosis Risk in Communities' (ARIC) study confirmed the association between influenza epidemics and hospitalizations for heart failure, reinforcing guideline-recommendations for vaccination[20]; an RCT is underway.[21] Extended follow-up (median 18.9 years) of the Women's Health Initiative Hormone Therapy trials, which randomized 27 347 women to various hormone replacement regimens, showed that they had no effect on the incidence of HFrEF or pEF.[22]

The ISCHEMIA trial (presented at the American Heart Association 2019) compared strategies of early coronary revascularization, predominantly percutaneous, with conservative management for stable CAD, some of whom had mild symptoms of heart failure and/or a reduced LVEF. Revascularization did not reduce the risk of myocardial infarction or death but increased the risk of stroke almost four-fold and did not reduce new-onset heart failure over the following 4 years.

*Radovi su dobijeni na objavljivanje u saradnji sa mrežom urednika nacionalnih časopisa iz oblasti kardiologije pod okriljem i uz odobrenje ESC-a.

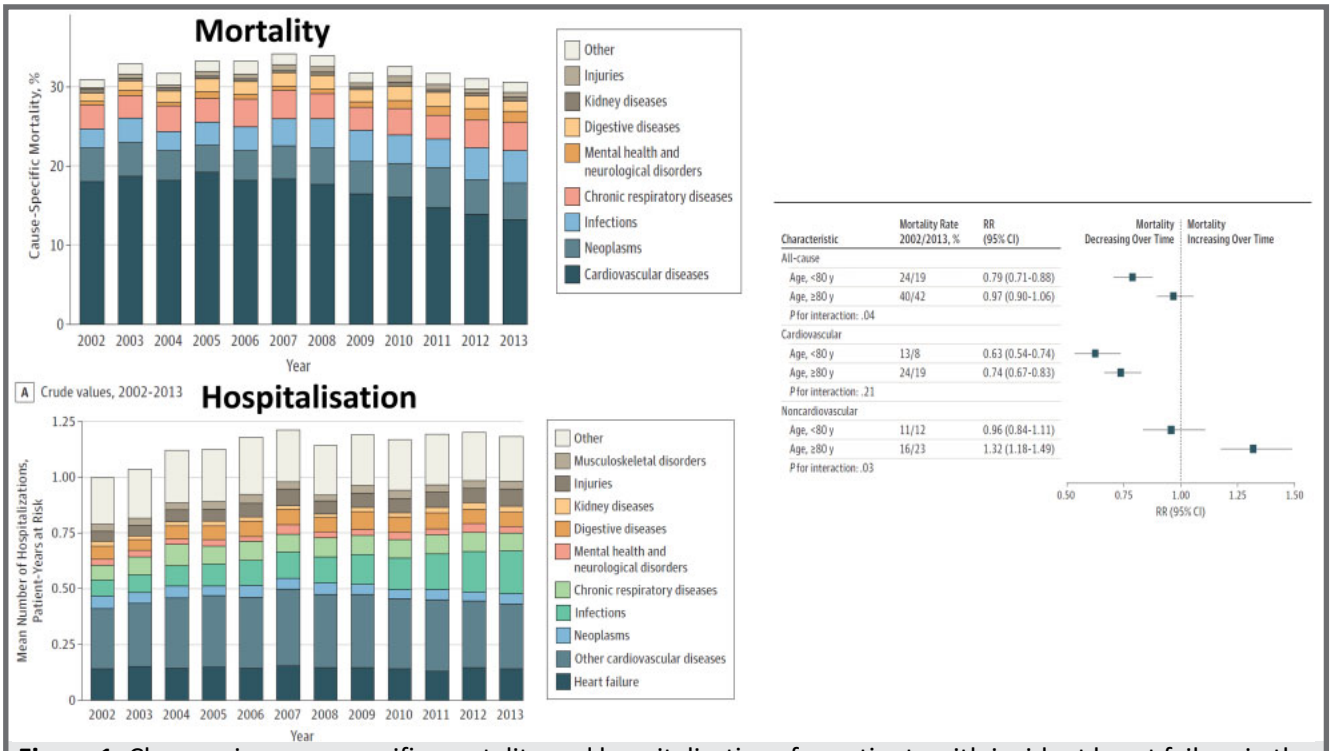


Figure 1: Changes in cause-specific mortality and hospitalizations for patients with incident heart failure in the UK between 2002 and 2013. Reproduced with permission from ref.[5]

Diagnosis

The Heart Failure Association of the European Society of Cardiology has proposed a new scoring system for the diagnosis of HFpEF.[23] Its practical utility awaits confirmation.[24] Simpler approaches may be preferred.[4]

Congestion

Congestion lies at the heart of failure.[25–27] Imaging has long been used to identify dilation of the atria and venous system, which might be termed haemodynamic congestion, for which natriuretic peptides are a useful biomarker.[25] More recently imaging has been used to identify accumulation of fluid in tissues (tissue congestion),[25,28–32] which may be associated with increases in the biomarker, (bio)-adrenomedullin.[33] Imaging and biomarkers in combination are both sensitive and specific for detecting a failing heart, a useful guide to the severity of congestion and prognosis and a potential therapeutic target indicating successful management. Imaging remains the preferred method for identifying the cause of heart failure. If congestion is central to the management of heart failure, then better monitoring[34] and more effective (diuretic) interventions (perhaps acetazolamide?[35]) should improve outcome (*Take home figure*).

Age and prognosis

Analysis of a large primary care database suggested that the cardiovascular (CV) prognosis of new-onset heart failure improved substantially between 2002 and 2014 [hazard ratio (HR): 0.73; 95% CI 0.68–0.80] for patients above and below the age of 80 years.[5] However, in those aged >80 years, the fall in CV mortality was entirely offset by non-CV mortality. In other words, treatment changed the way that elderly patients died but not overall mortality (*Figure 1*). Unfortunately, information on LVEF was not available; many patients will have had HFpEF and, therefore, caution should be exercised in attributing the reduction in CV mortality to treatment of heart failure. A systematic review of survey and registry data also suggested that the prognosis of heart failure had improved; important determinants of outcome were age and cardiology input to management.[36] Frailty, which might be considered a biological rather than chronological measure of age, may be an even more powerful predictor of disability and death.[37]

Guideline-recommendations for the treatment of HFrEF do not discriminate by age. The Swedish Heart Failure Registry found that prescription of ACE inhibitors or beta-blockers to patients with HFrEF aged >80 years was associated with a lower mortality.[38,39] However, observational associations have many explanations other than a therapeutic effect.[40] An individual patient-data meta-analysis of three RCTs of MRA (RALES, EMPHASIS, and TOPCAT-Americas)[13] suggested that MRAs exerted a similar reductions in mortality (by about ~25%) for patients with HFrEF above and below age 75 years but benefit was less certain for HFpEF.

The diversity of heart failure phenotypes

Precision-medicine, which should also be accurate, requires patients to be classified in a way that informs management. For oncology, this has focused on the genetic cause, tumour location, and spread. For heart failure, a multi-system disorder, it is much more complex.[41–47]

Current, therapeutically relevant classifications of heart failure include the severity of congestion (based on symptoms, signs, blood biomarkers, and imaging), CAD,

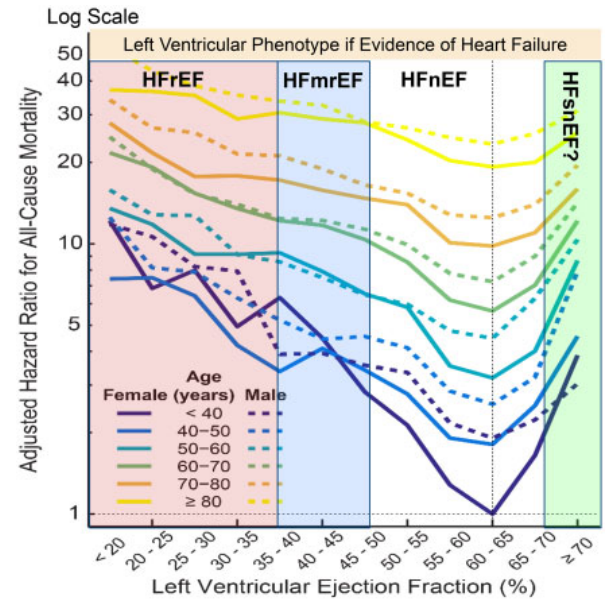


Figure 2: All-cause mortality according to left ventricular ejection fraction reported on >350 000 routine echocardiograms stratified by age and sex. HFmrEF, heart failure with mildly reduced ejection fraction; HFnEF, heart failure with normal ejection fraction; HFrEF, heart failure with reduced ejection fraction; HFsnEF, heart failure with supra-normal ejection fraction. Reproduced with permission from ref.[50]

heart rate and rhythm and QRS duration, blood pressure, serum potassium, renal function, indices of iron deficiency, mitral regurgitation, infiltrative myocardial disease (e.g. amyloid), and ventricular phenotype.[41,48] Optimal management of heart failure, with a few rare exceptions, requires only a modest amount of information but this still creates many thousands of patient-subgroups or clusters that might have different therapeutic needs.[45,46] Such subgroups will increase exponentially with the introduction of each new class of treatment. Despite this heterogeneity of substrate and wealth of interventions, precision-medicine is in its infancy in heart failure.

One therapeutically relevant classification of heart failure is by LVEF, a surrogate for left ventricular (LV) dilation. Prior to the 1980s, imaging of cardiac function was available only in expert centres. Clinical trials relied on the chest X-ray rather than the echocardiogram to support a diagnosis of heart failure. The success of trials such as SOLVD, MERIT, and CHARM, which all had a reduced LVEF as an inclusion criterion, led to the adoption of LVEF <40% as the European Society of Cardiology (ESC) Guideline definition for HFrEF.[49] Values ≥40% were termed HFpEF, comprising patients with a mid-range or mildly-reduced (HFmrEF), normal (HFnEF) and, perhaps, supra-normal (HFsnEF) LVEF.[50] Analyses of >350 000 routinely collected echocardiograms suggested that the nadir of risk, whether or not the patient has a diagnosis of heart failure, lies in the range 60–65% both for men and women. Interestingly, an LVEF of >70% was associated with similar risk as an LVEF of 30–40% (*Figure 2*).[50] The ESC Guidelines of 2016 introduced the concept of HFmrEF, for two main reasons. Firstly, because of imprecision, an echocardiographic measurement could not reliably distinguish between two measurements of LVEF within 10% of each other. Creating a buffer-zone between HFrEF and HFnEF meant that misclassification was less likely. This innovation meant that a trial of HFpEF could not claim benefit for all patients with an LVEF >40% based solely on an effect in those with an LVEF 40–49%. Secondly, the introduction of HFmrEF challenged the convention that an LVEF <40% was the correct threshold for HFrEF. Some analyses subsequent to the ESC 2016 Guideline suggest that patients with an LVEF <50% may respond to treatment similarly to those with an LVEF <40%.[51] However, this interpretation could reflect confirmation-bias amongst enthusiastic proponents of HFmrEF (*Table 1*). The evidence is not so consistent when looked at in its entirety, especially if mortality is considered a key outcome. In the future, many trials will probably include both HFrEF and HFmrEF, others will include HFmrEF, HFnEF, and HFsnEF, but NT-proBNP should be used routinely to stratify risk and potentially exclude low-risk patients who have little to gain from yet another 'pill'. Assuming we continue to use LVEF to classify patients, which seems likely since we cannot undo the past, then the major issue is where to set thresholds. For HFrEF, these have ranged from <25% in COPERNICUS, <30% in MADIT-II, and RAFT to <35–40% for the bulk of other trials.[51] For HFpEF, LVEF has generally been set at >40% or >45% with no upper limit. Analyses of recent trials have led some to suggest that, for patients with an elevated NT-proBNP, the upper limit of LVEF for HFmrEF should be increased to 55% or even 60% but this seems premature until consistency is demonstrated across multiple interventions and end-points and measurement precision for LVEF improves.

In a substantial observational study of patients with HFpEF and pulmonary hypertension, progression of right rather than left ventricular dysfunction was observed and was associated with an increased risk of atrial fibrillation (AF) and death.[52] Although right ventricular (RV) dysfunction is a powerful prognostic marker, remarkably few trials focusing on RV dysfunction have been done (SERENADE: https://clinicaltrials.gov/ct2/show/NCT03153111).

Atrial fibrillation

About a third of outpatients, perhaps more for those with HFpEF,[53] and more than half of those admitted with heart failure will be in AF, which is associated with an adverse prognosis even after correcting for age and other risk factors.[54] Controversy continues over whether medical management focused on rate control or restoration of sinus rhythm is the better strategy for AF and heart failure. In practice, the strategy needs to be tailored to the patient. When AF is the driver of symptoms and worsening cardiac function, restoration of sinus rhythm might be appropriate but when AF reflects the progression of underlying cardiac dysfunction, it may not.[55] For new-onset or paroxysmal AF associated with a clear deterioration in symptoms, restoration of sinus

Table 1: Evidence supporting or refuting the benefits of treatments for heart failure with a left ventricular ejection fraction in the "mid-range" (HFmrEF: 40–49%)

	LVEF	Symptoms	Hospitalization for heart failure[a]	CV death or HFH[a]	CV mortality	All-cause mortality
Diuretics						
Perindopril		Improved		**0.38 (0.19–0.75)**[b]		
Candesartan		Improved	**0.72 (0.55–0.95)∏**	**0.76 (0.61–0.96)**	0.81 (0.60–1.11)	0.79 (0.60–1.04)
Irbesartan				0.98 (0.85–1.12)Δ		
ARNI (Sac/Val) vs. Val[c]		Improved	0.77 (0.58–1.02)	0.81 (0.64–1.03)	0.94 (0.69–1.28)	NYR
MRA (overall)[c]			0.76 (0.46–1.27)	0.72 (0.50–1.05)	0.69 (0.43–1.12)	0.73 (0.49–1.10)
MRA (Americas)[c]			0.60 (0.32–1.10)	**0.55 (0.33–0.91)**	**0.46 (0.23–0.94)**	**0.58 (0.34–0.99)**
ß-Blocker (SR)	Improved		0.95 (0.68–1.32)	0.83 (0.60–1.13)	**0.48 (0.24–0.97)**	0.59 (0.34–1.03)
ß-Blocker (AF)	Improved		1.15 (0.57–2.32)	1.06 (0.58–1.94)	0.86 (0.36–2.03)	1.30 (0.63–2.67)
Ivabradine						
Digoxin			0.80 (0.63–1.03)	0.96 (0.79–1.17)	1.24 (0.94–1.64)	1.08 (0.85–1.37)
Rivaroxaban vs. aspirin			0.65 (0.40–1.05)			0.75 (0.53–1.06)
Rivaroxaban+ Aspirin vs. aspirin			0.87 (0.56–1.35)			**0.63 (0.44–0.90)**
CRT						
ICD						
BNP-guided therapy				Reduction from 67% to 44% patients with an event		

Statistically significant results are shown in bold on a blue background. Blank cells indicate no relevant information reported. Other data shown are not significant, although may not be heterogeneous with the effect in patients with a reduced left ventricular ejection fraction (HFrEF). Data for sacubitril/valsartan taken from reference for LVEF >42.5% to 52.5%.[98]
AF, atrial fibrillation; ARNI, angiotensin receptor-neprilysin inhibitors; BNP, brain natriuretic peptide; CRT, cardiac resynchronization therapy; ICD, implantable cardioverter defibrillator; LVEF, left ventricular ejection fraction; MRA, Mineralocorticoid receptor antagonist; SR, sinus rhythm, [A]Recurrent event analyses used when available, [B]The PEP-CHF trial specified inclusion of patients with LVEF 40–49% as was LVEF >49% but did not report effects in this subgroup. However, it did report effects in patients with a prior myocardial infarction who were more likely to have HFmrEF, [C]Stronger effect in women.

rhythm may be warranted to improve symptoms. For long-standing AF and heart failure with markedly dilated atria, sustained restoration of sinus rhythm and atrial contraction is less likely. Optimal pharmacological management includes anticoagulation, avoiding toxic antiarrhythmic agents and lenient ventricular rate control. Beta-blockers are the agent of choice for rate control, a resting day-time ventricular rate of 70–90 b.p.m. is preferred,[49] which may require only modest doses; digoxin should be used sparingly, if at all. Unfortunately, RCTs of rate vs. rhythm control for AF have failed to optimize the rate control strategy in the above fashion.

A meta-analysis of RCTs of rate vs. rhythm control included four trials (*n* = 2486) comparing pharmacological rhythm to rate control found no difference in mortality or thromboembolic events but an increase in hospitalizations, often due to recurrent AF, in the rhythm control group.[56] Six trials (*n* = 1112) comparing AF ablation with rate control reported reductions in mortality (0.51; 95% CI 0.36–0.74), hospitalizations (0.44; 95% CI 0.26–0.76), and stroke (0.59: 95% CI 0.23–1.51) and an improved quality of life.[56] However, none of the trials individually had a robust result, patients were highly selected and the rate control strategy was not optimal. As such, this meta-analysis should be considered hypothesis generating. Further trials are required with greater involvement of heart failure physicians.

Implanted electrical devices

The controversy over the role of high-energy devices for heart failure continues. Long-term follow-up of cardiac resynchronization therapy (CRT) in a French Registry showed a low rate of sudden death amongst patients who received CRT-Pacing (without a defibrillator).[57–59] A systematic review of observational studies and RCTs reported that differences in the rate of sudden death with CRT-Pacing and CRT-D were narrowing.[58] RCTs comparing CRT-Pacing and CRT-D are underway[59] (*Take home figure*). Whether myocardial scar found on cardiac magnetic resonance imaging identifies patients with more to gain from an implantable cardioverter defibrillator (ICD) is also under investigation[60] (CMR_GUIDE; https://clinicaltrials.gov/ct2/show/NCT01918215). Retrospective analysis of SCD-HeFT found that patients with T2DM did not benefit from an ICD.[61] An individual patient-data meta-analysis confirmed a reduction in sudden death with MRA.[62] A systematic review identified 22 studies

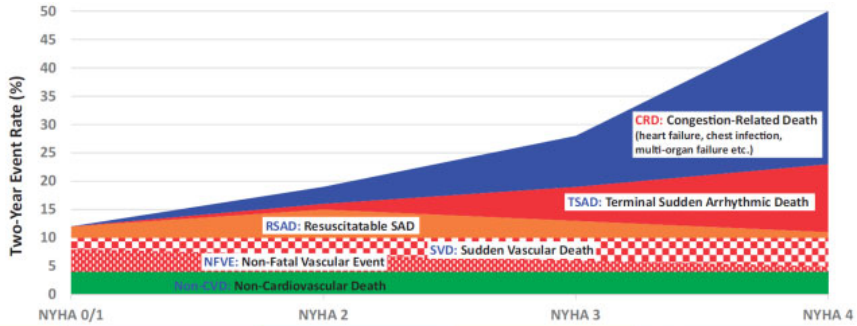
with post-mortem interrogation of ICDs; the analysis suggested that 24% of sudden deaths were not arrhythmic.[63] A substantial multi-point pacing trial failed, so far, to show improvements in the clinical or echocardiographic response to CRT.[64]

Mitral regurgitation

COAPT suggested that a percutaneously delivered mitral clip could reduce functional (secondary) regurgitation with a subsequent substantial improvement in morbidity and mortality that was moderately cost-effective in a US healthcare context (US$40 361 per life-year gained and $55 600 per quality-adjusted life year).[65–68] Two-year follow-up of MITRA.fr suggested no benefit.[69] A possible explanation for the apparent discrepancy could be the ratio of the severity of LV dysfunction to the severity of mitral regurgitation. When regurgitation is disproportionate to the severity of LV dysfunction it may drive disease progression and correction may improve outcome.[70,71] When regurgitation is proportionate to the severity of LV dysfunction, fixing the mitral regurgitation may be less useful because myocardial dysfunction drives disease progression. The concept is simple and plausible but application in practice may be difficult. Mitral regurgitation offloads the LV and may mask dysfunction. It is also likely that there is a spectrum of primary and secondary mitral regurgitation, with some patients having a mixed picture. More experience and further data from RCTs may improve patient selection (RESHAPE-HF2: https://clinicaltrials.gov/ct2/show/NCT02444338). However, optimizing guideline-recommended therapy, including diuretic dose, may cause mitral regurgitation secondary to dilation of the LV and mitral ring to improve or resolve. Other technologies for secondary mitral[72] and tricuspid regurgitation[73,74] are being developed.

Coronary artery disease

In COMPASS (*n* = 27 395), 5902 with CAD, in sinus rhythm and with a diagnosis of heart failure (predominantly HFpEF) were randomly assigned them to aspirin 100 mg/day, rivaroxaban 5 mg bd or aspirin and rivaroxaban 2.5 mg bd.[75,76] The study was stopped early for benefit on the primary endpoint (a composite of CV death, stroke, or myocardial infarction) with the combination compared with aspirin alone. Further analysis suggested a reduction in all-cause mortality for patients with heart failure, especially HFpEF, assigned to combination therapy (HR: 0.63; 0.44–0.90) or rivaroxaban alone (HR: 0.75; 0.53–1.06) with an estimated 4% absolute difference at 2 years; rather similar to the magnitude of effect in HFrEF for sacubitril-valsartan[77] or dapagliflozin[78] (*Figure 3*). This suggests that coronary events might be an important driver of death in HFpEF (*Take home figure*), although effects of rivaroxaban on endothelial function, inflammation, and fibrosis should not be discounted. The analysis also suggests that those who do not have heart failure have little to gain from additional treatment with rivaroxaban.
However, for patients with HFrEF, CAD in sinus rhythm with a recent hospital discharge for worsening heart failure, addition of rivaroxaban 2.5 mg bd to background anti-platelet therapy did not improve overall prognosis, although a composite of vascular outcomes (stroke, myocardial infarction, and sudden death) was reduced, driven mainly by a reduction in stroke.[79,80] This suggests



	NYHA 0/1		NYHA 2		NYHA 3		NYHA 4	
	Absolute Rate	% of Events	Absolute Rate	% of Events	Absolute Rate	% of Events	Absolute Rate	% of Events
CRD	0%	0%	3%	16%	9%	32%	27%	54%
TSAD	<1%	<1%	1%	5%	6%	21%	12%	24%
RSAD	2%	17%	5%	26%	3%	11%	1%	2%
SVD	2%	17%	3%	16%	4%	14%	5%	10%
NFVE	4%	33%	3%	16%	2%	7%	1%	2%
Non-CVD	4%	33%	4%	21%	4%	14%	4%	8%

Take home figure: Two-year cause-specific mortality and non-fatal vascular events for patients with cardiovascular disease according to New York Heart Association (NYHA) class. Numbers and proportions are a conceptual representation of absolute and relative risk and are not strictly evidence-based. Note that for patients in NYHA Class 4, interventions for sudden arrhythmic death may be ineffective or fail to lead to a meaningful prolongation of life because the patient is likely soon to die of worsening heart failure. CRD, congestion-related death, otherwise called death due to worsening heart failure; NFVE, non-fatal vascular event (e.g. myocardial infarction and stroke; note that events are more likely to be suddenly fatal as heart failure progresses); non-CVD, non-cardiovascular death; RSAD, resuscitatable sudden arrhythmic death; SVD, sudden vascular death; TSAD, terminal (non-resucitatable) sudden arrhythmic death. Reproduced with permission from ref.[59]

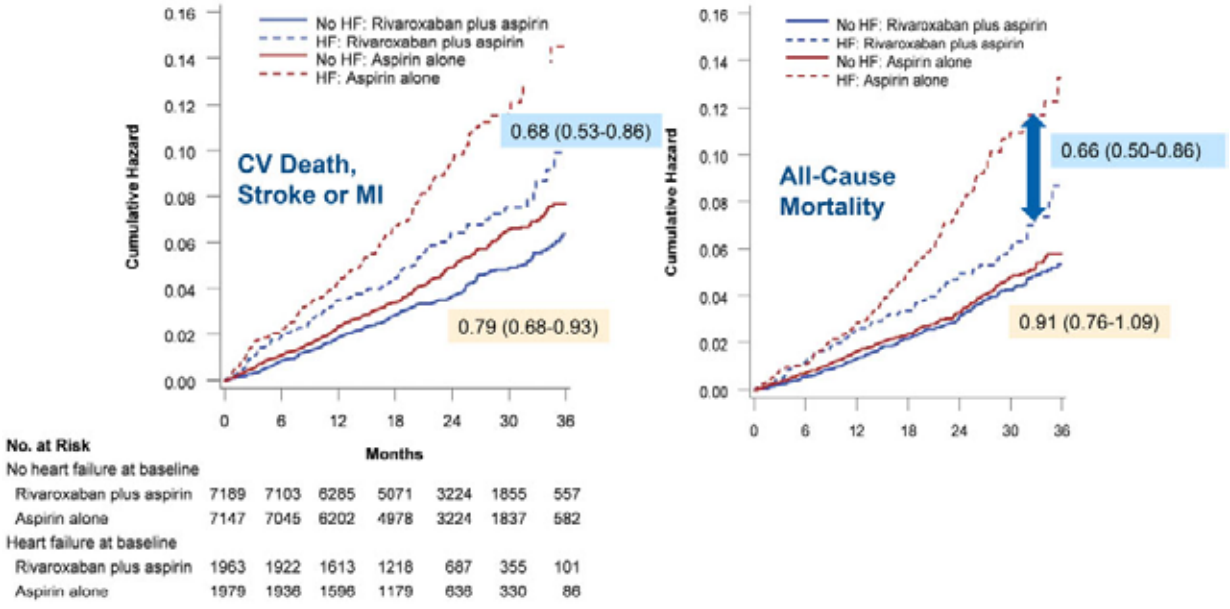


Figure 3: Effect of rivaroxaban 2.5 mg bd and aspirin 100 mg/day compared with aspirin alone for stable CAD, sinus rhythm and heart failure (predominantly heart failure with preserved ejection fraction) in COMPASS-HF. Reproduced with permission from ref.[75]

that for patients with stable CAD and more advanced heart failure, hospitalizations, and deaths due to worsening heart failure are not greatly influenced by antithrombotic therapy (*Take home figure*).

Angiotensin receptor-neprilysin inhibitors

Heart failure with reduced ejection fraction

As experience in the implementation of angiotensin receptor-neprilysin inhibitors (ARNIs) grows, both in clinical trials and in clinical practice, there is a strong argument to consider them as first-line agents, rather than angiotensin converting-enzyme inhibitors (ACEi) or angiotensin receptor blockers (ARB), for the treatment of HFrEF. In PIONEER-HF,[81] 881 patients with an LVEF ≤40% who were hospitalized for worsening heart failure were randomly assigned, without a run-in period, to sacubitril/valsartan or enalapril prior to discharge and followed for 8 weeks to determine the effect on plasma concentrations of NT-proBNP; about one-third had new-onset heart failure. Sacubitril-valsartan exerted a greater reduction in NT-proBNP. Reductions in markers of myocardial injury or stress, high-sensitivity cardiac troponin-T and soluble ST2, were also observed. These effects appeared early after randomization (within 1–4 weeks). Moreover, patients assigned to sacubitril/valsartan were less likely to experience adverse outcomes within the first 8 weeks. TRANSITION[82] randomly assigned 1002 patients to pre- or post-discharge initiation of sacubitril/valsartan, showing no adverse consequences to earlier administration.
EVALUATE[83] compared the effects of sacubitril/valsartan and enalapril on aortic stiffness in HFrEF most of whom were already chronically treated with an ACEi or ARB. After 24 weeks treatment, no differences in aortic stiffness were observed but slightly greater reductions in LV end-diastolic and systolic volumes were observed with sacubitril/valsartan compared with enalapril, although changes in LVEF were similar. Mitral E-velocity and left atrial volume declined, consistent with a fall in left atrial pressure. PROVE-HF,[84] an observational study, had similar findings and showed that most of the decline in NT-proBNP occurred within 14 days consistent with the rapid onset of clinical benefit observed with sacubitril/valsartan in trials and clinical practice. PRIME[85] was an RCT (n = 118) comparing the effects of sacubitril/valsartan or valsartan on functional mitral regurgitation in patients with an LVEF between 25% and 49% who were already receiving an ACEi or ARB. Those assigned to sacubitril/valsartan had greater reductions in mitral regurgitation and LV end-diastolic and left atrial volumes but LVEF increased by a similar small amount in each group (about 2.5%).
Further reports from PARADIGM-HF suggest that, compared with enalapril, sacubitril/valsartan may improve markers of collagen metabolism, in particular, decreasing synthesis of type-I collagen, which makes an important contribution to myocardial stiffness.[86] In I-PRESERVE, irbesartan (an ARB) did not affect collagen biomarkers compared with placebo.[87]

Heart failure with preserved ejection fraction

PARAGON-HF investigated the effect of sacubitril/valsartan compared to valsartan alone on morbidity and mortality in patients with HFpEF (defined as an LVEF >45%).[88] It was the first RCT since PEP-CHF[89] to require patients to be treated with diuretics, the first-line treatment for the relief of symptoms and signs of congestion, and to have echocardiographic evidence of cardiac dysfunction. It was also the first large trial of HFpEF to require all patients to have raised plasma concentrations of natriuretic peptides, the most powerful, widely available prognostic marker in HFpEF. Sacubitril/valsartan was compared with valsartan rather than placebo be-

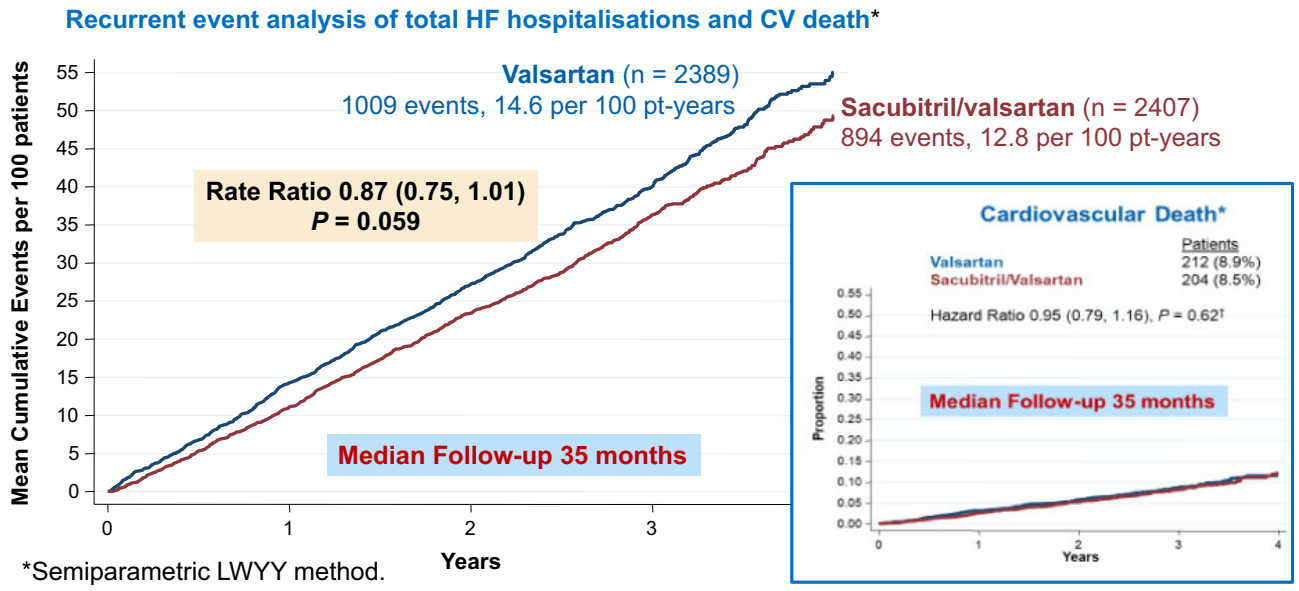


Figure 4: Effect of sacubitril/valsartan compared with valsartan for heart failure with preserved ejection fraction in PARAGON-HF. Reproduced with permission from ref.[91]

cause many patients eligible for PARAGON-HF had indications for ACE inhibitors and ARBs such as hypertension and CAD. The only trial comparing valsartan to placebo in HFpEF was of modest size and neutral.[90] Previous RCTs of other ARBs, including candesartan (CHARM-Preserved) and irbesartan (I-PRESERVE) failed to show substantial benefit for HFpEF.[88] Patients had to tolerate, sequentially, both valsartan and sacubitril/valsartan at half the intended target dose before randomization. This simulates clinical practice (doctors do not usually prescribe medicines to patients unwilling or unable to take them) and reduces the risk of a neutral trial-outcome due to low adherence. Of 10 539 patients screened, 4822 were randomized.

PARAGON-HF was neutral for its primary endpoint (CV death or the total number of recurrent hospitalizations for heart failure[91]; *Figure 4*). Some have argued that the *P*-value was very close to 0.05 and that it was 'almost' positive. This misses the point. The trial shows that the size of the potential benefit of sacubitril/valsartan for HFpEF is modest, regardless of the *P*-value and that the treatment is, overall, unlikely to be cost-effective. Accordingly, we should look for more effective treatments or, more controversially, subgroups that obtain greater benefit. After a median follow-up of 35 months, 23% of patients experienced a primary event but the annual incidence of CV and all-cause mortality were, respectively, only about 3% and 5%, which is similar to those for previous trials of HFpEF and for elderly patients with resistant hypertension assigned to placebo in HYVET.[92] Although <3% of patients were reported to have heart failure in HYVET, a combination of indapamide and perindopril reduced all-cause mortality and cut the incidence of heart failure by >50%. Many of these patients probably had undiagnosed HFpEF prior to randomization. Higher rates of hospitalization for heart failure in trials of HFpEF compared to hypertension may well reflect ascertainment bias, as clinicians who are interested or expert in the management of heart failure are more likely to diagnose or report heart failure events. Overall, these trials suggest that the mortality rate and possibly the rates of cardiovascular and all-cause hospitalization may be similar in patients with and without a diagnosis of HFpEF, if they have a similar burden of co-morbidities. However, it is also likely that many patients with hypertension, CAD and T2DM have undiagnosed heart failure.

Subgroup analysis suggested that the effect of sacubitril/valsartan on the primary endpoint was greater for patients with an LVEF below the median (57%), but this was driven almost entirely by an effect on hospitalization for heart failure rather than on CV death.[93] The effect of sacubitril/valsartan on the primary endpoint was also greater for women and this was true throughout the studied range of LVEF, but again this was driven by a difference in hospitalization for heart failure and not CV mortality.[94] Reductions in NT-proBNP were similar for each sex. Sacubitril/valsartan appeared to have a favourable effect on quality of life for men but not for women. Patients with a recent heart failure hospitalization may also have benefited more.[95] These observations should be interpreted in the light of a trial that was neutral for its primary endpoint. No effect was observed on mortality and the benefits of treatment on quality of life and hospitalizations for heart failure according to sex were inconsistent. In PARADIGM-HF, no difference in treatment effect according to sex was observed. A further sizeable RCT in HFpEF, PARALLAX-HF, investigating the effects of sacubitril/valsartan on quality of life and exercise capacity will provide more evidence in 2020 (https://clinicaltrials.gov/ct2/show/NCT03066804).

Do women and men respond differently to treatment?

An analysis of 12 058 patients with HFrEF in two large trials found that women had more severe symptoms,

similar LVEF but a substantially better prognosis than men, even after adjusting for key prognostic variables including aetiology and NT-proBNP (HR: 0.68; 0.62–0.89).[96] A combined analysis of PARAGON-HF and PARADIGM-HF suggested that patients with HFrEF and HFpEF had similarly impaired quality of life but that women generally reported a worse quality of life than men.[97] In an observational analysis of patients with HFrEF, the BIOSTAT survey also found that women generally had a better prognosis than men despite being prescribed lower doses of beta-blockers and ACE inhibitors.[98] Interestingly, men and women had the same heart rate, the pharmacodynamic marker of beta-blocker dose. For patients with HFpEF in the TOPCAT trial, reductions in mortality, but not hospitalizations for heart failure, were greater for women, although the interaction was statistically significant only for all-cause mortality.[99] In the PARAGON-HF trial (HFpEF), women obtained greater benefit than men throughout the studied range of LVEF but the difference was driven by differences in the rate of hospitalization for heart failure rather than mortality.[94] One obvious difference between men and women, on average, is size. Cardiac resynchronization therapy is reputed to be more effective in women than men, but differences disappear once adjusted for height.[100] Many medicines are cleared by the kidney. Estimated glomerular filtration rate (eGFR) is indexed to body surface area (BSA) but doses of treatment are usually not. A woman (or small man) weighing 64 kg and 160 cm tall has BSA of 1.67 m^2 using the Dubois formula and a man (or large woman) weighing 85 kg and 180 cm tall has a BSA 2.05 m^2. If both have an eGFR of

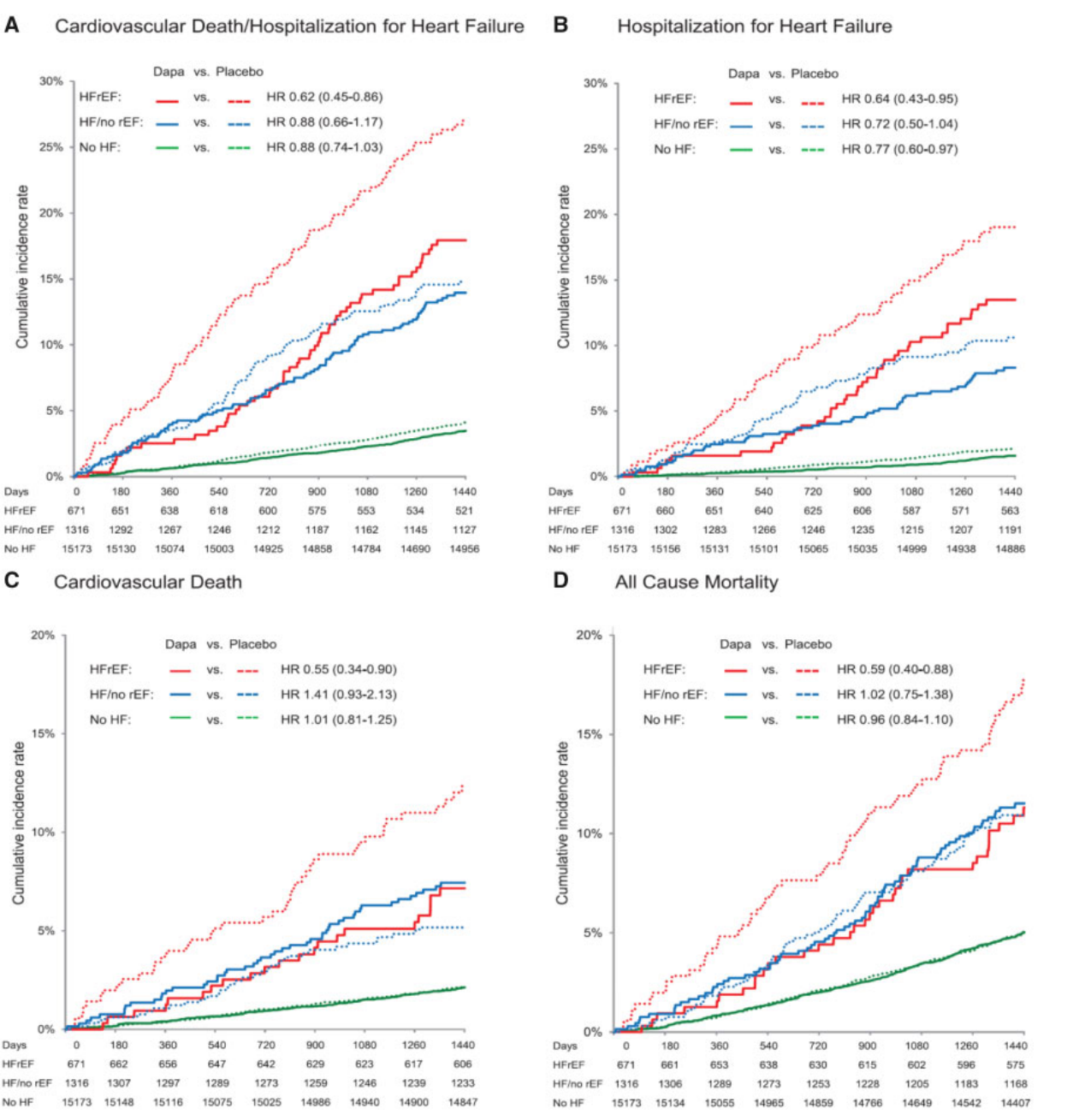


Figure 5: Effect of dapagliflozin compared with placebo in type-2 diabetes mellitus in patients with heart failure with reduced ejection fraction, heart failure with preserved ejection fraction, or without heart failure in DECLARE. Reproduced with permission from ref.[111]

60 mL/kg/m^2, then the woman (or small man) has an un-indexed eGFR of 100 mL/min and the man (or large woman) has an un-indexed eGFR of 123 mL/min. If a medicine is cleared by the kidney then perhaps smaller people require lower doses to achieve the same plasma therapeutic concentration and clinical benefit?

Sodium-glucose cotransporter-2 inhibitors

Sodium-glucose cotransporter protein-2 (SGLT2) is found mainly in the proximal renal tubule and to a lesser extent in other organs. SGLT1 is abundant in the intestine and myocardium. SGLT2 inhibitors (SGLT2i) cause glycosuria, improving glycaemia, which led to their development for the treatment of T2DM, and an osmotic diuresis, leading to a contraction of plasma volume.[101,102] SGLT1 inhibitors reduce intestinal glucose absorption, which can cause diarrhoea but might have favourable effects on myocardial energy-utilization.[103] Most SGLT2i are highly selective, including dapagliflozin and empagliflozin, but sotagliflozin is less selective.[103]

EMPA-REG enrolled 7020 patients with T2DM, about 10% of whom had heart failure (LVEF was not measured) and showed that empagliflozin reduced the risk of hospitalization for heart failure and mortality.[104] Within a few weeks of initiating empagliflozin, body weight, and blood pressure fell and haematocrit rose, consistent with a diuretic effect. Subsequent RCTs of other SGLT2i in T2DM had similar findings. Meta-analyses suggested that SGLT2i were the hypoglycaemic agents most likely to reduce incident heart failure,[105–107] whilst observational data raises concerns about insulin therapy.[108] A meta-analysis of RCTs of empagliflozin, canagliflozin, and dapagliflozin for T2DM, including >30 000 patients, showed benefit, at least for those with established CV disease.[109] For the outcome of hospitalization for heart failure or CV death, the annual rate was about 0.6% for the 13 672 patients with multiple risk factors but without established CV disease, about 3% for the 20 650 patients with established atherosclerotic disease and about 6% for 3891 patients with heart failure at baseline; the relative risk reductions with SGLT2i in these populations were 16%, 24%, and 29%, respectively, without evidence of heterogeneity amongst agents. The largest of these trials, DECLARE,[110] included 17 160 patients of whom 671 had HFrEF and 1316 had HFpEF or an unspecified LVEF. In a subgroup analysis,[111] dapagliflozin reduced hospitalizations for heart failure and CV mortality for HFrEF but not for other patient-groups (*Figure 5*).

DAPA-HF[78,112] enrolled 4744 patients and followed them for a median of 18.3 months, demonstrating that addition of dapagliflozin to guideline-recommended therapy for HFrEF-reduced hospitalizations for heart failure by 30% and mortality (mainly cardiovascular) by 18%, preventing 3–5 hospitalizations and 1–2 deaths per 100 patients treated per year (*Figure 6*). Patients were somewhat less likely to experience serious adverse events, especially renal, with dapagliflozin compared with placebo. The benefits appeared consistent across subgroups, although patients with evidence of more severe congestion (worse NYHA class or higher NT-proBNP) may have received less benefit. Importantly, benefits were similar for those with and without T2DM and regardless of age.[113] Dapagliflozin also improved quality of life,[114] an effect that was confirmed in a smaller RCT (DEFINE)[115] that followed 263 patients for 12 weeks; about one in six patients got a meaningful benefit, either prevention of worsening or an improvement in symptoms, compared with placebo.

In DAPA-HF, the placebo-corrected decline in weight between baseline and 8 months was 0.87 kg and this was associated with a small fall in NT-proBNP and systolic blood pressure and a small increase in haematocrit and serum creatinine. These findings are again consistent with the belief that SGLT2i exert at least some of their benefits by enhancing diuresis, either through an osmotic effect of glycosuria or by interfering with sodium-hydrogen exchange in the nephron.[116] The effects of SGLT2i appear early, consistent with an immediate haemodynamic effect. However, alternative or additional explanations for the effect of SGLT2i have been proposed. A small RCT suggested that empagliflozin stimulated production of erythropoietin leading to a rise in haematocrit and a fall in ferritin, a marker of inflammation and iron deficiency, although not transferrin saturation, a marker of iron deficiency alone.[117] However, administration of exogenous erythropoietin did not reduce morbidity or mortality in the RED-HF trial.[118] Others have suggested that SGLT2i increase the production of ketones, which may be a more efficient myocardial energy substrate, or block myocardial sodium–hydrogen exchanger-3, which may improve myocardial function and reduce fibrosis.[119,120] An RCT of empagliflozin in patients with T2DM but not heart failure[121] suggested little effect on cardiac function or remodelling; RCTs of the effects of SGLT2i on cardiac function in patients with HFrEF and HFpEF are awaited. Future trials will confirm whether the benefit observed in DAPA-HF is a class effect and whether they are effective for HFpEF or when congestion is severe.[122,123]

Acute heart failure

Two large RCTs of serelaxin failed to confirm the results of the original RELAX-AHF trial. RELAX-AHF-EU,[124] an open-label RCT (n = 2688), reported a similar and low rate for mortality (≤2%) and re-admissions for heart failure (<1%) at 14 days for patients assigned placebo or serelaxin, despite a reduction in worsening heart failure at day 5 [6.7–4.5% (P < 0.008)]. The RELAX-AHF-2 trial,[125] a double-blind RCT (n = 6545), reported that the rates of worsening heart failure in the first 5 days (about 7%) and 180-day mortality (about 11%) were similar for placebo and serelaxin. The failure of so many short-term interventions for AHF may reflect failed therapeutic concepts, ineffective interventions, or problems with trial design. RCTs of AHF are difficult to implement, especially if conducted double-blind. Indeed, GALACTIC, a trial of personalized, early intensive and sustained vasodilation with nitrates and hydralazine, also failed to

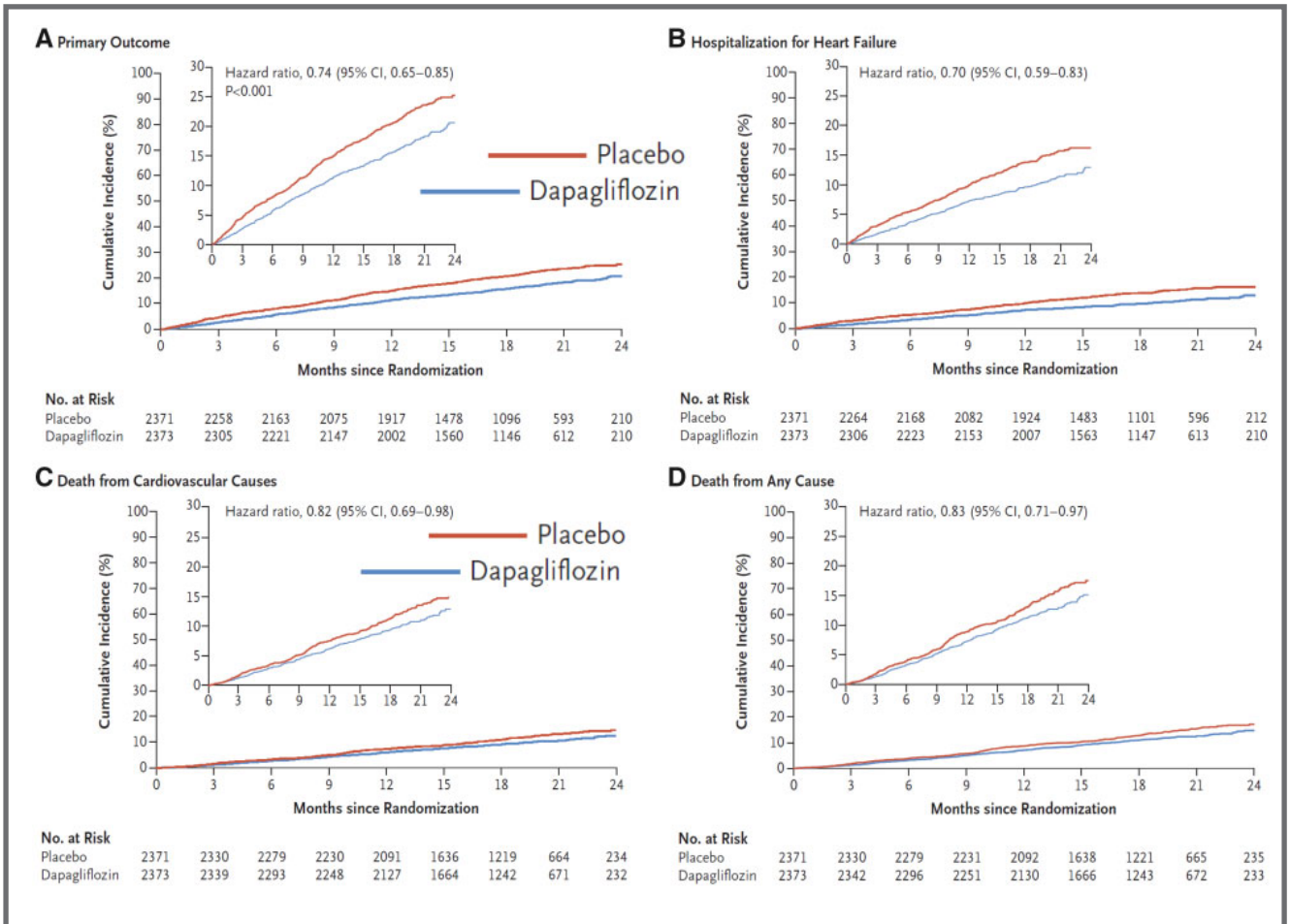


Figure 6: Effect of dapagliflozin compared with placebo in patients with heart failure with reduced ejection fraction, with or without type-2 diabetesmellitus in DAPA-HF. Reproduced with permission from ref.[78]

show benefit, calling into question the concept of vasodilator therapy for the routine management of acute heart failure.[126] Many patients present with acute breathlessness in the middle of the night. It is difficult to have research staff available '24/7' when there is no 'gateway' similar to a coronary care unit or catheter laboratory. Compassionate investigators may also be unwilling to enrol frail elderly patients who are most at risk of adverse outcomes. Moreover, breathlessness usually responds to oxygen and diuretics within hours,[127] especially for patients with a systolic blood pressure ≥125 mmHg, as required in the serelaxin trials. On the other hand, patients with extensive peripheral oedema,[26] renal dysfunction, and a low blood pressure, who often do not constitute an acute emergency have a poor prognosis and an unmet need for more effective interventions; pharmacological, or device.[127,128]

Stem cell therapy

Intra-myocardial injection of stem cells failed to improve weaning from left ventricular assist devices.[130]

Heart failure in patients with cancer

Interest in cardio-oncology reflects increasing survival after treatment for cancer, growing awareness of the CV toxicity associated with both established and new treatments for cancer, and interest in personalized risk-profiling prior to chemotherapy. People with cardiomyopathy-related gene mutations may be more prone (7.5% of those with compared to 1.1% of those without a titin gene mutation) to develop ventricular dysfunction after the administration of chemotherapy.[131]

Interruption of trastuzumab is associated with a higher risk of cancer recurrence in women with early invasive HER2^{+ve} breast cancer; about 60% of interruptions are for cardiotoxicity.[132] An observational study showed that of 30 women receiving HER2-targeted therapies who developed an LVEF of 40–49% and were treated prospectively with beta-blockers and ACE inhibitors, only three went on to develop severe heart failure or a LVEF <35%.[133] Cardiac function rarely returned to normal after completion of treatment, challenging the view that trastuzumab-related LV dysfunction is usually reversible. A recent study reported high rates of CV events, especially heart failure, amongst patients with multiple myeloma receiving potent proteasome inhibitors, such as carfilzomib and bortezomib,[134] which were associated with much poorer survival. Risk factors for developing a CV event included elevated pre-treatment NT-proBNP or an increase during treatment. A systematic review of prophylactic use of renin–angiotensin–aldosterone antagonists and beta-blockers identified 22 relevant RCTs, of which the largest had only 206 patients,[135,136] but found no convincing evidence of clinical efficacy

Implementation of therapy

Analyses of administrative data from primary care in the UK suggest that implementation of therapy has improved substantially over the last decade, with 72% now prescribed a beta-blocker, although many patients remain on less than target doses.[6] Amongst hospital discharges in England and Wales, 89% of those with HFrEF were discharged on a beta-blocker (https://www.nicor.org.uk/wp-content/uploads/2019/09/Heart-Failure-2019-Report-final.pdf), which is very similar to that observed in patients with HFrEF selected for enrolment in the ESC-EURObservational Heart Failure Long-Term Registry.[137] However, an analysis of Medicare beneficiaries in the USA found that only 51% of patients with HFrEF were prescribed a beta-blocker after a first or recurrent hospitalization for heart failure and only 12% received at least ≥50% of the target dose by 1 year.[138] This suggests that the organization of care for HFrEF makes an important difference to treatment and, consequently, outcome. However, a cluster RCT (*n* = 2494) of service redesign aiming to improve hospital-to-home transition, which included self-care education, a structured hospital discharge summary, family physician follow-up within 1 week, and, for high-risk patients, home-visits, did not substantially improve patient well-being or outcome.[139] An RCT (*n* = 110) showed that frequent (several times per month) visits to participating community pharmacies could improve medication adherence and well-being.[140] An RCT of 450 patients found benefits of e-Health intervention on self-care behaviour and quality of life in the first 3 months after initiation but not thereafter,[141] with no effect on hospitalizations or mortality. There are many reasons why RCTs of complex interventions fail including inadequate power, suboptimal trial design, already excellent or unintended improvements in care for the control group, lack of long-term engagement and motivation of staff and patients, inclusion of patients for whom pharmacological intervention is largely ineffective (e.g. HFpEF) but sometimes we just have to admit that what should work does not. More evidence is required; learning from past experience.[142]

Rehabilitation

Systematic reviews suggest that exercise-based rehabilitation can improve patients' well-being and exercise capacity and reduce heart failure-related and all-cause hospitalization but may not reduce mortality, despite potentially improving adherence to treatment.[143–147] The best and most cost-effective service-model is a topic of active research.[148,149]

Palliative care

Morphine relieves chronic breathlessness in patients with chronic lung disease but data for heart failure are sparse. An RCT of 45 patients failed to demonstrate important clinical benefits of morphine administration to patients with HFrEF or HFpEF predominantly in NYHA functional class III.[150]

Withdrawing treatment for heart failure after recovery

Withdrawing treatment from patients with idiopathic or genetically determined dilated cardiomyopathy who have experienced full recovery of ventricular function should be done with great caution if at all.[151] Although patients with a recovered LVEF (HFrcEF) may have a better prognosis, it may still not be good.[152] Further research is required for peripartum and other specific types of cardiomyopathy. A recent report from an old trial (DIG), suggested that withdrawal of digoxin was associated with an increased risk of hospitalization for heart failure but did not affect mortality.[153] An RCT of 188 patients with stable heart failure from Brazil suggested that 75% of patients could be withdrawn from loop diuretics for at least 90 days without deterioration in symptoms, need for reinstitution of diuretic therapy, or a rise in plasma NT-proBNP.[154] This is in stark contrast to a smaller RCT from the UK, where withdrawal of diuretics and other therapies for 48 h led to a doubling of plasma concentrations of NT-proBNP, an increase in LV and left atrial volumes and worsening symptoms.[155]

Conclusion

Great progress in the understanding and management of heart failure has been made over the last year. New controversies and new evidence challenge many old assumptions. As ever, some will resist progress and others will embrace it. You, the reader, must help our professions and patients find the correct balance between reckless enthusiasm and diagnostic and therapeutic inertia.

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