Article/Review

Polipill yurak qon-tomir kasalliklarini oldini olishda: samaradorlik va istiqbollari

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Xulosa:
Yurak-qon tomir kasalliklari (YuQTK) dunyo bo'ylab kasallanish va o'limning yetakchi sabablaridan biri hisoblanadi. Profilaktikaning samaradorligini oshirish maqsadida bir nechta dorivor moddalarni o'z ichiga olgan polipill konsepsiyasi ilgari surilgan. Ushbu maqolada polipillning birlamchi va ikkilamchi profilaktikadagi o'rni, uning afzalliklari va kamchiliklari tahlil qilinadi. Polipill birlamchi profilaktikada arterial gipertenziya, dislipidemiya va tromboz rivojlanishini oldini olish orqali YuQTK xavfini kamaytirishi mumkin. Ikkilamchi profilaktikada esa yurak xuruji va insult kabi holatlarning qayta yuzaga kelish ehtimolini pasaytirishga yordam beradi. Shuningdek, polipill dori qabul qilish tartibini yaxshilash va umumiy iqtisodiy xarajatlarni kamaytirish imkonini beradi.

Kalit so'zlar: polipill, arterial gipertoniya, dislipidemiya, past zichlikdagi lipoproteid xolesterin, ateroskleroz, yurak qon-tomir kasalliklari, profilaktika, davo chorasiga moyillik, insult, samaradorlik.

Polypill in Cardiovascular Disease Prevention: Efficacy and Perspectives

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Abstract:
Cardiovascular diseases (CVDs) are among the leading causes of morbidity and mortality worldwide. To enhance the effectiveness of prevention, the concept of a polypill containing multiple active pharmaceutical components has been introduced. This review explores the role of the polypill in primary and secondary prevention, along with its advantages and limitations. In primary prevention, the polypill may help reduce the risk of developing hypertension, dyslipidemia, and thrombosis. In secondary prevention, it aids in lowering the likelihood of recurrent cardiovascular events such as myocardial infarction and stroke. Additionally, the polypill improves medication adherence and reduces overall healthcare costs

Keywords: polypill, arterial hypertension, dyslipidemia, low-density lipoprotein cholesterol, atherosclerosis, cardiovascular diseases, prevention, medication adherence, stroke, efficacy.

Kirish

Epidemiologik tadqiqotlardan olingan dalillar Shimoliy Amerikadagi arterial gipertenziya (AG) bilan og'rigan bemorlarning >90% ekanligini ko'rsatadi. Yevropa va Yaqin Sharq va >80%

Avstraliyada, Lotin Amerikasi va Osiyoda kamida bitta qo'shimcha yurak-qon tomir xavf omili mavjudligi haqida ta'kidlangan [1]. Xususan, gipertenziya bilan og'rigan odamlarda dislipidemiya (DLP) tarqalishi umumiy aholi soniga qaraganda 1,2-1,5 baravar yuqori. Epidemiologik tadqiqotlar natijalariga asosan gipertenziya va dislipidemiya kasalliklarining kombinasiyasi nafaqat YuQT kasalliklarining salbiy oqibatlariga, balki ushbu aterosklerotik kasalliklarning rivojlanish xavfini 2-3 marotabagacha oshirishi Framingem [2], MRFIT(Multiple risk factor intervention trial) [3], INTERHEART (Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries) [4] kabi bir nechta tadqiqotida isbotlangan. Randomizasiyalangan Mendeley tadqiqot xulosalaridan foydalangan holda Zanetti D. ning eng so'nggi va eng katta tadqiqoti (2020) shuni ta'kidlaydiki "haqiqiy xavf omillari" deb past zichlikdagi lipoprotein xolesterinning (PZLP-XS) triglitseridlar (TG), lipoprotein (a) va apolipoprotein B patogenetik rolini tasdiqlashgan[5].Shu bilan birga Mendeley randomizasiyasidan meta-regeressiya tahlilidan foydalanga holda ishonchli ravishdagi natijalar shuni ko'rsatadiki PZLP-XS va Sistolik AQB ning butun umr davomida pastligi yoki pasayishi YuQTKlari xavfini uzoqlashtiradi [6].

YuQTK ga tegishli bo'lgan xavf omillari (birinchi navbatda bular arterial gipertoniya, dislipidemiya va chekish) uzoq vaqtdan beri ma'lum. YuQTK dan gospitalizasiya va o'lim xavflarini kamaytirish maqsadida nomedikamentoz va medikamentoz chora-tadbirlarning samaradorligi ilmiy tadqiqotlarda isbotlangan. Ammo ushbu dori darmonlarni qabul qilish chastotasi, davolashga rioya qilishning juda pastligi sababli dislipidemiya va AG kabi xavf omillarning maqsadli ko'rsatgichlarga erishishga ta'sir qilishi mumkin. Oxirgi yillarda ko'plab xalqaro forumlarda "polypill" haqidagi ko'plab muhokamalar olib borilayapti ushbu termin 2003-yil N.J.Wald va M.R.Low tomonidan taklif etilgan bo'lib, [7] ushbu polipill tarkibi o'z ichiga antiagregant (aspirin 75 mg), antigipertenziv dorilardan (b-blokator, AAF ingibitor va diuretik) va 0,8 mg foliy kislotasini o'z ichiga olgan. Ushbu kombinasiyada foliy kislota gomosistein darajasini kamaytirish maqsadida qo'llanilgan bo'lib, ushbu tarkibli dorilar kombinasiyasi bemorlarda insult va MI kabi xavflarni kamaytirishi isbotlanmagan va tadqiqot muvaffaqiytatsiz deb topilgan [8–10]. N.J.Wald va M.R.Low 15 ta katta tadqiqotlar metatahlilidan keyin shuni xulosa qilib ta'kidlashganki, 55 yoshdan katta barcha bemorlarda polipill YuQTK xavfini 80% ga kamaytiradi [7]. Aynan shu metatahlildan so'ng birlamchi YuQTK profilaktikasi maqsadida polipill konsepsiyasi paydo bo'la boshladi. Mualliflar o'z metatahlillari natijalaridan kelib chiqqan holda PZLP-XS ning statin orqali 1,8 mmol/l gacha pasaytirish YuIK xavfini 61% gacha va insult xavfini 17% gacha kamaytirishini ta'kidlashgan. Polipill tarkibidagi antigipertenziv dorilarning yarim dozada kiritilishi diastolik AQB ning 11 mm.sim.ust.gacha pasaytirishi va shu bilan birga YuIKni 46% gacha va insult xavfini esa 63% gacha kamaytirishi tasdiqlagan. Natijada mualliflarning taxminiga ko'ra polipill yordamida YuIK xavfi 88% gacha va insult xavfi 80% gacha kamaytirish mumkinligi aytilgan. Bundan tashqari agar polipillni 55-64 yoshdagi xavf omillari bo'lmagan (xavf omillari bo'lishidan qat'iy nazar) bemorlar qabul qilishi kelajakda 10-12 yil davomida YuIK va insult rivojlanish xavfini uzoqlashtiradi. Keyinchalik esa polipillni nafaqat birlamchi YuQTK profilaktikasida balki ikkilamchi YuQTK profilaktikasidagi (anamnezidagi MI bo'lgan bemorlar) samaradorligini o'rganish boshlanib, bemorlar kontingentidan kelib chiqqan holda polipill tarkibi ham o'zgartirib borildi. Masalan: anamnezida MI o'tqazgan bemorlarga statin, antiagregant, b-blokatorlar va AAF ingibitori tarkibli polipill maqsadga muvofiq deb topildi. Ushbu tarkibli polipill Fransiyada 2119 nafar MI o'tqazgan bemorlarda samaradorligi baholandi va unga ko'ra polipill qabul qilgan bemorlarda bir yillik omon qolish ko'rsatgichi 97% ni tashkil qilgan [11]. Centro Nacional De Investigaciones Cardiovasculares (CNIC)-polipill nomi bilan tanilgan Yevropada yurak qon-tomir kasalliklarining ikkilamchi profilaktikasi uchun sotiladigan birinchi polipill bu 100 mg Asetilsalitsil kislotasi (ASK), 20 yoki 40 mg atorvastatin va 2,5, 5 yoki 10 mg Ramiprildan iborat edi [12]. Klinik amaliyotda ikkilamchi YuQTK profilaktikasi maqsadida CNIC-polipill AQB va PZLP-XS ning pasayishi va umumiy lipid profilining yaxshi tomonga o'zgarishi ko'rsatilgan [13–16]. YuQTK aniqlangan bemorlarda o'tqazilgan retrospektiv kuzatuv natijalari (NEPTUNO) taqdqiqoti shuni ko'rsatadiki: uchta alternativ variantlarga nisbatan (bir xil individual monokomponentlar, ekvivalent dorilar va boshqa kogortaga kiritilmagan dorilar) ga nisbatan CNIC-polipill jiddiy YuQT hodisalarining umumiy tezligini sezilarli darajada kamaytiradi [17]. NEPTUNO tadqiqoti quyidagi guruhlarni o'z ichiga olgan: YuIK(O'MI va stabil/nostabil stenokardiya), bosh miyya serebrovaskulyar kasalliklari(ishemik insult, TIX) va periferik arteriya

kasalliklari bor bemorlar.Ushbu tadqiqot maqsadi: Aspirin, ramipril va atorvastatinni (CNIC-Polypill) o'z ichiga olgan polipillning yurak-qon tomir kasalliklari (YuQTK) ning qaytalanish darajasi va aterosklerotik yurak-qon tomir kasalliklari bo'lgan bemorlarda xavf omillarini nazorat qilish bo'yicha samaradorligini baholash va turli farmakologik davolash strategiyalari bilan solishtirish edi.Tadqiqot o'z ichiga 6456 nafar bemorni o'z ichiga olib, har bir guruh(1-guruh polipill, 2- guruh bir xil individual monokomponentlar, 3-guruh ekvivalent dorilar 4- guruh boshqa kogortaga kiritilmagan dorilarni qabul qilgan) o'z ichiga 1614 nafardan bemorni tashkil etgan va tadqiqot 2 yil yoki jiddiy YuQT hodisalarining paydo bo'lgunicha davom etgan. Natija shuni ko'rsatadiki nazoratdagi guruhlarga nisbatan polipill guruhidagi bemorlarda YuQT asoratlari pastroq bo'lgan (22%; p = 0,017, 25%; p = 0,002, 27%; p = 0,001), AQB va PZLP-XS ning maqsadli ko'rsatgichlariga erishish CNIC-polipill guruhida boshqa guruh vakillariga nisbatan sezilarli ravishda yuqori bo'lgan AQB: + 12,5% nisbatan + 6,3%; p < 0,05, + 2,2%; p < 0,01, +2,4%; p < 0,01. PZLP-XS: + 10,3% nisbatan + 4,9%; p < 0,001 , +5,7%; < 0,001, +4,9%; < 0,001 ishonchli ravishda). Tadqiqot so'ngida CNIC-polipill qabul qilayotgan guruhda davo chorasiga moyillikning qolgan guruhlarga nibatan sezilarli ortganligi kuzatilgan CNIC-Polypill (72,1% nisbatan 62,2%, 60,0% 54,2% ishonchli ravishda; p < 0,001) [18]. Bundan tashqari, NEPTUNO tadqiqoti samaradorligi ma'lumotlariga asoslangan MERCURY (CEA) va model CEA xarajatlari samaradorligini tahlil qilishda o'tkazilgan sog'liqni saqlashning iqtisodiy baholari CNIC-polipill boshqa yondashuvlarga nisbatan iqtisodiy jihatdan samarali terapevtik strategiya degan xulosaga keldi [19–21]. Ushbu topilmalar polipillarni yurak-qon tomir kasalliklarini parvarish qilishga kiritishni qo'llab-quvvatlovchi dalillarning ortib borayotganini ta'kidlaydi. [22,23]. ROZALIA (Vengeriya ko'p tarmoqli nazoratdagi nointervension tadqiqot) tadqiqotida lizinopril/amlodipin 5/10 mg, 5/20mg, 10/20 mg dozada va rozuvastatin 10 va 20 mg dozada polipill tarkibidagi dorilarning samaradorligi va xavfsizligi o'rganilgan [24] bo'lib, bemorlarga tavsiya etilgan. Tadqiqotda 2452 nafar bemor AG 1-2 daraja va giperxolesterinemiya (93,2%) yoki juda yuqori YuQTK xavfi (6,8%) ya'ni QD (34%), metabolik sindrom(38%), periferik arteriya kasalliklari (35%) bor bemorlar ishtirok etgan. Bundan tashqari 68% bemor tadqiqotga kiritilishidan oldin gipotenziv terapiyani qabul qilgan, ammo AQB ning maqsadli ko'rsatgichlariga erisha olmagan. AQB va xolesterinning maqsadli ko'rsatgichlarga erishilganligi 6 oydan so'ng nazorat qilinganda tadqiqot oxiriga kelib 91% bemorlar AQB <140/90 mm.sim.ust maqsadli ko'rsatgichiga va 57% bemorning AQB 130/80 mm.sim.ust.dan pasaygani aniqlangan. 80 yoshdan oshgan bemorlarning 94% da AQB <150/90 mm.sim.ust.ni qayd etgan. Olib borilgan davo chorasi natijalari QD, metabolik sindrom va periferrik arteriya kasalliklari bor bemorlarda farq qilmagan. 1 oydan so'ng UXS va PZLP-XS darajalari dinamikasi ko'rilib, tadqiqotning oxirida UXS 6,4±1,1 mmol/l dan 4,8±0,9 mmol/l gacha(p<0,05), PZLP-XS 3,8±1,1 mmol/l dan 2,6±0,8 mmol/l gacha (p<0,05) kamaygan, bundan tashqari ishonchli ravishda (p<0,05) Trigliseridlar darajasi (23% ga) pasayib,YuZLP-XS darajasi (6%) gacha ko'paygan bo'lib, jigar fermentlari va kreatinin darajasi sezilarli ortmagan. Bu esa ushbu tarkibli polipillning metabolik neytralligidan dalolat beradi. Bemorlarda ushbu dorilarning nojo'ya ta'siri umumiy 4,5% hollarda kuzatilib, undan 3,1% yo'tal, 2,2% oyoqlardagi shish, 1,1% mushakdagi og'riq va 0,2% holda esa bosh aylanishi kuzatilgan. Shu bilan birga JUPITER tadqiqotida [25] kuzatilganidek, tadqiqot ohiriga kelib ushbu tadqiqotda ham C-reaktiv oqsili darajasining kamayganligi kuzatilgan.

Davo-chorasiga moyillikning ortishi

Polipillning antigipertenziv fiksasiyalangan kombinasiyali dorilardan asosiy farqi bu: aksariyat antigipertenziv fiksasiyalangan kombinasiyalar ikkita guruh antigipertenziv dorilardan iborat bo'lgan dorilardir, polipill esa 2 va undan ortiq turli guruhli (masalan antigipertenziv va statinlar) dorilarni o'z ichiga olgan komponentlar majmuasidir. Komorbid holatlarning tarqalishi esa aynan polipillarni yaratish va qabul qilishni talab etadi. Ya'ni bemorlarda dori darmonlarni bir necha mahal qabul qilishning o'rniga polipillni qabul qilish davo chorasiga moyillikni va shu bilan birga bemorning sog'ligini yaxshilaydi. Davo chorasiga moyillikning polipill guruhlarida yaxshilanishi bir nechta tadqiqotlarda o'z tasdig'ini topgan bo'lib, ular quyidagilar: Polipillning barcha YuQTK laridan o'lim xavfini kamaytirishini baholash maqsadida beshta klinik tadqiqotlaar o'tqazildi: TIPS,CRUCIAL,UMPIRE,IMPACT va KanyiniGAP [26–29].TIPS tadqiqotida YuQTK laridan nohush holatlarni profilaktikasi maqsadida bemorlarda har xil tarkibli polipill qo'llangan bo'lib, bittadan 5 ta turdagi dorilar polipill tarkibiga kiritilgan. Ushbu ko'p tarmoqli tadqiqot shuni ko'rsatdiki

kamroq tarkibli dorilar birlashmasiga nisbatan polipill SAB darajasini yaxshilaydi va bemorlar tomonidan yaxshi o'zlashtirilishi va doriga moyillikni ortishi tasdiqlangan [27]. CRUCIAL tadqiqoti davolashga moyillikni, gipertenziya va dislipidemiya kabi yondosh kasalliklarda yurak-qon tomir tizimini yaxshilanishi, umumiy YuQTK xavfiga polipillning ta'siri haqida olib borilgan tadqiqot edi[28].IMPACT tadqiqotida esa davolashga moyillikni baholashni bemorlar individual ravishda o'zlari bajargan bo'lib, UMPIRE randomizasiyalashgan klinik tadqiqotida YuQTK aniqlangan yoki YuQTK rivojlanish xavfi yuqori bo'lgan 2004 nafar bemorlar ikki guruhga bo'lingan holda 1-guruh (n=1002) Aspirin 75 mg, simvastatin 40 mg, lizinopril 10 mg va atenolol 50mg tarkibli polipill va 2- guruh (n=1002) polipill tarkibidagi dorilarni alohida qabul qilgan holda, 15 oy davomida o'rganilgan. Natija shuni ko'rsatadiki: Polipill guruhida davo chorasiga moyillik nazoratdagi guruhga nisbatan sezilarli darajada oshgan (86% nisbatan 65%). Shu bilan birga tadqiqot oxirida SAB -4.9 mm.sim.ustgacha ($p<0,001$) va PZLP-XS -6,7 mg/dl gacha ($p<0,001$) ishonchli ravishda pasaygan[30]. Kayni-GAP tadqiqotida antigipertenziv, antitrombositar va statinlarning hujjatlashtirilgan YuQTK diagnozi bor bemorlarda qabul qilinishi va davo chorasiga moyillikning ortishi baholangan bo'lib, standart terapiyaga nispatan polipill qabul qilayotgan bemorlarda davo chorasiga moyillikning ortishi kuzatilgan. Ammo YuQTK larining ikkilamchi profilaktikasida ustunligi kuzatilmagan [31]. SECURE (Secondary Prevention of Cardiovascular Disease in the Elderly) qariyalarda YuQTKlari ikkilamchi profilaktikasi nomli tadqiqotida ushbu CNIC-polipill dorisi ananaviy davo chorasi bilan solishtirilgan holda 2499 nafar 65 yoshdan katta bemorlarda o'rganilgan. Moriskiy shkalasi yordamida davo chorasiga moyillik baholanganda, 6 oydan so'ng CNIC-polipill guruhida, nazoratdagi guruhga nibatan davo chorasiga moyillik yuqori bo'lgan (70% nisbatan 62,7%)[32]. Shu bilan birga, yurak-qon tomir kasalliklarining ikkilamchi profilaktikasi (FOCUS) uchun belgilangan dozali kombinatsiyalangan preparatni o'rganishning ikkinchi bosqichi CNIC-FS-FERRER polipillini (aspirin 100 mg, simvastatin 40 mg va ramipril 2,5/5/10 mg) qo'llash ushbu uchta dorini alohida qo'llash bilan solishtirganda davolanishga rioya qilishni 22% ga oshiradi (41% ga nisbatan 50,8%; $p = 0,019$) [33].Yana bir tadqiqotlardan biri TEMPUS randomizasiyalashgan klinik tadqiqotida polipill va alohida komponentli dorilarni kunduzgi va tungi vaqtlarda qabul qilayotgan bemorlarda Moriskiy shkalasi yordamida davo chorasiga moyillik baholanganda: polipillni kunduzgi vaqtda qabul qilayotgan bemorlarda, alohida komponentlarda dorilarni qabul qilayotgan bemorlarga nisbatan moyillik 5,2% yuqori va kechgi vaqtda polipill qabul qiluvchilar uchun esa 5,0% yuqori moyillik aks etgan [34].

Polipillning noqulayliklari:

Shifokorlar amaliyotida YuQTKi turli xavf guruhlari uchun dorilarni titrasiyalash va dori dozalarini individual ravishda tanlashi lozimdir. Shifokorlar amaliyotidan kelib chiqib polipill tarkibidagi aniq bir dorini titrasiyalash imkoni yo'qligi bu uning asosiy kamchiliklaridan biri hisoblanadi. Biroq so'ngi tavsiyalarga asosan xolesterin darajasi va AQB darajasidan qat'iy nazar xavf guruhiga asoslangan holda gipolipidemik terapiyaning olib borilishi tavsiya etiladi [35,36]. Ushbu davo chorasi HOPE-3 tadqiqotida o'rganilgan bo'lib, tadqiqotda 55 yoshdan katta erkaklar va 65 yoshdan katta ayollar shu bilan birga barcha bemorlarda bitta qo'shimcha YuQTK xavfi bor bemorlar kiritilgan. Bemorlar ikkita guruhga bo'linib, har bir guruh ham ikki guruhga bo'lingan: 1-guruh 10 mg/sut rozuvastatin yoki plasebo, 2- guruh esa kandesartan 16 mg/sut va gidroxlortiazid 12,5 mg/sut fiksasiyalashgan kombinasiya va ikkita tarkibli alohida dorilar plasebo qabul qilishgan. Tadqiqot shuni ko'rsatdiki, fiksasiyalangan terapiya qabul qilgan bemorlarda yurak-qon tomir o'limi xavfi ikki tarkibli alohida plasebo terapiyasini olgan bemorlarga nisbatan 29% ga kamaygan va fatal MI va nofatal insult holatlari ko'rsatgichi kamaygan ($p = 0,005$). Shu bilan birga gipolipidemik terapiya qabul qilayotgan bemorlarda YuQTK laridan o'lim xavfi 24% ga kamaygan bo'lib, fiksasiyalashgan antigipertenziv davoning asosiy noqulayligi o'rtacha AQB 143,5 mm.sim.ust.dan yuqori bo'lgan, umumiy bemorlarning uchdan bir qismida samarasiz deb topilgan [37]. Polipillning yana bir noqulayliklaridan biri: polipill tarkibidagi dorining nojo'ya ta'siri barcha dorilardan voz kechishga olib keladi. Bunga misol qilib Kokreynov metatahlili shuni ko'rsatadiki: polipill qabul qilayotgan guruhda boshqa nazoratdagi guruhlarga nisbatan polipilldan voz kechish 26% holatda kuzatilgan [38]. Ammo nazoratdagi guruh o'z ichiga oddiy va plasebo dorilarni qabul qilayotgan ishtirokchilarni o'z ichiga olgan. Ammo polipillning YuQTK xavfini kamaytirish, davo chorasiga moyillikning ortishi kabi ko'plab klinik tadqiqotlar natijalari polipillni ushbu noqulayliklarini o'rnini

bosa oladi.

Munozara

Polipill YuQTK xavfini, jumladan: insult xavfi, YuQTKlaridan o'lim xavfini kamaytiradi, polipillning uzoq ta'sir davomiyligi sababli AQB va UXS ning samarali va xavfsiz maqsadli ko'rsatgichlargacha kamaytiradi. Bundan tashqari antigipertenziv va gipolipidemik terapiyaning bitta dori tarkibida bo'lishi AG va dislipidemiyali bemorlarning doriga bo'lgan moyilligini oshiradi. . Biroq, uning universal qo'llanilishi individual yondashuv zarurati va ayrim farmakologik cheklovlar tufayli hali ham muhokama qilinmoqda. Kelgusida polipillni shaxsiylashtirilgan tibbiyot tamoyillariga mos ravishda rivojlantirish hamda uning uzoq muddatli samaradorligi va xavfsizligini baholash bo'yicha qo'shimcha tadqiqotlar talab etiladi.

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Authors' contribution.

Conceptualization, Sh.F. and G.X.; methodology, G.X.; software, G.A.; validation, G.X., G.A. and X.Y.; resources, Sh.F.; data curation, G.X.; writing—original draft preparation, Sh.F.; writing—review and editing, Sh.F.; visualization, G.X.; supervision, G.X.; project administration, Sh.F.; funding acquisition, Sh.F. All authors have read and agreed to the published version of the manuscript.

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Data Availability Statement

Since this article is a review article, no new empirical data were created or analyzed.

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Conflict of interest

The authors declare no conflicts of interest regarding this study.

Qisqartmalar

DLP	Dislipidemiya
UXS	Umumiy xolesterin
PZLP-XS	Past zichlikdagi lipoprotein xolesterin
TG	Trigliserid
YuQTK	Yurak qon-tomir kasalligi
YuIK	Yurak ishemik kasalligi
O'MI	O'tkir miokard infarkti
MI	Miyokard infarkti
TIX	Tranzitor ishemik xuruj
AG	Arterial gipertoniya
AQB	Arterial qon bosim
QD	Qandli diabet
AAFi	Angiotenzinga aylantiruvchi ferment ingibitori
ASK	Asetilsalitsil kislota

Adabiyot

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