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Klinički učinci metoprolola kroz kardiovaskularni kontinuum

Clinical Effects of Metoprolol Across the Cardiovascular Continuum

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SAŽETAK: *Blokatori beta-adrenergičkih receptora ostvaruju povoljne učinke kroz čitav kardiovaskularni kontinuum. U odnosu na neselektivne beta-blokatore, kardioselektivni beta-1 blokatori imaju prednost u bolesnika u kojih želimo izbjeći blokadu beta-2 receptora u bronhima i perifernim krvnim žilama, u bolesnika s bronhoopstruktivnom i/ili perifernom arterijskom bolesti. Selektivnim djelovanjem pokušava se izbjeći i negativan utjecaj na homeostazu glukoze te erektilnu funkciju. Metoprolol je u svijetu dugo i dobro poznat te široko primjenjivan i provjeren kardioselektivni beta-blokator. Brojnim kliničkim istraživanjima jasno je dokazan terapijski učinak metoprolola u arterijskoj hipertenziji, akutnim i kroničnim oblicima koronarne bolesti srca, postinfarktnoj profilaksi, srčanim aritmijama i sindromu kroničnog zatajivanja srca. U svim ispitivanjima metoprolol je imao dobru podnošljivost i sigurnost. Uz ispravno doziranje i vođenje bolesnika, nuspojave su rijetke, blage i reverzibilne. Danas je metoprolol sukcinat i u Hrvatskoj dostupan u obliku s produljenom apsorpcijom i postupnim plazmatskim klirensom, s mogućnošću doziranja jednom na dan koje osigurava stabilnu koncentraciju lijeka u plazmi i djelovanje tijekom 24 sata. Time se postiže sigurniji učinak i bolja suradljivost bolesnika neophodna za uspjeh liječenja.*

KLJUČNE RIJEČI: *kardiovaskularne bolesti, beta-adrenergički blokatori, metoprolol sukcinat.*

SUMMARY: *Beta-adrenergetic receptor antagonists cause positive effects across the whole cardiovascular continuum. Compared to non-selective beta-blockers, cardioselective beta-1 blockers have an advantage in patients in whom we wish to avoid beta-2 receptor blockade in the bronchi and peripheral blood vessels, in patients with bronchoobstructive and/or peripheral arterial disease. A negative impact on blood glucose homeostasis and erectile function is to be avoided by selective application. Metoprolol has been internationally known as widely applied and checked cardioselective beta-blocker for a long time. A series of clinical studies have clearly proved the therapeutic effect of metoprolol in the hypertension, acute and chronic types of coronary heart disease, postinfarction prophylaxis, heart arrhythmia and chronic heart failure syndrome. In all researches, metoprolol has showed good tolerance and safety. If taking proper doses and managing patients properly, the side-effects are rare and reversible. Today, metoprolol succinate is available in Croatia in the form with sustained absorption and gradual plasma clearance with a possibility of a one-day dosage which ensures stable concentration of the drug in the plasma and effects during a period of 24 hours. This is how a safer effect and better cooperation of a patient required for the success of the treatment is achieved.*

KEYWORDS: *cardiovascular diseases, beta-blockers, metoprolol succinate.*

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Blokatori beta-adrenergičkih receptora (beta-blokatori) su skupina kardiovaskularnih lijekova s povoljnim terapijskim učincima kroz cijeli kardiovaskularni kontinuum: u arterijskoj hipertenziji (AH), akutnim i kroničnim oblicima koronarne bolesti srca (KBS), postinfarktnoj profilaksi (prevenciji reinfarkta i iznenadne srčane smrti), srčanim aritmijama i sindromu kroničnog zatajivanja srca (KZS)[1-4]. U odnosu na neselektivne beta-blokatore, kardioselektivni beta-1 blokatori imaju prednost u bolesnika u kojih želimo izbjeći blokadu beta-2 receptora u bronhima i perifernim krvnim žilama, u bolesnika s bronhoopstruktivnom i/ili perifernom arterijskom bolesti. Selektivnim djelovanjem pokušava se izbjeći i negativan utjecaj na homeostazu glukoze te erektilnu funkciju. Od beta-1 kardioselektivnih beta-blokatora u Hrvatskoj su prisutni atenolol, bisoprolol, nebivolol i metoprolol.

Metoprolol je u svijetu dugo i dobro poznat te široko primjenjivan i provjeren kardioselektivni beta-blokator. Ranije je niz godina u Hrvatskoj bio prisutan u konvencionalnom, brzo oslobađajućem obliku te se morao uzimati u dvije do tri pojedinačne doze. Danas je dostupan u obliku s produljenim oslobađanjem, s mogućnošću propisivanja

Beta-adrenergic receptor antagonists (beta-blockers) are the group of cardiovascular drugs with favorable therapeutic effects across the whole cardiovascular continuum: in hypertension, acute and chronic types of coronary heart disease (CHD), postinfarction prophylaxis (prevention of re-infarction and sudden cardiac death), heart arrhythmia and chronic heart failure syndrome (CHF)[1-4]. Compared to non-selective beta-blockers, cardioselective beta-1 blockers have an advantage in patients in whom we wish to avoid beta-2 receptor blockade in the bronchi and peripheral blood vessels, in patients with bronchoobstructive and/or peripheral arterial disease. A negative impact on blood glucose homeostasis and erectile function is to be avoided by selective application. Out of beta-1 cardio-selective beta blockers, atenolol, bisoprolol, nebivolol and metoprolol are present in Croatia.

Metoprolol has been internationally known as widely used and studied cardioselective beta-blocker for many years. Some time ago, it was in Croatia long present as a conventional, quick-release form and had to be taken in two to three individual doses. Today it is accessible in the sustained-release form with a possibility of prescribing it

jedanput na dan. Ovakav oblik metoprolol sukcinata osigurava stabilnu koncentraciju lijeka u plazmi i trajanje učinka tijekom 24 sata, što omogućava bolju suradljivost bolesnika, neophodnu za uspjeh liječenja. Brojna klinička istraživanja jasno su dokazala povoljno terapijsko djelovanje metoprolola kroz čitav kardiovaskularni kontinuum.

Metoprolol u arterijskoj hipertenziji

Učinkovitost metoprolola analizirana je u nizu kliničkih ispitivanja u bolesnika s blagom do umjerenom AH[5]. Neka od tih istraživanja bila su placebom kontrolirana[6], u drugima je uspoređivan učinak pripravka metoprolola s produljenim oslobađanjem u odnosu na standardni pripravak[7-9], a u nekima je uspoređivan antihipertenzivni učinak metoprolola u odnosu na druge beta-blokatore, najčešće atenolol[10-14]. Duljina ispitivanja kretala se od 4 do 12 tjedana, a doze su obično bile fiksne, iako su neki protokoli dozvoljavali prilagodbu u slučaju nedovoljnog kliničkog odgovora, do maksimalne dnevne doze od 200 mg[8,9,12.] Sva su ispitivanja jasno pokazala da metoprolol izaziva značajno sniženje povišenog arterijskog tlaka (AT)[5]. Postotak bolesnika sa željenim antihipertenzivnim učinkom (dijastoličkim AT <90 mmHg) u studijama kretao se od 51% do 89%[8,9,10-13,16]. Antihipertenzivni učinak metoprolola u obliku s produljenim djelovanjem bio je značajno bolji u odnosu na ekvivalentne doze standardnog pripravka[8] i atenolola[12].

Učinci metoprolola u koronarnoj bolesti srca

Na osnovu velikog kliničkog iskustva i brojnih randomiziranih kliničkih istraživanja, Europsko kardiološko društvo (ESC) danas preporuča beta-blokatore kao prvi lijek izbora u gotovo svim kliničkim oblicima KBS[15-18]. Kao jedan od najšire ispitivanih i praktično primjenjivanih kardioselektivnih beta-blokatora, metoprolol je dokazano učinkovit u stabilnoj i nestabilnoj angini pektoris, nijemoj ishemiji, ishemijom uzrokovanim srčanim aritmijama, akutnom infarktu miokarda, postinfarktnoj profilaksi reinfarkta i iznenadne srčane smrti te kroničnom zatajivanju srca uslijed ishemijske kardiomiopatije[15-18].

Učinci sporo oslobađajućeg oblika metoprolol sukcinata istraživani su u bolesnika sa stabilnom anginom pektoris u dvjema randomiziranim studijama, usporedbom sa standardnim brzodjelujućim oblikom[19] te s postupno oslobađajućim oblikom metoprolol tartarata[20]. Ovisno o prethodnoj dozi beta-blokatora, bolesnici su primali dnevnu dozu od 100 mg ili 200 mg postupno djelujućeg metoprolol sukcinata. Bolesnici liječeni ovim oblikom u dozi od 200 mg na dan imali su najbolju toleranciju napora, određivanu nastupom anginozne boli i promjena ST-segmenta. Postignut je odličan antianginozni učinak tijekom 24 sata, što omogućava bolju kvalitetu života koronarnih bolesnika.

Smjernice ESC za liječenje akutnog koronarnog sindroma ističu važnost primjene beta-blokatora, među njima i metoprolola[15-18]. Smanjenjem AT i frekvencije srca metoprolol smanjuje potrošnju kisika u akutno ishemičnom miokardu i deficit kisika u ugroženom području. Pravodobno primjenjen, metoprolol smanjuje učestalost ishemi-

once a day. Such type of metoprolol succinate ensures a stable concentration of a drug in the plasma and the duration of effects during 24 hours which ensures better cooperation with patients required for the success of treatment. A number of clinical studies clearly showed favorable therapeutic effects of metoprolol across the entire cardiovascular continuum.

Metoprolol in hypertension

The efficacy of metoprolol has been analyzed in a series of clinical studies in patients with a mild to moderate hypertension[5]. Some of the researches were placebo controlled[6], some other studies compared the effect of sustained-release metoprolol preparations to the standard preparation[7-9], while some antihypertensive effect of metoprolol compared to some other beta-blockers, most frequently atenolol[10-14]. The length of studies ranged from 4 to 12 weeks, while the doses were usually fixed, although some protocols allowed adjustment in case of insufficient clinical response, up to maximum daily dose of 200 mg[8,9,12]. All those researches clearly showed that metoprolol causes significant lowering of increased blood pressure (BP)[5]. The rate of patients with desired antihypertensive effect (diastolic BP <90 mmHg) in the studies ranged from 51% to 89%[8,9,10-13,16]. Antihypertensive effect of metoprolol in the form with sustained effect was much better compared to equivalent doses of standard preparations[8] and atenolol[12].

Effects of metoprolol in coronary heart disease

Based on an extensive clinical experience and a number of randomized clinical researches, the European Society of Cardiology (ESC) today recommend beta-blockers as the first choice drug in almost all types of CHD[15-18]. As one of most extensively researched and practically applied cardio-selective beta-blockers, metoprolol has been proven as efficient in stable and unstable angina pectoris, silent ischemia, ischemia caused by heart arrhythmia, acute myocardial infarction, postinfarction prophylaxis of re-infarction and sudden cardiac death as well as chronic heart failure as a consequence of ishaemic cardiomyopathy[15-18].

The effects of slow-release metoprolol succinate have been investigated in patients with stable angina pectoris in the two randomized studies, by comparing it with fast acting form[19] and gradually releasing form of metoprolol tartarate[20]. Depending on the previous dose of beta-blockers, the patients received a daily dose of 100 mg or 200 mg gradually acting metoprolol succinate. The patients treated with this type in dose of 200 mg a day had the best effort tolerance determined by occurrence of anginal pain and ST-segment changes. Excellent antianginal effect during 24 hours was achieved which enables a better life quality of coronary patients.

The ESC guidelines for the treatment of acute coronary syndrome emphasize the importance of application of beta-blockers, including metoprolol[15-18]. Due to lowering of BP and heart frequency, metoprolol reduces the consumption of oxygen in acute ischemic myocardium and deficit of oxygen in the affected area. If properly applied, meto-

jom induciranih malignih ventrikulskih aritmija, reducira konačnu veličinu infarkta i poboljšava postinfarktnu funkciju lijeve klijetke. U postinfarktnih bolesnika metoprolol smanjuje rizik reinfarkta i iznenadne srčane smrti[15-18]. Postupno djelujući oblik metoprolol sukcinata zbog jednostavne primjene olakšava obveznu doživotnu profilaksu beta-blokatorom.

Metoprolol u kroničnom zatajivanju srca

Pored povećanja perifernog vaskularnog otpora, hiperadrenergičko stanje u KZS djeluje direktno kardiotoksično, izazivajući apoptozu kardiomiocita. Dokazan je proporcionalan odnos između koncentracije kateholamina u plazmi i smrtnosti bolesnika[21]. U više multicentričnih randomiziranih studija (US Carvedilol Program i COPERNICUS studija s karvedilolom, CIBIS-II studija s bisoprololom i MERIT-HF studija s metoprololom) dokazan je terapijski učinak navedenih beta-blokatora na kvalitetu i duljinu života bolesnika s kroničnim sistoličkim zatajivanjem srca[22-25]. Povoljni učinci beta-blokatora objašnjavaju se njihovim antiishemijskim i antiaritmičkim djelovanjem, smanjenjem hemodinamskog opterećenja srca, blokadom kardiotoksičnih učinaka kateholamina, suzbijanjem apoptoze i progresivne disfunkcije miokarda te ventrikulskog remodeliranja[18,26].

Učinci metoprolol sukcinata u bolesnika s KZS srca istraživani su u tri randomizirane, dvostruko slijepe, placebom kontrolirane studije[24,27-29]. U sva tri istraživanja bili su uključeni stabilni bolesnici s istisnom frakcijom (EF) lijeve klijetke ≤40%[24,27,28]. Prije randomizacije bolesnici su bili stabilizirani diuretikom i ACE inhibitorom te eventualno digitalisom[30].

RESOLVD studija

U RESOLVD studiji randomizacija je vršena u dvije faze: 1) bolesnici (n=768) su randomizirani na kandesartan (4-16 mg/dan), enalapril (20 mg/dan) ili kombinaciju oba lijeka tijekom 17 tjedana, 2) uz liječenje iz prve faze, odgovarajući bolesnici (n=426) su zatim primali metoprolol sukcinat do dnevne doze od 200 mg (n=214) ili placebo (n=212) te bili praćeni tijekom dodatna 24 tjedna[27]. Primarni cilj druge faze studije bila je učinkovitost i sigurnost metoprolol sukcinata dodanog blokatoru angiotenzinskih receptora, ACE inhibitoru ili kombinaciji oba lijeka, analizom 6-minutnog testa hodanja i neurohumoralnih parametara. Iako metoprolol nije pokazao učinak na 6-minutni test hodanja i NYHA funkcionalni stupanj, uočeno je značajno poboljšanje ventrikulske funkcije, u smislu smanjenja volumena lijeve klijetke na kraju sistole i dijastole te povećanja EF[27]. Iako studija nije bila dizajnirana da dokaže utjecaj na smrtnost, u bolesnika liječenih metoprolol sukcinatom uočen je trend smanjenja smrtnosti (3,7% vs. 8,1%)[27].

MERIT-HF Pilot studija

Ova pilot studija analizirala je učinke metoprolola na EF lijeve klijetke u 61 bolesnika sa zatajivanjem srca. Bolesnici su primali metoprolol sukcinat, titriran tijekom osam tjedana do dnevne doze od 150 mg (n=42) ili placeprolol reduces the frequency of ischemia-induced malign ventricular arrhythmia, reduces final size of infarction and improves postinfarction ventricular function. In postinfarction patients, metoprolol reduces a risk of re-infarction and sudden cardiac death[15-18]. Gradually acting form of metoprolol succinate facilitates compulsory lifelong prophylaxis with beta-blocker due to its simple application.

Metoprolol in chronic heart failure

Besides the increased peripheral vascular resistance, hyperadrenergic condition in CHF is active directly cardiotoxically, causing cardiomyocyte apoptosis. The proportionate relation between concentration of catecholamines in plasma and mortality of patients has been proven[21]. In several multicentric randomized studies (US Carvedilol Program and COPERNICUS study with carvedilol, CIBIS-II study with bisoprolol and MERIT-HF study with metoprolol) the therapeutic effect of the above beta-blockers on the quality and length of life of patients with chronic systolic heart failure has been proven[22-25]. Favorable effects of beta-blockers are explained by their anti-ischemic and arrhythmic effect, reduction of hemodynamic heart load, blockade of cardiotoxic effects of catecholamines, combating apoptosis and progressive myocardial dysfunction and ventricular remodelling[18,26].

The effects of metoprolol succinate in patients with CHF were studied in three randomized, double blind, placebo-controlled studies[24,27-29]. Stable patients with left ventricular ejection fraction (EF) of the ≤40%[24,27,28] were included in all three studies. Prior to randomization, the patients were stabilized by diuretic and ACE inhibitor and eventually by digitalis[30].

RESOLVD study

Randomization was performed in two stages in the RESOLVD study: 1) patients (n=768) are randomized on candesartan (4-16 mg/day), enalapril (20 mg/day) or the combination of the two drugs during 17 weeks, 2) besides the first-stage treatment, respective patients then received (n=426) metoprolol succinate up to daily dose of 200 mg (n=214) or placebo (n=212) and were followed-up during 24 weeks[27]. The primary goal of the second stage was the efficacy and safety of metoprolol succinate added to angiotensin receptor blocker, ACE inhibitor or the combination of the two medicines, by analysis of the 6-minute walk test and neurohumoral parameters. Although metoprolol showed no effect on the 6-minute walk test and NYHA functional class, significant improvement of ventricular function was observed in terms of reduction of the volume of the left ventricle at the end of systole and diastole and increase in EF[27]. Although the study was not designed to prove the impact on mortality, in patients treated with metoprolol succinate, the falling trend of mortality (3.7% vs. 8.1%) was perceived[27].

MERIT-HF Pilot study

This pilot study has analyzed the effects of metoprolol on the EF left ventricles in 61 patients with heart failure. The patients received metoprolol succinate, titrated during

bo (n=19), a nakon toga su praćeni kroz šest mjeseci[28]. Bolesnici liječeni metoprololom (srednjom postignutom dozom od 99 mg/dan) nakon 26 tjedana imali su značajno veću EF (36,3% vs. 27,9%, p<0.015) te značajno manje EKG epizoda nepostojane ventrikulske tahikardije i parova ventrikulskih ekstrasistola. Ova pilot studija pokazala je povoljan učinak metoprolola na funkciju lijeve klijetke, uz dobru sigurnost i podnošljivost u bolesnika s KZS[28,30] te podržala planiranje odgovarajućeg većeg istraživanja.

MERIT-HF studija

Radilo se o randomiziranoj, placebom kontroliranoj, dvostruko slijepoj studiji u 3.391 bolesnika sa simptomatskim zatajivanjem srca (NYHA II-IV) i EF ≤40%, prethodno stabilnih na diuretiku i ACE inhibitoru[24]. Inicijalna doza metoprolol sukcinata u NYHA II bolesnika bila je 25 mg/dan, a u NYHA III-IV bolesnika 12,5 mg/dan. Titriranje doze vršeno je tijekom osam tjedana do maksimalne ciljne doze od 200 mg/dan ili maksimalno podnošljive doze. Primarni ishodi studije bili su ukupna smrtnost te smrtnost i hospitalizacije zbog svih uzroka. Iako je planirano vrijeme liječenja bilo tri godine, nakon prosječno jedne godine trajanja studija je prijevremeno prekinuta iz etičkih razloga. Prosječna dnevna doza metoprolola iznosila je 159 mg, a ciljna doza od 200 mg postignuta je u 64% bolesnika. Metoprolol je smanjio ukupnu smrtnost za 34% (7,2% vs. 11%, p=0,00009). Liječenje metoprololom 27 bolesnika tijekom jedne godine spriječilo je jedan smrtni ishod. Značajno su smanjeni i posebni uzroci smrti: kardiovaskularna smrtnost, iznenadna smrt, smrt zbog pogoršanja zatajivanja srca[24]. Metoprolol je također značajno smanjio i kombinirani primarni ishod, ukupnu smrtnost i hospitalizacije zbog svih uzroka (32,2% vs. 38,3%, p<0,001). Kod kombiniranog primarnog ishoda smanjenje rizika u korist metoprolola iznosilo je 19% (p<0,001)[24]. Liječenje metoprololom 16 bolesnika tijekom jedne godine spriječilo je jednu smrt ili jednu hospitalizaciju. Značajno smanjenje rizika u korist metoprolola utvrđeno je i za brojne sekundarne kombinirane ishode (ukupnu smrtnost ili hospitalizacije zbog pogoršanja zatajivanja srca, smrtni ishod ili transplantaciju srca, kardiovaskularnu smrt ili nefatalni akutni infarkt miokarda, ukupnu smrtnost ili hospitalizaciju ili posjetu zbog pogoršanja zatajivanja srca)[20]. Povoljni učinci metoprolola u smanjenju smrtnosti i poboljšanju kvalitete života bili su prisutni u svim podskupinama (u starijih bolesnika, žena, dijabetičara, najtežih — NYHA IV bolesnika, u bolesnika s preboljelim infarktom miokarda i onih s prethodnom AH)[24].

Zaključak

Metoprolol je kardioselektivni beta-1 adrenergički blokator s dokazanim terapijskim učincima kroz čitav kardiovaskularni kontinuum. Široko je propisivan u svijetu, posebno u zemljama Europske unije i SAD. Ranije je u Hrvatskoj postojao konvencionalan, brzodjelujući oblik metoprolola, što je zahtjevalo uzimanje dvije do tri pojedinačne doze te smanjivalo suradljivost bolesnika. Danas je dostupan metoprolol sukcinat u sporo djelujućem obliku, s postupnim klirensom iz plazme, što osigurava ravnomjeran 24-satni učinak jedne dnevne doze. Trenutno se u nas

a period of eight weeks up to daily dose of 150 mg (n=42) or placebo (n=19), and subsequently they were followed up during the period of six months[28]. The patients treated with metoprolol (mean achieved dose 99 mg/day) had after 26 weeks significantly higher EF (36.3% vs. 27.9%, p<0.015) and significantly fewer ECG episodes of non-sustained ventricular tachycardia and ventricular couplets. This pilot study has showed a positive effect of metoprolol on the left ventricular function with good safety and tolerance of patients with CHF[28,30] and supported planning on relevant more extensive research.

MERIT-HF study

It was randomized, placebo controlled, double blind study in 3391 patients with symptomatic heart failure (NYHA II-IV) and EF ≤40%, previously stable on diuretics and ACE inhibitor[24]. The initial dose of metoprolol succinate in NYHA II patients was 25 mg/day, and in NYHA III-IV patients it was 12.5 mg/day. Titrating the dose was performed during a period of eight weeks up to maximum target dose of 200 mg/day or maximal tolerated dose. The primary outcomes of the study were total mortality and mortality and hospitalization due to all causes. Although the planned time of treatment was three years, after averagely one year of the duration of the study, the study was early stopped for ethical reasons. The average daily dose of metoprolol was 159 mg and the target dose of 200 mg was achieved in 64% patients. Metoprolol has reduced total mortality by 34% (7.2% vs. 11%, p=0.00009). The treatment of 27 patients during one year by metoprolol prevented one death. Special causes of deaths were greatly reduced: cardiovascular mortality, sudden death, death due to worsening of the heart failure[24]. Metoprolol has also significantly reduced the combined primary outcome, total mortality and hospitalizations due to all causes (32.2% vs. 38.3%, p<0.001). In case of combined primary outcome, the reduction of the risk in favor of metoprolol was 19% (p<0.001)[24]. The treatment of 16 patients with metoprolol during one year prevented another death or one hospitalization. Significant decrease in risk in favor of metoprolol has been determined for numerous secondary combined outcomes (total mortality or hospitalizations due to worsening of heart failure, deadly outcome or heart transplantation, cardiovascular death or non-fatal acute myocardial infarction, total mortality or hospitalization or visit due to worsening of heart failure)[20]. Positive effects of metoprolol in reducing mortality and improving life quality were present in all sub-groups (elderly patients, women, diabetics and the most serious — NYHA IV patients, in patients with survived myocardial infarction and those with previous hypertension)[24].

Conclusion

Metoprolol is a cardioselective beta-1 adrenergic blocker with proven therapeutic effects across the entire cardiovascular continuum. It is widely prescribed in the world, especially in the countries of the European Union and USA. A conventional, fast-acting form of metoprolol was applied earlier in Croatia, which required taking two to three individual doses thus reducing cooperation with

najviše propisuje u bolesnika s KBS, u postinfarktnoj profilaksi te u prevenciji i terapiji srčanih aritmija.

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patients. Today, metoprolol succinate in slow-acting form with gradual clearance from the plasma is available ensuring equal 24-hour effect of one daily dose. Currently, it is most prescribed in patients with CHD, in post-infarction prophylaxis and in prevention and therapy of heart arrhythmia in Croatia.

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