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PROMENA PARADIGME ZA STABILNU KORONARNU BOLEST U HRONIČNI KORONARNI SINDROMI. NOVINE U VODIČU EVROPSKOG UDRUŽENJA KARDIOLOGA IZ 2019. GODINE.

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SAŽETAK: Iako je engleski lekar Heberden opisao anginu pectoris (AP) još pre 2 i po veka, naše razumevanje ovog sindroma, kako uzroka, optimalnog dijagnostičkog pristupa tako i lečenja, nastavlja da se razvija. Novi vodič Evropskog udruženja kardiologa iz 2019 godine donosi pre svega promenu paradigme za stabilnu koronarnu bolest (SKB) u sveobuhvatni termin hronični koronarni sindromi (HKS), koja suštinski znači da hronična koronarna bolest (HKB) ili ishemična bolest srca (IBS) ima kompleksne kliničke scenarije i može imati periode nestabilnosti u bilo kojoj evolucionoj fazi. Rezultati esencijalne COURAGE studije te najnovijih studija: ISHEMIA, ORBITA i metanaliza o HKS kao i ključne poruke Evropskog Vodiča za dijagnostiku i lečenje hroničnih koronarnih sindroma (HKS) bacaju svetlo na problematiku koronarne bolesti, bolesti koja još uvek prednjači u svetskom mortalitetu. Koronarna bolest (KB) ima duge stabilne perode ali zbog akutnih aterotrombotskih događaja, erozije ili rupture aterosklerotskog plaka može preći u neki od akutnih koronarnih sindroma (AKS). Bolest je hronična, najčešće progresivna i zato ozbiljna čak i u asimptomatskim fazama. Dinamična priroda KB ispoljava se u različitim kliničkim prezentacijama, koje kategorizujemo u bilo akutne, bilo hronične koronarne sindrome. Promena paradigme naglašava činjenicu da dinamički procesi akumulacije u aterosklerotske plakove i funkcionalne alteracije koronarne cirkulacije, mogu biti modifikovani promenom životnih navika, farmakološkom terapijom i revaskularizacijom miokarda (RM), koje dovode do stabilizacije ili regresije bolesti ali nažalost ne i do potpunog izlečenja. Od kardinalnog značaja je pažljiva evaluacija anamneze, karakterizacija anginoznih i drugih simptoma i evaluacija rizik faktora i manifestacija predhodnih kardiovaskularnih bolesti (KVB), kao i procena adekvatnosti fizičke aktivnosti i tolerancije napora. U sadašnjem vodiču za HKS je prepoznato 6 vodećih i najčešćih kliničkih sindroma-scenarija : 1. Pacijenti sa suspektom KB i stabilnom anginom pectoris i/ili dispnejom na napor; 2. Pacijenti sa novonastalom srčanom insuficijencijom (SI) ili disfunkcijom leve komore (DLK) i suspektom KB; 3. Asimptomatski i simptomatski bolesnici sa stabilizovanim simptomima koji traju manje od jedne 1 godine posle AKS ili skorašnje revaskularizacije miokarda (KRM); 4. Asimptomatski i simptomatski pacijenti više od 1 godine protekle posle AKS ili RM; 5. Pacijenti sa anginom pectoris i suspektom vazospastičnom ili mikrovaskularnom bolešću; 6. Asimptomatske osobe u kojih je KB otkrivena na skriningu. Svaki od ovih scenarija je klasifikovan kao HKS i posledice su različitih evolucionih faza hronične KB, te imaju različit rizik za buduće neželjene kardiovaskularne (KV) događaje. Pretest verovatnoća (PTP) koronarne bolesti, bazirana na starosti, polu i kvalitetima simptoma, podvrgnuta je reviziji i izmenjena u odnosu na predhodni vodič iz 2013. godine. Uveden je i novi termin: Klinička verovatnoća KB (KPKB) koji uključuje kako PTP tako i razne rizik faktore aterosklerotske KB i služi da isključi ili potvrdi sumnju na KB. Opšti metodološki pristup za inicijalnu dijagnozu za pacijente sa AP i suspektom opstruktivnom KB uključuje 6 koraka. KORAK 1-Procena simptoma i znakova za identifikaciju pacijenata sa mogućom nestabilnom AP i drugim formama AKS; KORAK 2 je procena opšteg stanja i kvaliteta života koji odlučuju o planiranju lečenja; KORAK 3 uključuje osnovne dijagnostičke procedure i procenu funkcije leve komore (LK) srca; KORAK 4 čini određivanje Pre-test i Kliničke verovatnoće opstruktivne KB; KORAK 5 je izbor dijagnostičkog testa fizičkim ili farmakološkim opterećenjem putem EKG i vizuelizacionih (slikovnih, imidžing) metoda uključujući MSCT (MDCT) koronarnu angiografiju (CTKA, CTA) za ustanovljavanje

diagnoze KB. Na kraju, KORAK 6 je procena rizika od neželjenih KV događaja, posebno mortaliteta i na bazi toga donošenje definitivne terapijske odluka uz invazivnu koronarografiju (ICA) i eventualnu RM. Ako opstruktivna KB ne može biti isključena kliničkom evaluacijom, radi se bilo neinvazivni funkcionalni imidžing test bilo anatomske imidžing putem CTKA kao inicijalni test za isključenje ili potvrdu dijagnoze KB. Za odluku o RM treba razmotriti i anatomske i funkcionalne procene, izuzev kod teških koronarnih stenoza >90%. Visok rizik neželjenih KV događaja identifikuje pacijente koji bi imali veliku prognostičku korist od RM, čak i ako su asptomatski. Uloga revaskularizacije miokarda (RM) je stavljena u kontekst novijih dokaza koji se odnose na prognostičku ulogu perkutanih koronarnih intervencija (PCI) ili koronarnog arterijskog premošćavanja graftom (CABG) u ovoj niskorizičnoj populaciji. RM je rezervisana za pacijente gde postoje jaki dokazi da bi se njom poboljšala prognoza na bazi dokaza regionalne ishemije perfuzionim imidžingom. Pacijenti sa visokim rizikom -mortalitetom od 3% godišnje i više podvrgavaju se frakcionoj rezervi koronarnog protoka (FFR) ili koronarnoj rezervi protoka (CFR) zbog RM čak i ako nemaju simptome. Primena zdravog načina života smanjuje rizik od naknadnih neželjenih KV događaja i spada u adekvatnu terapiju sekundarne prevencije. Neophodna je redovna vakcinacija protiv gripa kod svih sa HKS. Optimalnoj medikalnoj terapiji (OMT): nefarmakološkoj i farmakološkoj terapiji HKS poklanja se ogromna pažnja kao glavnoj vrsti lečenja HKS, a ne RM. Istaknuta je savremena uloga anti-ishemijskih (antianginalnih lekova): Prve linije- betablokatori (BB) i antagonisti kalcijuma (CCB) uz sublingvalni nitroglicerina, i Druge linije- dugodelujući nitrati (LAN), uz novije opcije: ivabradin, nikorandil, trimetazidine, ranolazine, alopuronol i drugo. Lekovi koji poboljšavaju prognozu HKS jesu statini i acetilsalicilna kiselina (ASA) i drugi antitrombotični lekovi i od skora male doze rivaroksabana a dodatno inhibitori angiotenzin konvertaze (ACEI) i ponovo BB u specifičnim indikacijama. Anti-ishemijski tretman mora se prilagoditi pojedinačnom pacijentu na osnovu komorbiditeta, druge konkomitantne terapije, očekivane tolerancije i pridržavanja i sklonosti pacijenta. Izbor anti-ishemijskih lekova za lečenje HKS-a treba da bude prilagođen srčanom ritmu, krvnom pritisku i funkciji srca. BB i ACEI se preporučuju pacijentima sa DLK ili SI sa smanjenom ejekcionom frakcijom leve komore (HFrEF). Antitrombotska terapija je ključni deo sekundarne prevencije kod pacijenata sa HKS-om. Pacijente sa prethodnim infarktom miokarda, koji su pod visokim rizikom od ishemijskih događaja i niskim rizikom od smrtnog krvarenja, trebalo bi razmotriti dugoročnu dvostruku antiagregacionu terapiju aspirinom i bilo inhibitorom P₂Y₁₂ receptora ili rivaroksabanom sa vrlo malim dozama, osim ako nemaju indikacija za oralnu antikoagulaciju kao što je atrijska fibrilacija (AF). Inhibitori protonske pumpe preporučuju se kod pacijenata koji primaju i samo aspirin ili kombinaciju antitrombotske terapije koji su pod rizikom od gastrointestinalnog krvarenja. Statini se preporučuju svim pacijentima sa HKS-om bez obzira na nivo LDL. ACEI (ili blokatori receptora angiotenzina- ARB) preporučuju se u prisustvu SI, dijabetesa i hipertenzije i treba ih razmotriti kod pacijenata sa visokim rizikom za neželjene događaje.

KLJUČNE REČI: Hronični koronarni sindromi, stabilna angina pectoris, koronarna arterijska bolest, ishemijska bolest srca, EKG test fizičkim opterećenjem, stres ehokardiografski farmakološki testovi, MSCT-skenerska koronarografija, invazivna koronarografija, farmakoterapija, anti-ishemijski lekovi, antitrombotični lekovi, statini, perkutana revaskularizacija miokarda, perkutane koronarne intervencije, hirurška revaskularizacija miokarda.

Ključne reči: angina pectoris/stabilna, Angina Pectoris/Nestabilna, Mikrovaskularna angina, angina pectoris sa normalnim koronarnim arteriogramom (INOCA), ishemijska bolest srca, koronarna bolest, Akutni koronarni sindrom, Infarkt miokarda, Ishemija miokarda/dijagnoza/prevenција i kontrola/farmakoterapija, Revaskularizacija miokarda/perkutana koronarna intervencija/CABG

UVOD I ZNAČAJ PROBLEMA

Novi vodič Evropskog udruženja kardiologa (ESC) iz 2019 godine za dijagnozu, terapiju i zbrinjavanje hroničnih koronarnih sindroma [1] se fokusira na novi sveobuhvatni termin Hronični koronarni sindromi (HKS) za sve oblike hronične koronarne bolesti (HKB) izuzev akutnih koronarnih sindroma [2,3], pre nego samo na stabilnu koronarnu arterijsku bolest (SKB), kao predhodni ESC vodič iz 2013 [4]. Novi vodič ESC 2019. donosi pre svega promenu

paradigme za stabilnu koronarnu bolest u sveobuhvatni termin hronični koronarni sindromi (HKS), koja suštinski znači da HKB ima kompleksne kliničke scenarije i može imati periode nestabilnosti u bilo kojoj evolucionoj fazi. Suštinski klinička prezentacija koronarne bolesti se kategorizuje ili na akutne koronarne sindrome (ACS, AKS) [2,3,5] ili hronične koronarne sindrome (HKS) [1]. Koronarna bolest (KB) je dinamički patološki proces pojave i rastežanja aterosklerotskih plakova u epikardnim

koronarnim arterijama, ali i u njihove manjim intramiokardnim granama [6,7,8,9] (mikrovaskularna bolest) sa ili bez koronarnog vazospazma [10-13], bez obzira da li su funkcionalno fiksno opstruktivne (stenotične) ili neopstruktivne [14,15]. Ovaj dinamički proces dovodi do funkcionalne alteracije koronarnog krvotoka odnosno ishemije miokarda. Išemija miokarda može da se redukuje, stabilizuje ili da se postigne stagnacija ili regresija aterosklerotičnih plakova putem terapijskih intervencija: optimalnom neinvazivnom medikalnom tj. (medicinskom terapijom-OMT)

koja se sastoji od promene životnih navika, redukcije faktora rizika i optimalne farmakoterapije (OFT) te optimalnim invazivnim intervencijama - perkutanom ili hirurškom revaskularizacijom miokarda (RM). [16-21]. HKB ima duge stabilne periode, ali takođe može da postane nestabilna u nekom period zbog akutnih aterotrombotičnih događaja -rupture ili erozije aterosklerotskog plaka. Ipak bolest je hronična, najčešće progresivna i zato ozbiljna, čak i u klinički asimptomatskim periodima [1] (slika 1).

SLIKA 1: KLINIČKA PREZENTACIJA - KLINIČKI SCENARIJI HRONIČNIH KORONARNIH SINDROMA

Preuzeto i prevedeno sa sajta <https://www.escardio.org/Guidelines/Clinical-Practice-Guidelines/Chronic-Coronary-Syndromes>

Dinamička priroda procesa KB ima za rezultat različite kliničke prezentacije ili kliničke scenarije, akutne koronarne sindrome (AKS) [2,3,5] ili hronične koronarne sindrome (HKS) [1].

KLINIČKA PREZENTACIJA - KLINIČKI SCENARIJI HRONIČNIH KORONARNIH SINDROMA(HKS).

Klinička prezentacija HKS se sastoji iz 6 vodećih i najčešćih kliničkih scenarija [1]:

1. Pacijenti sa suspektom KB i stabilnom anginom pectoris (AP) i/ili dispnejom na napor.

2. Pacijenti sa novonastalom srčanom insuficijencijom (SI) ili disfunkcijom leve komore (DLK) i suspektom KB.

3. Asimptomatski i simptomatski pacijenti sa stabilizovanim simptomima do 1 godine protekle posle AKS ili revaskularizacije miokarda (RM).

4. Asimptomatski i simptomatski pacijenti više od 1 godine protekle posle AKS ili RM.

5. Pacijenti sa AP i suspektom vazospastičkom ili mikrovaskularnom bolešću.

6. Asimptomatske osobe u kojih je KB otkrivena na skriningu.

Svaki od ovih scenarija je klasifikovan kao HKS i posledice su različitih evolucionih faza KB te imaju različit rizik za buduće neželjene KV događaje (smrt ili infarkt miokarda etc) a taj rizik se može menjati tokom vremena [1].

NOVI KONCEPTI I PREPORUKE ZA HKS

Novi koncepti i preporuke za HKS i revidirani koncepti i preporuke iz predhodnog ESC vodiča 2013. godine [4], u ovom 2019 ESC vodiču [1], na bazi savremenih raspoloživih dokaza iz velikog broja randomizovanih studija, registara i konsenzusa eksperata (citiran ogroman broj naučnih radova: 529 refrenci) imaju holistički pristup, daju dosta jasne smernice za dijagnostiku i terapiju HKB i sistematično obrađuju sve kliničke prezentacije HKB na jasan i klinički parktično primenjiv način. Ovaj ESC Vodič i njegove preporuke treba da olakšaju kliničko odlučivanje lekarima u svakodnevnoj praksi [1].

NOVE GLAVNE PREPORUKE KLASA I (Postoje dokazi i/ili opšta saglasnost da su određeni tretman ili procedura delotvorni, korisni i efektni):

1. Neinvazivni funkcionalni vizuelizacioni (imidžing) dijagnostički testovi za detekciju ishemijske miokarda ili koronarna MSCT angiografija (CTKA) treba da bude inicijalni test za dijagnozu KB u simptomatskih pacijenata kod kojih opstruktivna koronarna bolest ne može da se isključi samo kliničkim prosuđivanjem.
2. Preporučuje se da selekcija optimalnog testa za dijagnozu KB bude bazirana na Kliničkoj verovatnoći KB i ostalim karakteristikama pacijenta koje utiču na izvođenje testa, lokalnoj dostupnosti i ekspertizi.
3. Neinvazivni funkcionalni vizuelizacioni test za ishemijsku miokarda je preporučen ako koronarna MSCT angiografija pokaže KB neizvesnog funkcionalnog značaja ili je nedijagnostička, inkonkluzivna.
4. Invazivna koronarografija (ICA) se preporučuje kao alternativni test za dijagnozu koronarne bolesti (KB) u bolesnika sa visokom kliničkom verovatnoćom i teškim simptomima, refrakternim na medikalnu terapiju (nefarmakološku i farmakološku) ili tipičnu anginu na malom fizičkom opterećenju i kad klinička evaluacija upućuje na visok rizik od neželjenih KV događaja. Invazivna funkcionalna procena (FFR, iwFR) mora biti dostupna i korišćena za evaluaciju stenoze pre koronarne revaskularizacije, osim u slučaju vrlo visokog

stepena koronarne stenoze $\geq 90\%$ dijametra stenoze.

5. U bolesnika sa atrijalnom fibrilacijom (AF) sa skorom $CHA_2DS_2-VASc \geq 2$ za muški pol i ≥ 3 za ženski pol, prednost se daje Ne-vitamin K antagonistima (NOAK, DOAK) ako nema kontraindikacija.

6. Posle perkutane koronarne revaskularizacije (post PCI) kod bolesnika sa AF, NOAK lekovi: Apiksaban 2 x 5 mg, Dabigatran 2 x150 mg, Edoksaban 60 mg i Rivaroksaban 20 mg jednom dnevno imaju prednost nad vitamin K antagonistima (VKA) u kombinaciji sa antitrombocitnom terapijom (mono ili dvostrukom-DAPT kod visokog hemoragijskog rizika).

7. Blokatori protonске pumpe su preporučeni u bolesnika sa visokim rizikom od gastrointestinalnih krvarenja, prema HAS-BLED skor, u terapijskim podgrupama: bolesnika sa monoterapijom aspirinom, dvostrukom antitrombocitnom terapijom (DAPT) ili monoterapijom oralnim antikoagulantima (OAK).

8. Ako se ne postigne ciljna vrednost LDL holesterola u serumu sa maksimalnom dozom statina, preporučuje se kombinovanje sa ezetimibom, a kod VRLO VISOKOG RIZIKA I nepostizanja ciljnog nivoa LDL, dodaje se treći lek PCSK9-inhibitor (Proprotein konvertaza subtilizin/kexin tipa 9) parenteralno.

9. Inhibitori natrijum-glikoza-2-kotransportera (SGLT2-I): empagliflozin, kanagliflozin ili dapagliflozin su preporučeni kod pacijenata sa dijabetes melitusom (DM) i HKS i kardiovaskularnom bolešću.

10. Agonisti receptora glukagonu-sličnom peptidu-1 (GLP-1) liraglutid ili semaglutid se preporučuju kod pacijenata sa DM i HKS i kardiovaskularnom bolešću.

NOVE i /ili IZMENJENE GLAVNE PREPORUKE KLASA IIa (Postoje protivrečni dokazi i/ili različiti stavovi o korisnosti/efikasnosti određenog tretmana ili procedure, ali najveći broj dokaza govori u prilog korisnosti/efikasnosti)

1. Invazivna koronarografija (ICA) sa dostupnošću invazivne funkcionalne evaluacije treba da se razmotri za potvrđivanje dijagnoze KB kod pacijenata sa neizvesnom ili inkonkluzivnom dijagnozom na neinvazivnim testovima.

2. Koronarna MSCT angiografija (CTKA) treba se razmotriti kao alternativa invazivnoj koronarografiji (ICA) ako su drugi neinvazivni testovi dvosmisleni ili nedijagnostički.

3. Dodavanje drugog antitrombotičnog leka aspirinu za dugotrajnu sekundarnu prevenciju treba razmotriti u bolesnika sa **visokim ishemijskim rizikom** i bez visokog rizika od krvarenja.

4. Dugotrajna oralna antikoagulantna terapija (OAK) treba da se razmotri kod AF i CHA₂DS₂-VASc=1 za muški pol i 2 za ženski pol, prednost se daje Ne-vitamin K antagonistima (NOAK), ako nema kontraindikacija

5. Kod bolesnika sa AF i NOAK-om, gde prevladava hemoragijski rizik nad rizikom tromboze stenta ili ishemijskog moždanog udara treba dati nižu dozu NOAK-a (Rivaroksaban 15 mg jednom dnevno ili Dabigatran 2 x 110 mg u kombinaciji sa mono ili dvostrukom antitrombotičnom terapijom (DAPT).

6. Kod post-PCI pacijenata sa AF ili drugim indikacijama za OAK, trostruka terapija sa aspirinom, klopogrelom i OAK najmanje mesec dana ili duže treba se razmotriti kada rizik tromboze stenta prevladava hemoragijski rizik, sa ukupnim trajanjem do 6 meseci, što se odlučuje prema proceni oba rizika i **jasno se iskazuje na otpustu iz bolnice!**

7. Inhibitori angiotenzin konvertaze (ACEI) treba da se razmotre u HKS pacijenata sa vrlo visokim rizikom od neželjenih KV događaja.

8. Ranolazin, nikorandil, ivabradin i trimetazidin prelaze u IIa (iz IIb klasa-korisnost / efikasnost je mnogo manje zasnovana na dokazima / stavovima).

KLASA III (Postoje dokazi i/ili opšta saglasnost da su određeni tretman ili procedura nekorisni / neefikasni i u izvesnim slučajevima mogu biti štetni i zato su kontraindikovani)

1. Koronarna MSCT angiografija se ne preporučuje kada postoje ekstenzivne koronarne kalcifikacije, iregularna srčana frekvencija, značajna gojaznost, nesposobnost pacijenta da zadrži dah dovoljno dugo i bilo koje drugi faktori koji bi uticali da se ne dobije kvalitetna slika.

2. Promene u ST segmentu EKG za vreme PSVT ne treba koristiti kao dokaz KB.

3. Ambulatorni EKG monitoring (Holter EKG) ne bi trebalo rutinski koristiti u ispitivanju pacijenata sa suspektom HKS.

4. Koronarni kalcijumski skor putem MSCT nije preporučen za identifikaciju osoba sa opstruktivnom KB.

5. EKG test fizičkim opterećenjem (ergometrijski EKG stres test na pokretnoj traci ili biciklu) u pacijenata sa $\geq 0,1\text{mV}$ (1mm) depresijom ST

segmenta na EKG u miru, ili kod lečenja digitalisom, ne preporučuje se za dijagnostičke svrhe kod HKS.

6. Invazivna koronarografija (ICA) nije preporučena kao jedina metoda za stratifikaciju rizika kod HKS.

7. Nitrati nisu preporučeni za lečenje HKS kod pacijenata sa hipertrofičnom opstruktivnom kardiomiopatijom ili u istovremenoj terapiji sa inhibitorima fosfodiesteraze (Sildenafil i ostali).

8. Korišćenje tikagrelora ili prasugrela nije preporučeno kao deo trojne antitrombotičke terapije sa acetyl-salicylicnom kiselinom (ASA) i oralnom antikoagulantnom terapijom (OAK).

9. Koronarna MSCT angiografija nije preporučena kao rutinski test za praćenje pacijenata sa utvrđenom dijagnozom hroničnog koronarnog sindroma (HKS).

10. Kolor Dopler Karotidna ehosonografija sa određivanjem debljine intimomedijalnog sloja (IMT) nije preporučena za stratifikaciju rizika HKS.

11. U niskorizičnih asimptomatskih odraslih ne-dijabetičara, koronarna MSCT angiografija ili funkcionalni vizuelizacioni (imidžing) testovi za detekciju ishemije nisu indikovani za dalju dijagnostičku procenu.

12. Rutinsko određivanje cirkulišućih srčanih biomarkera nije preporučeno za stratifikaciju KV kod pacijenata sa HKS.

13. Kombinacija lekova iz grupa ACEI i ARB nije preporučena kod HKS i arterijske hipertenzije (HTA) ili disfunkcije leve komore (DLK) i srčane insuficijencije (SI).

14. Kod teške bolesti srčanih ventila, testove opterećenja (stress) ne treba koristiti rutinski za detekciju KB, zbog niskog dijagnostičkog benefita i potencijalne opasnosti od komplikacija.

15. Supstitucionalna terapija polnim hormonima nije preporučena za redukciju rizika kod postmenopauzalnih žena.

16. Transmiokardna revaskularizacija nije preporučena za pacijente sa teškom AP refrakternom na optimalno medikalno lečenje (OMT) i strategije revaskularizacije miokarda (RM).

SCENARIO 1: PACIJENTI SA SUSPEKTNOM Koronarnom bolesti (HKS) I STABILNOM ANGINOM PEKTORIS i/ ili DISPNEJOM NA NAPOR.

Postupak (algoritam) u 6 koraka u pristupu inicijalnom zbrinjavanju pacijenata sa suspektom HKS i stabilnom AP ili dispnejom na napor je dat na SLICI 2.

SLIKA 2. Postupak (algoritam) u 6 koraka u pristupu inicijalnom zbrinjavanju pacijenata sa suspektnim HKS i stabilnom AP ili dispnejom

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Umesto ranijih 3 koraka po ESC vodiču iz 2013 [4, 22], sada je uveden postupak ili algoritam u 6 KORAKA [1] u pristupu inicijalnom zbrinjavanju pacijenata sa suspektnim HKS:

KORAK 1: Procena simptoma (TABELA 1) koristi tradicionalnu kliničku klasifikaciju suspektnih anginoznih simptoma: tegoba u grudima-nelagodnost (stezanje, pečenje, žarenje,

teskoba, osećaj pritiska, težine ili nejasan bol) pri naporu obično kraći od 10 minuta, (bol koji traje sekundama najčešće nije anginozni) i izvođenje kliničkih ispitivanja, identifikovanje bolesnika sa nestabilnom AP i ostalih formi AKS. AP može paradoksalno da se smanji sa daljim naporom (walk-through angina) ili pri sledećem naporu (warm-up angina) [23].

TABELA 1: tradicionalna klinička klasifikacija suspektnih anginalnih simptoma,

TABELA 1

Tipična angina pectoris (definitivna Dg)

Atipična angina (verovatna Dg)

Neanginozni bol

Tradicionalna klinička klasifikacija bola u grudima

BOL TREBA DA IMA SVE TRI SLEDEĆE KARAKTERISTIKE:

1. Substernalnu tegobu ili nelagodnost karakterističnog kvaliteta: Stezanje, pritisak, teskoba, težina ili pečenje i trajanja nekoliko minuta do maksimalno 20min
2. Provociran naporom ili emotivnim stresom
3. Prestaje u odmoru ili /i na nitrat unutar nekoliko minuta

Treba da ima dve od tri karakteristike

Bez ovih karakteristika ili ima samo jednu karakteristiku

Ne treba naglašavati koliko je važno brzo isključiti druga hitna akutna kardiološka stanja: akutni koronarni sindrom (AKS) -nestabilna angina pectoris- identičan bol kao u AP ali traje >20 minuta. Uvek treba misliti na

disektnu aneurizmu aorte tj Akutne aortne sindrome (AAS), plućne embolije, perikarditis i miokarditis. U diferencijalnoj dijagnozi razmotriti nekardijalne bolesti koje mogu da liče na anginozni bol. Najčešće bolesti koje mogu da

imitiraju anginu pectoris: gastroezofagealne bolesti (40%), sindromi vezani za zid toraksa (Costochondritis i Titz-ov sindrom), neke plućne bolesti, pneumotoraks, pleuritis i herpes zoster intercostalis.

KORAK 2- Razmatranje opšteg stanja i kondicije pacijenta, procena kvaliteta života i prisustva komorbiditeta koji potencijalno utiču na terapijsku odluku. Ako je izvođenje testova opterećenja i koronarna revaskularizacija malo verovatna zbog opšteg stanja, uvesti odmah OMT posebno antianginalnu farmakološku terapiju.

KORAK 3. Osnovno kliničko dopunsko ispitivanje.

Uključuje osnovno ispitivanje: elektrokardiogram (EKG), u selektovanih pacijenata ambulatorni EKG Holter monitoring, biohemijske analize, radiografiju toraksa u selekcioniranih pacijenata. EKG je ključan za dijagnozu ishemije miokarda, tipično revrezibilna horizontalna depresija ST segmenta u dva ili više susednih EKG odvođa u toku ili neposredno posle anginoznog napada. Manje je specifična nishodna depresija ST segmenta a sporo ushodna je najmanje specifičnosti za dijagnozu ishemije, dok je brzo-ushodna depresija ST segmenta normalna varijanta pri tahikardiji [24]; Često se na Holteru EKG otkriva asimptomatska ishemija miokarda u vidu horizontalne depresije ST segmenta pri naporu [24, 25, 26]; EKG takođe može da ukaže na

indirektne znakove KB: patološki Q zubac [27]; blok leve grane Hissovog snopa (BLG) ili atrio-ventrikularne (AV) blokove, ekstrasistole [27]; Kod epizode atrijalne fibrilacije (AF) sa asimptomatskom ishemijom miokarda: ST-depresijom [28, 29, 30]. Nasuprot AF, ST depresija za vreme paroksizmalne supraventrikularne tahikardije (PSVT) nije prediktivna za ishemiju. Obavezna je ehokardiografska procena funkcije leve komore srca (LK) prvenstveno ejekcione frakcije leve komore (EF). Kada je EF<50% pacijent se direktno šalje na invazivnu koronarografiju (ICA). Transtoraksna ehokardiografija (TTE) kao pojedinačna najinformativnija dijagnostička metoda u kardiologiji ima ključnu ulogu u isključenju alternativnih uzroka nelagodnosti u grudima [30] i za stratifikaciju rizika. U slučaju suboptimalne eho slike (<10% slučajeva) pribegava se transezofagealnoj ehokardiografiji (TEE) i kardiomagnetnoj rezonanci (CMR) [31].

KORAK 4 Procena pre-test verovatnoće i kliničke verovatnoće KB

Evropski Vodič 2019 daje povećan i obnovljen značaj određivanju pre-test verovatnoće (PTP) opstruktivne koronarne bolesti, ali klasična PTP, autora Diamond-a i Forrester-a bazirana na starosti, polu i prirodi simptoma [31] podvrgnuta je promeni na osnovu novih dokaza [32]. Srednja PTP iznosi 15% do 85%. Korišćenjem nove tabele (TABELA 2) smanjuje se procenjivanje incidence koronarne bolesti. [1, 31, 32].

TABELA 2. NOVA REVIDIRANA PRETEST VEROVATNOĆA

Foldyna B, Udelson JE, Karady J, et al. insights from the PROMISE trial. Eur Heart J Cardiovasc Imaging 2018; 20:574- 581.

SIMPTOMI	TIPIČNI		ATIPičNI		NEANGINOZNI		DISPNEJA	
STAROST	MUŠKARCI	ŽENE	MUŠKARCI	ŽENE	MUŠKARCI	ŽENE	MUŠKARCI	ŽENE
30–39	3%	5%	4%	3%	1%	1%	0%	3%
40–49	22%	10%	10%	6%	3%	2%	12%	3%
50–59	32%	13%	17%	6%	11%	3%	20%	9%
60–69	44%	16%	26%	11%	22%	6%	27%	14%
70+	52%	27%	34%	19%	24%	10%	32%	12%

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Uvodi se novi termin Klinička verovatnoća opstruktivne koronarne bolesti (KPKB) koji koristi različite rizik faktore KB kao modifikatore PTP verovatnoće.

Smanjenje verovatnoće za opstruktivnu KB:

A) normalan EKG test fizičkim opterećenjem

B) normalan kalcijumski skor koronarnih arterija (Agatston=0) [1, 33].

Faktori koji povećavaju KPKB:

A) dislipidemija, DM, HTA, pušenje, porodična anamneza za KB i naprasna smrt.

B) Promene u EKG u miru: Q zubac i promene u ST segmentu i T talasu.

C) Disfunkcija leve komore (DLK) koja upućuje na KB
 D) Abnormalan EKG test fizičkim opterećenjem (EKG TFO)
 E) povećan kalcijumski skor putem CTKA
 Selekcija inicijalnog neinvazivnog dijagnostičkog testa (funkcionalnog ili anatomskog imidžinga) je bazirana na PTP odnosno KPKB

KORAK 5. Izbor optimalnog dijagnostičkog testa za postavljanje dijagnoze KB

Selekcija optimalnog dijagnostičkog testa za postavljanje dijagnoze KB, bazirana je na profilu pacijenta, lokalnoj dostupnosti i ekspertizi. [1, 36-42] prikazana je na **SLICI 3**.

SLIKA 3. GLAVNI DIJAGNOSTIČKE PUTANJE U SIMPTOMATSKIH PACIJENATA SA SUSPEKTNOM OPSTRUKTIVNOM KB-HKS

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Kod pacijenata kod kojih je revaskularizacija "uzaludna" zbog komorbiditeta i ukupnog kvaliteta života (KORAK 2), dijagnoza KB može se postaviti klinički a potrebna je samo OMT: optimalna medikalna terapija (medicinska: promena stila života, redukcija rizik faktora I farmakološka). Ako je dijagnoza KB neizvesna, postavljanje dijagnoze pomoću neinvazivnih funkcionalnih testova snimanja ishemije miokarda pre lečenja je razumna opcija; s druge strane kod pacijenta sa velikom kliničkom verovatnoćom KB, kada simptomi nisu reagovali na medicinsku terapiju ili je prisutna teška tipična AP pri niskom stepenu opterećenja i/ili početna klinička procena (uključujući ehokardiogram i kod odabranih pacijenata EKG test fizičkim opterećenjem -TFO ili Ergometrijski EKG test) ukazuje na visok rizik neželjenih događaja, preći direktno na invazivnu koronarografiju (ICA) bez daljeg dijagnostičkog

testiranje. Pod takvim okolnostima, indikacija za RM treba da se zasniva na odgovarajućoj invazivnoj potvrdi hemodinamičkog značaja stenoze: FFR, ivFR, CFR [43,44]. Postojeće smernice preporučuju upotrebu bilo neinvazivnih funkcionalnih vizuelizacionih snimanje ishemije ili anatomskog imidžinga pomoću CTKA kao početni test za dijagnozu KB.

Funkcionalni neinvazivni testovi ishemije za dijagnozu opstruktivne KB dizajnirani su za otkrivanje ishemije miokarda putem EKG promena, nepravilnosti pokreta zida pomoću CMR-a stresa ili stresne ehokardiografije (SEHO), ili hipoperfuzija do aperfuzija scintigrafijom miokarda (SPECT), pozitronsko-emisionom tomografija (PET), kontrastnom miokardnom ehokardiografijom ili kontrastnom CMR. Ishemija se može izazvati fizičkim opterećenjem (ergometrijski) ili farmakološkim stresorima, bilo putem povećanog rada

miokarda i potrebe za kiseonikom, ili heterogenošću u perfuziji miokarda vazodilatacijom. **Neinvazivni funkcionalni testovi imaju visoku tačnost za otkrivanje koronarne stenoza koja ograničava protok u poređenju sa invazivnim funkcionalnim ispitivanjem frakcionom rezervom koronarnog protoka (FFR) [1, 45].** Međutim, nesignifikantne koronarne stenozе i aterosklerotski plakovi koji nisu povezani sa ishemiјom ostaju **neotkrivene funkcionalnim testiranjem** i u prisustvu negativnog funkcionalnog testa, pacijenti bi trebalo da dobiju modifikaciju faktora rizika na osnovu ESC preporuka za KV prevenciju uz periodično retestiranje [1, 6].

Anatomska neinvazivna procena

Anatomska neinvazivna procena vizuelizacijom koronarnih arterija, prikazivanjem i lumena i zida koronarnih arterija može se izvesti pomoću intravenskog kontrastnog sredstva koronarnom MSCT angiografijom (KCTA, najbolje sa 128 ili 256 slajsova /sekundi), koji pruža visoku tačnost za otkrivanje opstruktivnih koronarnih stenoza, kao i invazivna koronarografija (ICA) [1,45] jer se oba snimanja zasnivaju se na anatomiji. **Međutim, stenozе koje iznose od 50% do 90% vizuelnim pregledom nisu nužno funkcionalno značajne, tj. one ne izazivaju uvek ishemiјu miokarda.** [45,46]. Stoga se neinvazivno ili invazivno funkcionalno ispitivanje preporučuje za dalje **procenu angiografske stenozе** otkrivene koronarnom CTA ili ICA-om, osim ako je stenozа visokog stepena (> 90% prečnika) otkrivena putem ICA. Prisustvo ili odsustvo neopstruktivne koronarne ateroskleroze na koronarnoj CTA pruža prognostičke informacije i može se koristiti u svrhu preventivne terapije. [47].

Uloga EKG testa fizičkim opterećenjem (TFO) ili EKG Ergometrijski stres test (ERGO)

EKG Ergometrijski stres test ima lošiju dijagnostičku performansu u poređenju sa dijagnostičkim vizuelizacionim testovima i ima ograničenu moć da isključi opstruktivna KB [1,45]. Zbog toga ove smernice preporučuju upotrebu dijagnostičkih slikovnih testova umesto TFO EKG-om kao početni test za dijagnozu opstruktivne KB. EKG TFO može se smatrati alternativom za dijagnozu opstruktivni KB, ako nisu dostupni vizuelizacioni (slikovni testovi), **imajući na umu rizik od lažno negativnih i lažno pozitivnih rezultata testa.** [45,48,49]. EKG TFO nema dijagnostičku vrednost kod pacijenata sa EKG nenormalnostima u miru (rest) koje sprečavaju interpretaciju promena ST-segmenta.

Uticaj kliničke verovatnoće na izbor dijagnostičkog testa

Svaki neinvazivni dijagnostički test ima određeni opseg kliničke verovatnoće za opstruktivnu KB, gde je korisnost njegove primene maksimalna. Koeficijenti verovatnoće testova predstavljaju korisne parametre njihove sposobnosti da pravilno klasifikuju pacijente i kojima se olakšava **izbor najkorisnijeg testa** kod bilo kog pacijenta. [1, 45]. S obzirom na kliničku verovatnoću opstruktivne KB (KPKB) i koeficijenta verovatnoće određenog testa, može se proceniti POST-TEST verovatnoća za opstruktivnu KB nakon obavljanja takvog testa. Koristeći ovaj pristup, može se proceniti optimalni opseg kliničke verovatnoće za svaki test, gde mogu **reklasifikovati pacijente iz srednje (15—85%) u bilo koju: nisku (<15%) ili visoku verovatnoću KB >85% posle testa** [45]. Koronarnoj CTA se daje prednost kod pacijenata sa nižim opsegom kliničke verovatnoće KB (ranije brojčano PTP 15-65%), bez prethodne dijagnoze KB i važnih uslova povezanih sa velikom verovatnoćom za dobar kvalitet slike. CTKA otkriva **subkliničku koronarnu aterosklerozu**, ali takođe može da isključi i anatomske i funkcionalno značajnu KB. Neinvazivni funkcionalni testovi za ishemiјu imaju prednost jer direktno prikazuju oblast ishemiјe miokarda putem provokacije ishemiјe [1,45]. **Pre revaskularizacije, funkcionalna procena ishemiјe (neinvazivnom ili invazivnom metodom) je potrebna kod većine pacijenata.** Pored dijagnostičke tačnosti i kliničke verovatnoće, izbor neinvazivnog testa zavisi od drugih karakteristika pacijenta, lokalne edukacije ordinirajućeg kardiologa za ekspertizu evaluacije ishemiјe putem stress imidžinga i lokalne dostupnosti testova, odnosno potebe za slanjem u više ustanove. Neki dijagnostički testovi mogu kod izvesnih pacijenata imati prednost i biti najbolji izbor. Na primer, tahiaritmija i prisutnost ekstenzivne koronarne kalcifikacije su povezana sa povećanom verovatnoćom ne-dijagnostičkog kvaliteta slike koronarne CTA i ne preporučuje se kod takvih bolesnika. [50,51]. Stresna ehokardiografija ili SPECT perfuzijsko snimanje miokarda mogu se kombinovati sa dinamičkim TFO i može biti poželjno ako su dodatne informacije dostupne tokom testa TFO EKG. TFO EKG TEST se ne može koristiti u dijagnostičke svrhe kod prisustvo EKG abnormalnosti koje sprečavaju procenu ishemiјe. Rizici u vezi sa različitim dijagnostičkim testovima moraju se odmeriti ZA I PROTIV korisnosti za **određenog pacijenta.** [52]. Slično tome, kontraindikacije za

farmakološke stresore i kontrastna sredstva (kontrastna sredstva na bazi joda i gadolinijuma, helati) treba uzeti u obzir. Kada se testiranje koristi na odgovarajući način, klinička korist od tačne dijagnoze i terapije premašuje projektovane rizike samog testiranja [52].

Invazivno kardiološko ispitivanje

U striktno dijagnostičke svrhe ICA je potrebna samo kod pacijenata za koje se sumnja da imaju opstruktivnu KB u slučaju neubedljivog, dvosmislenog ili inkonkluzivnog neinvazivnog ispitivanja ili, izuzetno, kod pacijenata iz određenih javnih zanimanja od posebnog značaja (vozači, piloti, radnici na mašinama, policajci i slično), zbog bezbednosnih i regulatornih pitanja. [53]. Međutim, ICA može biti neophodna i **kada neinvazivna procena sugeriše vrlo visok rizik neželjenih događaja radi određivanja opcija za revaskularizaciju.** [53]. Kod pacijenta sa velikom kliničkom verovatnoćom za KB i simptomi ne reaguje na medicinsku terapiju ili sa tipičnom anginom na niskom nivou napora, a početna klinička procena ukazuje na visok rizik od događaja, rana ICA bez prethodne neinvazivne stratifikacije rizika može biti razumno rešenje da bi se identifikovale lezije koje mogu biti pogodne za revaskularizaciju miokarda (**SLIKA 3**). Invazivna funkcionalna procena bi trebalo da dopuni ICA, posebno kod pacijenata sa koronarnim stenozama od 50 do

90% ili višesudovne (multivesel) bolesti, **s obzirom na česte neusklađenosti stepena angiografske i hemodinamske ozbiljnosti koronarnih stenoz.** [53-58]. ICA ne bi trebalo da se izvodi kod pacijenata sa anginom koji odbijaju invazivne procedure i izbegavaju revaskularizaciju, koji nisu kandidati za perkutane koronarne intervencije (PCI) ili baj-pass premošćavanje koronarnih arterija (CABG), ili kod koga se ne očekuje da revaskularizacija miokarda poboljša funkcionalni status ili kvalitet života.

KORAK 6. Postavljena dijagnoza HKS, te se vrši se stratifikacija rizika od neželjenih događaja putem funkcionalnih stress testova: stress-rest (SPECT) perfuzionu scintigrafiju miokarda, najdostupniji farmakološki stress eho dobutaminom ili dipiridamolom i najmanje dostupno kardiomagnetna rezonanca (CMR) stress sa dobutaminom i perfuzijom kontrasta. **Na određivanju nivou rizika se bazira odluka o daljem lečenju** [1]. Definicija nivoa rizika prema godišnjem mortalitetu: nema ishemijske, mortalitet od neželjenih događaja manji od 1%; srednji rizik - godišnji mortalitet između 1% i 3%; visok godišnji mortalitet je preko 3% (TABELA 3).

TABELA 3. Definicija nivoa rizika za funkcionalne slikovne (imidžing) testove i neinvazivne anatomske CT koronarna angiografija

Definicija NIVOA RIZIKA za razne modalitete testova za stratifikaciju KV rizika za HKS

EKG TEST FIZIČKIM OPTEREĆENJEM Duke TM (Treadmill Score) = T(min)- 5 x dep ST -4 x (nivo imtom)	VISOK RIZIK	KV MORTALITET > 3% GODIŠNJE (TM scor < -11)
	SREDNJI RIZIK	KV ≥ 1% i ≤ 3% GODIŠNJE (TM scor između +5 i -11)
	NIZAK RIZIK	KV MORTALITET < 1% GODIŠNJE (TM scor > +5)
Vizuelizacija veličine ishemije Stres tetovima Ergo ili farmakol. testovima : SPECT MIBI STRESS ECHO STRESS CMR	VISOK RIZIK	Area ishemije >10% (>10% za SPECT, INDUKCIJA DISFUNKCIJE (hipo ili akinezija) ≥ 3 segmenta LV na dobutamin SEHO CMR-verovatno ≥ 2/16 STRES PERFUZIONI DEFJEKT ILI 3/16 INDUK. DISFUNKCIJE SEGMENTA
	SREDNJI RIZIK	Area ishemije 1-10% SPECT STRES ishemija na stress EHO INDUKCIJA DISFUNKCIJE 1 ILI 2 SEGMENTA CMR manja nego visoko-rizična
	NIZAK RIZIK	nema ishemije
Neinvazivna skenerska koronarna angiografija	VISOK RIZIK	Signifikantne lezije kategorije visokog rizika (trosudovna bol sa proks stenozama, glavno stablo i proksimalna LAD)
	SREDNJI RIZIK	Signifikantne lezije u velikim i proksimalnim arterijama ali ne u kategoriji visokog rizika

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SLIKA 4 DIJAGRAM 3. Komparacija nivoa KV rizika asimptomatskih osoba u primarnoj prevenciji neželjenih KV događaja i kod ustanovljenog HKS u sekundarnoj prevenciji

Ako je angina vrlo teška, ali nije nestabilna, prema poznatoj Klasifikaciji kanadskog KV udruženja klasa IV -(TABELA 4), kod pretest verovatnoće veće od 85% po Bayesovoj teoremi,

sprovodi se odmah ICA bez predhodnih neinvazivnih testova, ali uz procenu koronarne frakcione rezerve protoka (FFR) [45, 56, 59].

TABELA 4. Klasifikacija težine angine pektoris i/ili dispneje na napor prema Kanadskom kardiovaskularnom udruženju

ccsc	KLASIFIKACIJA TEŽINE ANGINE PEKTORIS i/ili dispneje (prim autora D.B.) prema Kanadskom Kardiovaskularnom udruženju
KLASA I	Uobičajena fizička Aktivnost , kao što je pešačenje ili penjanje uz stepenice ne dovodi do nastanka angine pektoris i/ili dispneje . Angina se javlja pri teškom, brzom i produženom fizičkom naporu na poslu ili pri rekreaciji
KLASA II	BLAGO OGRANIČENJE UOBIČAJENIH AKTIVNOSTI. Angina i/ ili dispneja nastaje pri brzom pešačenju ili penjanju uz stepenice, hodanju uzbrdo, pešačenju ili penjanju nakon jela ili na hladnoći i vetru, pri emotivnom stresu, ili u prvih par sati nakon budjenja. Tegoba u grudima nastaje pri pešačenju više od dva bloka-200 m po ravnom ili penjanjem uz stepenice više od jednog sprata pri normalnom hodu i uslovima
KLASA III	ZNAČAJNO OGRANIČENJE UOBIČAJENIH AKTIVNOSTI. Angina nastaje pri pešačenju jednog do dva bloka(100-200m) po ravnom ili penjanju uz stepenice do jednog sprata pri normalnom hodu i u normalnim uslovima
KLASA IV	NEMOGUĆNOST OBAVLJANJA BILO KAKVE FIZIČKE AKTIVNOSTI BEZ ANGINOZNIH TEGOBA – ANGINA i/ili dispneja MOŽE NASTATI I U MIRU

Uloga koronarne MSCT angiografije je da isključi signifikantnu bolest u pacijenata sa nižom intermedijarnom verovatnoćom od 15 do 65%. Finalno se U KORAKU 6 vrši izbor adekvatne

terapije: promena životnog stila, farmakološka terapija KB i revaskularizacija miokarda(RM), bazirane na simptomima i riziku od neželjenih KV događaja.

NEFARMAKOLOŠKE MERE U LEČENJU HRONIČNIH KORONARNIH SINDROMA (u principu za sve HKS, POSEBNO ZA SCENARIO 1)

Vodič podvlači krucijalnu ulogu zdravog načina ili stila života i ostalih preventivnih mera za smanjenje rizika od posledičnih kardiovaskularnih događaja i mortaliteta [1], kao što je prikazano u esencijalnim studijama COURAGE [60] i FAME [44]. Redovno uzimanje lekova za lečenje hipertenzije, hiperlipidemije, dijabetesa i dr. treba da obezbedi postizanje ciljnih vrednosti krvnog pritiska, LDL holesterola, HDL, triglicerida i glikemije (HbA1c) što dovodi do stagnacije i regresije ateroskleroze što je detaljno obrađeno u ESC Vodiču za KV prevenciju 2016 [6].

Preporučuje se u preventivnom radu uključenost multidisciplinarnog tima: kardiolog, ordinirajući lekar opšte medicine (GP), medicinske sestre, nutricionista, psiholog, psihoterapeut i farmaceut (klasa I dokaz B) [1]. **Primena zdravog načina života, kao preventivna intervencija** smanjuje rizik od naknadnog razvoja neželjenih KV događaja i smrtnosti. Važna je primena zdravog ponašanja: prestanak pušenja, preporučena fizička aktivnost, zdrava ishrana, održavanje zdrave telesne mase čime se značajno smanjuje rizik od budućih kardiovaskularnih događaja i smrti, a što je zasnovano na dokazima. [1,61,62]. Koristi su očigledne već 6 meseci nakon indeksnog događaja [1,61,62]. Primarna zdravstvena zaštita ima važnu ulogu u prevenciji, u EUROACTION studiji pokazalo da je program koji koordinira medicinska sestra u primarnoj nezi poboljšava redukciju faktora rizika. [63].

Prestanak pušenja cigareta poboljšava prognozu kod pacijenata sa HKS, uključujući smanjenje rizika od smrti za 36% za one koji uspešno prekinu. Mere za promociju prestanka pušenja uključuju kratke savete i savete intervencije u ponašanju i farmakološku terapiju uključujući zamenu nikotina. Pacijenti takođe treba da izbegavaju pasivno pušenje. Kratki saveti lekara, udvostručuju verovatnoću prestanka pušenja u kratkom roku, ali intenzivniji savet i podrška (intervencije u ponašanju, telefonska podrška ili mere samopomoći) su efikasnije od kratkih saveta, posebno ako se nastavi u toku jednog meseca [62,63]. Svi oblici terapije zamene nikotina, bupropion i vareniklin su efikasniji u prestanku pušenja nego samokontrola; kombinovanje bihevioralnog i farmakološkog pristupa za prestanak pušenja je efikasno i preporučuje se. [64].

Zdrava ishrana [65]: Dijeta bogata povrćem, voćem i integralnim žitaricama. Ograničiti unos zasićenih masti na <10% ukupnog unosa. Ograničiti alkohol na <100 g / nedeljno ili 15 g / dan.

Zdrava telesna masa: dobiti i održavati zdravu masu (BMI <25 kg / m²) ili smanjiti masu kroz preporučeni unos energije i povećanje fizičke aktivnosti.

Gojaznost je povezana sa kraćim ukupnim životnim vekom i preterana telesna masa je povezana sa razvojem kardiovaskularnih bolesti (KVB) [66]. Obim struka je znak centralne gojaznosti i metaboličkog sindroma [30] i snažno je povezan sa razvojem KVB i dijabetesa. Preporučuje se obim struka ≤94 cm za muškarce i ≤80 cm za žene. Kod osoba sa KVB namerno mršavljenje povezano je sa značajno nižim rizikom od nepovoljnih događaja [67].

Umereni unos alkohola (1-2 pića dnevno) ne povećava rizik od AIM.

Fizička aktivnost. Vežba je nazvana "polipilom" zbog svojih mnogobrojnih korisnih efekata na KV faktore rizika i KV sistem [21, 68, 69, 70]. Fizička aktivnost redukuje težinu AP, poboljšava transport kiseonika u miokardu i povećanje kapaciteta za vežbanje i predstavlja nezavisni prediktor povećanog preživljavanja kod muškaraca i žene sa HKS [21,68,69,70]. Svaki 1 mL/kg/min povećanja vršne potrošnje kiseonika bio je povezan sa smanjenjem rizika za KVB za 14% i sve uzrok smrti kod žena i muškaraca. [21]. Preporuke za fizičku aktivnost za pacijente sa HKS su 30 do 60 min aerobne aktivnosti umerenog intenziteta ≥5 dana sedmično. [6,69]. Čak i nedovoljna fizička aktivnost u slobodno vreme smanjuje rizik smrtnosti kod ranije sedećih pacijenata [72] i sve veća aktivnost povezana je sa nižim KV mortalitetom [73]. Vežbe snage održavaju mišićnu masu i funkciju i uz aerobnu aktivnost (brzi hod, plivanje i dr), daju korisne efekte u pogledu sniženja insulinske rezistencije, nivoa lipida i krvnog pritiska.

KV rehabilitacija na osnovu fizičkog vežbanja konstantno je pokazala efikasnost u smanjenju KV mortaliteta i hospitalizacija u poređenju sa kontrolnom grupom kod pacijenata sa KB i ova korist ostaje i u sadašnje doba [74-77].

Psihosocijalni faktori. Pacijenti sa KB imaju dvostruko povećan rizik od depresije i anksioznih poremećaja u poređenju sa ljudima koji nemaju srčane bolesti [78]. Psihosocijalni stres, depresija i anksioznost su povezani sa lošijim ishodima HKS. Klinička ispitivanja pokazala su da su psihološka (npr. savetovanje i / ili kognitivno-bihevioralna terapija) i

farmakološke intervencije psihofarmacima imale blagotvoran uticaj na depresiju, anksioznost i stres, sa nekim dokazima smanjenja srčane smrtnosti i neželjenih događaja u poređenju sa placebom. [79,80,81].

Faktori životne sredine. Zagađivači vazduha se procenjuju kao jedan od 10 vodećih faktora rizika za globalnu smrtnost. Izloženost zagađenju vazduha takođe povećava rizik od AIM kao i hospitalizacija i smrti od SI (HF), moždanog udara i aritmija. [82]. Pacijenti sa HKS treba da izbegavaju područja sa velikim saobraćajnim gužvama zbog zagađenja i buke [82,83].

Seksualna aktivnost. Pacijenti sa HKS često se brinu zbog KV rizika seksualne aktivnosti i / ili seksualne disfunkcije [84,85]. Rizik od izazivanja iznenadne smrti ili AIM je veoma mali, naročito kada je seksualna aktivnost sa stabilnim partnerom u poznatom okruženju bez stresa ili bez prekomernog unosa hrane ili alkohola [86]. Iako seksualna aktivnost prolazno povećava rizik od MI, uzrok je samo <1% akutnog MI i <1,7% za iznenadnu smrti tokom seksualne aktivnosti. [86]. Potrošnja energije tokom seksualne aktivnosti je uglavnom niska do umerena (3-5 MET-a, metaboličkih ekvivalenata) i penjanje stepenicama na drugi sprat često se koristi kao ekvivalent aktivnosti u smislu potrošnje energije. Inhibitori fosfodiesteraze-5 za lečenje erektilne disfunkcije su obično bezbedni kod HKS pacijenata, ali su kontraindikovani kod oni koji uzimaju nitrate i koji imaju izraženu hipotenziju [86]. Zdravstveni radnici treba da pitaju pacijente o seksualnoj aktivnosti, da im daju informacije i pruže savete.

Pridržavanje modifikacijama životnog stila i redovnom uzimanju lekova je veliki izazov. Sistematski pregled epidemioloških studija pokazao je da se znatan deo pacijenata ne pridržava redovnog uzimanja KV lekova i da se 9% kardiovaskularnih neželjenih događaja u Evropi može pripisati lošoj prijemčivosti pacijenata (komplijansi) za redovnu terapiju [87, 88]. Kod starijih muškaraca sa KB, veće pridržavanje smernicama za lekove pozitivno je povezano sa boljim kliničkim ishodima, nezavisno od ostalih uslova. **Polifarmacija** igra negativnu ulogu u pridržavanju lečenju [88] i složenost režima uzimanja lekova je povezana sa nepridržavanjem i većom stopom hospitalizacija [89]. Lekari koji propisuju lekove treba da daju prednost lekovima koji su dokazali svoju korist sa najvišim nivoom dokaza i onima od kojih je najveća korist za pacijenta, a bez značajnih neželjenih efekata lekova. Pojednostavljenje režima pomaže u pridržavanju lečenju i postoje dokazi o koristima kognitivnih obrazovnih

strategija, elektronski nadziranih povratnih informacija i telefonska podrška medicinskih sestara i tehničara. Recenziranje i kontrola vrste i doze lekova od strane lekara iz primarne zdravstvene zaštite su značajan faktor pomoći svim pacijentima a posebno pacijentima sa više komorbiditeta, da bi se pojednostavio režim lečenja, otkrile interakcije lekova a rizik od neželjenih efekata lekova sveo na minimum [89, 90,91]. Dugoročna podrška (intenzivna prvih 6 meseci, zatim svakih 6 meseci tokom 3 godine) u GOSPEL- studiji (Globalne strategije sekundarne prevencije za ograničavanje ponavljanja događaja nakon infarkta miokarda) rezultiralo je značajnim poboljšanjima rizik faktora i smanjenja nekih neželjenih ishoda [20].

Supstituciona terapija polnim hormonima kod žena sa HKS u menopauzi se ne preporučuje. Godišnja vakcinacija protiv gripa je preporučena svim bolesnicima sa HKS jer poboljšava prevenciju AIM, redukuje KV mortalitet kod odraslih u dobi > 65 godina.

FARMAKOLOŠKA TERAPIJA HRONIČNIH KORONARNIH SINDROMA (SCENARIO 1)

Ciljevi farmakološkog lečenja bolesnika sa HKS su: smanjiti simptome AP i ishemijsku izazvanu fizičkim naporom i vežbanjem i sprečavanje neželjenih KV događaja. Anti ishemijski lekovi - ali i promene životnog stila, redovni treninzi za vežbanje, edukacija pacijenata i eventualna revaskularizacija - svi igraju ulogu u minimiziranju ili iskorenjivanju simptoma tokom dugoročne prevencije. Prevencija kardiovaskularnih neželjenih ishoda: AKS, AIM, SI (HFrEF, HFmEF, HFpEF), ventrikularnih aritmija i srčanih blokova, VT, AF, moždanog udara i KV smrti povezanih sa HKS se fokusira na smanjenje incidencije akutnih aterotrombotskih događaja i razvoja disfunkcije LK. Optimalna farmakološka terapija (OFT) može se definisati kao tretman koji zadovoljavajuće kontroliše simptome i sprečava neželjene KV događaje povezane sa HKS, sa maksimalnim pridržavanjem pacijenta lečenju i uz minimalne neželjene efekte lekova. Postoje dva glavna terapijska cilja u lečenju HKS:

1. Minimizovanje simptoma sa poboljšanjem kvaliteta života antiishemijskim - antianginalnim lekovima **prve linije:** betablokatori (BB) i antagonisti kalcijuma (CCB) te brzodelujući nitroglicerini sublingvalno po potrebi i **druge linije:** dugodelujući nitrat (LAN), uključujući nove opcije: ivabradin, nikorandil, trimetazidin i ranolazin (i eventualno alopurinol). **2. Poboljšanje prognoze smanjenjem rizika za progresiju**

ateroskleroze i sprečavanje akutnih koronarnih događaja i naprasne smrti i produženje života - sekundarna prevencija KVB (acetilsalicilna kiselina (ASA) i drugi antitrombocitni lekovi, statini, ACEI, BB).

ANTI-ISHEMIJSKI (ANTIANGINALNI) LEKOVI

Neposredno ublažavanje anginoznih simptoma ili prevencija simptoma pod okolnostima koje verovatno izazivaju anginu, obično se dobija brzodelujućim formulacijama nitroglicerina sublingvalnim putem, što spada u antianginalne lekove prve linije. Međutim, ne postoji univerzalna definicija optimalnog lečenja kod pacijenti sa HKS i terapija lekovima mora se prilagoditi individualnim karakteristikama i sklonostima pacijenta. **Početna terapija lekovima** obično sastoji se od jednog ili dva antianginalna leka uz lekove za sekundarnu prevenciju KVB. [92-95]. Početni izbor antianginalnih lekova zavise od očekivane tolerancije povezane sa profilom i komorbiditetima pacijenta, potencijalnih interakcije sa lekovima koji su istovremeno primenjuju u terapiji, preferencije pacijenta nakon obaveštenja o potencijalnim štetnim efektima lekova i dostupnosti lekova. Kombinovana terapija sa dva antianginalna leka npr. beta blokator (BB) i antagonist kalcijuma (CCB) je bolja od monoterapije bilo kojom klasom antianginalnih lekova, ali efekat u

smanjenju kliničkih događaja ostaje nejasan [95-98]. Kao lekovi prve linije se preporučuju BB ili CCB, mada do danas nijedna randomizovana kontrolisana studija (RCT) nije uporedila ovu strategiju sa alternativnim strategijama koja koristi početno propisivanje drugih antiishemijskih lekova ili kombinacije BB i CCB [92-95]. Rezultati meta-analize 46 studija i 71 komparacija tretmana, podržava početnu kombinaciju BB i CCB. [98]. Ista meta-analiza sugerirala je nekoliko drugih inicijalnih prvih linija kombinacije antiishemijskih lekova (nitrati dugog delovanja, ranolazin, trimetazidin i u manjoj meri, ivabradin) koje se mogu pokazati korisnim u kombinaciji sa BB ili CCB kao terapijom prve linije, a nema podataka za nikorandil. Nijedna studija ili metaanaliza još nije procenila sa dovoljno snage uticaj kombinovanja beta blokatora ili CCB-a sa drugom linijom antiishemijskih lekova protiv neželjenih događaja: morbiditeta ili smrtnosti [98]. Bez obzira na inicijalnu strategiju, odgovor na početnu antianginalnu terapiju treba da bude preispitan nakon 2-4 nedelje od započinjanja lečenja.

Algoritam lečenja antiishemijskim lekovima kod pacijenata sa suspektnim HKS i stabilnom anginom i/ili dispnejom na napor je prikazan na TABELI 5.

TABELA 5. Farmakološka terapija antiishemijskim lekovima hroničnih koronarnih sindroma

LEGENDA: BB=blokatori beta adrenergičkih receptora CCB =antagonisti kalcijuma ili blokatori kalcijumskih kanala DHP=dihidropiridinski NE-DHP= ne-dihidropiridinski LAN =dugodelujući nitrati etc....

Prevedeno i preuzeto sa sajta <https://www.escardio.org/Guidelines/Clinical-Practice-Guidelines/Chronic-Coronary-Syndromes>

LEKOVI PRVE LINIJE LEČENJA HKS

KRATKO DELUJUĆI NITRATI se daju za akutni napad AP na napor. Sublingvalne tablete (lingvate) i sprej nitroglicerina pružaju odmah ublažavanje angine na napor. Sprej nitroglicerina deluje brže nego sublingvalna tableta

nitroglicerina [99]. Na početku simptoma angine pacijent treba da se odmori u sedećem položaju (stajanje promoviše sinkopu) i da uzme nitroglicerina (tableta 0,3-0,6 mg sublingvalno, ne gutati se, ili 0,4 mg spreja pod jezik i ne gutati i ne udisati) svakih 5 min sve dok bol prestane ili je

uzeto najviše 1,2 mg unutar 15 min. U tom vremenskom okviru, ako angina potraje više od 15 minuta, pacijent mora da se javi hitnoj medicinskoj pomoći radi bolničkog lečenja, zbog sumnje na AKS. Za profilaksu se može primeniti nitroglicerina pre fizičkih aktivnosti za koje se zna da izazivaju anginu.

BETA BLOKATORI (BB-blokatori beta 1- β 1-adrenergičkih receptora).

Prednost u HKS daje se selektivnim blokatorima β 1- adrenergičkih receptora. Efikasnost OMT kod stabilne angine gde je BB centralna komponenta lečenja je slična efektu perkutane koronarne intervencije (PCI) sa stentom, po mišljenju W. Bodena, glavnog istraživača COURAGE studije [16,60]. Dozu beta blokatora treba prilagoditi da srčana frekvenca bude 55-60 otkucaja u minuti [100,101]. Prekid treba da bude postepenim smanjenjem doze i ne naglo. Nagli prestanak uzimanja zbog povećanja broja β 1 receptora u srcu izaziva pogoršanje angine, nekad čak i infarkt miokarda. Doziranje prema ciljnoj srčanoj frekvenci od 55-60/min je uobičajeno, ali je prihvatljivo je i ispod 50/min u individualnog pacijenta bez blokova. Ciljne doze β 1-blokatora kod HKS: metoprolol 2 x 100mg, maksimalno 400 mg, bisoprolol 1 x 1,25-10 mg, maksimalno u Evropi 30 mg, u USA čak do 40 mg; (L.Opie, Drugs for the Heart, 2013); nebivolol 1,25-5 mg x 1, maksimalno do 15 mg u praksi. BB su efikasni kod silent ishemije. Pri naporu je cilj da SF ne bude preko 100/min. Svi BB su potencijalno jednako efikasni u HKS i izbor se vrši prema komorbiditetima. BB se mogu kombinovati sa dihidropiridinskim (DHP) CCB da bi se smanjila tahikardija indukovana DHP-ima. Oprez je opravdan kada se beta-blokator kombinuje sa verapamilom ili diltiazemom zbog potencijala za razvoj pogoršanja SI, prekomerne bradikardije i / ili atrioventrikularnog bloka (ranije apsolutna, sada relativna kontraindikacija). Kombinacija beta blokator sa nitratom smanjuje refleksnu tahikardiju. Glavne nuspojave beta blokatora su umor, psihička depresija, bradikardija, AV blok, bronhospazam, periferna vazokonstrikcija, posturalna hipotenzija, impotencija i maskiranje simptoma hipoglikemije. Kod komorbiditeta, prednost imaju najselektivniji β 1 blokatori bisoprolol i nebivolol. Kod pacijenata sa nedavnim AIM i onih sa hroničnom SI sa smanjenom EF (HFrEF), BB su povezani sa značajnim smanjenjem smrtnosti i kardiovaskularnih događaja [102-104], oko 30% redukcija mortaliteta i reinfarkta, sličan efekat i kod ishemijske SI. Korist kod pacijenata sa KB bez prethodnog AIM ili SI je manje dobro ustanovljena i nedostaju placebo

kontrolisana ispitivanja. [105]. Retrospektivna analiza 21860 podudarnih pacijenata iz REACH registra nije pokazala smanjenje kardiovaskularne smrtnosti beta-blokatorima kod pacijenata sa KB i faktorima rizika, sa ili bez prethodnog AIM [106], ali je ovo još uvek predmet debate i daljih istraživanja.

ANTAGONISTI KALCIJUMA (CCB ili blokatori kalcijumovih sporih kanala).

Dok CCB poboljšavaju simptome ishemije miokarda, nije dokazano da se smanjuju neželjeni događaji i smrtnost kod pacijenata sa HKS [107]. Međutim pokazano je da imaju prednost u prevenciji ishemije pri naporu u odnosu na BB.

NE-DIHIDROPIRIDINSKI ANTAGONISTI KALCIJUMA (NE-DHP): VERAPAMIL I DILTIAZEM

Verapamil ima veliki broj odobrenih indikacija, uključujući sve vrste angine (na napor, vazospastične i nestabilne), supraventrikularne tahikardije i hipertenzija. Indirektni dokazi sugeriše dobru bezbednost, ali uz rizik od srčanih blokova, bradikardije i HF. U poređenju sa metoprololom, antianginalna aktivnost bila je slična. Kombinovana beta-blokada sa verapamilom se ne savetuje (ranije apsolutno kontraindikovana zbog rizika srčanih SA I AV blokova). Diltiazem, svojim profilom efekata, ima prednosti u poređenju sa verapamilom u lečenju angine napora. Kao verapamil, deluje perifernom vazodilatacijom, smanjuje afterload uz prevenciju koronarnog vazospazma. Posедуje umeren negativan inotropni, hronotropni i dromotropni efekat. Nije bilo rezultata ispitivanja koji su upoređivali diltiazem i verapamil. Upotreba ne-DHP-a ne preporučuje se CCB kod pacijenata sa disfunkcijom LV-a.

DIHDROPIRIDINSKI ANTAGONISTI KALCIJUMA (DHP-CCB). Nifedipin dugog delovanja

Nifedipin snažni arterijski vazodilatator posebno dobro testiran na hipertenzivnim anginalnim pacijentima kada se doda uz betablokadu. U velikoj placebo-kontroliranoj ACTION, dodavanje nifedipina dugog delovanja [60 mg jednom dnevno] na konvencionalno lečenje angine nije dalo efekta na prognozu. Nifedipin dugog delovanja pokazalo se bezbednim i umanjio je potrebu za koronarnom angiografijom i kardiovaskularnim intervencijama [108]. Relativne kontraindikacije za nifedipin su: mali minutni volumen srca (teška aortna stenoza, hipertrofična opstruktivna kardiomiopatija ili SI); Pažljiva kombinacija sa beta-blokadom je obično

izvodljiva i poželjna. Vasodilatatorni neželjeni efekti uključuju glavobolje i edeme gležnjeva.

Amlodipin.

Veoma dug poluvivot amlodipina i njegova dobra podnošljivost čine ga efikasnim antianginalnim i antihipertenzivnim lekom koji se uzima jednom dnevno. Neželjenih efekata je malo, uglavnom edem gležnja. U pacijenata sa HKS i bez SI, amlodipin u dozi 10 mg / dan smanjuje broj koronarnih revaskularizacija i hospitalizaciju zbog AP u studiji trajanja 24 meseca [109]. Ishemija izazvana vežbanjem efikasnije se smanjuje amlodipinom, 10 mg / dan, nego pomoću beta blokatora atenolola, 50 mg / dan a njihova kombinacija je još bolja. Međutim, CCB - BB kombinacija se nedovoljno koristi, kao i druge kombinacije antiishemijskih lekova, čak i u nekim studijama koje izveštavaju da je primenjeno „optimalno lečenje stabilne AP na napor“ [110].

LEKOVI DRUGE LINIJE

Dugodelujući nitrati za profilaksu angine (npr. Nitroglicerina flaster, izosorbid dinitrat i izosorbid mononitrat) su lekovi druge linije za ublažavanje AP, kada je početna terapija BB ili NE-DHP CCB kontraindikovana, slabo se toleriše ili je nedovoljna za kontrolu simptoma. Suštinski postoji nedostatak podataka koji upoređuju nitrata sa BB i CCB, da bi se izvukli čvrsti zaključci o njihovoj relativnoj efikasnosti [110]. Kada se uzmaju tokom dužeg perioda, nitrati sa dugim delovanjem izazivaju toleranciju sa gubitkom efikasnosti, zato je potrebno propisivanje intervala bez leka od 10- 14 sati. Bioraspoloživost izosorbid-dinitrata zavisi od inter-individualne varijabilnosti jetre dok je izosorbid-mononitrat, njegov aktivni metabolit 100% bioraspoloživ. Titracija doze je od suštinskog značaja za kako bi se dobila maksimalna kontrola simptoma u podnošljivoj dozi. Prestanak treba da bude postepenim smanjenjem doze i ne naglo da se izbegne pogoršanje AP. Najčešći neželjeni efekti su hipotenzija, glavobolja i crvenilo. Kontraindikacije uključuju hipertrofičnu opstruktivnu kardiomiopatiju, tešku stenozu aorte i istodobna primena inhibitora fosfodiesteraze (npr. sildenafil, tadalafil ili vardenafil) ili riociguata.

Molsidomin je nepravedno zanemaren lek, (čak i u novom ESC vodiču iz 2019 godine [1]), koji deluje slično nitratima, ali se na njegovo dejstvo ne razvija tolerancija, ima efikasno antiishemijsko dejstvo i dobru podnošljivost. Dozira se 3 x 2mg do 4mg ili rektalni oblik 2 x

8mg. Nažalost nema studija o efektu na prognozu HKS [111,112].

Ivabradin nije inferiorniji do atenolola ili amlodipina u lečenju angine i ishemije kod pacijenti sa HKS [111]. Dodavanjem ivabradina 7,5 mg dva puta dnevno terapija atenololom je omogućila bolju kontrolu otkucaja srca i anginalnih simptoma. U celini, rezultati studija podržavaju upotrebu ivabradina kao leka druge linije kod pacijenata sa HKS, kada ne podnose ili imaju kontraindikacije za BB.

Nikorandil je nitratni derivat nikotinamida, sa antianginalnim efektima sličnim onima nitrata ili beta blokatora. Nuspojave uključuju mučninu, povraćanje i potencijalno teške ulceracije oralne, crevne i sluzokože. U placebo-kontrolisanoj IONA studiji (n = 5126), nikorandil je značajno smanjio nefatalni AIM ili hospitalizaciju kod bolesnika sa HKS, ali nije bilo efekta na smrt od ishemijske srčane bolesti ili fatalnog AIM [113]. Ovi rezultati podržavaju upotrebu nikorandila kao lek druge linije kod pacijenata sa HKS.

Ranolazin je selektivni inhibitor kasne unutrašnje natrijumske struje. Neželjeni efekti uključuju vrtoglavicu, mučninu i zatvor. Pored toga, ranolazin povećava QTc, i stoga bi trebalo pažljivo se primenjuje kod pacijenata sa produženjem QTc ili sa lekovima koji produžuju QTc. U placebo-kontroliranom ispitivanju na 6560 pacijenata sa NSTEMI AKS, dodavanje ranolazina u standardni tretman nije dokazalo efikasno u smanjenju primarnih ishoda i KV mortaliteta, AIM ili rekurentne ishemije. [114]. Međutim, ranolazin u relativno velikoj podgrupi HKS (n = 3565), značajno smanjuje rekurentne ishemije i pogoršanje angine [115]. Ovi rezultati podržavaju upotrebu ranolazina kao leka druge linije kod bolesnika sa HKS sa anginom uprkos često korišćenim antianginalnim sredstva kao što su beta blokatori, CCB i / ili dugotrajno delovanje nitrati. Suprotno tome, postoji nedostatak dokaza koji bi podržali upotrebu ranolazina kod pacijenata sa HKS posle PCI sa nepotpunim revaskularizacijom.

Trimetazidin smanjuje ishemiju dejstvom na metabolizam miokarda a bez hemodinamskih efekata, za razliku od mnogih anti-ishemijskih lekova [116]. Trimetazidin 35 mg dva puta dnevno dodat BB (atenolol) redukuje ishemiju izazvanu naporom [117]. Kontraindikovan je kod Parkinsonove bolesti i poremećaja pokreta. Studija na 1628 pacijenata pokazala je da lečenje sa trimetazidinom uz druge antianginalne lekove rezultira sa manjim srednjim brojem napada angine, koji su lakšeg stepena.

Alopurinol, inhibitor ksantin-oksidadaze od skora je predložen u terapiju HKS. Alopurinol ima

dupli efekat konzervacije energije, redukuje potrošnju O₂ u miokardu inhibicijom ksantin oksidaze i vrši transfer iz kreatin fosfata u ATP. Norman i saradnici [118] u randomizovanoj studiji od 65 pacijenata sa HKS su našli da 600 mg/dan alopurinola produžava vreme do nastanka ST depresije i bola redukujući vaskularni oksidativni stress. U velikoj opservacionoj studiji od 29298 sa nenamernom upotrebom alopurinola dovodi do redukcije rizika za nastanak akutnog infarkta miokarda (AKS) kod starih, posebno kad se uzima duže od 2 godine [119]. Međutim, uloga alopurinola u smanjenju kliničkih događaja u KB ostaje nejasna [120].

PACIJENTI SA HKS I NISKIM KRVNIM PRITISKOM

Terapija antiishemijskim lekovima treba da se odpočne sa vrlo malim dozama, BB ili ne-DHP-CCB uz budno praćenje tolerancije na ove lekove, pri težoj hipotenziji prekinuti terapiju. Treba dati prednost lekovima koji ne utiču na krvni pritisak, kao što su: Trimetazidin, Ranolazin i Ivabradin kod pacijenata u sinusnom ritmu

PACIJENTI SA HKS I BRADIKARDIJOM

Povišena srčana frekvenca u miru jeste jak nezavisni rizik faktor za neželjeni ishod u bolesnika sa HKS i terapijski cilj je srčana frekvencom (SF) manja od 60/min. Ali kod SF<50/min treba izbeći lekove koji imaju negativno hronotropno dejstvo (BB i NE-DHP-CCB, ivabradin) ili da se koriste sa oprezom ako su neophodni. **Lečenje treba početi sa vrlo niskom dozom.** Lekovi koji nemaju efekat usporavanja srčane frekvence treba da imaju prednost (DHP-CCB, LAN, Trimetazidin, Ranolazin, Nikorandil)

FARMAKOLOŠKO LEČENJE SPREČAVANJEM NEŽELJENIH DOGAĐAJA I POBOLJŠANJEM PROGNOZE

LEKOVI PROTIV TROMBOCITA

Aktivacija i agregacija trombocita je pokretač simptomatske koronarne aterotromboze, što je osnova za upotrebu antiagregacionih - antitrombocitnih lekova kod pacijenata sa HKS-om s obzirom na povoljnu ravnotežu prevencije ishemijskih događaja i povećan rizik od krvarenja. Dvostruki antiagregacijski terapija (DAPT) sa aspirinom i oralnim inhibitorima P₂Y₁₂ je osnov antitrombotske terapije nakon AIM i / ili PCI.

ACETILSALICILNA KISELINA (ASPIRIN) U MALIM DOZAMA deluje nepovratno

inhibicijom trombocita ciklooksigenaze-1 i time tromboksana, što se dešava sa hroničnim doziranjem ≥75 mg / dan. Gastrointestinalni nuspojave pri većim dozama opravdavaju dnevnu dozu od 75-100 mg za prevenciju ishemijski događaji kod KB pacijenata sa ili bez anamneze AIM. Kako je inhibicija ciklooksigenaze-1 aspirinom konzistentna i predvidljiva kod adekvatnih bolesnika, ne postoji potreba za testiranjem funkcije trombocita.

INHIBITORI P₂Y₁₂ blokiraju trombocitne receptore P₂Y₁₂, koji igra ključnu ulogu u aktivaciji trombocita i formiranju arterijskog tromba. Klopidogetrel i prasugrel su prolektivi tienopiridina koji nepovratno blokiraju P₂Y₁₂ aktivnim metabolitima. Klopidogetrel je dobro poznati standardni antitrombociti lek, ali relativno često postoji rezistencija na njegovo dejstvo. Na Prasugrel se ne javlja značajno rezistencija, smanjuje ishemijske događaje i trombozu stenta, ali bez uticaja na mortalitet, ali zato na štetu pojačanih nefatalnih krvarenja. Tikagrelor je reverzibilno vezujući inhibitor P₂Y₁₂, koji ne zahteva metaboličku aktivaciju. Tikagrelor ima najpredvidljiviji i dosledno visok nivo inhibicije P₂Y₁₂ tokom terapije održavanja kod prijemčivih pacijenata i takođe ima brži početak dejstva u poređenju sa klopidogetrelom. Čini se da monoterapija tikagrelorom ima sličnu efikasnost i sigurnost kao i aspirin kod pacijenata sa prethodnim PCI. Tikagrelor povećava nefatalna, ali ne i fatalna krvarenja. Ekvivalentna efikasnost i slična bezbednost dve doze tikagrelora su objašnjene sličnim nivoima inhibicije trombocita. Tikagrelor može izazvati dispneju, koja je često prolazna i najčešće blaga i podnošljiva, ali ponekad je potreban prelazak na tienopiridin. Postoje mišljenja i ograničene farmakodinamske studije koje podržavaju nelicenciranu upotrebu prasugrela ili tikagrelora u stabilnih pacijenata koji su podvrgnuti elektivnoj PCI a koji imaju visok rizik od tromboze stenta.

TRAJANJE DVOSTRUKE ANTIAGREGACIONE TERAPIJE POSLE PCI

Posle 6 meseci DAPT-a postiže optimalnu ravnotežu efikasnosti i sigurnost kod većine pacijenata [121]. Preuranjeni prekid upotrebe P₂Y₁₂ inhibitora je povezan sa povećanim rizikom od tromboze stenta i ne preporučuje se [121]. Međutim, može se razmotriti kraće trajanje DAPT-a kod osoba sa visokim rizikom za krvarenje opasno po život s obzirom na vrlo nizak rizik od tromboze stenta posle 3 meseca.

Ipak zvanični stav je: preporučeno 12 meseci trajanja DAPT nakon AKS i PCI.

Veća korist od produžene terapije klopidogetrela ili prasugrela primećena je u pacijenti koji su lečeni od AIM. PEGASUS-TIMI 54 studija pokazala je da je dugotrajna terapija tikagrelorom 60 ili 90 mg 2 x 1, započeta kod stabilnih pacijenata više od 1 godine nakon AIM, smanjuje ishemijske događaje na račun povećanja više nefatalnih krvarenja [121]. Doza od 60 mg čini se da se bolje podnosi i odobrena je u mnogim zemljama za ovu indikaciju. Apsolutno smanjenje ishemijskih događaja kod HKS SCENARIO 4 s dugotrajnim tikagrelorom (60 mg 2 x 1) uz malu dozu ASA kod pacijenata sa visokim rizikom nakon AIM sa DM, perifernom arterijskom bolesti ili višesudovnom KB dokazali su Bhatt DL i saradnici u podgrupi spomenute studije PEGASUS-TIMI 54 [122].

ORALNI ANTIKOAGULANTNI LEKOVI (AOK)

ANTIKOAGULANTNI LEKOVI U SINUSNOM RITMU

Antikoagulantni lekovi inhibiraju delovanje i / ili stvaranje trombina, koja igra ključnu ulogu i u koagulaciji i u aktiviranju trombocita. Nedavno objavljena ispitivanja su obnovila interesovanje za kombinovanje nižih antikoagulantnih doza sa antitrombocitnom terapijom.

RIVAROKSABAN U MALIM DOZAMA.

Rivaroksaban je inhibitor faktora Xa koja je proučavan u maloj dozi od 2,5 mg 2 x 1 dnevno u nekoliko populacija pacijenata u sinusnom ritmu, a ova doza je 1/4 standardne doza koja se koristi za antikoagulaciju kod pacijenata sa AF. U studiji ATLAS ACS 2TIMI 51 rivaroksaban 2,5 mg 2 x 1, u poređenju sa placebom, je smanjio složeni ishod od AIM, moždanog udara ili KV smrti kod stabilizovanih pacijenata tretiranih aspirinom i klopidogetrelom nakon AKS, uz pojačano nefatalno krvarenje, ali uz dokaze smanjenja kardiovaskularne smrtnosti [123]. Nakon toga u COMPAS studiji [124], isti režim u kombinaciji sa aspirinom i klopidogetrelom, s ili bez rivaroksabana 2 x 5 mg, kod pacijenata sa HKS pokazali su smanjene ishemijske događaje na račun povećanog rizika pretežno nefatalnog krvarenja. [124].

ANTIKOAGULANTNI LEKOVI U ATRIJSKOJ FIBRILACIJI

OAK se preporučuje pacijentima sa AF i HKS za smanjenje ishemijskog moždanog udara i drugih ishemijskih događaja. OAK kod pacijenata sa AF pokazali su superiornost nad monoterapija aspirinom ili DAPT na bazi klopidogetrela za prevenciju moždanog udara i zato se

preporučuju za ovu indikaciju [124]. Kada uvodi OAK kod pacijenta sa AF i HKS, na osnovu CHADVASC skora i HASBLED skora, non vitamin Kantagonisti -NOAK (tj. apikaban, dabigatran, edoksaban ili rivaroksaban) imaju prednost nad antagonistima vitamina K (VKA). [1]

Inhibitori protonske pumpe

Inhibitori protonske pumpe smanjuju rizik od gastrointestinalnog krvarenja u pacijenti koji se leče antitrombocitnim lekovima i daju se svima sa visokim rizikom za krvarenje (HASBLED skor) i kod monoterapije, za poboljšanje sigurnosti. [124]

STATINI

Kada ciljne vrednosti LDL holesterola ne mogu biti postignute, pokazano je da je dodavanje ezetimiba redukuje LDL holesterol ali i smanjuje KV događaje kod pacijenata sa AKS, kod obolelih od dijabetesa [1] bez daljeg uticaja na smrtnost. Pored vežbanja, ishrane i kontrole težine, što bi trebalo preporučiti svim pacijentima dodaci ishrani, uključujući fitosteroles mogu u manjoj meri sniziti LDL-C, ali nije pokazano poboljšanje kliničkih ishoda [1]. Fitosteroli se takođe koriste kod pacijenata sa netolerancijom na statine koji čine grupu s većim rizikom za kardiovaskularne događaje. Studije od 2015. Pokazuju da inhibitori proprotein konvertaze subtilin-keksina tipa 9 (PCSK9) (evolocumab i alirocumab su vrlo efikasni u smanjenju holesterola, snižavajući LDL-C na konzistentan način stabilan način do < 1,3 mmol / L. U ispitivanjima ishoda, ovi agensi su pokazali smanjenje kardiovaskularnih i uglavnom ishemijskih događaja, sa malo ili bez uticaj na smrtnost. [1]. Vrlo nizak nivo holesterola se dobro podnosi i povezan je sa manje događaja, ali visokom cenom PCSK9 inhibitora i njihova nepoznata dugoročna sigurnost ograničila je njihovu upotrebu do danas. Niske gustine lipoproteinska afereza i nove terapije poput mipomersena i lomitapid treba dalje istraživanje. Za pacijente koji su podvrgnuti PCI, visoka doza atorvastatina smanjuje učestalost periproceduralnih događaja [1].

BLOKATORI SISTEMA RENIN ANGIOTENSIN ALDOSTERON

ACE INHIBITORI mogu smanjiti smrtnost, AIM, moždani udar i SI-HF među pacijentima sa disfunkcijom LK, prethodnim perifernim vaskularnim bolestima i kod DM visokog rizika. Preporučuje se da **ACE inhibitori (ili ARB, blokatori receptora angiotenzina AT₂ u**

slučajevima netolerancije ACEI) treba uzeti u obzir za lečenje pacijenata sa HKS sa koegzistirajućom hipertenzijom, LVEF <40%, DM ili hroničnom bubrežnom bolesti i insuficijencijom (CKD), osim ako su kontraindicirani (npr. Teška renalna oštećenja, hiperkalemija itd.). Međutim, nisu pokazala sva ispitivanja da ACE inhibitori smanjuju smrtnost od svih uzroka, kao ni kardiovaskularnu smrt, nefatalni AIM, moždani udar ili HF kod pacijenata sa aterosklerozom i bez oslabljene funkcije LK. Metaanaliza, uključujući 24 ispitivanja i 61961 bolesnika dokumentovala je kod bolesnika sa HKS bez SI-HF [1] da inhibitori renin-angiotenzin sistema (RAS) smanjuju kardiovaskularne događaje i smrt samo u poređenju sa placebo, ali ne i kada u poređenju sa aktivnim kontrolama. Otuda, terapija ACE inhibitorima u HKS pacijenat bez SI-HF ili visokog KV rizika se generalno ne preporučuje, osim ako nije potrebno zbog postizanja ciljnih vrednosti krvnog pritiska.

Neprilizin je endogeni enzim koji razgrađuje vazoaktivne peptide kao što su bradikinin i natriuretski peptidi. Farmakološka inhibicija neprilizina podiže nivo ovih peptida, pojačavajući diurezu, natriurezu, opuštanje miokarda i antiremodeliranje i smanjenje izlučivanje renina i aldosterona. Prvi lek u klasi je LCZ696, koji kombinuje valsartan i sakubitril (inhibitor neprilizina) u jednoj tableti. pacijenti sa HF (LVEF <35%) koji ostaju simptomatski uprkos optimalnom tretman ACE inhibitorom,

beta blokatorom i mineralokortikoidom antagonist receptora (MRA), **sakubitril / valsartan** je preporučuje se kao zamena za ACE inhibitor kako bi se dodatno smanjilo rizik od HF hospitalizacije i smrti kod ambulantnih pacijenata. **Preporučuje se blokada aldosterona spironolaktonom ili eplerenonom** za upotrebu kod post-MI pacijenata koji već primaju terapijske doze ACE inhibitora i beta blokatora I imaju LVEF <35%, ili dijabetes ili SI-HF. Treba biti oprezan se primenjuje kada se MRA koriste kod pacijenata sa oštećenom funkcijom bubrega [procenjeni GFR (eGFR) <45 mL / min / 1.73 m²] i kod onih sa nivo kalijuma u serumu > 5,0 mmol / L.340

Kombinacija anti-ishemijskih lekova i lekova koji utiču na prognozu i preživljavanje u praksi se nedovoljno primenjuju kako u svetu[110] tako i u delu Srbije -Timočkoj krajini. Takođe ne titriraju se doze za postizanje optimalnih efekata farmakološke terapije [112]. Iz kliničke prakse Ordinacije Dr Bastać prikazuje se analiza lečenja DE NOVO koronarne bolesti kod konsektivnih 101 pts . Pri prvom pregledu pacijenti , ranije vođeni ili shvaćeni kao stabilna angina pectoris , imali su farmakološku terapiju od strane ordinirajućeg lekara ili kardiologa (samo 26% imali definitivnu dijagnozu koronarne bolesti putem EKG testa fizičkim opterećenjem) prikano na TABELA 6

Tabela 6. Analiza propisanih lekova za lečenje suspektog hroničnog koronarnog sindroma (HKS) u Ordinaciji "Dr Bastać" na 101-nom kosektivnom pacijentu 2017. godine

Antiishemijski lekovi		Lekovi koji deluju na prognozu koronarne bolesti
I linije	II linije	
65% beta blokatori (imaju i hipertenziju)	36% dugodelujući nitrati nije propisan molsidomin	48% acetil salicilna kiselina (ASA) 9% Klopidoogrel
31% Ant CA (zbog hipertenzije)	16% trimetazidin	23% statin
20% Ntg sublinvalno po potrebi	Nisu propisani: ranolazin, ivabradin, nikorandil,	61% ACE inhibitori (imaju i hipertenziju) 65% beta blokatori (imaju i hipertenziju)

REVASKULARIZACIJA MIOKARDA (RM). Uloga koronarne revaskularizacije miokarda (RM) u lečenju hroničnih koronarnih sindroma SCENARIO 1. slika 5

Slika 5. Uloga koronarne revaskularizacije miokarda (RM) u lečenju hroničnih koronarnih sindroma SCENARIO 1

Prevedeno i preuzeto sa sajta <https://www.escardio.org/Guidelines/Clinical-Practice-Guidelines/Chronic-Coronary-Syndromes>

Kod pacijenata sa HKS-om optimalna medikalna terapija (promena stila života, redukcija rizik faktora i farmakološka-medikamentozna terapija, ne izjednačavati medikalnu i medikamentoznu terapiju)-OMT je ključna za smanjenje simptoma, zaustavljanja napredovanja ateroskleroze i sprečavanja aterotrombotskih događaja. Revaskularizacija miokarda (RM) igra centralnu ulogu u zbrinjavanju najtežih oblika HKS kao zadnja instanca, ali uvek kao dodatak optimalnoj medikalnoj terapiji (OMT), a bez njenog eliminisanja. Ciljevi RM su ublažavanje simptoma kod pacijenata sa anginom i / ili poboljšanje prognoze. Ove preporuke sugeriše da je revaskularizacija kod pacijenata sa AP i

značajnom stenozom često terapija druge linije kada OMT nije bila uspešna. Revaskularizacija miokarda: PCI ili CABG može kod jednog manjeg broja selekcionisanih pacijenata efikasno ublažiti anginu, smanjiti upotrebu antianginalnih lekova i poboljšati sposobnost fizičkog vežbanja i kvalitet života u poređenju sa strategijom samo sa OMT. Revaskularizacija bilo PCI-em ili CABG-om takođe ima za cilj da efikasno eliminiše ishemiju miokarda i njene nepovoljne kliničke manifestacije među pacijentima sa značajnim koronarnim stenozama i za smanjenje rizik od glavnih akutnih neželjenih KV događaja uključujući AIM i kardiovaskularnu smrt. Mnogobrojne metaanalize koje upoređuju strategiju RM putem PCI sa početnom OMT kod

pacijenata sa HKS-om, pokazuju ili da nema koristi [126,127] ili revaskularizacija miokarda pruža skromnu korist [128,129] u smislu preživljavanja ili manje incidence AIM i SI. S tim u vezi, prethodne ESC smernice iz 2013 [4] su identifikovale specifične podgrupe pacijenata (zasnovane na koronarnoj anatomiji, veličini zone ishemije miokarda, faktora rizika, stanju srčane funkcije itd.) kod kojih RM može poboljšati prognozu, što ukazuje na to da u drugim podgrupama ona nema efekta. SLIKA 5 rezimira praktični pristup indikacijama za RM u HKS prema prisustvu ili odsustvu simptoma i dokumentovane ishemija miokarda neinvazivnim funkcionalnim slikovnim testovima. Međutim, odnosa rizika i koristi kod individualnog slučaja treba uvek da se vrednuje i RM se razmatra samo ako očekivana korist nadmašuje potencijalni rizik. Takođe, aspekt zajedničkog timskog odlučivanja je ključan, sa potpunim informacijama datim pacijenta o očekivanim prednostima i nedostacima dve strategije, uključujući rizik od krvarenja vezan za DAPT u slučajevima revaskularizacija putem PCI. **Detaljna diskusija o najboljem izboru između modaliteta revaskularizacije PCI ili CABG za individualnog pacijenta na HEART timu je objavljena u ESC smernicama za revaskularizaciju miokarda iz 2018. godine** [131].

Uloga RM je stavljena u kontekst novijih dokaza koji se odnose na prognostičku ulogu perkutanih koronarnih intervencija (PCI) ili koronarnog arterijskog premoščavanja venskim graftom ili nativnom a. mammariom internom i drugim arterijama (CABG) u ovoj niskorizičnoj populaciji. Sada je RM rezervisana za pacijente gde postoje jaki dokazi da bi se njom poboljšala prognoza na bazi dokaza regionalne ishemije vizuelizacionim neinvazivnim testovima-perfuzionim imidžingom ili procenom FFR i iwFR [131]. Tipična konstelacija je kod pacijenta sa velikom oblašću ishemije miokarda koja odgovara stenozu glavnog stabla (left main stenosis>50%) i višesudovnoj bolesti koja uvek uključuje stenozu ≥70% proksimalne prednje-silazne grane leve koronarne arterije (LAD). Postoje nedvosmisleni dokazi da perkutana koronarna revaskularizacija (PCI) kod akutnih koronarnih sindroma sa ST-segment-elevacijom redukuje mortalitet u odnosu na fibrinolizu, a obe u odnosu na one gde nije urađena reperfuzija. U ostalim formama KB -hroničnim koronarnim sindromima (HKS) uloga PCI revaskularizacije je kontraverzna u smislu redukcije mortaliteta [132,133]. U najnovijoj meta-analizi 46 studija na 37 757 osoba ispitivan

je benefit PCI raznih kategorija koronarnih bolesnika, uključujući i pravu stabilnu anginu bez skorašnjeg infarkta. Kod stabilne angine pektoris, kategorije hronični koronarni sindrom PCI ne redukuje ukupni mortalitet (RR, 0.98, p=0.11]), srčanu smrt (RR, 0.89, p=0.33) niti pojavu infarkta miokarda (RR, 0.96; P=0.54). PCI sprečava smrt, srčanu smrt i AIM prvenstveno kod pacijenata sa nestabilnom AP. Za pacijente sa stabilnom KB, PCI ne pokazuje nikakve efekte na bilo koji od ovih ishoda. [132-134]. Međutim sada postaje evidentno da je OMT i dalje nedovoljno korišćena i u novijim studijama [132]. Mohee K. i saradnici pokazuju da je OMT ipak suboptimalna u bolesnika pred PCI a postaje optimalna tek posle PCI zbog povećane komplikacije. [132]. Argument: OMT je definitivna terapija za pacijente sa stabilnom koronarnom bolešću i niskim rizikom od KV događaja (mortalitet < 1% godišnje)

COURAGE STUDIJA [16,60,133,134]. **(Boden WE i saradnici, objavljena u NEJM 2007)**-inicijalna PCI sa stentom ne smanjuje rizik od smrtnog ishoda, AIM i hospitalizacije i nema prednost u stabilnoj AP prema OMT na 2287 randomizovanih pts sa poznatom značajnom stabilnom KB i dokazanom miokardnom ishemijom koji su bili samo na OMT ili OMT+PCI. Između 1999 i 2004, COURAGE (Clinical Outcomes Utilization Revascularization and aggressive Drug Evaluation) studija randomizovala 2287 pts sa objektivnim dokazom ishemije i proksimalne angiografske KB (≥ 70% vizualne stenozе) na OMT sa ili bez PCI. Cilj i dizajn studije bio je da testira strategiju rutinske, anatomske-indikovane PCI, ako je potrebna, za neuspeh inicijalne OMT. Praćenjem od 2,5 do 7 godina (medijana 4,6 g) pokazalo je da smrt ili AIM se dešava sa istom frekvencom u obe podgrupe (HR PCI+OMT vs OMT= 1,05, p=0,62). Nakon 4.6 godina praćenja nije bilo statistički značajne razlike među grupama za kumulativnu smrtnost i nefatalni infarkt miokarda -18,5 % vs 19%, kao i za moždani udar i hospitalizaciju zbog nove nestabilne AP. **VAŽNO:** pacijenti COURAGE studije su bili sa izraženim simptomima pri uključenju i imali značajne komorbiditete, visoku prevalencu objektivno utvrđene ishemije i ekstenzivnu angiografsku koronarnu bolest i spadali su u populaciju u kojoj se očekivao klinički benefit od PCI. Analiza podgrupa otkriva konzistentnost među klinički relevantnim subgrupama. Nema razlike samo OMT versus OMT+PCI u pogledu višesudovne bolesti, niske EF, klase III-IV angine i prisustva Dijabetes Mellitusa. Komparacijom nije bilo razlike ni u hospitalizaciji za AKS. Glavni

rezultat studije je pokazao da PCI kao inicijalna strategija u bolesnika sa stabilnom AP HKS ne redukuje smrt, AIM i ostale velike događaje (MACE), kada se doda OMT. Pacijent sa PCI imali su manje angine u prvoj i 3. godini ali ne i u 5. godini praćenja. Kao što se očekivalo inicijalno u OMT je češća bila revaskularizacija u 16,5% samo prve godine praćenja. Efikasnost OMT kod stabilne AP gde je optimalna doza betablokatora centralna komponenta je slična efektu perkutane koronarne intervencije (PCI) sa stentom (Boden, Courage, 2007). [133,134].

Komparacija između PCI i OMT (Braunwald s Heart disease, 2015- Morow D, Boden WE) [135]. n-) u smislu ranijih tehnika balon angioplastika vs medikalna terapija, pripada istoriji, sada u eri novih tehnika PCI i nove optimalne terapije lekovima. Na 16 studija oko 9000 pts, PCI vs OMT, invazivna strategija nije dala redukciju mortaliteta ili AIM, nego samo redukciju težine AP i bolji kvalitet života- QoL.

META-ANALIZA VINDECKER-A i saradnika objavljuje smanjenje smrtnosti i AIM revaskularizacijom nasuprot OMT samo kod bolesnika sa HKS-om kada je izvršena revaskularizacija CABG ili lekom obloženim stentom nove generacije (DES), za razliku od balon angioplastika, metalnih BMS stentova i starih, ranijih DES [129].

FAME 2 [130]: Statistički značajnija redukcija rizika sa PCI+OMT versus **samo OMT**, prekinuta posle 7 meseci, ali je imala značajne limitacije, nije randomizovana i nije bila duplo slepo kontrolisana studija. Ipak Xaplanteris P. I i saradnici godinu ukazuju na potencijalno širi prognostički uticaj strategije revaskularizacije kada se radi ciljano sa funkcionalnom invazivnom procenom koronarne stenozе putem FFR ili iwFR. Petogodišnje praćenje FAME 2 studije potvrdilo je kliničku korist kod podgrupe pacijenata koji su posebno lečeni sa PCI uz ciljanje samo stenozа koje proizvode ishemiju (tj. FFR <0.80) plus OMT, a to je dalo značajno niže stope hitne revaskularizacije i niža stopa spontanog AIM [130] ali bez jasnog efekta na mortalitet

ORBITA Nova studija ORBITA (randomizovana, kontrolisana, duplo slepa studija) komparacije OMT ili angioplastike sa stentom anatomske značajnih koronarnih stenozе (PCI) u stabilnoj angini, sa lažnom invazivnom procedurom (sham) u kontrolnoj grupi, nije utvrdila prednost PCI u značajnijem poboljšanju funkcionalnog kapaciteta [125]. Studija ističe značajnu komponentu placeba na kliničke efekte i upozorava nas na zamke tumačenja krajnjih ishoda studija (end-points)

koji su podložni pristrasnosti u odsustvu lažne kontrole. Međutim, rezultati ORBITA studije ne mogu da daju definitivne smernice zbog ograničene veličine studije, kratkog vremena posmatranja do ukrštanja tretmana i nedovoljne snage za procenu kliničkih krajnjih ishoda.

ISCHEMIA Najveća međunarodna randomizovana duplo-slepa kontrolisana studija praćenja ISCHEMIA [137-139] regrutovala je pacijente sa stabilnom KB sa umerenom ili ozbiljnom ishemijom na stress testu a imala je cilj da se proceni ima li razlike u kliničkim ishodima -mortalitetu i KV morbiditetu kod bolesnika sa stabilnom hroničnom koronarnom bolešću (SKB, to jest HKS) između invazivne strategije+OMT i samo OMT. Od ukupno regrutovanih 8518 pacijenata randomizacijom je nasumično odabrano 5179 i dalje su randomizovani po vrsti tretmana: Invazivna intervencija PCI sa stentom plus medikalna terapija (n=2588) versus samo medikalna terapija (n=2591). Koronarna CT angiografija izvedena je kod većine učesnika i pregledana je od strane osnovne laboratorije kako bi se isključila stenoza glavnog stable $\geq 50\%$. Randomizovani učesnici imali su srednju starost od 64 godine, sa 1168 žena (22,6%) i 2122 dijabetesa (41,0%). Među 3909 učesnika randomiziranih nakon funkcionalnih imidžing stresa testa na ishemiju, procena težine ishemije kod 3901 učesnika bila je sledeća: **teška 1748 (44,8%)**, umerena 1600 (41,0%) i blaga 317 (8,1%); **79,0% je imalo višesudovnu KB** (n = 2679 od 3390), a proksimalnu stenozu prednje silazne grane (LAD) 46,8%. Za vreme od prosečno 3,3 godine praćenja **nije bilo značajne statističke razlike između primarnih ishoda**: smrt od kardiovaskularnih uzroka, infarkta miokarda ili hospitalizacije za nestabilne angina, srčani zastoj -13.3% kod invazivne strategije u odnosu na 15,5% u grupi medikalnog lečenja (p=0.34). Ključni sekundarni ishod bila je smrt od kardiovaskularnih uzroka ili infarkt miokarda: 11.7% u rutinskoj invazivnoj grupi versus 13.9% OMT grupe (p=0.21). Ukupni mortalitet (kardiovaskularni i svi ostali uzroci): 6.4% u rutinskoj invazivnoj grupi versus 6.5% u OMT grupi (p=0.67). Periproceduralni AIM: 2,98%. Invazivni versus konzervativni odnos prema mortalitetu u bio je sličan bez obzira na stepen ishemije (p vredost za interakciju = 0.23), što važi i za AIM. (p vredost za interakciju = 0.15). Među pacijentima sa stabilnom KB i umerenom do teškom ishemijom na neinvazivnom vizuelizacionom stres testu, rutinski invazivni tretman je pokazao redukciju glavnih neželjenih ishoda u poređenju sa OMT.

Nema benefita od invazivne PCI terapije u pogledu složenog krajnjeg ishoda: Ukupnog, KV mortaliteta i nefatalnog infarkta miokarda.

ACC/AHA Američki vodič za hroničnu KB [140] odvrća od korišćenja PCI ili CABG za jednosudovnu ili dvosudovnu CAD bez signifikantnog zahvatanja proksimalne LAD u odsustvu neprihvatljive AP posle adekvatnog pokušaja vodičem usmerene OMT, posebno ako neinvazivni testovi pokazuju malu oblast vijabilnog miokarda ili nema ekstenzivne ishemijske ili redukovane EF.

KLINIČKI SCENARIO 2.

Pacijenti sa novonastalom srčanom insuficijencijom ili disfunkcijom leve komore i suspektom koronarnom arterijskom bolesti

KB je najčešći uzrok hronične srčane insuficijencije (HSI) u Evropi. Najveći broj studija daje dokaze koji podržavaju preporuke za proučavanje pts sa ishemijskom kardiomiopatijom (CMP) - patofiziološka osnova ishemijske CMP je sistolna disfunkcija EF<40%, mada pacijenti sa HKS mogu imati i HSI sa očuvanom EF. Pacijenti sa simptomatskom HSI treba da se dijagnostikuju prema 2016 ESC vodiču za HIS [141]. Uz standardnu anamnezu, fizikalni pregled, EKG i radiografiju toraksa, u imidžing treba uključiti ehokardiografiju sa Doplerom za evaluaciju dokaza dijagnoze ishemijske kardiomiopatije sa HSI sa: **a)** redukovanom EF; **b)** graničnom (mid-range) EF; **c)** očuvanom EF uz fokalne ili difuzne ehokardiografske znake sistolne disfunkcije leve i/ili desne komore, dokaze diastolne disfunkcije, kompenzatorne hipertrofije, funkcije zalistaka (ishemična mitralna regurgitacija) i dokaze sekundarne plućne hipertenzije [1]. Uz rutinske hematološke i biohemijske analize, posebno je važno procenjivati bubrežnu funkciju, kaliemiju i natriemiju inicijalno i u toku titracije farmakoterapije. Merenje serumskog nivoa natriuretskih peptide služi da isključi HIS, ako je nivo NT-proBNP normalan. Step povećanja titra BNP služi za procenu težine HIS [142]. Osnovno lečenje u klasi NYHA II-III je antianginozna ili antishemična terapija sa lekovima koji utiču na prognozu i prevenciju događaja. BB su i esencijalna komponenta u kupiranju anginoznih napada i prevenciji događaja kao i redukciji mortaliteta u HIS (Klasa I, nivo A) [142-149]. Amlodipin se može uključiti kao anti-ishemijski lek, kod onih koji ne tolerišu BB I jedini od antagonista kalcijuma se smatra sigurnim u HIS (preporuka klase IIb nivo B) [150-151]. Takođe se preporučuju kratkododelujući

nitriti sublingvalno ili transkutano flasterima. Pacijente sa simptomatskom HIS treba da se leče prema 2016 ESC vodiču za HIS [141], sa akcentom na dodavanje standardnoj terapiji novijeg leka angiotensin receptor-neprilysin inhibitor (sacubitril-valsartan) [141]. Doze lekova: diuretike [152], ACEI, BB, spironolaktone ili eplerenona eventualno i ivabradine postepeno povećavati da se izbegne, hipotenzija, bradikardija, azotemija i hiperkalemija. ACEI su ključni (KLASA I, NIVO A) u asimptomatskoj disfunkciji leve komore posle infarkta miokarda i kod simptomatske HIS za popravljavanje simptoma i redukciju morbiditeta i mortaliteta [153].

Implantabilni kardioverter-defibrilator (ICD) i kardijalna resinhronizaciona terapija (CRT) [154] mogu pružiti poboljšanje simptoma i popraviti preživljavanje [154]. Miokardnu revaskularizaciju treba razmatrati u pogodnih pacijenata sa ishemijskom HIS baziranu na simptomima, koronarnoj anatomiji i dokazima aktuelne ishemijske i vijabilnosti miokarda slikovnim testovima u zonama akinezijske cikatriksa, putem multidisciplinarnog tima. Miokardnu revaskularizaciju se preporučuje kada anginozne tegobe i/ili dispneja perzistiraju uprkos optimalnoj antianginoznoj terapiji (KLASA I, nivo dokaza A).

U GRUPU PACIJENATA SA DUGOTRAJNOM Dg HRONIČNIH KORONARNIH SINDROMA SPADAJU:

KLINIČKI SCENARIO 3. ASIMPTOMATSKI I SIMPTOMATSKI PACIJENTI SA STABILIZOVANIM SIMPTOMIMA DO 1 GODINE PROTEKLE POSLE AKS ILI KORONARNE REVASKULARIZACIJE.

KLINIČKI SCENARIO 4: ISTO SAMO NAKON GODINU DANA)

Zajedničko za obe grupe, klinički scenario 3 i 4 je doživotni tretman i praćenje [1]. Klinički tok može biti povoljan za duži period. Ipak, kod pacijenata sa HKS mogu se razviti različite KV komplikacije: episode de novo AKS, komplikacije usled terapijskih postupaka zbog KB ili zbog interakcija sa komorbiditetima. Rizik od komplikacija postoji i u asimptomatskih pacijenata pa se procena rizika mora primeniti i na simptomatske i na asimptomatske pacijente. Zato je razvijen i **validiran rizik skor** baziran na biomarkerima 2017. godine [155].

KLINIČKI SCENARIO 3

ASIMPTOMATSKI I SIMPTOMATSKI PACIJENTI UNUTAR 1 GODINE OD AKS ILI REVASKULARIZACIJE

Posle revaskularizacije ili stabilizacije AKS unutar godinu dana, pacijent mora biti budno praćen zbog povišenog rizika od komplikacija i potrebe podešavanja farmakološkog tretmana [35]. Preporuka je najmanje dve posete lekaru u prvoj godini praćenja, dok oni sa sistolnom disfunkcijom LK pre revaskularizacije ili posle AKS, treba da se jave na kardiološki pregled za 8-12 nedelja posle AKS ili revaskularizacije. Srčana funkcija se može poboljšati putem oporavka ošamućenog (stunning) ili hibernizovanog miokarda putem revaskularizacije a na osnovu rezultata ADVISE II studije invazivnom procenom da li su epikardne koronarne stenozе uzrok ishemije putem iwFR [52,53]. Međutim može doći i do pogoršanja zbog konkomitantnih KV poremećaja (valvularne bolesti, infekcije, aritmije i dr) i te poremećaje treba identifikovati i lečiti. Neinvazivna procena posle revaskularizacije može se razmatrati radi isključenja rezidualne ishemije ili dokumentovanja referentnog nalaza ishemije radi planiranja intenziviranja lečenja i daljeg periodičnog praćenja [1].

KLINIČKI SCENARIO 4.

ASIMPTOMATSKI I SIMPTOMATSKI PACIJENTI VIŠE OD 1 GODINE PROTEKLE OD AKS ILI REVASKULARIZACIJE.

Jednom godišnje je potrebna evaluacija pacijenta od strane kardiologa, čak i kada je pacijent bez tegoba. Preporuka je godišnji klinički pregled i procena pridržavanja farmakoterapiji i nefarmakološkim merama uz **određivanje profila rizika putem skorova rizika**. Laboratorijske analize: lipidni profil, bubrežna funkcija, krvna slika i srčani biomarkeri treba da se izvrše na svake dve godine [1,45]. Povišeni marker inflamacije hsCRP je udružen povišenim rizikom za neželjene događaje. Von Willebrandt factor, interleukin-6 i NTpro BNP su prediktori ishoda [25]. I ostali biomarkeri za pts sa HKS imaju prognostički značaj: srčana frekvenca, hemoglobin, broj leukocita [156]. Multipli biomarker skorovi su pokazali prognostički značaj: kombinujući: hsCRP, fibrin degradirajuće produkte i heat shock protein 70; [157]. Za pacijente sa pogoršanim rizikom skorom tokom praćenja opravdano je intenzivirati terapiju i dijagnostičku re-evaluaciju, mada za terapiju vođenu rizikom skorom još nije dokazano da poboljšava prognozu. Dvanaestokanalni EKG

treba da bude deo svakog kontrolnog pregleda da bi se registrovala srčana frekvenca i ritam i radi detekcije promena koje upućuju na simptomatsku ishemiju/infarkt miokarda i evaluacije PR, QRS i QT intervala. Bilo bi korisno ehokardiografski proceniti sistolnu i dijasolnu funkciju LK, stanje valvula, srčanih dimenzija i volumena u očigledno (prividno) asimptomatskih pacijenata na 3 do 5 godina. [1,52,53]. U slučaju neobjašnjene redukcije sistolne funkcije leve komore, posebno regionalne, bilo bi od koristi uraditi imidžing koronarne anatomije. Takođe treba tragati za asimptomatskom, silent ishemijom u prividno asimptomatskih pacijenata putem periodičnih stress imidžing testova [1,52].

KLINIČKI SCENARIO 5.

PACIJENTI SA ANGINOM PEKTORIS I SUSPEKTNOM VAZOSPASTIČKOM ILI MIKROVASKULARNOM BOLEŠĆU.

Angina bez opstruktivne bolesti u epikardnim koronarnim arterijama (engl INOCA). U kliničkoj praksi je primećen nesklad između nalaza koji se tiču koronarne anatomije, prisustvo simptoma i rezultata neinvazivnih testova se često javljaju [13]. Ovi pacijenti zaslužuju pažnju, jer su AP sa neobstruktivnom KB povezana sa povećanim rizikom od neželjenih kliničkih događaja [14,15]. Nizak dijagnostički doprinos ICA može se objasniti prisustvom: (1) blaga stenozа ili difuzno koronarno sužavanje, sa potcenjenim funkcionalnim značajem; (2) poremećaji mikrocirkulacije; (3) dinamičke stenozе epikardijalnih sudova uzrokovane koronarnim spazmom ili intramiokardijalnim mostovima koje nisu očigledne tokom CTA ili ICA. Intrakoronarno merenja pritiska je korisno u rešavanju u prvom slučaju. Pri dijagnostičkoj obradi, pacijenti sa anginom i / ili miokardijalnom ishemijom koji imaju koronarne stenozе sa neishemijskim vrednostima FFR ili iwFR mogu takođe biti označene kao neobstruktivne bolesti epikardnih koronarnih arterija. **Prisustvo jasno određenih anginoznih simptoma i patološki nalaz neinvazivnih testova kod pacijenata sa normalnim koronarnim epikardnim arterijama trebalo bi da dovode do sumnje na neobstruktivni uzrok ishemije.** Često i uglavnom kao rezultat upornosti simptoma, pacijenti sa anginom i bez opstruktivne KB prolaze višestruke dijagnostičke testove, uključujući ponovljeni koronarni CTA ili ICA, koji doprinose do povećanih troškova zdravstvene zaštite [158]. Važno je naglasiti da se u

svakodnevnoj praksi često dešava značajna diskrepanca između nalaza koronarne anatomije, prisustva simptoma, i rezultata neinvazivnih testova. Dijagnostički putevi koji istražuju mikrocirkulacijske ili vazomotorne koronarne poremećaje često se ne sprovedu pa je konačna dijagnoza podržana dokazima retko sprovedena. Zahvaljujući tome, zabrinutost pacijenta i depresija nije retka u ovoj kliničkoj populaciji [159]. CorMicA randomizovani kontrolisana studija iz 2018. godine ustanovila je kod pacijenata sa neobstruktivnom koronarnom bolešću, putem prilagođenog lečenja vođenim rezultatima intrakoronarnog ispitivanja: rezerva koronarnog protoka (CFR), mikrocirkulatorni otpor i ispitivanje acetilholinskim testom rezultirali su značajnim smanjenjem anginoznih simptoma u poređenju sa konvencionalnim, medicinski tretmanom [160].

Mikrovaskularna angina

Pacijenti sa mikrovaskularnom anginom tipično imaju tegobe u grudima na napor, pozitivan test na ishemiju, bilo EKG TFO ili neinvazivnim vizuelizacionim testovima, bez opstruktivne KB ili sa blagom do umerenom stenozom (40- 60%) epikardnih koronarnih arterija, što se otkriva putem ICA ili CTA i ove stenozе se smatraju funkcionalno neznаčajnim. Na mikrovaskularno poreklo angine se obično posumnja nakon isključenja opstruktivne koronarne epikardne stenozе, tokom dijagnostičke obrade pacijenata sa dokazanom miokardnom ishemijom na EKG TFO testu. **Regionalne nenormalnosti kretanja zida se retko razvijaju tokom vežbanja ili stresa kod pacijenata sa mikrovaskularnom anginom.** Neki pacijenti mogu imati mešoviti oblik angine mikrovaskularna + vazospastična, s povremenim epizodama u mirovanju, posebno povezanim sa izlaganjem hladnoći. Sekundarna mikrovaskularna angina, bez opstruktivne KB, može biti posledica srčanih ili sistemskih stanja, uključujući one koje izazivaju hipertrofiju LV-a (kao što je hipertrofična kardiomiopatija, aortna stenozа i hipertenzivna bolest srca) [161] ili upala (kao što su miokarditis ili vaskulitis) [162]. **Stratifikacija rizika kod mikrovaskularne AP je dosta kompleksna.** Prisustvo mikrocirkulacijske disfunkcije kod pacijenata sa HKS povlači za sobom goru prognozu nego što se prvobitno mislilo, bazirano na najnovijim dokazi zasnovani na praćenju pacijenata sa objektivnim poremećajima u mikrocirkulaciji dokazanih invazivnim ili neinvazivnim tehnikama. [163-167]. Disfunkcija mikrocirkulacije prethodi razvoju epikardnih koronarnih lezije, posebno kod žena i povezane

su sa oštećenjima i nepovoljnim ishodom događajima. Među pacijentima sa dijabetesom koji su podvrgnuti dijagnostičkoj obradi, one bez opstruktivne epikardijalne bolesti, ali sa nenormalnom koronarnom rezervom protoka (CFR) imaju slično lošu dugoročnu prognozu kao i oni sa opstruktivnom epikardijalnom bolesti [165]. Kod pacijenata sa značajnom KB sa signifikantnom stenozom na FFR-u ≤ 0.80 , prisustvo nenormalnog CFR-a < 2.0 je povezano sa dodatnim pogoršanjem i značajnijim brojem neželjenih događaja posebno kada je indeks mikrocirkulatorne rezistencije (IMR) takođe nenormalan [166].

Treba razmotriti mogućnost mikrocirkulacijskog porekla angine kod pacijenata sa jasnom anginom, nenormalnom neinvazivnim funkcionalnim testovima i koronarnim aretrijama koje su ili normalne ili sa blagim stenozama, koje se smatraju funkcionalno neznаčajnim na ICA ili CTA. Jedan od izazova u obavljanju sveobuhvatne procene mikrovaskularne funkcije je testiranje dva glavna mehanizma disfunkcije odvojeno:

1. Oslabljena mikrocirkulatorna provodljivost (ili povećana Mikrocirkulatorna rezistencija)

i

2. Arteriolarne disregulacije [168-170].

Ipak, treba raščistiti koji je od ova dva puta od kritične važnosti za izbor farmakološkog tretmana za minimizovanje simptoma ovih pacijenata. [160]. Oslabljena ili poremećena mikrocirkulatorna konduktivnost može se dijagnostikovati merenjem koronarne reserve protoka (CFR) ili minimalne mikrocirkulatorne rezistencije. CFR se može meriti neinvazivno transtorakalnom kolor i pulsnom Doppler ehokardiografijom [vizuelizacijom I merenjem brzine protoka bazalno I uz vazodilatirni test adenozinom ili dipiridamolom] [171] kao I magnetnom rezonancom (indeks perfuzije miokarda ili PET-om, što je manje dostupno). **Mikrocirkulatorna rezistencija** se može izmeriti u laboratoriji za kateterizaciju kombinovanjem intrakoronarnog pritiska sa podacima zasnovanim na termodiluciji (za izračunavanje IMR) ili doplerom brzina protoka (za izračunavanje hiperemičke mikrovaskularne otpornosti ili HMR) [172,173]. Odluka o abnormalnoj mikrocirkulaciji se donosi kada vrednost **indeksa mikrocirkulatorne rezistencije** bude veći od 25 jedinica (IMR > 25 J) ili **CFR < 2.0** . Suprotno tome, dijagnoza arteriolarne disregulacije zahteva procenu endotelne funkcije u koronarnoj mikrocirkulaciji selektivnom intrakoronarnom infuzijom

acetilholina. Acetilholin je endotelni zavisan vazodilatator koji deluje direktno na ćelije glatkih mišića arteriola i izaziva **paradoksalnu arteriolarnu vazokonstrikciju - mikrovaskularni spazam disfunkcionalnog vaskularnog endotela ili abnormalnu funkciju ćelija glatkih mišića** [174]. Ovaj arteriolarni odgovor na acetilholin izaziva anginalne simptome sa ili bez istovremenih ishemijske promene EKG-a i smanjenja koronarne brzina protoka krvi, ako se rade istovremeno doppler merenja. Tonometrija perifernog pulsa tokom reaktivne hiperemije može biti takođe otkrivaju nenormalnu sistemsku endotelnu funkciju kod pacijenata sa AP i ne-opstruktivnom KB [175].

Vasospastična angina

Na vazospastičnu angina treba posumnjati kod pacijenata sa AP kada se simptomi javljaju uglavnom u mirovanju, uz zadržanu toleranciju na napor. Verovatnoća vazospastične angine povećava se kada napadi prate cirkadijanski obrazac, sa više epizoda noću i u ranim jutarnjim časovima. Pacijenti su često mlađi i imaju manje faktora KV rizika nego pacijenti koji imaju AP na napor, osim što su najčešće pušači cigareta [176]. Koronarni vazospazam je suspektan i kod pacijenata sa prolaznim koronarnim stentovima i upornom AP. [177-178]. Dijagnoza vazospastične AP zasniva se na otkrivanju prolaznih ishemijskih promena depresije ili elevacije ST segmenta tokom napada angine (obično pri odmoru rest AP). Pacijenti sa Prinzmetalovom AP predstavljaju posebnu podgrupu gde AP u mirovanju prati prolazna elevacija ST-segmenta [176-179]. Ova elevacija ST na EKG-u je u korelaciji sa proksimalnom okluzijom vazospazmom. Kako je većina napada vazospastične AP samoograničavajuća, teško je registrovati bez višednevnog ambulatornog Holter monitoringa 12-kanalnim zapisom. Pojava promena segmenta ST pri normalnom puls podržava verovatnoću ishemije miokarda prouzrokovane spazmom. Kod pacijenata sa sumnjom na vazospastičnu AP i dokumentovanim EKG promenama, koronarna CTA ili ICA je važna da isključi prisustvo fiksnih koronarna stenoza. Angiografska dokumentacija koronarnog spazma zahteva upotrebu provokacionog testa u laboratoriji za kateterizaciju. S obzirom na nisku osetljivost hiperventilacionog testa i testa hladnom vodom, intrakoronarna primena acetilholina ili ergonovina tokom ICA su preferirani provokativni testovi. [176-179]. 176. Oba farmakološka sredstva su sigurna, pod uslovom da se selektivno ubace u leve ili desne koronarne

arterije i taj aktivirani spazam se lako kontroliše intrakoronarnim nitratima. Mali procenat pacijenata može razviti ventrikularna tahikardija / ventrikularna fibrilacija ili bradiaritmija tokom provokativni test (3,2 i 2,7% respektivno), sličan onome tokom spontanijih napada spazma (7%) [180]. Intravenozno davanje ergonovina za neinvazivne testove je kontarindikovano zbog rizika od izazivanja dugotrajnog spazma u više koronarnih arterija što može biti vrlo teško kupiranje i može biti fatalno. **Provokativni test za koronarni spazam smatra se pozitivnim kada izazove: (1) anginalne simptome, (2) ishemijske promene EKG-a i (3) tešku vazokonstrikciju epikardne koronarne arterije.** Ako test ne uspe pokretanje sve tri komponente, to bi trebalo smatrati dvosmislenim [176]. Razvoj AP kao odgovor na injekcije acetilholina u odsustvo angiografski evidentnog spazma, sa ili bez pratećih EKG promena ST-segmenta mogu ukazivati na mikrovaskularni spazam i često se primećuje kod pacijenata sa mikrovaskularnom AP [179]. Kod pacijenata sa epikardijalnim ili mikrocirkulacijskim vazomotorim poremećajima, CCB i dugodelujući nitrati (LAN) predstavljaju tretman izbora, pored kontrole KV faktora rizika i promene načina života. Nifedipin se pokazao efikasnim u smanjenju koronarnog spazam povezanim sa implantacijom stenta. Kod svih pacijenata sa vazospastičnom anginom treba postići optimalnu kontrolu rizik faktora, posebno prekid pušenja i primena aspirina. **Isključiti lekove koji mogu biti uzrok vazospazma -zloupotrebu kokaina ili amfetamina.** Hronični preventivni tretman vazospastične angine je uglavnom baziran na većim dozama antagonista kalcijuma. Prosečne doze ovih lekova verapamil ili diltiazem od 240 do 360 mg/dan ili nifedipin od 40 do 60 mg uobičajeno preveniraju spazam u oko 90% bolesnika. Nekada se moraju, radi prevencije spazama, dati visoke doze kalcijum antagonista: do 960 mg dan Verapamila ili Diltiazema odnosno do 100 mg /dan Nifedipina.. Nekim bolesnicima treba dodati dugodelujuće nitrate. Beta-blokatore treba izbeći, jer mogu pojačati spazam zbog toga što blokiranjem beta vazodilatatornih efekata preovlađuje vazokonstrikcija neblokiranim alfa receptorima. Oko 10% bolesnika su refrakterni na ovo lečenje, pa se retko može indikovati dodavanje gvanetidina ili klonidina. Implantacija stenta na mestu spazma i bez stenoze te hirurška ili hemijska simpatektomija su krajnje mere.

KLINIČKI SCENARIO 6. ASIMPTOMATSKE OSOBE U KOJIM JE KB OTKRIVENA NA SKRININGU.

U nastojanju da snizi veliko incidence koronarnih naprasnih smrti kod asimptomatskih odraslih osoba, brojna izučavanja faktora rizika i pokazatelja rizika, kao i stres testovi, često se izvode kao skrining ispitivanja. Evropske smernice za prevenciju KVB u 2016. godini u kliničkoj praksi detaljno su se usredsredili na ova pitanja. [15]. Uopšteno, preporučuje se upotreba sistema za procenu rizika kao što je ESC SCORE. Osobe sa porodičnom istorijom preuranjene KB treba da se pregledaju na porodičnu hiperholesterolemiju. Koronarni kalcijum skor, indeks ABI i Kolor dopler ehosonografija karotidnih arterija u otkrivanje plaka može pružiti korisne informacije o aterosklerotskom riziku kod odabranih pacijenata. Rutinska upotreba biomarkera ili vizuelizacionih testova za KB se ne preporučuje. Novi biomarkeri imaju rastuću prediktivnu vrednost u odnosu na klasične, ali neto poboljšanje reklasifikacijerizika je i dalje samo skromno (7.18%) upoređeno, na primer, sa koronarnom kalcijumskim skorom, koji ima neto poboljšanje reklasifikacije 66%. **Samo osobe sa velikim rizikom od događaja trebaju biti uzeti u obzir za dalje neinvazivno ili invazivno ispitivanje.** Nema podataka o tome kako da se tretiraju asimptomatski ispitanici sa pozitivnim testom na KB izvan preporuka navedenih u ovim smernicama. Međutim, principi stratifikacije rizika, kako je gore opisano za simptomatske pacijente, takođe se odnose na ove osobe. Važno je znati da nema podataka koji su pokazali poboljšanu prognozu nakon odgovarajućeg zbrinjavanja zasnovanog na novim biomarkerima. Važno je napomenuti da su pacijenti oboleli od karcinoma i oni koji su u toku lečenje raka, hroničnih inflamatornih i sistemskih autoimunih bolesti zaslužuje intenzivniju evaluaciju rizika. Osobe čija zanimanja uključuju javnu sigurnost (npr. piloti ili vozači kamiona ili autobusa, radnici) ili profesionalni sportisti, obično se podvrgavaju periodičnim testiranjima radi procene EKG testom TFO i procene mogućih srčanih bolesti, uključujući KB, mada nema dovoljno podataka koji bi to opravdali. Međutim, ove evaluacije mogu se izvršiti iz medicinsko-pravnih razloga. Prag za obavljanje vizuelizacionog stress testa na KB kod takvih osoba je niži nego kod prosečnog pacijenta.

REFRAKTORNA ANGINA PEKTORIS (RAP)

RAP kao oblik hroničnog koronarnog sindroma (HKS) se definiše kao hronično stanje izazvano klinički ustanovljenom reverzibilnom ishemijom u prisustvu KB, koje se ne može adekvatno kontrolisati kombinacijom medikalne terapije, angioplastike sa stentingom (PCI) ili hirurškom koronarnom revaskularizacijom (CABG) [1, 120]: Dolaze u obzir sledeće opcije lečenja:

- 1- Forsirana eksterna kontrapulzacija (EECP) treba da se uzme u obzir za olakšanje i minimizovanje tegoba u bolesnika sa AP Refrakternom na optimalnu farmakološku terapiju i revaskularizacionu strategiju
- 2-Transkutana električna stimulacija nerva (TENS) se može koristiti da bi se ublažili simptomi refraktorne AP na optimalnu farmakoterapiju i revaskularizacionu strategiju
- 3-Stmulacija kičmene moždine (SCS) se može koristiti da bi se ublažili simptomi refraktorne angine na optimalnu farmakol Th i revaskularizacionu strategiju
- 4-Transmiokardna revaskularizacija (TMR) nije indikovana u pacijenata sa simptomima refraktorne angine na optimalnu farmakološku Th i revaskularizacionu strategiju

BUDUĆE PERSPEKTIVE HRONIČNIH KORONARNIH SINDROMA HKS - Citat iz Braunaldovog udžbenika kardiologije, autori Dejvid Morou, Dž. J. A. De Lemos i Vilijam Boden [135]:

Naše razumevanje HRONIČNIH KORONARNIH SINDROMA (HKS), kako uzroka, optimalnog pristupa tako i lečenja, kontinirano se razvija.

1. Kompleksni i verovatno heterogeni uzroci ishemije miokarda zahtevaju kontinuirano multidisciplinarno istraživanje putem eksperimentalnih studija iz genetike, molekularne biologije, biohemije, morfoloških i funkcionalnih aspekata koronarne cirkulacije, te patološke morfologije i patofiziologije ishemije miokarda, što zatim treba potvrditi u randomizovanim duplo-slepim kontrolisanim kliničkim studijama sa dovoljnom statističkom snagom da se iznedre nove smernice za precizniju i jednostavniju dijagnostiku i efikasnu terapiju HKS. Danas se konfrontiramo sa suštinskim podacima koji su izazov paradigmi da Ishemijska KB zahteva kritičnu koronarnu aterosklerozu subepikardne koronarne arterije ili drugu strukturnu bolest srca koja rezultuje u dramatičnom povećanju potrošnje kiseonika. Preklinički,

translacioni i klinički epidemiološki podaci demonstriraju anomalije u funkciji koronarne arterije, koji mogu da dovedu do ishemije miokarda u odsustvu aterosklerotske opstrukcije.

2. Ipak, do sada, lečenja predložena za ovaj važni sindrom-HRONIČNI KORONARNI SINDROM su se pokazala nedovoljnim. Dodatni uvid u patobiologiju ishemije mogao bi dovesti do novih pravaca u lečenju.
3. Inicijalni pristup vodičem usmerene sekundarno-preventivne terapije i koronarne revaskularizacije, kada je neophodno, jeste najbolji pristup za većinu pacijenata sa HKS. Postoje podgrupe pacijenata sa indikatorima visokog rizika za koje bi koronarna revaskularizacija miokarda trebala da bude logična. **Ipak, klinička kontradikcija i nedoumica ostaje u pogledu da li takve pacijente, uključujući one sa umerenom ili teškom ishemijom na neinvazivnom testu, treba rutinski podvrgnuti koronarnoj revaskularizaciji miokarda u odsustvu simptoma refrakternosti na optimalnu preventivnu i farmakološku terapiju (OMT).**
4. Definitivni dokazi za zbrinjavanje pacijenata sa stabilnim HKS i ostalih posledica ishemije, posebno disfunkcije leve komore i mitralne ishemijske regurgitacije, ostaju još uvek nekompletni. Po našem mišljenju, kompletna revaskularizacija miokarda, obično hirurška -CABG, ostaje razumna opcija za pacijente sa višesudovnom KB, disfunkcijom LK i vijabilnim miokardom, posebno kad postoji objektivni dokaz ishemije. Ipak, neke skorašnje studije taj stav dovode u pitanje. Uprkos našem dobrom iskustvu sa HKS, na važna pitanja nema odgovora [135].

ZAKLJUČAK:

Pažljiva i studiozna evaluacija anamneze, uključujući karakterizaciju anginalnih simptoma i procenu rizik faktora i manifestacija kardiovaskularnih bolesti, kao i odgovarajući fizikalni pregled i osnovno dopunsko, bazično ispitivanje je esencijalno za dijagnozu hroničnih koronarnih sindroma. Ako samo kliničkom evaluacijom ne može da se isključi opstruktivna koronarna arterijska bolest (srednja pre-test

verovatnoća) kao inicijalni test za isključenje ili postavljanje dijagnoze hroničnih koronarnih sindroma (klinički scenario 1) treba koristiti neinvazivne dijagnostičke funkcionalne vizuelizacione testove fizičkim ili farmakološkim opterećenjem ili anatomske vizuelizacije putem koronarne CT angiografije. Izbor inicijalnog neinvazivnog dijagnostičkog testa je zasnovan na pretest verovatnoći za opstruktivnu koronarnu bolest (PTP), kliničkoj verovatnoći iste, karakteristika i dostupnosti testa. Za odluku o revaskularizaciji treba uraditi i anatomske i funkcionalne evaluacije. Zahteva se bilo neinvazivna ili invazivna funkcionalna evaluacija za procenu veličine ishemije miokarda udružene sa angiografskom stenozom koronarne arterije, osim za stenoze vrlo viokog stepena (>90% stenoze dijametra). Procena rizika za neželjene događaje i mortalitet služi da odredi za koje pacijente sa HKS se predviđa prognostička korist od revaskularizacije. Procena funkcije leve komore ehokardiografijom je obavezni deo stratifikacije rizika. Pacijenti u velikom riziku od neželjenih događaja se podvrgavaju invazivnom ispitivanju zbog razmatranja revaskularizacije, čak i kad su asimptomatski. Primena zdravog načina života smanjuje rizik od naknadnih KV događaja i smrtnosti i uvek je uključena u program odgovarajućih mera i terapije sekundarne prevencije. Kliničari bi trebalo da savetuju i podstaknu neophodne promene načina života pri svakom kliničkom susretu sa pacijentima. Kognitivno-bihevioralne psihološke intervencije kao što su podrška pacijentima da postave realne ciljeve, samokontrola, planiranje sprovođenja promena, suočavanje sa teškim situacijama, prilagođavanje životnoj sredini i uključivanje socijalne podrške jesu efektivne intervencije za promenu ponašanja. Multidisciplinarni timovi mogu pružiti pacijentima podršku za promenu ka zdravom načinu života i uputiti ga na izbegavanje rizika i rizičnog ponašanja. Anti-ishemijsko lečenje mora biti prilagođeno pojedinačnom pacijentu na osnovu komorbiditeta, istovremene terapije, očekivane tolerancije i pridržavanja terapiji ali i sklonosti pacijenta. Izbor anti-ishemijskih lekova za lečenje HKS-a treba da bude prilagođen srčanoj frekvenci, krvnom pritisku i funkciji leve komore. Beta blokatori i /ili antagonisti kalcijuma ostaju lekovi prve linije kod pacijenata sa HKS-om. Antitrombotska terapija je ključni deo sekundarne prevencije kod pacijenata sa HKS-om i zahteva pažljivo razmatranje. Pacijentima sa prethodnim infarktom miokarda, sa ili bez revaskularizacije, koji su pod visokim

rizikom od ishemijskih događaja i niskim rizikom od teškog ili fatalnog krvarenja, trebalo bi razmotriti dugotrajnu (i posle 12 meseci) dvostruku antitrombocitnu terapiju (DAPT) sa aspirinom ili bilo inhibitorom P2I12 ili rivaroksabanom s vrlo malim dozama, osim ako nemaju indikaciju za oralnom antikoagulantnom terapijom (OAK) kao što je prisustvo atrijske fibrilacije (AF). Statini se preporučuju svim pacijentima sa HKS-om, bez obzira na nivo LDL holesterola. ACE inhibitori (ili ARB) se preporučuju u prisustvu srčane insuficijencije (SI), dijabetesa ili hipertenzije i treba da se razmotre kod svih visokorizičnih pacijenata. Inhibitori protonske pumpe preporučuju se kod pacijenata koji primaju aspirin ili kombinaciju antitrombotske terapije koji su pod visokim rizikom od gastrointestinalnog krvarenja. Treba uložiti napore da se pacijentima objasni važnost redovnog uzimanja propisanih lekova, što je zasnovano na dokazima da redovno pridržavanje lečenju sprečava neželjene događaje, oslobađa pacijenta od bolova i popravlja kvalitet života. Ponovljena terapijska edukacija pacijenata je od suštinskog značaja za svaki klinički susret. Pacijenti sa dugogodišnjom dijagnozom HKS trebalo bi da periodično posećuju lekara radi procene mogućih promena statusa rizika, pridržavanja ciljeva lečenja i razvoja komorbiditeta. Preporučuje se ponavljano izvođenje testova fizičkim ili farmakološkim opterećenjem, najbolje vizulizacionih stresa testova ili invazivne koronarografije s funkcionalnim testiranjem u slučaju pogoršanja simptoma i / ili povećanog statusa rizika. Procena funkcije i dimenzija srčanih šupljina, miokarda i zalistaka, kao i funkcionalni test za odbacivanje značajne asimptomatske(silent) ishemije miokarda, treba da se razmotre svakih 3–5 godina kod asimptomatskih bolesnika sa dugogodišnjom

dijagnozom HKS. Procena koronarne vazomotorne funkcije treba da se razmotriti kod pacijenata bez opstruktivne koronarne bolesti ili sa neznajnom epikardijalnom koronarnom bolesti koji imaju objektivne dokaze ishemije miokarda. Ciljevi lečenja hroničnih koronarnih simptoma (HKS): poboljšanje prognoze tj. smanjenje mortaliteta putem smanjenja rizika za progresiju ateroskleroze i sprečavanje akutnih koronarnih događaja i naprasne smrti te minimizovanje simptoma sa poboljšanjem kvaliteta života. Treba uložiti napore da se pacijentima objasni važnost preporuka-smernica i uputstava zasnovanih na dokazima za pridržavanje lečenju.

Svim bolesnicima sa stabilnom koronarnom bolesti potrebna je promena životnog stila, redukcija rizik faktora i farmakološka terapija ali svi bolesnici sa stenozama koronarnih arterija nemaju benefit od revaskularizacije, koji zavisi od veličine ishemije i načina anatomske zahvatanja koronarnih arterija. Optimalna medikalna terapija je definitivna terapija za pacijente sa stabilnom koronarnom bolesti i niskim rizikom od kardiovaskularnih događaja. Revaskularizacija i optimalna medikalna terapija treba da se smatraju kao komplementarni a ne kompetitivni tretmani.

Kod bolesnika sa HKS sa visokim rizikom gde je mortalitet >3% godišnje ili AP refrakternom na OMT potreban je dokaz ishemije putem testa fizičkim ili farmakološkim opterećenjem, najbolje stres ehokardiografijom radi određivanja veličine ishemije na stres eho testu I anatomska procena radi utvrđivanja načina zahvatanja koronarki, da bi se indikovala revaskularizacija koja dovodi do kliničkog benefita.

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PARADIGM CHANGE FOR STABLE CORONARY DISEASE IN CHRONIC CORONARY SYNDROME. NOVELTIES IN THE GUIDELINES OF THE EUROPEAN SOCIETY OF CARDIOLOGISTS FROM 2019

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SUMMARY: Although the English physician Heberden described angina pectoris (AP) two and a half centuries ago, our understanding of this syndrome, as a cause, an optimal diagnostic approach and treatment, continues to develop. The new guidelines of the European Society of Cardiology (ESC) from year 2019 brings, first of all, a paradigm shift for stable coronary artery disease (SCAD) to the comprehensive term chronic coronary syndromes (CCS), which essentially means that chronic coronary artery disease (CAD) has complex clinical scenarios and may have periods of instability, at any evolutionary stage. The results of the essential COURAGE study and the latest studies: ISCHEMIA, ORBITA and meta-analysis on CCS as well as the key messages of the European Guidelines for Diagnosis and Treatment of Chronic Coronary Syndromes (CCS) shed light on the issue of coronary heart disease. Chronic coronary artery disease (CCAD) has long stable periods but due to acute atherothrombotic events, erosion or rupture of atherosclerotic plaque can progress to some of the acute coronary syndromes (ACS). The disease is chronic, usually progressive and therefore serious even in asymptomatic stages. The dynamic nature of CAD is manifested in various clinical presentations, which we categorize into either acute or chronic coronary syndromes. The paradigm shift emphasizes the fact that the dynamic processes of accumulation in atherosclerotic plaques and functional alterations of the coronary circulation can be modified by lifestyle changes, pharmacological therapy and myocardial revascularization (MR), which lead to stabilization or regression of the disease but unfortunately not complete cure. Careful evaluation of the anamnesis, characterization of anginal and other symptoms and evaluation of risk factors and manifestations of previous cardiovascular diseases (CVD), as well as assessment of the adequacy of physical activity and exercise tolerance, are of cardinal importance. The current guide to CCS identifies 6 leading and most common clinical syndromes: 1. Patients with suspected CCS and stable angina pectoris and / or dyspnea on exertion; 2. Patients with newly developed heart failure (HF) or left ventricular dysfunction (LVD) and suspected CAD; 3. Asymptomatic and symptomatic patients with stabilized symptoms lasting less than one 1 year after ACS or recent myocardial revascularization (MR); 4. Asymptomatic and symptomatic patients more than 1 year after ACS or MR; 5. Patients with AP and suspected vasospastic or microvascular disease; 6. Asymptomatic individuals in whom CAD was detected at screening. Each of these scenarios is classified as CCS and is a consequence of different evolutionary phases of chronic CAD, and has a different risk for future adverse cardiovascular (CV) events. Pre-test probability (PTP) of CAD, based on age, sex and quality of symptoms, has been revised and changed from the previous guide from year 2013. A new term has been introduced: Clinical probability of obstructive coronary artery disease (CPCAD) which includes both PTP and various risks factors of atherosclerotic CAD and serves to exclude or confirm the suspicion of CAD. The general methodological approach for initial diagnosis for patients with AP and suspected obstructive CAD involves 6 steps. STEP 1-Assessment of symptoms and signs to identify patients with possible unstable AP and other forms of ACS; STEP 2 is an assessment of the general condition and quality of life that decide on treatment planning; STEP 3 includes basic diagnostic procedures and assessment of left ventricular (LV) function of the heart; STEP 4 makes the determination of Pre-test and Clinical probability of obstructive CAD; STEP 5 is the selection of a

diagnostic test by physical or pharmacological stress via ECG and imaging methods including MSCT coronary angiography (CTA) to establish the diagnosis of CAD. Finally, STEP 6 is the assessment of the risk of adverse CV events, especially mortality, and based on that, make definitive therapeutic decisions with invasive coronary angiography (ICA) and possible MR. If obstructive CAD cannot be ruled out by clinical evaluation, either a noninvasive functional imaging test or anatomical imaging by CTA is performed as an initial test to exclude or confirm the diagnosis of CAD. Anatomical and functional assessment should be considered for a decision on MR, except in severe coronary stenosis > 90%. A high risk of adverse CV events identifies patients who would have great prognostic benefit from MR, even if asymptomatic. The role of myocardial revascularization (MR) has been placed in the context of recent evidence relating to the prognostic role of percutaneous coronary interventions (PCI) or coronary artery bypass graft (CABG) in this low-risk population. MR is reserved for patients where there is strong evidence to improve prognosis based on evidence of regional ischemia by perfusion imaging. Patients at high risk of mortality of 3% per year or more undergo coronary flow fractional reserve (FFR) or coronary flow reserve (CFR) due to perform MR even if they have no symptoms. The application of a healthy lifestyle reduces the risk of subsequent adverse CV events and is part of adequate secondary prevention therapy. Regular vaccination against influenza is necessary for everyone with CCS. Optimal medical therapy (OMT): non-pharmacological and pharmacological therapy of CCS is given great attention as the main type of treatment of CCS, not MR. The modern role of anti-ischemic (antianginal) drugs is emphasized: First lines - beta-blockers (BB) and calcium antagonists (CCB) with sublingual nitroglycerin, and Second lines - long-acting nitrates (LAN), with newer options: ivabradine, nicorandil, trimethazidine, allopurinol, etc. Drugs that improve the prognosis of CCS are statins and acetylsalicylic acid (ASA) and other antiplatelet drugs and recently low dose rivaroxaban and additionally angiotensin converting enzyme inhibitors (ACEI) and again BB in specific indications. Anti-ischemic treatment must be tailored to the individual patient based on comorbidities, other concomitant therapies, expected tolerances and adherence, and patient preferences. The choice of anti-ischemic drugs for the treatment of CCS should be adjusted to the heart rhythm, blood pressure and heart function. BB and ACEI are recommended for patients with LVD or HF with reduced left ventricular ejection fraction (HFrEF). Antithrombotic therapy is a key part of secondary prevention in patients with CCS. Patients with previous acute myocardial infarction (AMI), who are at high risk of ischemic events and low risk of fatal bleeding, should consider long-term dual antiplatelet therapy with aspirin and either P₂Y₁₂ receptor inhibitor or a very low-dose rivaroxaban, unless there is an indication for oral anticoagulation, is atrial fibrillation (AF). Proton pump inhibitors are recommended in patients receiving only aspirin or a combination of antithrombotic therapy who are at risk of gastrointestinal bleeding. Statins are recommended for all patients with CCS, regardless of LDL level. ACEIs (or angiotensin receptor blockers, ARBs) are recommended in the presence of SI, diabetes, and hypertension and should be considered in patients at high risk for adverse events.

Keywords: Angina pectoris/stable, Angina Pectoris/Unstable, microvascular angina, angina pectoris with normal coronary arteriogram, ischemic heart disease, coronary heart disease, Acute coronary syndrome, Myocardial infarction, Myocardial ischemia/diagnosis/prevention and control/pharmacotherapy, Myocardial revascularization/percutaneous coronary intervention-PCI/coronary artery bypass-CABG

INTRODUCTION AND SIGNIFICANCE OF THE PROBLEM

The new 2019 European Society of Cardiology (ESC) guide for the diagnosis and management of chronic coronary syndromes [1] focuses on the new comprehensive term Chronic Coronary Syndromes (CCS) for all forms of chronic coronary artery disease (CCAD) except acute coronary syndromes [2,3], rather than only stable coronary artery disease (SCAD), as a previous ESC guide from 2013 [4]. The new guide of the European Association of Cardiologists from 2019 primarily brings a paradigm shift for stable coronary heart disease to the comprehensive term chronic coronary

syndromes (CCS), which essentially means that CAD has complex clinical scenarios and can have periods of instability at any evolutionary stage. Essentially, the clinical presentation of coronary heart disease is categorized into either acute coronary syndromes (ACS) [2,3,5] or chronic coronary syndromes (CCS) [1]. Coronary heart disease (CAD) is a dynamic pathological process of appearance and growth of atherosclerotic plaques in epicardial coronary arteries, but also in their smaller intramyocardial branches [6,7, 8,9] (microvascular disease) with or without coronary vasospasm [10-13], without whether they are functionally fixed obstructive (stenotic) or non-obstructive [14,15]. This dynamic process leads to a functional alteration of the

coronary blood flow or myocardial ischemia. Myocardial ischemia can be reduced, stabilized or stagnation or regression of atherosclerotic plaques can be achieved through therapeutic interventions: optimal non-invasive medical ie. (medical therapy-OMT) which consists of lifestyle changes, reduction of risk factors and optimal pharmacotherapy (OPhT) and optimal invasive interventions - percutaneous or surgical

myocardial revascularization (RM). [16-21]. CAD has long stable periods, but may also become unstable at some period due to acute atherothrombotic events — breakup or erosion of atherosclerotic plaque. However, the disease is chronic, most often progressive and therefore serious, even in clinically asymptomatic periods [1] (FIGURE 1).

FIGURE 1: CLINICAL PRESENTATION - CLINICAL SCENARIOS OF CHRONIC CORONARY SYNDROMES

Retrieved from <https://www.escardio.org/Guidelines/Clinical-Practice-Guidelines/Chronic-Coronary-Syndromes>

The dynamic nature of the CAD process results in different clinical presentations or clinical scenarios, acute coronary syndromes (ACS) [2,3,5] or chronic coronary syndromes (CCS) [1].

CLINICAL PRESENTATION - CLINICAL SCENARIOS OF CHRONIC CORONARY SYNDROMES (CCS).

The clinical presentation of CCS consists of 6 leading and most common clinical scenarios [1]:

1. Patients with suspected CAD and stable angina pectoris (AP) and / or dyspnea on exertion.
2. Patients with newly developed heart failure (HF) or left ventricular dysfunction (LVD) and suspected CAD.
3. Asymptomatic and symptomatic patients with stabilized symptoms up to 1 year after ACS or myocardial revascularization (RM).

4. Asymptomatic and symptomatic patients more than 1 year after ACS or RM.

5. Patients with AP and suspected vasospastic or microvascular disease.

6. Asymptomatic individuals in whom CAD was detected at screening.

Each of these scenarios is classified as CCS, is a consequence of different evolutionary phases of CAD and has a different risk for future adverse CV events (death or myocardial infarction) and this risk may change over time [1].

NEW CONCEPTS AND RECOMMENDATIONS FOR CCS

New concepts and recommendations for CCS and revised concepts and recommendations from the previous ESC guide in 2013 [4], in this 2019 ESC

guide [1], based on current available evidence from a large number of randomized studies, registers and expert consensus (cited a huge number of scientific papers: 529 references) have a holistic approach, give quite clear guidelines for the diagnosis and therapy of CCAD and systematically process all clinical presentations of CCAD in a clear and clinically applicable way. This ESC Guide and its recommendations should facilitate clinical decision-making by physicians in their day-to-day practice [1].

NEW MAIN RECOMMENDATIONS OF CLASS I

(There is evidence and / or general agreement that a given treatment or procedure is beneficial, useful and effective: Wording to use: Is recommended or is indicated)

1. Non-invasive functional imaging diagnostic test for the detection of myocardial ischemia or coronary MSCT angiography should be the initial test for the diagnosis of CAD in symptomatic patients in whom obstructive coronary heart disease cannot be ruled out by clinical judgment alone.
2. It is recommended that the selection of the optimal test for the diagnosis of CAD be based on the Clinical Probability of CAD and other patient characteristics that affect test performance, local availability, and expertise.
3. Non-invasive functional imaging test for myocardial ischemia is recommended if coronary MSCT angiography shows CAD of uncertain functional significance or is non-diagnostic, inclusive.
4. Invasive coronary angiography (ICA) is recommended as an alternative test for the diagnosis of coronary artery disease (CHD) in patients with high clinical probability and severe symptoms refractory to medical therapy (nonpharmacological and pharmacological) or typical angina at low exercise and when clinical evaluation indicates at high risk of adverse CV events. Invasive functional assessment (FFR, iwFR) must be available and used to evaluate stenosis prior to coronary revascularization, except in the case of a very high degree of coronary stenosis $\geq 90\%$ of the stenosis diameter.
5. In patients with atrial fibrillation (AF) with a CHA₂DS₂-VASc score ≥ 2 for males and ≥ 3 for females, non-vitamin K antagonists (NOAC, DOAC) are preferred if there are no contraindications.
6. After percutaneous coronary revascularization (postPCI) in patients with AF, NOACs: Apixaban 2 x 5 mg, Dabigatran 2 x150

mg, Edoxaban 60 mg and Rivaroxaban 20 mg once daily have an advantage over vitamin K antagonists (VKA) in combination with in combination with antiplatelet therapy (mono- or dual-DAPT at high hemorrhagic risk).

7. Proton pump inhibitors are recommended in patients at high risk of gastrointestinal bleeding, according to the HAS-BLED score, in the following subgroups: patients with aspirin monotherapy, dual antiplatelet therapy (DAPT) or oral anticoagulant monotherapy.

8. If the target value of serum LDL cholesterol is not reached with the maximum dose of statins, combination with ezetimibe is recommended, and in VERY HIGH RISK, a third drug PCSK9-inhibitor (Proprotein convertase subtilisin / kexin type 9) is added parenterally.

9. Sodium glucose-2-cotransporter inhibitors (SGLT2-I): empagliflozin, canagliflozin or dapagliflozin are recommended in patients with diabetes mellitus (DM) and CCS and cardiovascular disease.

10. Glucagon-like peptide-1 (GLP-1) receptor agonists liraglutide or semaglutide are recommended in patients with DM and CCS and cardiovascular disease.

NEW AND / OR REVISED CLASS IIa MAIN RECOMMENDATIONS (There is conflicting evidence and / or divergence of opinion about the usefulness / efficacy of a given treatment or procedure, but weight of evidence/opinion favor of usefulness / efficacy. Wording to use: Should be considered)

1. Invasive coronary angiography with the availability of invasive functional evaluation should be considered to confirm the diagnosis of CAD in patients with an uncertain diagnosis on noninvasive tests.
2. Coronary MSCT angiography should be considered as an alternative to invasive coronary angiography if other non-invasive tests are ambiguous or non-diagnostic.
3. The addition of another antiplatelet drug to aspirin for long-term secondary prevention should be considered in patients with a high ischemic risk and without a high risk of bleeding.
4. Long-term oral anticoagulant therapy (OAC) should be considered with AF and CHA₂DS₂-VASc = 1 for males and 2 for females, non-vitamin K antagonists (NOAC) are preferred, if there are no contraindications
5. In patients with AF and NOAC, where the risk of haemorrhagic risk outweighs the risk of stent thrombosis or ischemic stroke, a lower dose of NOAC should be given (Rivaroxaban 15 mg once

daily or Dabigatran 2 x 110 mg in combination with mono or double antiplatelet therapy).

6. In post-PCI patients with AF or other indications for OAC, triple therapy with aspirin, clopidogrel, and OAC should be considered for at least one month or longer when the risk of stent thrombosis outweighs the haemorrhagic risk, with a total duration of up to 6 months. both risks and is clearly stated on discharge from the hospital!

7. Angiotensin converting enzyme (ACEI) inhibitors should be considered in CCS patients at very high risk of adverse cardiovascular events.

8. Ranolazine, nicorandil, ivabradine and trimetazine are converted to IIa (from class IIb-utility / efficacy is much less based on evidence / views).

CLASS III MAIN RECOMMENDATIONS. There is evidence and / or general agreement that a given treatment or procedure is not useful/ effective and in some cases may be harmful: Wording to use: Is not recommended

1. Coronary MSCT / MDCT angiography is not recommended when there are extensive coronary calcifications, irregular heart rate, significant obesity, inability of the patient to hold his breath long enough and any other factors that would affect the failure to obtain a quality image.

2. Changes in the ST segment of the ECG during PSVT should not be used as evidence of CAD.

3. Outpatient ECG monitoring (Holter ECG) should not be routinely used in the examination of patients with suspected CCS.

4. Coronary calcium score via MSCT is not recommended for identification of persons with obstructive CAD.

5. Exercise ECG test (ergometric ECG stress test on a treadmill or bicycle) in patients with $\geq 0.1\text{Mv}$ (1mm) ST segment depression on an ECG at rest, or digitalis treatment is not recommended for diagnostic purposes of CCS.

6. Invasive coronary angiography (ICA) is not recommended as the only method for risk stratification in CCS.

7. Nitrates are not recommended for the treatment of CCS in patients with hypertrophic obstructive cardiomyopathy or in concomitant therapy with phosphodiesterase inhibitors (Sildenafil et al.).

8. The use of ticagrelor or prasugrel is not recommended as part of triple antithrombotic therapy with acetyl-salicylic acid (ASA) and oral anticoagulant therapy (OAC).

9. Coronary MSCT angiography is not recommended as a routine test to monitor patients diagnosed with chronic coronary syndrome (CCS).

10. Carotid echosonography with determination of intimomedial layer thickness is not recommended for CCS risk stratification.

11. In low-risk asymptomatic adult non-diabetics, coronary MSCT angiography or functional imaging tests for ischemia are not indicated for further diagnostic evaluation.

12. Routine determination of circulating cardiac biomarkers is not recommended for stratification of cardiovascular risk in patients with CCS.

13. The combination of drugs from the ACEI and ARB groups is not recommended for CCS.

14. In severe heart valve disease, stress tests should not be used routinely to detect CAD, due to low diagnostic benefit and potential risk of complications.

15. Sex hormone replacement therapy is not recommended for risk reduction in postmenopausal women.

16. Transmyocardial revascularization is not recommended for patients with severe AP refractory to optimal medical treatment (OMT) and myocardial revascularization (RM) strategies.

SCENARIO 1: PATIENTS WITH SUSPECT CAD-CCS AND STABLE AP and / or EFFORT DYSPNEA.

The procedure (algorithm) in 6 steps in the approach to initial care of patients with suspected CCS and stable AP or dyspnea on exertion is given in Figure 2.

FIGURE 2. **6-step procedure (algorithm)** in the approach to initial care of patients with suspected CCS and stable AP or dyspnea Retrieved from <https://www.escardio.org/Guidelines/Clinical-Practice-Guidelines/Chronic-Coronary-Syndromes>

Instead of the previous 3 steps according to the ESC guide from 2013 [4,22], a procedure or algorithm has now been introduced in 6 STEPS [1] in the approach to initial care of patients with suspected CCS:

STEP 1: Assessment of symptoms (TABLE 1) uses the traditional clinical classification of suspected anginal symptoms: chest discomfort -

discomfort (pain) on exertion usually shorter than 10 minutes (pain lasting seconds is usually not anginal) and conducting clinical trials, identifying patients with unstable angina and other forms of ACS. AP can paradoxically decrease with further effort (walk-through angina) or with the next effort (warm-up angina) [23].

TABLE 1. The traditional clinical classification of suspected anginal symptoms: chest discomfort

Patients with angina and/or dyspnoea and suspected coronary artery disease

Clinical classification of suspected angina

Typical angina	Meets the following three characteristics: 1. Constricting discomfort in the front of the chest or in the neck, jaw, shoulder, or arm; 2. Precipitated by physical exertion; 3. Relieved by rest or nitrates within 5 min.
Atypical angina	Meets two of these characteristics.
Non-anginal chest pain	Meets only one or none of these characteristics.

It should not be emphasized how important it is to quickly rule out other acute cardiac conditions: acute coronary syndrome (ACS) -

unstable angina pectoris- identical pain as in AP but lasting > 20 minutes. One should always think of a dissecting aortic aneurysm, ie Acute

aortic syndrome (AAS), pulmonary embolism, pericarditis and myocarditis. In the differential diagnosis, consider non-cardiac diseases that may resemble anginal pain. The most common diseases that can mimic angina pectoris: gastroesophageal diseases (40%), thorax wall syndromes (Costochondritis and Titz syndrome), some lung diseases, pneumothorax, pleuritis and herpes zoster intercostalis

STEP 2- Consider the general condition and condition of the patient,

assess the quality of life and the presence of comorbidities that potentially affect the therapeutic decision. If performance of load tests and coronary revascularization are unlikely due to the general condition, immediately introduce OMT, especially antianginal pharmacological therapy.

STEP 3. Basic clinical supplementary trial.

Includes basic examination: electrocardiogram (ECG), in selected patient ambulatory ECG Holter monitoring, biochemical analysis, radiography of the thorax in selected patients. An ECG is crucial for the diagnosis of myocardial ischemia, typically a reversible horizontal depression of the ST segment in two or more adjacent ECG leads during or immediately after an anginal attack. The descending ST-segment depression is less specific and the slow-ascending depression is the least specific for the diagnosis of ischemia, while the fast-ascending ST-segment depression is a normal variant in tachycardia [24]; Holter ECG often reveals asymptomatic myocardial ischemia in the form of horizontal depression of the ST segment on exertion [24,25,26]; The ECG

may also indicate indirect signs of CAD: pathological Q tooth [27]; left bundle branch block (LBBB) or atrioventricular (AV) blocks, extrasystoles [27]; In an episode of atrial fibrillation (AF) with asymptomatic myocardial ischemia - ST depression [28,29]. In contrast to AF, ST depression during paroxysmal supraventricular tachycardia (PSVT) is not predictive of ischemia. Echocardiographic assessment of left ventricular function (LV), primarily left ventricular ejection fraction (EF), is mandatory. When the EF is <50% the patient is referred directly for invasive coronary angiography (ICA). Transthoracic echocardiography (TTE) as the single most informative diagnostic method in cardiology has a crucial role in excluding alternative causes of chest discomfort [30] and for risk stratification. In the case of suboptimal echo imaging (<10% of cases), transesophageal echocardiography (TOE) and cardiomagnetic resonance imaging (CMR) are used [31].

STEP 4 Assessment of pre-test probability and clinical probability of CAD-CHD

The European Guide 2019 gives increased and renewed importance to the determination of pre-test probability (PTP) of obstructive coronary heart disease, but the classic PTP, Diamond and Forrester based on age, sex and nature of symptoms [31] have undergone major changes based on new evidence [32]. The mean PTP is 15% to 85%. Using the new table (TABLE 2) reduces the overestimation of the incidence of coronary heart disease. [1, 31, 32].

TABLE 2. NEW REVISED PRETEST PROBABILITY

Foldyna B, Udelson JE, Karady J, et al. insights from the PROMISE trial. Eur Heart J Cardiovasc Imaging 2018; 20:574-581.

Patients with angina and/or dyspnoea and suspected coronary artery disease

Pre-test probability of coronary artery disease

Age	Typical		Atypical		Non-anginal		Dyspnoea ^a	
	M	W	M	W	M	W	M	W
30-39	3%	5%	4%	3%	1%	1%	0%	3%
40-49	22%	10%	10%	6%	3%	2%	12%	3%
50-59	32%	13%	17%	6%	11%	3%	20%	9%
60-69	44%	16%	26%	11%	22%	6%	27%	14%
70+	52%	27%	34%	19%	24%	10%	32%	12%

^a In addition to the classic Diamond and Forrester classes, patients with dyspnoea only or dyspnoea as the primary symptom are included. The dark green shaded regions denote the groups in which non-invasive testing is most beneficial (pre-test probability >15%). The light green shaded regions denote the groups with pre-test probability of CAD between 5-15% in which the testing for diagnosis may be considered after assessing the overall clinical likelihood based on modifiers of pre-test probability.

A new term, Clinical Probability of Obstructive Coronary Disease (CPCAD), is introduced, which uses different risk factors for CAD as modifiers of PTP probability. Reduction of probability for obstructive CAD: normal ECG test with physical load and normal calcium score of coronary arteries (Agatston = 0) [1, 33]. Factors that increase CPCAD:

A) dyslipidemia, diabetes, hypertension, smoking, family history of CAD and sudden death.

B) Changes in the ECG at rest: Q wave and changes in the ST segment and T wave.

C) Left ventricular dysfunction referring to CAD

D) Abnormal exercise ECG test

E) increased calcium score by CT

The selection of the initial non-invasive diagnostic test (functional or anatomical image) is based on PTP or CPCAD.

STEP 5. Selection of the optimal diagnostic test for diagnosing CAD

Selection of the optimal diagnostic test for diagnosing CAD, based on patient profile, local availability and expertise. [1, 36-42] is shown in Figure 3.

Figure 3. MAIN DIAGNOSTIC PATHWAYS IN SYMPTOMATIC PATIENTS WITH SUSPECT OBSTRUCTIVE CAD CCS

Retrieved from <https://www.escardio.org/Guidelines/Clinical-Practice-Guidelines/Chronic-Coronary-Syndromes>

In patients in whom revascularization is “futile” due to comorbidity and overall quality of life (STEP 2), the diagnosis of CAD can be made clinically and only OMT- optimal medical therapy is required. If the diagnosis of CAD is uncertain, making a diagnosis using non-invasive functional tests to record myocardial ischemia before treatment is a reasonable option; on the other hand in a patient with a high clinical probability of CAD, when symptoms have not responded to medical therapy or severe typical low-grade angina is present and / or initial clinical assessment (including echocardiogram and in selected patients ECG exercise test or Ergometric ECG test) indicates a high risk of adverse events, switch directly to

invasive coronary angiography (ICA) without further diagnostic testing. Under such circumstances, the indication for MR should be based on appropriate invasive confirmation of the hemodynamic significance of the stenosis: FFR, CFR [43, 44].

Existing guidelines recommend the use of either noninvasive functional imaging of ischemia or anatomical imaging using coronary CT angiography (CTA) as an initial test for the diagnosis of CAD. Functional non-invasive ischemia tests for the diagnosis of obstructive CAD are designed to detect myocardial ischemia by ECG changes, irregularities of wall movement using CMR stress or stress echocardiography, or perfusion changes by myocardial scintigraphy

(SPECT), positron emission cardiography or contrast CMR. Ischemia can be caused by physical exertion (ergometrically) or pharmacological stressors, either through increased myocardial function and oxygen demand, or by heterogeneity in myocardial perfusion by vasodilation. Non-invasive functional tests have high accuracy for detecting coronary stenosis that restricts flow compared to invasive functional examination by fractional flow reserve (FFR) [45].

However, insignificant coronary stenoses and atherosclerotic plaques not associated with ischemia remain undetected by functional testing and in the presence of a negative functional test, patients should receive risk factor modification based on ESC recommendations for CV prevention [6].

Anatomical non-invasive assessment

Anatomical noninvasive assessment by visualization of coronary arteries, imaging and lumen of the coronary artery wall can be reported using intravenous contrast agent by coronary CT angiography (CTA), which provides high accuracy for detecting obstructive coronary stenoses, as well as invasive coronary angiography [45A] the recordings are based on anatomy. However, stenoses that amount to 50 to 90% by visual examination are not necessarily functionally significant, ie. they do not always cause myocardial ischemia. [45.46]. Therefore, non-invasive or invasive functional testing is recommended for further assessment of angiographic stenosis detected by coronary CTA or ICA, unless high-grade stenosis (> 90% of diameter) is detected by invasive angiography. The presence or absence of non-obstructive coronary atherosclerosis on coronary CTA provides prognostic information and can be used for preventive therapy. [47].

The role of Exercise (ergo) ECG test

The ECG ergometric stress test has poorer diagnostic performance compared to diagnostic visualization tests and has limited power to rule out obstructive CAD. [45]. Therefore, these guidelines recommend the use of diagnostic imaging tests instead of exercise ECG as an initial test for the diagnosis of obstructive CAD. Exercise ECG test can be considered as an alternative for the diagnosis of obstructive CAD, if visualization (imaging tests) are not available, bearing in mind the risk of false negative and false positive test results. [45]. Exercise ECG has no diagnostic value in patients with ECG abnormalities that prevent the interpretation of ST-segment changes.

Influence of clinical probability on the choice of diagnostic test

Each non-invasive diagnostic test has a certain range of clinical probability for obstructive CAD where the usefulness of its application is maximum. Test probability coefficients are a useful parameter of their ability to properly classify patients and can be used to facilitate the selection of the most useful test for any patient. [45]. Given the clinical probability of obstructive CAD and the probability coefficient of a particular test, a post-test probability for obstructive CAD after performing such a test can be assessed.

Using this approach, the optimal range of clinical probability for each test can be estimated, where patients can be reclassified from medium (15–85%) to any: low (<15%) or high probability of CAD > 85% after the test [45]. Coronary CTA is preferred in patients with a lower range of clinical probability of CAD (previously numerically PTP 15-65%), without prior diagnosis of CAD and important conditions associated with a high probability of good image quality. Coronary CTA detects subclinical coronary atherosclerosis, but can also rule out anatomically and functionally significant CAD.

Non-invasive functional tests for ischemia have the advantage because they directly show the area of myocardial ischemia by provoking ischemia. Before revascularization, functional assessment and [45]. schemes (non-invasive or invasive method) is required in most patients.

In addition to diagnostic accuracy and clinical probability, the choice of a non-invasive test depends on other patient characteristics, local expertise, and test availability. Some diagnostic tests may be better in some patients than others. For example, tachyarrhythmia and the presence of extensive coronary calcification are associated with an increased likelihood of non-diagnostic quality of the coronary CTA image and are not recommended in such patients. [51]. Stress echocardiography or SPECT myocardial perfusion imaging may be combined with dynamic TFO and may be desirable if additional information is available during the TFO ECG test. TFP cannot be used for diagnostic purposes in the presence of ECG abnormalities that prevent the assessment of ischemia. The risks associated with different diagnostic tests must be weighed for and against the benefit to the particular patient [52]. Similarly, contraindications for pharmacological stressors and contrast agents (iodine- and gadolinium-based contrast agents) chelates) should be considered. When testing is used appropriately, the clinical benefit of

accurate diagnosis and therapy outweighs the projected risks of testing itself [52].

Invasive examination

For strictly diagnostic purposes, ICA is required only in patients suspected of having obstructive CB in the case of unconvincing, ambiguous or inclusive non-invasive testing or, exceptionally, in patients of certain public occupations of special importance (drivers, pilots, machine workers, police officers). and the like), due to security and regulatory issues. [53]. However, ICA may also be necessary when a noninvasive assessment suggests a very high risk of adverse events to determine revascularization options. [53]. In a patient with a high clinical likelihood of CAD and symptoms not responding to medical therapy or with typical low-effort angina, and an initial clinical assessment indicating a high risk of events, early ICA without prior noninvasive risk stratification may be a reasonable solution to identify lesions that may be suitable for myocardial revascularization (FIGURE 3). Invasive functional assessment should complement the ICA, especially in patients with 50 to 90% coronary stenosis or multivessel

disease, given the frequent discrepancies in the angiographic and hemodynamic severity of coronary stenosis. [53-58]. ICA should not be performed in patients with angina who refuse invasive procedures and avoid revascularization, who are not candidates for percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG), or in whom myocardial revascularization is not expected to improve functional status or quality of life

STEP 6 After the diagnosis of CCS is made, the risk of adverse events is stratified by functional stress tests: isotopic stress-rest SPECT, the most available pharmacological stress echo dobutamine or dipyridamole and the least available cardiomagnetic resonance (CMR) stress with dobutamine and contrast perfusion. The decision on further treatment is based on determining the level of risk [1]. Definition of risk levels according to annual mortality: no ischemia, mortality from adverse events less than 1%; medium risk - annual mortality between 1% and 3%; high annual mortality is over 3% (Table 3).

TABLE 3. DEFINITION OF HIGH RISK LEVEL (HIGH EVENT RISK) FOR FUNCTIONAL IMAGE TESTS AND NON-INVASIVE ANATOMICAL CT CORONARY ANGIOGRAPHY

Patients with angina and/or dyspnoea and suspected coronary artery disease

Definitions of high event risk for different tests

Exercise ECG	Cardiovascular mortality >3% per year according to Duke Treadmill Score.
SPECT or PET perfusion imaging	Area of ischaemia ≥10% of the left ventricle myocardium.
Stress echocardiography	≥3 of 16 segments with stress-induced hypokinesia or akinesia.
CMR	≥2 of 16 segments with stress perfusion defects or ≥3 dobutamine-induced dysfunctional segments.
Coronary CTA or ICA	Three-vessel disease with proximal stenoses, LM disease, or proximal anterior descending disease.
Invasive functional testing	FFR ≤0.8, iwFR ≤0.89.

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29

Figure 4. COMPARISON OF CV RISK LEVELS OF ASYMPTOMATIC PERSONS IN PRIMARY PREVENTION OF ADVERSE CV EVENTS AND IN ESTABLISHED CCS IN SECONDARY PREVENTION

Retrieved from <https://www.escardio.org/Guidelines/Clinical-Practice-Guidelines/Chronic-Coronary-Syndromes>

If the angina is very severe but not unstable, according to the well-known Canadian Classification of the Canadian Class IV Association (TABLE 4), with a pretest probability greater than 85% according to

Bayes' theorem, ICA is performed immediately without previous noninvasive tests, but with coronary fractional flow reserve assessment. (FFR) [45, 56, 59].

TABLE 4. Classification of severity of angina pectoris and / or dyspnea on exertion according to the Canadian Cardiovascular Association

Patients with angina and/or dyspnoea and suspected coronary artery disease

Canadian Cardiovascular Society grading of effort angina severity

Class	Description of angina severity	
I	Angina only with strenuous exertion	Presence of angina during strenuous, rapid, or prolonged ordinary activity (walking or climbing the stairs).
II	Angina with moderate exertion	Slight limitation of ordinary activities when they are performed rapidly, after meals, in cold, in wind, under emotional stress, or during the first few hours after waking up, but also walking uphill, climbing more than one flight of ordinary stairs at a normal pace, and in normal conditions.
III	Angina with mild exertion	Having difficulties walking one or two blocks, or climbing one flight of stairs, at normal pace and conditions.
IV	Angina at rest	No exertion needed to trigger angina.

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16

The role of coronary MSCT angiography is to rule out significant disease in patients with a lower intermediate probability of 15 to 50%.

Finally, the choice of adequate therapy is made: lifestyle change, pharmacological therapy of CAD

and myocardial revascularization (MR), based on symptoms and risk of adverse CV events.

NON-PHARMACOLOGICAL MEASURES IN THE TREATMENT OF CHRONIC CORONARY SYNDROMES (for all CCS, especially for scenario 1)

The guide underlines the crucial role of a healthy lifestyle or other preventive measures to reduce the risk of consequent cardiovascular events and mortality [1], as shown in the essential studies COURAGE [60] and FAME [44]. Regular taking of medications for the treatment of hypertension, hyperlipidemia, diabetes, etc. should ensure the achievement of target values of blood pressure, LDL cholesterol, HDL, triglycerides and glycemia (HbA1c), which leads to stagnation and regression of atherosclerosis, which is discussed in detail in the ESC Guide for CV prevention 2016 [6].

The involvement of a multidisciplinary team in preventive work is recommended: cardiologist, general practitioner (GP), nurses, nutritionist, psychologist, psychotherapist and pharmacist (class I evidence B) [1]. The use of a healthy lifestyle, as a preventive intervention, reduces the risk of subsequent development of adverse CV events and mortality. The application of healthy behavior is important: smoking cessation, recommended physical activity, healthy diet, maintaining a healthy weight, which significantly reduces the risk of future cardiovascular events and death, and which is based on evidence. [1, 61, 62]. The benefits are obvious as early as 6 months after the index event [1, 61, 62]. Primary health care plays an important role in prevention, the EUROACTION study showed that a program coordinated by a primary care nurse improves the reduction of risk factors. [63].

Smoking cessation improves the prognosis in patients with HCV, including a 36% reduction in the risk of death for those who successfully quit. Measures to promote smoking cessation include brief tips and advice on behavioral intervention and pharmacological therapy including nicotine replacement. Patients should also avoid passive smoking. Short doctor's advice doubles the likelihood of smoking cessation in the short term, but more intensive advice and support (behavioral interventions, telephone support or self-help measures) is more effective than short advice, especially if continued for one month [62,63]. All forms of nicotine replacement therapy, bupropion, and varenicline are more effective in smoking cessation than self-control; combining a behavioral and pharmacological

approach to smoking cessation is effective and recommended. [64].

Healthy eating [65]: Diet rich in vegetables, fruits and whole grains. Limit saturated fat intake to <10% of total intake. Limit alcohol to <100 g / week or 15 g / day.

Healthy body mass gain and maintain a healthy mass (BMI <25 kg / m²) or lose weight through recommended energy intake and increased physical activity.

Obesity is associated with shorter overall life expectancy and overweight is associated with the development of cardiovascular disease (CVD) [66]. Waist circumference is a sign of central obesity and metabolic syndrome [30] and is strongly associated with the development of CVD and diabetes. The recommended waist circumference is ≤94 cm for men and ≤80 cm for women. In people with CVD, intentional weight loss is associated with a significantly lower risk of adverse events [67].

Moderate alcohol intake (1-2 drinks per day) does not increase the risk of AMI.

Physical activity. The exercise is called "pollypill" because of its many beneficial effects on CV risk factors and the CV system [21, 68, 69, 70]. Physical activity reduces AP severity, improves oxygen transport in the myocardium and increases exercise capacity, and is an independent predictor of increased survival in men and women with CCS [21, 68, 69, 70]. Every 1 mL / kg / min increase in peak oxygen consumption was associated with a 14% reduction in CVD risk and an all-cause cause of death in women and men. [21]. Recommendations for physical activity for patients with CCS are 30 to 60 min of moderate-intensity aerobic activity ≥5 days per week. [6, 69]. Even irregular physical activity in leisure time reduces the risk of mortality in previously seated patients [72] and increasing activity is associated with lower CV mortality [73]. Strength exercises maintain muscle mass and function, and in addition to aerobic activity (fast walking, swimming, etc.), they give beneficial effects in terms of lowering insulin resistance, lipid levels and blood pressure.

CV rehabilitation based on physical exercise has constantly shown efficacy in reducing CV mortality and hospitalizations compared to the control group in patients with CAD and this benefit remains at the present time [74,75,76, 77].

Psychosocial factors. Patients with CAD have a twice-increased risk of depression and anxiety disorders compared to people without heart

disease [78]. Psychosocial stress, depression and anxiety are associated with poorer CCS outcomes. Clinical trials have shown that psychological (eg, counseling and / or cognitive-behavioral therapy) and pharmacological interventions with psychopharmaceuticals have had beneficial effects on depression, anxiety, and stress, with some evidence of reduced cardiac mortality and adverse events compared with placebo. [79,80,81].

Environmental factors. Air pollutants are estimated as one of the 10 leading risk factors for global mortality. Exposure to air pollution also increases the risk of AMI as well as hospitalization and death from HF, stroke and arrhythmias. [82]. Patients with CCS should avoid areas with heavy traffic due to pollution and noise [82,83]

Sexual activity. Patients with CCS are often concerned about the CV risk of sexual activity and / or sexual dysfunction. [84,85]. The risk of causing sudden death or AMI is very small, especially when sexual activity with a stable partner in a known environment is stress-free or without excessive food or alcohol intake [86]. Although sexual activity transiently increases the risk of MI, it causes only <1% of acute MI and <1.7% for sudden death during sexual activity. [86]. Energy expenditure during sexual activity is generally low to moderate (3 - 5 METs, metabolic equivalents) and climbing stairs to the second floor is often used as equivalent activity in terms of energy expenditure. Phosphodiesterase-5 inhibitors for the treatment of erectile dysfunction are usually safe in CCS patients, but are contraindicated in those who take nitrates and who have severe hypotension [86]. Healthcare professionals should ask patients about sexual activity, give them information and provide advice

Adhering to lifestyle modifications and taking medication regularly is a big challenge. A systematic review of epidemiological studies has shown that a significant proportion of patients do not adhere to regular CV medications and that 9% of cardiovascular adverse events in Europe can be attributed to poor patient adherence (compliance) to regular therapy [87, 88]. In older men with CKD, greater adherence to medication guidelines was positively associated with better clinical outcomes, independent of other conditions. Polypharmacy plays a negative role in adherence to treatment [88] and the complexity of the medication regimen is associated with non-adherence and a higher hospitalization rate [89]. Physicians who prescribe drugs should give preference to drugs

that have proven their benefit with the highest level of evidence and those that are most beneficial to the patient, without significant side effects of the drug. Regime simplification helps adhere to treatment and there is evidence of the benefits of cognitive education strategies, electronically monitored feedback, and telephone support from nurses and technicians. Reviewing and controlling the type and dose of drugs by primary care physicians is a significant factor in helping all patients, especially patients with more comorbidities, to simplify the treatment regimen, detect drug interactions and minimize the risk of drug side effects [89,90,91]. Long-term support (intensive for the first 6 months, then every 6 months for 3 years) in the GOSPEL study (Global Secondary Prevention Strategies to Limit Recurrence after Myocardial Infarction) resulted in significant improvements in risk factors and a reduction in some adverse outcomes [20].

Sex hormone replacement therapy in menopausal women with CCS is not recommended.

Annual vaccination against influenza is recommended for all patients with CCS because it improves the prevention of AMI, reduces CV mortality in adults aged > 65 years

PHARMACOLOGICAL THERAPY OF CHRONIC CORONARY SYNDROMES SCENARIO 1

PHARMACOLOGICAL THERAPY OF CHRONIC CORONARY SYNDROMES: CLINICAL SCENARIO 1- Patients with suspected coronary heart disease and stable angina and / or dyspnea on exertion.

The goals of pharmacological treatment of patients with CCS are: to reduce the symptoms of angina and ischemia caused by physical exertion and exercise and to prevent unwanted CV events. Anti-ischemic drugs - but also lifestyle changes, regular exercise training, patient education and eventual revascularization - all play a role in minimizing or eradicating symptoms during long-term prevention. Prevention of cardiovascular adverse events: ACS, AMI, HFrEF, HFmEF, HFpEF), ventricular arrhythmias and heart blocks, VT, AF, stroke and CV deaths associated with CCS focuses on reducing the incidence of acute atherothrombotic events and and the development of LV dysfunction. Optimal pharmacological therapy (OPhT) can be defined as a treatment that satisfactorily controls symptoms and prevents CAD-related adverse events, with maximum patient adherence to treatment and with minimal drug side effects.

The modern role of first-line antianginal drugs: beta-blockers (BB) and calcium antagonists (CCB) and second-line long-acting nitrates (LANs) was highlighted, including new options: ivabradine, nicorandil, trimetazidine and ranolazine (and possibly allopurinol), and drugs that improve prognosis (acetylsalicylic acid (ASA) and other antiplatelet drugs, statins, ACEI, BB). There are two therapeutic goals in the treatment of CCS:

1. Improving the prognosis by reducing the risk of atherosclerosis progression and preventing acute coronary events and sudden death and prolonging life
2. Minimize symptoms with improved quality of life.

ANTI-ISCHEMIC (ANTIANGINAL) DRUGS

Immediate alleviation of anginal symptoms or prevention of symptoms under circumstances that are likely to cause angina is usually obtained by fast-acting formulations of nitroglycerin sublingually, which is one of the first-line antianginal drugs. However, there is no universal definition of optimal treatment in patients with HCV and drug therapy must be tailored to the individual characteristics and preferences of the patient. Initial drug therapy usually consists of one or two antianginal drugs in addition to drugs for the secondary prevention of CVD. [92-95]. The initial choice of antianginal drugs depends on the expected tolerance associated with the patient's profile and comorbidities, potential drug interactions used concomitantly in therapy, patient preferences after notification of potential

adverse drug effects, and drug availability. Combination therapy with two antianginal drugs e.g. beta-blocker (BB) and calcium antagonist (CCB) are better than monotherapy with any class of antianginal drugs, but the effect in reducing clinical events remains unclear [95-98]. BB or CCB are recommended as first-line drugs, although to date no randomized controlled trial (RCT) has compared this strategy with alternative strategies that use initial prescribing of other anti-ischemic drugs or a combination of BB and CCB [92-95]. The results of a meta-analysis of 46 studies and 71 treatment comparisons, support the initial combination of BB and CCB. [98]. The same meta-analysis suggested several other initial first-line combinations of antiischemic drugs (long-acting nitrates, ranolazine, trimetazidine, and to a lesser extent, ivabradine) that may prove useful in combination with BB or CCB as first-line therapy, with no data for nicorandil. No study or meta-analysis has yet sufficiently assessed the impact of combining beta-blockers or CCBs with another line of anti-ischemic drugs against adverse events: morbidity or mortality [98]. Regardless of the initial strategy, the response to initial antianginal therapy should be reconsidered 2 to 4 weeks after starting treatment.

The algorithm of treatment with antiischemic drugs in patients with suspected CCS and stable angina and / or dyspnea on exertion is shown in TABLE 5.

TABLE 5 PHARMACOLOGICAL THERAPY OF CHRONIC CORONARY SYNDROMES

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FIRST LINE TREATMENTS CCS

SHORT-ACTING NITRATES are given for an acute AP attack on exertion. Sublingual tablets (lingualete) and nitroglycerin spray provide immediate relief of angina on exertion. The nitroglycerin spray works faster than the sublingual nitroglycerin tablet [99]. At the onset of angina symptoms, the patient should rest in a sitting position (standing promotes syncope) and take nitroglycerin (tablet 0.3-0.6 mg sublingually, not swallowed, or 0.4 mg spray under the tongue and not swallowed and not swallowed. inhale) every 5 min until the pain ceases or a maximum of 1.2 mg is taken within 15 min. Within that time frame, if the angina lasts for more than 15 minutes, the patient must call an ambulance for hospital treatment, due to the suspicion of ACS. Nitroglycerin can be used for prophylaxis before physical activities that are known to cause angina

BETA BLOCKERS (BB-blockers of beta 1- β 1-adrenergic receptors).

Selective β 1-adrenergic receptor blockers are preferred in CCS. The efficacy of OMT in stable angina where BB is the central component of treatment is similar to the effect of percutaneous coronary intervention (PCI) with a stent, according to W. Boden, principal investigator of the COURAGE study [16, 60]. The dose of beta-blockers should be adjusted so that the heart rate is 55-60 beats per minute [100, 101]. Discontinuation should be gradual dose reduction and not abrupt. Abrupt cessation of intake due to an increase in the number of β 1 receptors in the heart causes worsening of angina, sometimes even myocardial infarction. Dosing according to the target heart rate of 55-60 / min is common, but is acceptable below 50 / min in an individual patient without blocks. Target doses of β 1-blockers in CCS: metoprolol 2 x 100mg. maximum 400 mg, bisoprolol 1 x 1.25-10 mg, maximum in Europe 30 mg, in the USA up to 40 mg; (L.Opie, Drugs for the Heart, 2013); nebivolol 1.25-5 mg x 1, up to a maximum of 15 mg in practice. BBs are effective in silent ischemia. During the effort, the goal is for the heart rate not to be over 100 / min. All BBs are potentially equally effective in CCS and selection is made according to comorbidities. BBs can be combined with dihydropyridine (DHP) CCBs to reduce DHP-induced tachycardia. Caution is warranted when a beta-blocker is combined with verapamil or diltiazem due to the potential for the development of worsening SI, excessive bradycardia, and / or atrioventricular block (formerly an absolute, now a relative

contraindication). The combination of a beta blocker with nitrate reduces reflex tachycardia. The main side effects of beta blockers are fatigue, mental depression, bradycardia, AV block, bronchospasm, peripheral vasoconstriction, postural hypotension, impotence, and masking the symptoms of hypoglycemia. In comorbidities, the most selective β 1 blockers bisoprolol and nebivolol are preferred. In patients with recent AMI and those with chronic SI with reduced EF (HFrEF), BB is associated with a significant reduction in mortality and cardiovascular events [102-104], about a 30% reduction in mortality and reinfarction, and a similar effect in ischemic SI. The benefit in patients with CAD without previous AMI or SI is less well established and placebo-controlled trials are lacking. [105]. A retrospective analysis of 21860 matching patients from the REACH registry did not show a reduction in cardiovascular mortality with beta-blockers in patients with CAD and risk factors, with or without previous AMI [106], but this is still the subject of debate and further research.

CALCIUM ANTAGONISTS (CCBs or calcium channel blockers).

While CCB improves the symptoms of myocardial ischemia, it has not been shown to reduce adverse events and mortality in patients with CCS [107]. However, they have been shown to have an advantage in the prevention of exercise ischemia over BB.

NON-DIHYDROPYRIDINE CALCIUM ANTAGONISTS (NE-DHP): VERAPAMIL AND DILTIAZEM

Verapamil has a number of approved indications, including all types of angina (on exertion, vasospastic and unstable), supraventricular tachycardia and hypertension. Indirect evidence suggests good safety, but with the risk of heart blocks, bradycardia and HF. Compared with metoprolol, antianginal activity was similar. Combined beta-blockade with verapamil is not recommended (previously absolutely contraindicated due to the risk of cardiac SA and AV blocks). Diltiazem, with its profile of effects, has advantages over verapamil in the treatment of exertion angina. Like verapamil, it acts by peripheral vasodilation, reducing afterload while preventing coronary vasospasm. It has a moderate negative inotropic, chronotropic and dromotropic effect. There were no test results comparing diltiazem and verapamil. The use of non-DHP is not recommended for CCB in patients with LV dysfunction

CALCIUM DIHYDROPYRIDINE ANTAGONISTS (DHP-CCB)

Long-acting nifedipine

Nifedipine, a potent arterial vasodilator, is particularly well tested in hypertensive anginal patients when added with beta-blockade. In large placebo-controlled ACTION, the addition of long-acting nifedipine [60 mg once daily] to conventional angina treatment had no effect on prognosis. Long-acting nifedipine has been shown to be safe and has reduced the need for coronary angiography and cardiovascular interventions [108]. Relative contraindications for nifedipine are: small cardiac output (severe aortic stenosis, hypertrophic obstructive cardiomyopathy or HF); Careful combination with beta-blockade is usually feasible and desirable. Vasodilator side effects include headaches and ankle edema.

Amlodipine.

The very long half-life of amlodipine and its good tolerability make it an effective antianginal and antihypertensive drug taken once a day. There are few side effects, mostly ankle edema. In patients with CCS and without SI, amlodipine at a dose of 10 mg / day reduced the number of coronary revascularizations and hospitalization for AP in a 24-month study [109]. Exercise-induced ischemia is reduced more effectively with amlodipine, 10 mg / day, than with the beta-blocker atenolol, 50 mg / day, and their combination is even better. However, the CCB-BB combination is underused, as are other combinations of antichemical drugs, even in some studies that report that "optimal treatment of stable AP on exertion" has been applied [110]

SECOND LINE DRUGS

Long-acting nitrates for the prophylaxis of angina (eg, nitroglycerin patch, isosorbide dinitrate, and isosorbide mononitrate) are second-line drugs for relieving AP, when initial therapy with BB or NE-DHP CCB is contraindicated, poorly tolerated, or insufficient to control symptoms. There is essentially a lack of data comparing nitrates with BB and CCB, in order to draw firm conclusions about their relative efficacy [110]. When taken over a long period of time, long-acting nitrates cause tolerance with loss of efficacy, so it is necessary to prescribe a drug-free interval of 10-14 hours. The bioavailability of isosorbide dinitrate depends on inter-individual liver variability while isosorbide mononitrate, its active metabolite, is 100% bioavailable. Dose titration is essential to obtain maximum symptom control at a tolerable dose. Discontinuation should be a

gradual dose reduction and not abruptly avoid worsening of AP. The most common side effects are hypotension, headache and redness. Contraindications include hypertrophic obstructive cardiomyopathy, severe aortic stenosis, and concomitant use of phosphodiesterase inhibitors (e.g., sildenafil, tadalafil, or vardenafil) or riociguata.

Molsidomin is an unfairly neglected drug (even in the new ESC guide from 2019 [1]), which acts similarly to nitrates, but does not develop tolerance to its action, has an effective anti-ischemic effect and good tolerability. Dosage 3 x 2mg to 4mg or retractable form 2 x 8mg. Unfortunately, there are no studies on the effect on the prognosis of CCS [111,112]

Ivabradine is not inferior to atenolol or amlodipine in the treatment of angina and ischemia in patients with CCS [111]. By adding ivabradine 7.5 mg twice daily, atenolol therapy provided better control of heart rate and anginal symptoms. Overall, the results of the study support the use of ivabradine as a second-line drug in patients with CCS, when they do not tolerate or have contraindications for BB.

Nicorandil is a nitrate derivative of nicotinamide, with antianginal effects similar to those of nitrates or beta blockers. Side effects include nausea, vomiting, and potentially severe ulceration of the oral, intestinal, and mucous membranes. In a placebo-controlled IONA study (n = 5126), nicorandil significantly reduced nonfatal AMI or hospitalization in patients with CCS, but there was no effect on death from ischemic heart disease or fatal AMI [113]. These results support the use of nicorandil as a second-line drug in patients with CCS.

Ranolazine is a selective inhibitor of late internal sodium current. Side effects include dizziness, nausea and constipation. In addition, ranolazine increases QTc, and should therefore be used with caution in patients with QTc prolongation or with QTc prolonging drugs. In a placebo-controlled study in 6560 patients with NSTEMI ACS, the addition of ranolazine to standard treatment did not prove effective in reducing primary outcomes and CV mortality, AMI, or recurrent ischemia. [114]. However, ranolazine in the relatively large CCS subgroup (n = 3565) significantly reduced recurrent ischemia and worsening angina [115]. These results support the use of ranolazine as a second-line drug in patients with CCS with angina despite frequently used antianginal agents such as beta-blockers, CCB, and / or long-acting nitrates. In contrast, there is a lack of evidence to support the use of

ranolazine in patients with CCS after PCI with incomplete revascularization

Trimetazidine reduces ischemia by affecting myocardial metabolism without hemodynamic effects, unlike many anti-ischemic drugs [116]. Trimetazidine 35 mg twice daily BB (atenolol) reduces exertion-induced ischemia [117]. It is contraindicated in Parkinson's disease and movement disorders.

A study of 1628 patients showed that treatment with trimetazidine along with other antianginal drugs resulted in a lower mean number of mild angina attacks.

Allopurinol, a xanthine oxidase inhibitor, has recently been proposed for the treatment of CCS. Allopurinol has a double effect of energy conservation, reduces the consumption of O₂ in the myocardium by inhibiting xanthine oxidase and transfers from creatine phosphate to ATP. Norman et al [118] in a randomized study of 65 patients with CCS found that 600 mg / day of allopurinol prolongs the time to onset of ST depression and pain by reducing vascular oxidative stress. the development of acute myocardial infarction (ACS) in the elderly, especially when taken for more than 2 years [119]. However, the role of allopurinol in reducing clinical events in CAD remains unclear [120].

PATIENTS WITH CCS AND LOW BLOOD PRESSURE

Therapy with anti-ischemic drugs should be started with very low doses, BB or non-DHP-CCB with vigilant monitoring of tolerance to these drugs, and in case of severe hypotension, therapy should be discontinued. Preference should be given to drugs that do not affect blood pressure, such as: Trimetazidine, Ranolazine and Ivabradine in patients with sinus rhythm

PATIENTS WITH CCS AND BRADICARDIA

Elevated resting heart rate is a strong independent risk factor for adverse events in patients with CCS and the therapeutic goal is a heart rate (SF) of less than 60 / min. But with HR <50 / min, drugs that have a negative chronotropic effect (BB and NON-DHP-CCB, ivabradine) should be avoided or used with caution if necessary. Treatment should begin with a very low dose. Drugs that do not have a heart rate slowing effect should be preferred (DHP-CCB, LAN, Trimetazidine, Ranolazine, Nicorandil)

PHARMACOLOGICAL TREATMENT TO IMPROVE PROGNOSIS AND PREVENT ADVERSE EVENTS

ANTI-PLATELET MEDICINES

Platelet activation and aggregation is the initiator of symptomatic coronary atherothrombosis, which is the basis for the use of antiplatelet - antiplatelet drugs in patients with CCS, given the favorable balance of prevention of ischemic events and increased risk of bleeding. Dual antiplatelet therapy (DAPT) with aspirin and oral P2Y₁₂ inhibitors is the basis of antithrombotic therapy after AMI and / or PCI.

ACETYSALICYLIC ACID (ASPIRIN) IN SMALL DOSES acts by irreversibly inhibiting platelet cyclooxygenase-1 and thus thromboxane, which occurs with a chronic dosage of ≥75 mg / day. Gastrointestinal side effects at higher doses justify a daily dose of 75-100 mg for the prevention of ischemic events in CAD patients with or without a history of AMI. As inhibition of cyclooxygenase-1 by aspirin is consistent and predictable in adequate patients, there is no need to test for platelet function.

P2Y₁₂ INHIBITORS block platelet receptors P2Y₁₂, which plays a key role in platelet activation and arterial thrombus formation. Clopidogrel and prasugrel are thienopyridine prodrugs that irreversibly block P2Y₁₂ with active metabolites. Clopidogrel is a well-known standard antiplatelet drug, but relatively often there is resistance to its action. Prasugrel does not show significant resistance, reduces ischemic events and stent thrombosis, but without affecting mortality, but therefore to the detriment of increased nonfatal bleeding. Ticagrelor is a reversibly binding inhibitor of P2Y₁₂, which does not require metabolic activation. Ticagrelor has the most predictable and consistently high level of P2Y₁₂ inhibition during maintenance therapy in susceptible patients and also has a faster onset of action compared to clopidogrel. Ticagrelor monotherapy appears to have similar efficacy and safety as aspirin in patients with previous PCI. Ticagrelor increases non-fatal but not fatal bleeding. Equivalent efficacy and similar safety of two doses of ticagrelor were explained by similar levels of platelet inhibition. Ticagrelor can cause dyspnoea, which is often transient and usually mild and tolerable, but sometimes a switch to thienopyridine is required. There are opinions and limited pharmacodynamic studies that support the unlicensed use of prasugrel or

ticagrelor in stable patients undergoing elective PCI who are at high risk for stent thrombosis.

DURATION OF DOUBLE ANTIAGREGATION THERAPY AFTER PCI

After 6 months, DAPT achieves an optimal balance of efficacy and safety in most patients [121]. Premature discontinuation of P2Y12 inhibitors is associated with an increased risk of stent thrombosis and is not recommended [121]. However, a shorter duration of DAPT may be considered in individuals at high risk for life-threatening bleeding given the very low risk of stent thrombosis after 3 months. However, the official position is: 12 months of DAPT recommended after ACS and PCI.

Greater benefit from prolonged therapy with clopidogrel or prasugrel has been observed in patients treated with AMI. The PEGASUS-TIMI 54 study showed that long-term therapy with ticagrelor 60 or 90 mg 2 x 1, initiated in stable patients more than 1 year after AMI, reduced ischemic events at the expense of increased multiple nonfatal bleeding. [121]. The 60 mg dose appears to be better tolerated and has been approved in many countries for this indication. Absolute reduction of ischemic events in CCS SCENARIO 4 with long-term ticagrelor (60 mg 2 x 1) with a low dose of ASA in high-risk patients after AMI with DM, peripheral arterial disease or multivessel CAD was demonstrated by Bhatt DL and associates in the subgroup of the mentioned study PEGASUS- TIMI 54. [122].

ORAL ANTICOAGULANT MEDICINES (AOK)

ANTICOAGULANT DRUGS IN SINUS RHYTHM

Anticoagulant drugs inhibit the action and / or production of thrombin, which plays a key role in both coagulation and platelet activation. Recently published studies have renewed interest in combining lower anticoagulant doses with antiplatelet therapy.

RIVAROXABANE IN SMALL DOSES. Rivaroxaban is a factor Xa inhibitor that has been studied at a low dose of 2.5 mg 2 x 1 daily in several populations of patients with sinus rhythm, and this dose is 1/4 of the standard dose used for anticoagulation in patients with AF. In the ATLAS ACS 2TIMI 51 study, rivaroxaban 2.5 mg 2 x 1, compared with placebo, reduced the complex outcome of AMI, stroke, or CV death in stabilized patients treated with aspirin and clopidogrel after ACS, with increased nonfatal bleeding, but with evidence reductions in cardiovascular mortality [123]. Subsequently, in

the COMPAS study [124], the same regimen in combination with aspirin and clopidogrel, with or without rivaroxaban 2 x 5 mg, in patients with CCS showed reduced ischemic events at the expense of an increased risk of predominantly nonfatal bleeding. [124].

ANTICOAGULANT DRUGS IN ATRIAL FIBRILLATION

OAC is recommended for patients with AF and CCS to reduce ischemic stroke and other ischemic events. OAC in patients with AF has shown superiority over aspirin monotherapy or clopidogrel-based DAPT for stroke prevention and is therefore recommended for this indication. [124]. When administering OAC to a patient with AF and CCS, based on the CHA₂DS₂-VAS score and HASBLED score, non-vitamin K antagonists -NOAC (i.e., apicaban, dabigatran, edoxaban, or rivaroxaban) have an advantage over vitamin K (VKA) antagonists. [1]

Proton pump inhibitors

Proton pump inhibitors reduce the risk of gastrointestinal bleeding in patients treated with antiplatelet drugs and are given to anyone with a high risk of bleeding (HASBLED score) and monotherapy, to improve safety. [124]

STATINS

When target LDL cholesterol values cannot be achieved, it has been shown that the addition of ezetimibe reduces LDL cholesterol but also reduces CV events in patients with ACS, in diabetics [1] without further impact on mortality. In addition to exercise, diet, and weight control, which should be recommended to all patients, dietary supplements, including phytosterols, may lower LDL-C to a lesser extent, but no improvement in clinical outcomes has been shown [1]. Phytosterols are also used in patients with statin intolerance, which is a group with a higher risk of cardiovascular events. Studies from 2015 show that subtilisin-kexin type 9 proprotein convertase inhibitors (PCSK9) (evolocumab and alirocumab) are very effective in lowering cholesterol, lowering LDL-C in a consistently stable manner to <-1.3 mmol / L. In outcome studies, these agents have been shown to reduce cardiovascular and mostly ischemic events, with little or no effect on mortality. [1] Very low cholesterol is well tolerated and associated with fewer events, but the high cost of PCSK9 inhibitors and their unknown long-term safety has limited their low-density lipoprotein apheresis and new therapies such as mipomersen and lomitapid need further investigation. For patients undergoing PCI, a

high dose of atorvastatin reduces the incidence of periprocedural events [1].

RENIN ANGIOTENSIN ALDOSTERONE SYSTEM BLOCKERS

ACE INHIBITORS can reduce mortality, AMI, stroke, and HF among patients with LV dysfunction, previous peripheral vascular disease, and high-risk DM. It is recommended that ACE inhibitors (or ARBs, angiotensin AT2 receptor blockers in cases of ACEI intolerance) be considered for the treatment of patients with CCS with coexisting hypertension, LVEF <40%, DM or chronic renal disease and insufficiency (CKD), unless contraindicated (eg severe renal impairment, hyperkalaemia, etc.). However, not all studies have shown that ACE inhibitors reduce all-cause mortality, as well as cardiovascular death, nonfatal AMI, stroke, or HF in patients with atherosclerosis and without impaired LC function. A meta-analysis, including 24 trials and 61961 patients, documented in CCS patients without HF [1] that renin-angiotensin system (RAS) inhibitors reduced cardiovascular events and death only compared to placebo, but not when compared to active controls. . Therefore, ACE inhibitor therapy in CCS patients without HF or high CV risk is generally not recommended unless necessary to achieve target blood pressure values.

Neprilysin is an endogenous enzyme that degrades vasoactive peptides such as bradykinin and natriuretic peptides. Pharmacological inhibition of neprilysin raises the level of these peptides, enhancing diuresis, natriuresis, myocardial relaxation, and antiremodeling and

reducing renin and aldosterone secretion. The first drug in the class is LCZ696, which combines valsartan and sacubitril (a neprilysin inhibitor) in one tablet. patients with HF (LVEF <35%) who remain symptomatic despite optimal treatment with ACE inhibitor, beta blocker and mineralocorticoid receptor antagonist (MRA), sacubitril / valsartan is recommended as a replacement for ACE inhibitor to further reduce the risk of HF hospitalization and death in outpatients.³³⁷ Aldosterone blockade with spironolactone or eplerenone is recommended for use in post-MI patients who are already receiving therapeutic doses of ACE inhibitors and beta blockers and have LVEF <35%, or diabetes or SI-HF. Caution should be exercised when using MRA in patients with impaired renal function [estimated GFR (eGFR) <45 mL / min / 1.73 m²] and in those with serum potassium > 5.0 mmol / L.

The combination of anti-ischemic drugs and drugs that affect the prognosis and survival in practice are insufficiently used both in the world [110] and in the part of Serbia - Timok region. Doses are not titrated to achieve optimal effects of pharmacological therapy [112]. The analysis of the treatment of DE NOVO coronary heart disease in consecutive 101 pts is presented from the clinical practice of the Dr. Bastać Practice. At the first examination, patients, previously treated or understood as stable angina pectoris, had pharmacological therapy by the attending physician or cardiologist (only 26% had a definitive diagnosis of coronary heart disease by exercise ECG test) attached to TABLE 6.

Table 6. Analysis of prescribed drugs for the treatment of suspected chronic coronary syndrome (CCS) in the Practice "Dr Bastać" on the 101st consecutive patient in 2017

Antiischemic drugs		Drugs that act on the prognosis of coronary heart disease
I lines	II lines	
65% beta blockers (also have hypertension)	36% long-acting nitrates molsidomin is not prescribed	48% acetyl salicylic acid (ASA) 9% Clopidogrel
31% Ant CA (due to hypertension)	16% trimetazidine	23% statin
20% Ntg sublinvally as needed	Not prescribed: ranolazine, ivabradine, nicorandil	61% ACE inhibitors (also have hypertension) 65% beta blockers (also have hypertension)

MYOCARDIAL REVASCULARIZATION (MR). The role of coronary myocardial revascularization (MR) in the treatment of chronic coronary syndromes SCENARIO 1. Figure 5

FIGURE 5. The role of coronary myocardial revascularization (RM) in the treatment of chronic coronary syndromes SCENARIO 1

Retrieved from <https://www.escardio.org/Guidelines/Clinical-Practice-Guidelines/Chronic-Coronary-Syndromes>

In patients with CCS, optimal medical therapy (lifestyle change, risk factor reduction and pharmacological-drug therapy, do not equate medical and drug therapy) -OMT is key to reducing symptoms, stopping the progression of atherosclerosis and preventing atherothrombotic events. Myocardial revascularization (RM) plays a central role in the management of the most severe forms of CCS as a last resort, but always as an adjunct to optimal medical therapy (OMT), without its elimination. The goals of MR are to alleviate symptoms in patients with angina and / or to improve the prognosis. These recommendations suggest that revascularization in patients with AP and significant stenosis is often second-line therapy when OMT has not been successful. Myocardial revascularization: PCI or CABG can effectively alleviate angina, reduce the use of antianginal drugs, and improve exercise ability and quality of life in a small number of selected patients compared to the OMT-only strategy. Revascularization with either PCI or CABG also aims to effectively eliminate myocardial ischemia and its adverse clinical manifestations among patients with significant coronary stenosis and to reduce the risk of major acute adverse CV events including AMI and cardiovascular death.

Numerous meta-analyzes comparing MR strategy by PCI with initial OMT in patients with CCS show either no benefit [126, 127] or myocardial revascularization provides a modest benefit [128, 129,] in terms of survival or lower incidence of AMI and SI. In this regard, previous ESC guidelines from 2013 [4] identified specific subgroups of patients (based on coronary anatomy, size of myocardial ischemia zone, risk factors, cardiac status, etc.) in whom MR may improve prognosis, indicating that in other subgroups it has no effect. FIGURE 5 summarizes the practical approach to MR indications in CCS according to the presence or absence of symptoms and documented myocardial ischemia by noninvasive functional imaging tests. However, the risk-benefit relationship in an individual case should always be evaluated and the MR is considered only if the expected benefit outweighs the potential risk. Also, the aspect of joint team decision-making is crucial, with complete information given to the patient about the expected advantages and disadvantages of the two strategies, including the risk of bleeding associated with DAPT in cases of revascularization via PCI.

A detailed discussion of the best choice between PCI or CABG revascularization modalities for an individual patient on the HEART team was published in the 2018 ESC guidelines for myocardial revascularization [131].

The role of MR has been placed in the context of recent evidence relating to the prognostic role of percutaneous coronary interventions (PCI) or coronary artery bypass grafting or native a. mammario internal and other arteries (CABG) in this low-risk population. MR is now reserved for patients where there is strong evidence to improve prognosis based on evidence of regional ischemia by visual noninvasive tests - perfusion imaging or assessment of FFR and iwFR [131]. The typical constellation is in a patient with a large area of myocardial ischemia corresponding to left main stenosis (left main stenosis > 50%) and multivessel disease that always involves stenosis $\geq 70\%$ of the proximal anterior-descending branch of the left coronary artery (LAD). There is unequivocal evidence that percutaneous coronary revascularization (PCI) in acute coronary syndromes with ST-segment elevation reduces mortality relative to fibrinolysis, and both relative to those where no reperfusion has been performed.

In other forms of CAD -chronic coronary syndromes (CCS), the role of PCI revascularization is controversial in terms of mortality reduction [132, 133]. A recent meta-analysis of 46 studies in 37,757 individuals examined the PCI benefit of various categories of coronary patients, including true stable angina without a recent heart attack. In stable angina pectoris, the chronic coronary syndrome PCI categories did not reduce overall mortality (RR, 0.98, $p = 0.11$), cardiac death (RR, 0.89, $p = 0.33$), or myocardial infarction (RR, 0.96; $P = 0.54$). PCI prevents death, cardiac death, and AMI primarily in patients with unstable AP. For patients with stable CAD, PCI shows no effects on any of these outcomes. [132-134]. However, it is now becoming evident that OMT is still underused in recent studies [132]. Mohee K. et al show that OMT is still suboptimal in patients before PCI and becomes optimal only after PCI due to increased compliance. [132]. Argument: OMT is the definitive therapy for patients with stable coronary heart disease and low risk of CV events (mortality <1% per year).

COURAGE STUDIES [16,60,133,134]. (Boden WE et al., Published in NEJM 2007) - initial PCI with a stent does not reduce the risk of death, AMI and hospitalization and has no advantage in

stable AP according to OMT on 2287 randomized pts with known significant stable CAD and proven myocardial ischemia who were only on OMT OR OMT + PCI. Between 1999 and 2004, a COURAGE (Clinical Outcomes Utilization Revascularization and Aggressive Drug Evaluation) study randomized 2287 pts with objective evidence of ischemia and proximal angiographic CAD ($\geq 70\%$ visual stenosis) to OMT with or without PCI. The aim and design of the study was to test the strategy of routine, anatomically-indicated PCI, if necessary, for the failure of the initial OMT. Follow-up of 2.5 to 7 years (median 4.6 g) showed that death or AMI occurred with the same frequency in both subgroups (PCI + OMT vs OMT = 1.05, $p = 0.62$). After 4.6 years of follow-up, there was no statistically significant difference between the groups for cumulative mortality and nonfatal myocardial infarction -18.5% vs 19%, as well as for stroke and hospitalization due to new unstable AP. Important: COURAGE study patients had marked symptoms at enrollment and had significant comorbidities, a high prevalence of objectively established ischemia, and extensive angiographic coronary heart disease, and were in the population where clinical benefit from PCI was expected.

Subgroup analysis reveals consistency among clinically relevant subgroups. There is no difference only OMT versus OMT + PCI in terms of multidisciplinary disease, low EF, class III-IV angina and the presence of Diabetes Mellitus. By comparison, there was no difference in hospitalization for ACS either. The main result of the study showed that PCI as an initial strategy in patients with stable AP CCS does not reduce death, AMI and other major events (MACE) when OMT is added. Patients with PCI had less angina in the first and 3rd year, but not in the 5th year of follow-up. As initially expected, revascularization was more common in OMT in 16.5% of the first year of follow-up alone. The efficacy of OMT in stable AP where the optimal dose of beta-blocker is a central component is similar to the effect of percutaneous coronary intervention (PCI) with a stent (Boden and Courage, 2007). [133,134].

Comparison between PCI and OMT (Braunwald's Heart disease, 2015- Morow D, Boden WE) [135]. n-) in terms of earlier techniques balloon angioplasty vs medical therapy, belongs to history, now in the era of new PCI techniques and new optimal drug therapy. In 16 studies of about 9000 pts, PCI vs OMT, the invasive strategy did not provide a reduction in mortality

or AMI, but only a reduction in AP severity and a better quality of life- QoL.

META-ANALYSIS OF VINDECKER et al. Reports reduction in death and AMI by revascularization versus OMT only in patients with CCS when CABG revascularization or next-generation drug-coated stent (DES) was performed, as opposed to balloon angioplasty, metal BMS stents, and old earlier DES [129].

FAME 2 [130]: Statistically significant risk reduction with PCI + OMT versus OMT alone, discontinued after 7 months, but had significant limitations, was not randomized, and was not a double-blind controlled study. Nevertheless, Xaplanteris P. I et al. Indicate a potentially broader prognostic impact of the revascularization strategy when targeted with a functional invasive assessment of coronary stenosis via FFR or iwFR. A five-year follow-up of the FAME 2 study confirmed clinical benefit in a subset of patients specifically treated with PCI targeting only ischemia-producing stenoses (i.e., FFR <0.80) plus OMT, which yielded significantly lower rates of emergency revascularization and lower rates of spontaneous AMI [130] but without a clear effect on mortality.

ORBITA A new ORBITA study (a randomized, controlled, double-blind study) comparing OMT or angioplasty with an anatomically significant coronary stenosis (PCI) stent in stable angina, with a false invasive procedure (sham) in the control group, found no advantage of PCI in significantly improving functional capacity. [125]. The study highlights a significant placebo component on clinical effects and warns us of the pitfalls of interpreting end-points that are subject to bias in the absence of false control. However, the results of the ORBITA study cannot provide definitive guidance due to the limited size of the study, the short observation time to treatment crossover, and insufficient strength to assess clinical outcomes.

ISCHEMIA The largest international randomized double-blind controlled follow-up study ISCHEMIA [137-139] recruited patients with stable CAD with moderate or severe ischemia on a stress test and aimed to assess whether there were differences in clinical outcomes - mortality and CV morbidity in patients with stable chronic coronary heart disease (SCAD) between the invasive strategy + OMT and OMT alone. Out of a total of 8518 recruited patients, 5179 were randomly selected by randomization and were still randomized by type of treatment: Invasive

PCI with stent plus medical therapy (n = 2588) versus only medical therapy (n = 2591). Coronary CT angiography was performed in most participants and was examined by the baseline laboratory to rule out main stable stenosis $\geq 50\%$. Randomized participants had a mean age of 64 years, with 1168 women (22.6%) and 2122 diabetes (41.0%). Among the 3909 participants randomized after the functional imaging stress test for ischemia, the assessment of the severity of ischemia in 3901 participants was as follows: severe 1748 (44.8%), moderate 1600 (41.0%) and mild 317 (8.1%); 79.0% had multivessel CAD (n = 2679 of 3390) and anterior descending branch (LAD) proximal stenosis 46.8%. During an average of 3.3 years of follow-up, there was no significant statistical difference between primary outcomes: death from cardiovascular causes, myocardial infarction, or hospitalization for unstable angina, cardiac arrest -13.3% in the invasive strategy versus 15.5% in the medical treatment group. (p = 0.34). The key secondary outcome was death from cardiovascular causes or myocardial infarction: 11.7% in the routine invasive group versus 13.9% of the OMT group (p = 0.21). Total mortality (cardiovascular and all other causes): 6.4% in the routine invasive group versus 6.5% in the OMT group (p = 0.67). Periprocedural AMI: 2.98%. The invasive versus conservative relationship to mortality was similar regardless of the degree of ischemia (p value for interaction = 0.23), which is also true for AMI. (p value for interaction = 0.15). Among patients with stable CAD and moderate to severe ischemia on a noninvasive visualization stress test, routine invasive treatment showed a reduction in major adverse outcomes compared with OMT. There is no benefit from invasive PCI therapy in terms of a complex end result: Overall, CV mortality, and nonfatal myocardial infarction.

The ACC / AHA American Guide to Chronic CAD [140] discourages the use of PCI or CABG for single-vessel or double-vessel CAD without significant proximal LAD involvement in the absence of unacceptable AP after adequate guidance-guided OMT, especially if noninvasive tests show a small area of exacerbated viable ischemia or reduced EF.

CLINICAL SCENARIO 2.

Patients with new-onset heart failure or left ventricular dysfunction and suspected coronary artery disease

CAD is the most common cause of chronic heart failure (HSI) in Europe. Most studies provide evidence to support recommendations for the

study of pts with ischemic cardiomyopathy (CMP) - the pathophysiological basis of ischemic CMP is systolic dysfunction EF <40%, although patients with CCS may also have HSI with preserved EF. Patients with symptomatic HF should be diagnosed according to the 2016 ESC HF Guide [141]. In addition to standard medical history, physical examination, ECG and chest radiography, Doppler echocardiography should be included in the image to evaluate the evidence of diagnosis of ischemic cardiomyopathy with HF with: a) reduced EF; b) mid-range EF; C) preserved EF with focal or diffuse echocardiographic signs of left and / or right ventricular systolic dysfunction, evidence of diastolic dysfunction, compensatory hypertrophy, valve function (ischemic mitral regurgitation) and evidence of secondary pulmonary hypertension [1]. In addition to routine hematological and biochemical analyzes, it is especially important to assess renal function, potassium, and sodium initially and during pharmacotherapy titration.

Measurement of serum natriuretic peptide levels serves to rule out HF if NT-proBNP levels are normal. The degree of increase in GNP titer is used to estimate the severity of HF [142]. The basic treatment in the NYHA II-III class is antianginal or antischemic therapy with drugs that affect the prognosis and prevention of events. BBs are also an essential component in the relief of anginal attacks and event prevention as well as mortality reduction in HF (Class I level A) [142-149]. Amlodipine may be included as an anti-ischemic drug, in those who do not tolerate BB I the only calcium antagonist is considered safe in HIS (Class IIb level B recommendation) [150-151]. Short-acting nitrates by sublingual or transcutaneous patches are also recommended. Patients with symptomatic HF should be treated according to the 2016 ESC Guide to HF [141], with an emphasis on adding to the standard therapy the newer drug angiotensin receptor-neprilysin inhibitor (sacubitril-valsartan) [141]. Doses of drugs: diuretics [152], ACEI, BB, spironolactone or eplerenone possibly and ivabradine should be gradually increased to avoid hypotension, bradycardia, azotemia hyperkalemia. ACEIs are crucial (CLASS I, LE 54 A) in asymptomatic left ventricular dysfunction after myocardial infarction and in symptomatic HF for symptom relief and reduction of morbidity and mortality [153].

Implantable cardioverter-defibrillator (ICD) and cardiac resynchronization therapy (CRT) [154] can provide improvement in symptoms and

improve survival [154]. Myocardial revascularization should be considered in suitable patients with ischemic HF based on symptoms, coronary anatomy, and evidence of current ischemia and myocardial viability by imaging tests in akinesia-cicatricial zones, through a multidisciplinary team. Myocardial revascularization is recommended when anginal discomfort and / or dyspnoea persist despite optimal antianginal therapy (CLASS I, level of evidence A).

THE GROUP OF PATIENTS WITH LONG-TERM Dg CHRONIC CORONARY SYNDROMES INCLUDE:

CLINICAL SCENARIO 3. ASYMPTOMATIC AND SYMPTOMATIC PATIENTS WITH STABILIZED SYMPTOMS UP TO 1 YEAR LAST AFTER ACS OR CORONARY REVASCULARIZATION.

CLINICAL SCENARIO 4: THE SAME ONLY AFTER A YEAR)

Common to both groups, clinical scenarios 3 and 4 are lifelong treatment and follow-up [1]. The clinical course may be favorable for a longer period. However, patients with CCS may develop various CV complications: episode de novo ACS, complications due to therapeutic procedures due to CAD or due to interactions with comorbidities. The risk of complications also exists in asymptomatic patients, so the risk assessment must be applied to both symptomatic and asymptomatic patients. Therefore, a risk based on biomarkers in 2017 was developed and validated [155].

CLINICAL SCENARIO 3 ASYMPTOMATIC AND SYMPTOMATIC PATIENTS WITHIN 1 YEAR OF ACS OR REVASCULARIZATION

After revascularization or stabilization of ACS within one year, the patient must be closely monitored due to the increased risk of complications and the need to adjust pharmacological treatment [35]. It is recommended to have at least two visits to the doctor in the first year of follow-up, while those with systolic LC dysfunction before revascularization or after ACS should report for cardiac examination 8-12 weeks after ACS or revascularization. Cardiac function can be improved by recovering from stunning or hibernating myocardium by revascularization based on the results of the ADVISE II study by invasively assessing whether epicardial coronary stenosis is the cause of ischemia by iwFR [52,53]. However, exacerbations can occur

due to concomitant CV disorders (valvular diseases, infections, arrhythmias, etc.) and these disorders need to be identified and treated. Non-invasive post-revascularization assessment may be considered to rule out residual ischemia or to document a reference ischemia finding to plan treatment intensification and further periodic follow-up [1].

CLINICAL SCENARIO 4.

ASYMPTOMATIC AND SYMPTOMATIC PATIENTS MORE THAN 1 YEAR LAST OF ACS OR REVASCULARIZATION.

Once a year, the patient needs to be evaluated by a cardiologist, even when the patient is without problems. The recommendation is an annual clinical examination and assessment of adherence to pharmacotherapy and non-pharmacological measures with the determination of risk profiles through risk scores. Laboratory analyzes: lipid profile, renal function, blood count and cardiac biomarkers should be performed every two years [1, 45]. An elevated marker of hsCRP inflammation is associated with an increased risk of adverse events. Von Willebrandt factor, interleukin-6 and NTpro BNP are predictors of outcome [25]. Other biomarkers for pts with CCS also have prognostic significance: heart rate, hemoglobin, leukocyte count [156]. Multiple biomarker scores showed prognostic significance: combining: hsCRP, fibrin degrading products, and heat shock protein 70; [157]. For patients with an exacerbated risk score during follow-up, it is warranted to intensify therapy and diagnostic re-evaluation, although risk-guided therapy has not yet been shown to improve prognosis. A 12-channel ECG should be part of each follow-up to record heart rate and rhythm and to detect changes suggestive of symptomatic myocardial ischemia / infarction and to evaluate PR, QRS, and QT intervals. It would be useful to echocardiographically assess systolic and diastolic LV function, valve status, heart size, and volume in apparently (seemingly) asymptomatic patients at 3 to 5 years of age. [1,52,53]. In case of unexplained reduction of left ventricular systolic function, especially regional, it would be useful to do an image of coronary anatomy. Asymptomatic, silent ischemia should also be sought in seemingly asymptomatic patients through periodic stress imaging tests [1, 52].

CLINICAL SCENARIO 5.

PATIENTS WITH ANGINA PECTORIS AND SUSPECT VASOPASTIC OR MICROVASCULAR DISEASE.

Angina without obstructive disease in the epicardial coronary arteries (INOCA). In clinical practice, there is a discrepancy between the findings concerning coronary anatomy, the presence of symptoms and the results of non-invasive tests often occur [13]. These patients deserve attention because APs with nonobstructive CAD are associated with an increased risk of adverse clinical events [14,15]. The low diagnostic contribution of ICA can be explained by the presence of: (1) mild stenosis or diffuse coronary narrowing, with underestimated functional significance; (2) microcirculation disorders; (3) dynamic epicardial vessel stenosis caused by coronary spasm or intramyocardial bridges that are not apparent during CTA or ICA. Intracoronary pressure measurements are useful in resolving the first case. At diagnostic processing, patients with angina and / or myocardial ischemia who have coronary stenoses with nonischemic FFR or ivFR values may also be referred to as non-obstructive diseases of the epicardial coronary arteries. The presence of clearly defined anginal symptoms and pathological findings of non-invasive tests in patients with normal coronary epicardial arteries should lead to suspicion of a non-obstructive cause of ischemia. Often and mainly as a result of persistence of symptoms, patients with angina and without obstructive CAD undergo multiple diagnostic tests, including repeated coronary CTA or ICA, which contribute to increased health care costs [158]. It is important to emphasize that in everyday practice, there is often a significant discrepancy between the findings of coronary anatomy, the presence of symptoms, and the results of noninvasive tests. Diagnostic pathways investigating microcirculatory or vasomotor coronary disorders are often not performed, so a definitive, evidence-based diagnosis is rarely made. Due to that, patient anxiety and depression are not uncommon in this clinical population. [159]. A 2018 randomized controlled trial of CorMicA found in patients with nonobstructive coronary heart disease, through customized treatment guided by the results of an intracoronary trial: coronary flow reserve (CFR), microcirculatory resistance, and acetylcholine test resulted in a significant reduction in anginal symptoms compared with treatment [160].

Microvascular angina

Patients with microvascular angina typically have chest pain on exertion, a positive ischemia test, either exercise ECG test or noninvasive

imaging tests, without obstructive CAD or with mild to moderate stenosis (40-60%) of the epicardial coronary arteries, which is detected by IC CTA and these stenoses are considered functionally insignificant. The microvascular origin of angina is usually suspected after the exclusion of obstructive coronary epicardial stenosis, during the diagnostic processing of patients with proven myocardial ischemia on the exercise ECG test. Regional abnormalities of wall movement rarely develop during exercise or stress in patients with microvascular angina. Some patients may have a mixed form of microvascular + vasospastic angina, with occasional episodes at rest, especially associated with exposure to cold. Secondary microvascular angina, without obstructive CAD, may be due to cardiac or systemic conditions, including those that cause LV hypertrophy (such as hypertrophic cardiomyopathy, aortic stenosis, and hypertensive heart disease) [161] or inflammation (such as myocarditis or vasculitis). [162]. Risk stratification in microvascular AP is quite complex. The presence of microcirculatory dysfunction in patients with CCS entails a worse prognosis than originally thought, based on the latest evidence based on monitoring patients with objective microcirculation disorders proven by invasive or noninvasive techniques. [163-167]. Microcirculation dysfunction precedes the development of epicardial coronary lesions, especially in women, and is associated with impairment and adverse outcome events. Among diabetic patients undergoing diagnostic processing, those without obstructive epicardial disease but with abnormal coronary flow reserve (CFR) have a similarly poor long-term prognosis as those with obstructive epicardial disease [165]. In patients with significant CAD with significant stenosis at FFR ≤ 0.80 , the presence of abnormal CFR < 2.0 is associated with additional exacerbation and a significant number of adverse events especially when the microcirculatory resistance index (IMR) is also abnormal [166].

The possibility of microcirculatory origin of angina should be considered in patients with clear angina, abnormal non-invasive functional tests, and coronary arteries that are either normal or with mild stenosis, which are considered functionally insignificant on ICA or CTA. One of the challenges in performing a comprehensive assessment of microvascular function is to test the two main mechanisms of dysfunction separately:

1. Weakened microcirculatory conductivity (or increased microcirculatory resistance) and

2. Arteriolar dysregulation. [168-170].

However, it should be clarified which of these two pathways is critical to the choice of pharmacological treatment to minimize the symptoms of these patients. [160]. Weakened or disturbed microcirculatory conduction can be diagnosed by measuring coronary flow reserve (CFR) or minimal microcirculatory resistance. CFR can be measured by noninvasive transthoracic color and pulsed Doppler echocardiography [visualization and measurement of basal flow rate and with vasodilatation test with adenosine or dipyridamole] [171] as well as magnetic resonance imaging (myocardial perfusion index is less available or PET). Microcirculatory resistance can be measured in a catheterization laboratory by combining intracoronary pressure with thermodilution-based data (to calculate IMR) or Doppler flow rates (to calculate hyperemic microvascular resistance or HMR) [172,173]. The decision on abnormal microcirculation is made when the value of the microcirculatory resistance index is greater than 25 units (IMR > 25 J) or CFR < 2.0 . In contrast, the diagnosis of arteriolar dysregulation requires assessment of endothelial function in coronary microcirculation by selective intracoronary infusion of acetylcholine. Acetylcholine is an endothelium-dependent vasodilator that acts directly on arteriole smooth muscle cells and causes paradoxical arteriolar vasoconstriction — microvascular spasm of dysfunctional vascular endothelium or abnormal smooth muscle cell function [174]. This arteriolar response to acetylcholine causes anginal symptoms with or without concomitant ischemic ECG changes and a decrease in coronary blood flow velocities if simultaneous Doppler measurements are performed. Peripheral pulse tonometry during reactive hyperemia may also reveal abnormal systemic endothelial function in patients with AP and non-obstructive CAD [175].

Vasospastic angina

Vasospastic angina should be suspected in patients with AP when the symptoms occur mainly at rest, with maintained tolerance to exertion. The likelihood of vasospastic angina increases when the attacks follow a circadian pattern, with multiple episodes at night and in the early morning hours. Patients are often younger and have fewer CV risk factors than patients who have AP on exertion, except that

they are most often cigarette smokers [176]. Coronary vasospasm is also suspected in patients with transient coronary stents and persistent AP. [177-178]. The diagnosis of vasospastic AP is based on the detection of transient ischemic changes in depression or elevation of the ST segment during an angina attack (usually at rest rest AP). Patients with Prinzmetal's AP represent a special subgroup where resting AP is accompanied by transient ST-segment elevation [176-179]. This ST elevation on the ECG correlates with proximal occlusion by vasospasm. As most vasospastic AP attacks are self-limiting, it is difficult to register without multi-day ambulatory Holter monitoring by 12-channel recording. The appearance of ST-segment changes at normal pulse supports the probability of myocardial ischemia caused by spasm. In patients with suspected vasospastic AP and documented ECG changes, coronary CTA or ICA is important to rule out the presence of fixed coronary stenosis. Angiographic documentation of coronary spasm requires the use of a provocation test in a catheterization laboratory. Due to the low sensitivity of the hyperventilation test and the cold water test, intracoronary administration of acetylcholine or ergonovine during ICA are preferred provocative tests. [176-179]. 176. Both pharmacological agents are safe, provided that they are selectively inserted into the left or right coronary arteries and that activated spasm is easily controlled by intracoronary nitrates. A small percentage of patients may develop ventricular tachycardia / ventricular fibrillation or bradyarrhythmia during a provocative test (3.2 and 2.7%, respectively), similar to that during spontaneous spasm attacks (7%) [180]. Intravenous administration of ergonovine for non-invasive tests is contraindicated due to the risk of causing long-term spasm in multiple coronary arteries, which can be very difficult to stop and can be fatal.

A provocative test for coronary spasm is considered positive when it causes: (1) anginal symptoms, (2) ischemic ECG changes, and (3) severe vasoconstriction of the epicardial coronary artery. If the test fails to run all three components, this should be considered ambiguous [176]. The development of AP in response to acetylcholine injections in the absence of angiographically evident spasm, with or without concomitant ECG changes in the ST segment, may indicate microvascular spasm and is often seen in patients with microvascular AP [179]. In patients with epicardial or

microcirculatory vasomotor disorders, CCB and long-acting nitrates (LANs) are the treatment of choice, in addition to controlling CV risk factors and lifestyle changes. Nifedipine has been shown to be effective in reducing coronary spasm associated with stent implantation. In all patients with vasospastic angina, optimal control of risk factors should be achieved, especially smoking cessation and aspirin use. Exclude drugs that may be narrow vasospasm - cocaine or amphetamine abuse. Chronic preventive treatment of vasospastic angina is mainly based on higher doses of calcium antagonists. Average doses of these drugs verapamil or diltiazem from 240 to 360 mg / day or nifedipine from 40 to 60 mg usually prevent spasm in about 90% of patients. Sometimes high doses of calcium antagonists must be given to prevent spasms: up to 960 mg a day of Verapamil or Diltiazem or up to 100 mg / day of Nifedipine. Long-acting nitrates should be added to some patients. Beta-blockers should be avoided, as they may increase spasm because by blocking the beta-dilating effects, vasoconstriction by unblocked alpha receptors predominates. About 10% of patients are refractory to this treatment, so the addition of guanethidine or clonidine may rarely be indicated. Stent implantation at the site of spasm and without stenosis, as well as surgical or chemical sympathectomy, are extreme measures.

CLINICAL SCENARIO 6. ASYMPTOMATIC PERSONS IN WHICH CAD WAS DETECTED AT SCREENING.

In an effort to reduce the high incidence of coronary sudden death in asymptomatic adults, numerous studies of risk factors and risk indicators, as well as stress tests, are often performed as screening tests. The European guidelines for CVD prevention in 2016 in clinical practice focused in detail on these issues. [15]. In general, the use of a risk assessment system such as ESC SCORE is recommended. People with a family history of premature CAD should be screened for familial hypercholesterolemia. Coronary calcium score, ABI index, and Color Doppler echosonography of the carotid arteries in plaque detection may provide useful information on atherosclerotic risk in selected patients. Routine use of biomarkers or imaging tests for CAD is not recommended. New biomarkers have an increasing predictive value compared to classical ones, but the net improvement in reclassification risk is still only modest (7.18%) compared, for example, with the coronary calcium score, which has a net

improvement in reclassification of 66%. Only persons at high risk of events should be considered for further non-invasive or invasive examination. There are no data on how to treat asymptomatic subjects with a positive CAD test outside the recommendations outlined in these guidelines. However, the principles of risk stratification, as described above for symptomatic patients, also apply to these individuals. It is important to know that there is no data that showed an improved prognosis after appropriate care based on new biomarkers. It is important to note that cancer patients and those undergoing treatment for cancer, chronic inflammatory and systemic autoimmune diseases deserve a more intensive risk evaluation. People whose occupations include public safety (eg pilots or truck or bus drivers, workers) or professional athletes are usually periodically tested to assess the ECG with a TFO test and assess possible heart disease, including CAD, although there is insufficient data to justify this. However, these evaluations can be performed for medical-legal reasons. The threshold for performing a visualization stress test for CAD in such persons is lower than in the average patient.

REFRACTORY ANGINA PEKTORIS (RAP)

RAP as a form of chronic coronary syndrome (CCS) is defined as a chronic condition caused by clinically established reversible ischemia in the presence of CAD, which cannot be adequately controlled by a combination of medical therapy, angioplasty with stenting (PCI) or surgical coronary revascularization (CABG) [1]: The following treatment options are considered:

- 1- Forced external counterpulsation (EECP) should be considered to alleviate and minimize discomfort in patients with AP Refractory to optimal pharmacological therapy and revascularization strategy
- 2-Transcutaneous electrical nerve stimulation (TENS) can be used to alleviate the symptoms of refractory AP on optimal pharmacotherapy and revascularization strategy
- 3-Spinal cord stimulation (SCS) can be used to alleviate the symptoms of refractory angina to optimal pharmacol Th and revasculariza strategy
- 4-Transmyocardial revascularization (TMR) is not indicated in patients with symptoms of refractory angina on optimal pharmacological Th and revascularization strategy

FUTURE PERSPECTIVES OF CHRONIC CORONARY SYNDROMES CCS - Quote from Brownwald's textbook of cardiology, authors

David Morrow, J. J. A. De Lemos and William Boden [135]:

Our understanding of CHRONIC CORONARY SYNDROMES (CCS), both as a cause, optimal approach and treatment, is constantly evolving.

1. Complex and probably heterogeneous causes of myocardial ischemia require continuous multidisciplinary research through experimental studies in genetics, molecular biology, biochemistry, morphological and functional aspects of coronary circulation, and pathological morphology and pathophysiology of myocardial ischemia, which should then be confirmed in clinical studies with sufficient statistical power to generate new guidelines for more precise and simpler diagnosis and effective therapy of CCS. Today, we are confronted with the essential data that challenge the paradigm that Ischemic CAD requires critical coronary atherosclerosis of the subepicardial coronary artery or other structural heart disease that results in a dramatic increase in oxygen consumption. Preclinical, translational and clinical epidemiological data demonstrate abnormalities in coronary artery function, which can lead to myocardial ischemia in the absence of atherosclerotic obstruction.

2. However, so far, the treatments proposed for this important syndrome-CHRONIC CORONARY SYNDROME have proved insufficient. Additional insight into the pathobiology of ischemia could lead to new directions in treatment.

3. An initial approach to targeted secondary-preventive therapy and coronary revascularization, when necessary, is the best approach for most patients with CCS. There are subgroups of patients with high-risk indicators for whom coronary myocardial revascularization should be logical. However, clinical controversy and doubt remains as to whether such patients, including those with moderate or severe ischemia on a noninvasive test, should be routinely subjected to coronary myocardial revascularization in the absence of symptoms of refractory to optimal preventive and pharmacological therapy (OMT).

- 4.. Definitive evidence for the care of patients with stable CCS and other consequences of ischemia, especially left ventricular dysfunction and mitral ischemic regurgitation, remains incomplete. In our opinion, complete myocardial revascularization, usually surgical -CABG, remains a reasonable option for patients with multivessel CAD, LC dysfunction, and viable myocardium, especially when there is objective evidence of ischemia. However, some recent studies call this view into question. Despite our

good experience with CCS, there are no answers to important questions [135].

FUTURE PERSPECTIVES OF CHRONIC CORONARY SYNDROME CCS - quote from Braunwald's textbook of cardiology, authors David Morrow and William Boden [181]: Our understanding of CCS, as a cause, optimal approach and treatment, is constantly evolving.

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myocardium, especially when there is objective evidence of ischemia. However, some recent studies call this view into question. Despite our good experience with CCS, there are no answers to important questions [181].

CONCLUSION:

Careful and studious evaluation of the anamnesis, including characterization of anginal symptoms and assessment of risk factors and manifestations of cardiovascular diseases, as well as appropriate physical examination and basic supplementary, basic examination is essential for the diagnosis of chronic coronary syndromes. If obstructive coronary artery disease (mean pre-test probability) cannot be ruled out by clinical evaluation alone, noninvasive diagnostic functional imaging tests with physical or pharmacological loading or anatomical imaging should be used as the initial test to exclude or diagnose chronic coronary syndromes (clinical scenario 1). via coronary CT angiography. The selection of the initial non-invasive diagnostic test is based on the probability test for obstructive coronary heart disease (PTP), its clinical probability, characteristics and test availability. An anatomical and functional evaluation should be performed to decide on revascularization. Either non-invasive or invasive functional evaluation is required to assess the size of myocardial ischemia associated with angiographic coronary artery stenosis, except for very high-grade stenosis (> 90% of diameter stenosis). The risk assessment for adverse events and mortality serves to determine for which patients with CCS the prognostic benefit of revascularization is predicted.

Assessment of left ventricular function by echocardiography is a mandatory part of risk stratification. Patients at high risk of adverse events undergo invasive examination to consider revascularization, even when asymptomatic. The application of a healthy lifestyle reduces the risk of subsequent CV events and mortality and is always included in the program of appropriate measures and therapy of secondary prevention. Clinicians should advise and encourage the necessary lifestyle changes at each clinical encounter with patients. Cognitive-behavioral psychological interventions such as supporting patients to set realistic goals, self-control, planning to implement change, coping with difficult situations, adapting to the environment, and

including social support are effective behavioral change interventions.

Multidisciplinary teams can support patients to change to a healthy lifestyle and guide them to avoid risk and risky behavior. Anti-ischemic treatment must be tailored to the individual patient based on comorbidity, concomitant therapy, expected tolerance and adherence to therapy, but also the patient's preference. The choice of anti-ischemic drugs for the treatment of CCS should be adjusted to heart rate, blood pressure and left ventricular function. Beta-blockers and / or calcium antagonists remain first-line drugs in patients with CCS. Antithrombotic therapy is a key part of secondary prevention in patients with CCS and requires careful consideration. Long-term (and after 12 months) dual antiplatelet therapy (DAPT) with aspirin or any P2I12 inhibitor should be considered in patients with previous myocardial infarction, with or without revascularization, who are at high risk of ischemic events and low risk of severe or fatal bleeding. or rivaroxaban with very low doses, unless they have an indication for oral anticoagulant therapy (OAK) such as the presence of atrial fibrillation (AF). Statins are recommended for all patients with CCS, regardless of the level of LDL cholesterol. ACE inhibitors (or ARBs) are recommended in the presence of heart failure (SI), diabetes, or hypertension and should be considered in all high-risk patients. Proton pump inhibitors are recommended in patients receiving aspirin or a combination of antithrombotic therapies that are at high risk for gastrointestinal bleeding. Efforts should be made to explain to patients the importance of taking prescribed medication regularly, based on evidence that regular adherence to treatment prevents adverse events, relieves the patient of pain, and improves quality of life. Repeated therapeutic education of patients is essential for every clinical encounter. Patients with a long-term diagnosis of CCS should visit a doctor periodically to assess possible changes in risk status, adhere to

treatment goals, and develop comorbidities. Repeated physical or pharmacological stress tests, preferably imaging stress tests, or invasive coronary angiography with functional testing in case of worsening symptoms and / or increased risk status are recommended. Assessment of the function and dimensions of the heart cavities, myocardium and valves, as well as a functional test to rule out significant asymptomatic (silent) myocardial ischemia, should be considered every 3–5 years in asymptomatic patients with a long-term diagnosis of CCS. Assessment of coronary vasomotor function should be considered in patients without obstructive coronary disease or with minor epicardial coronary disease who have objective evidence of myocardial ischemia. Objectives of treatment of chronic coronary symptoms (CCS): improving prognosis, ie. reducing mortality by reducing the risk of progression of atherosclerosis and preventing acute coronary events and sudden death; and minimizing symptoms while improving quality of life. Efforts should be made to explain to patients the importance of evidence-based guidelines and guidelines for adherence to treatment.

All patients with stable coronary heart disease need lifestyle changes, risk factor reduction and pharmacological therapy, but all patients with coronary artery stenosis do not benefit from revascularization, which depends on the size of the ischemia and the anatomical involvement of the coronary arteries. Optimal medical therapy is the definitive therapy for patients with stable coronary heart disease and low risk of cardiovascular events. Revascularization and optimal medical therapy should be considered as complementary rather than competitive treatments.

In high-risk CCS patients with mortality > 3% per year or AP refractory to OMT, evidence of physical or pharmacological stress ischemia is required, preferably stress echocardiography to determine the size of ischemia on the stress echo test and anatomical assessment to determine coronary artery disease. to indicate revascularization leading to clinical benefit.

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