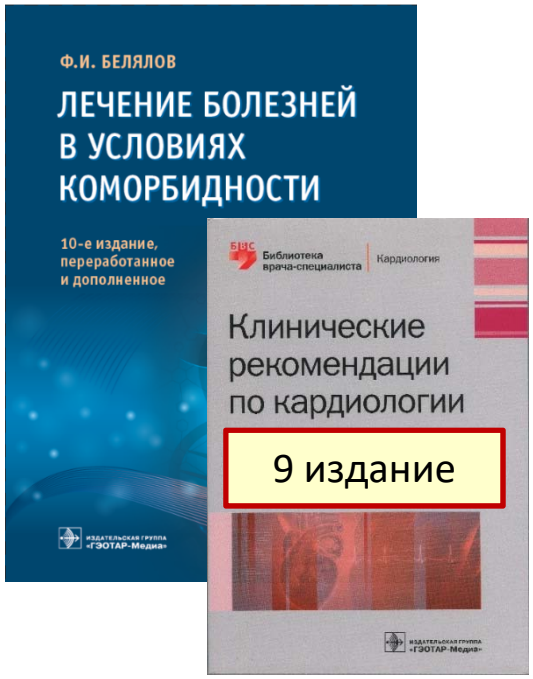
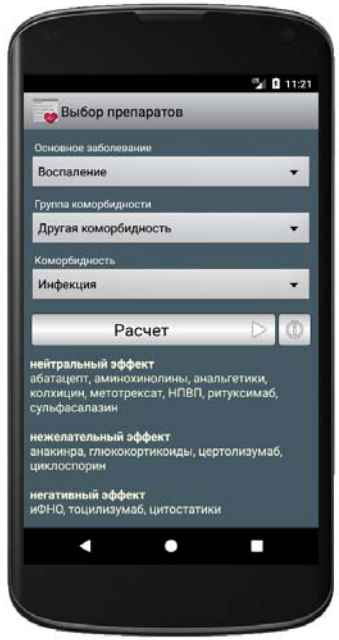
РОССИЙСКОЕ КАРДИОЛОГИЧЕСКОЕ ОБЩЕСТВО

Фарид Исмагильевич Белялов

Коморбидные чтения

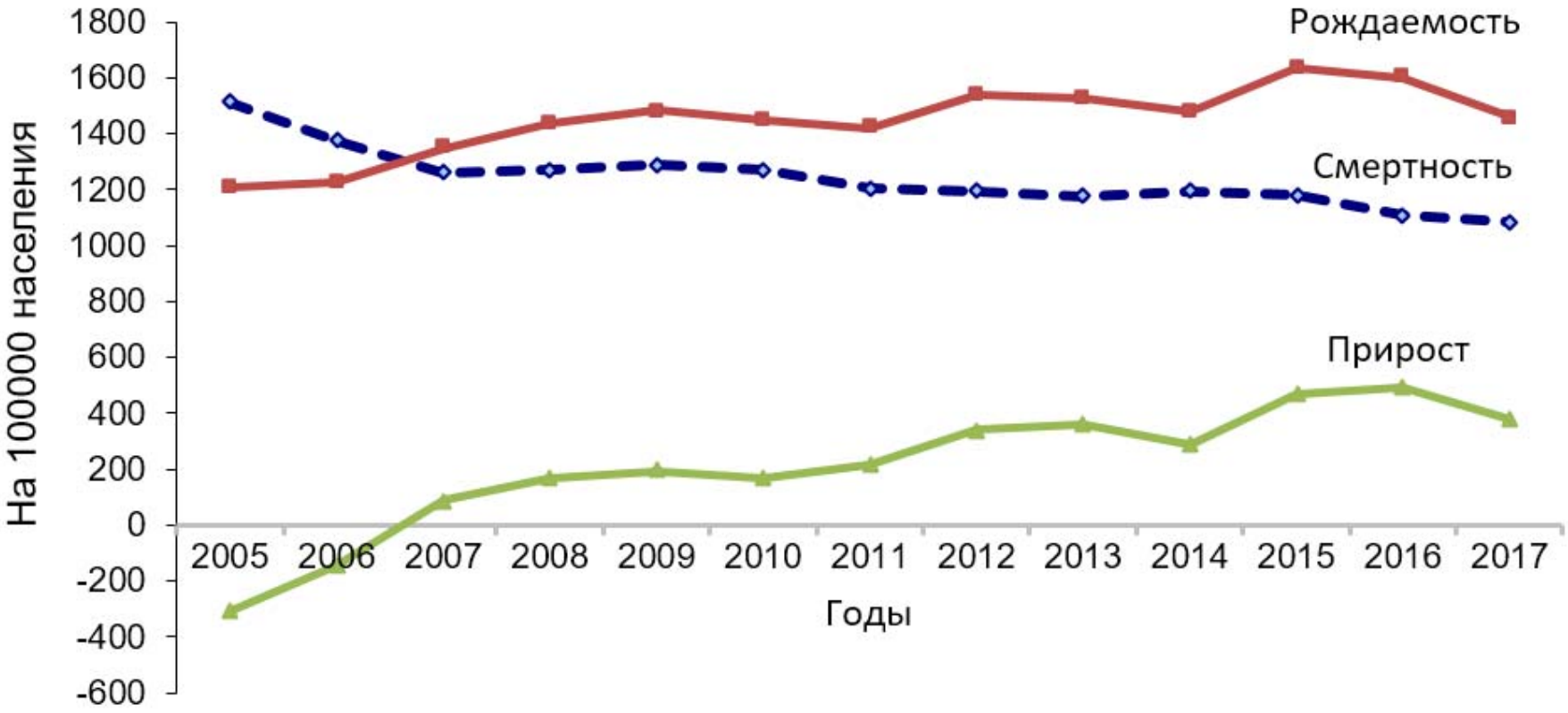


КардиоЭксперт

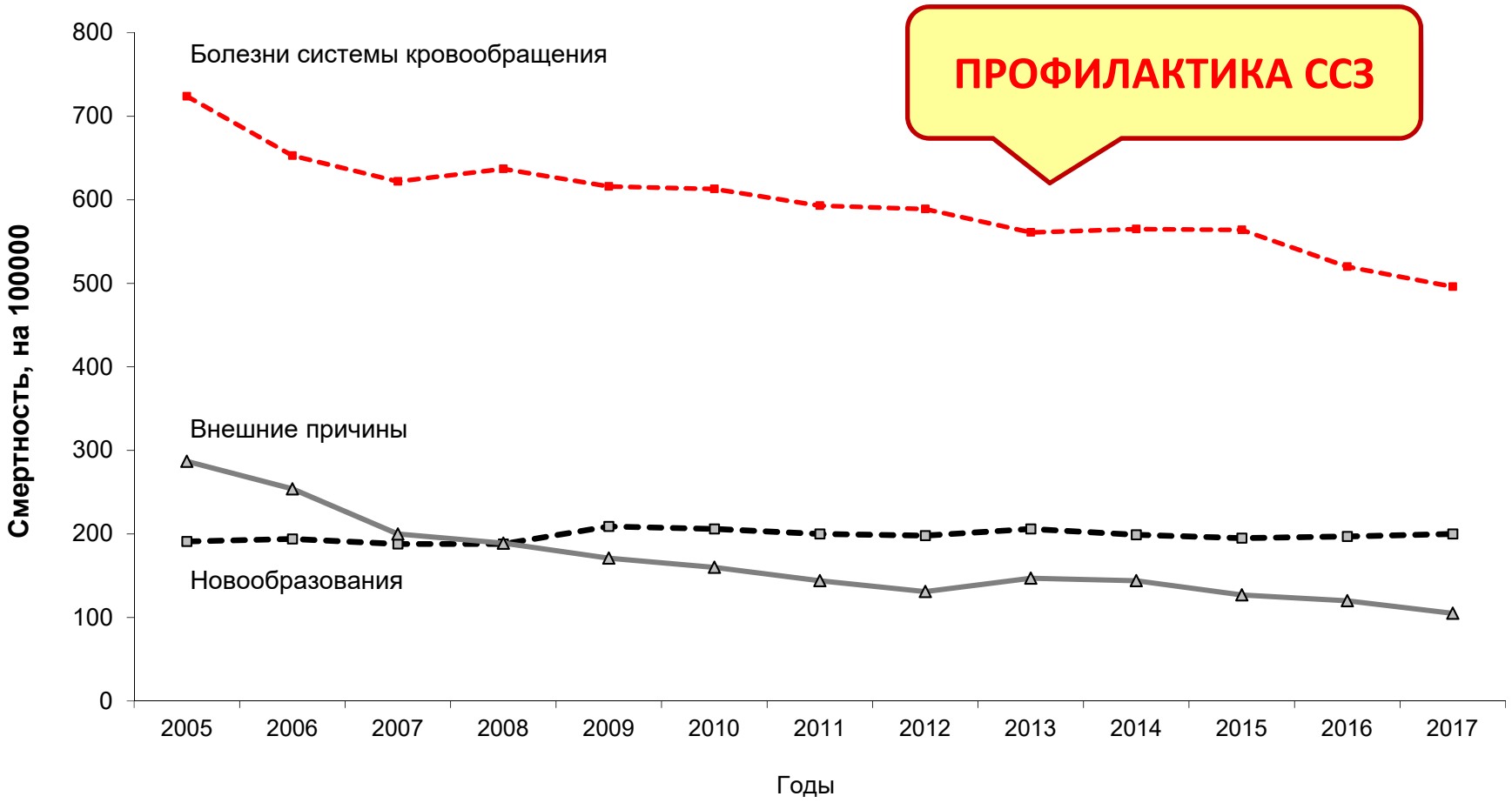


Братск 08.06.2018

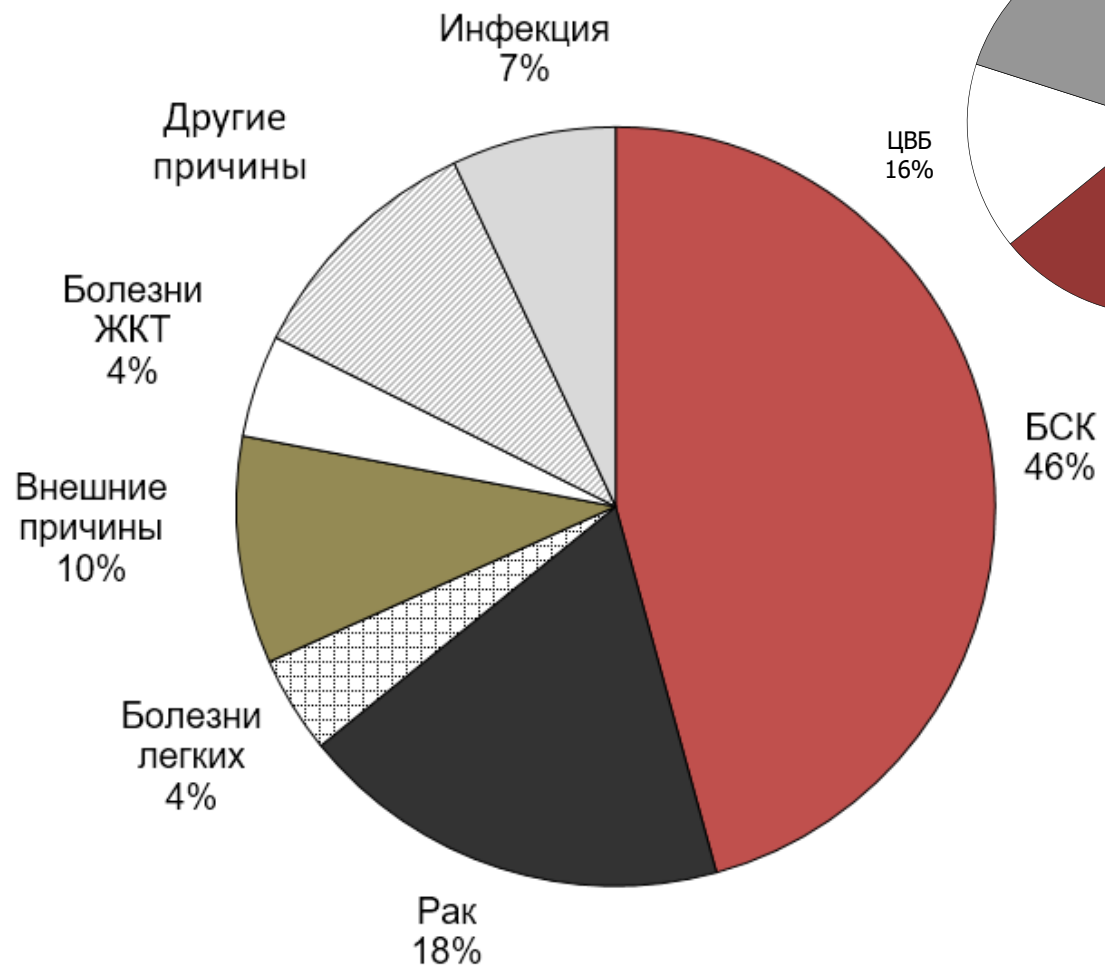
Естественное движение населения Иркутска

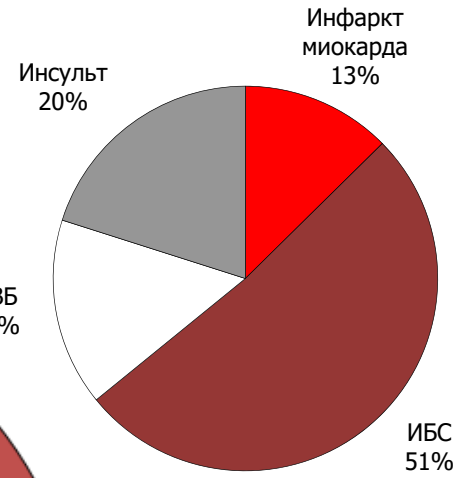


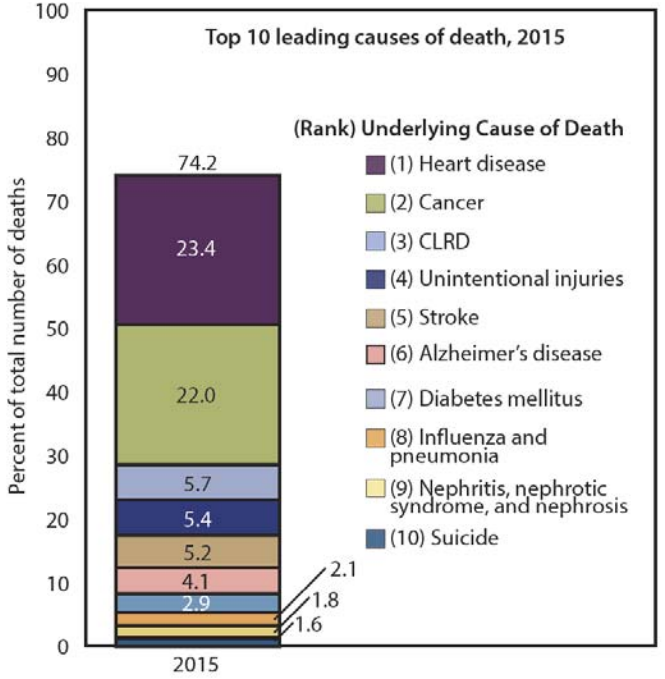
Смертность в Иркутске в 2017 году



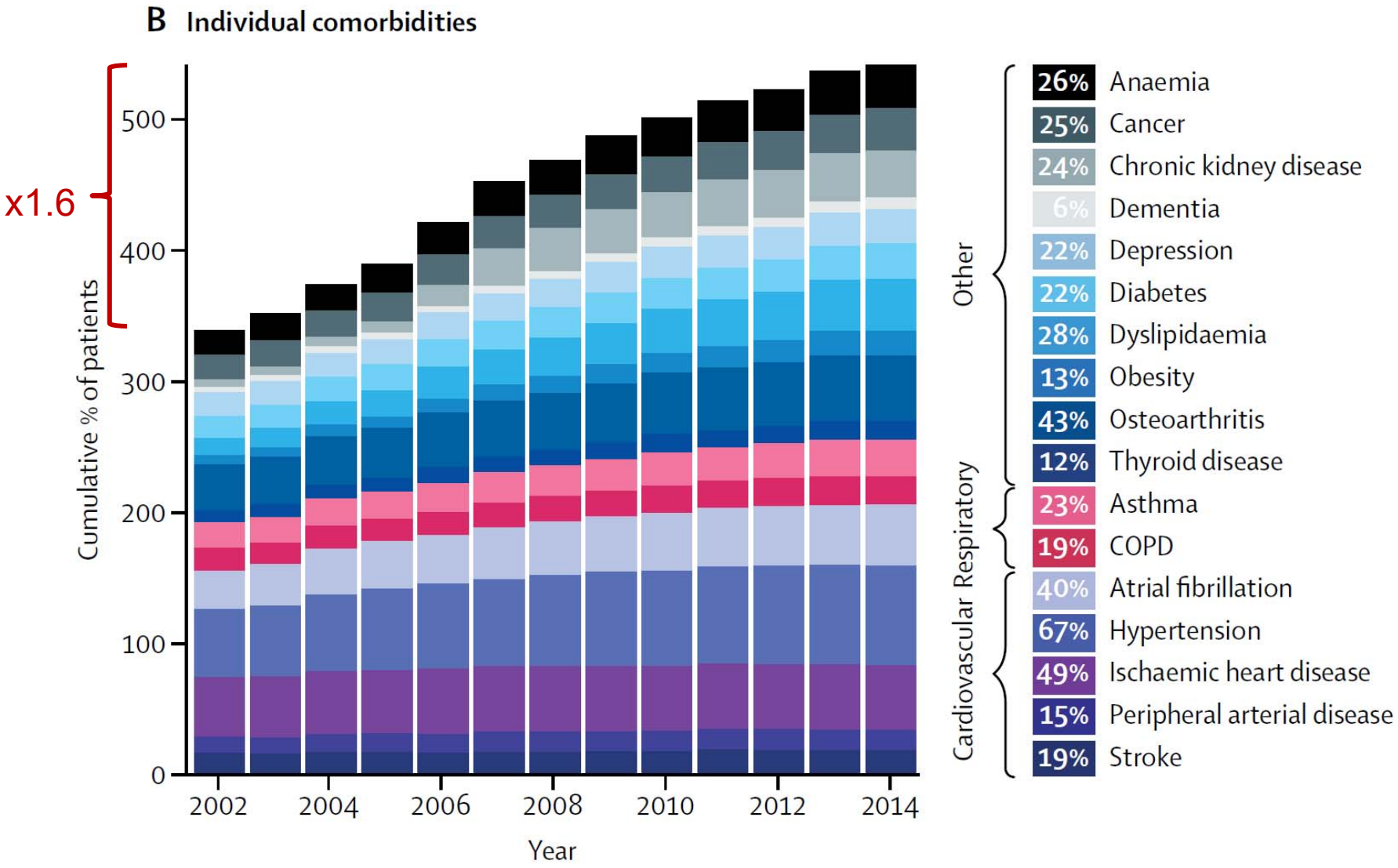
Смертность в Иркутске в 2017 году







Динамика коморбидных болезней



Conrad N, Judge A, Tran J, et al. Temporal trends and patterns in *heart failure* incidence: a population-based study of 4 million individuals. The Lancet. 2018;391(10120):572-580.


ПЕРСОНАЛИЗИРОВАННАЯ МЕДИЦИНА
КОМОРБИДНОСТЬ
ПСИХОСОМАТИКА
ПОЗИЦИЯ ПАЦИЕНТА
ПРОГНОЗИРОВАНИЕ
ХРОНОМЕДИЦИНА
РАСА, ВОЗРАСТ, ПОЛ
ГЕНЕТИКА
ВНЕШНЯЯ СРЕДА
ГУМАНИЗМ
Ф.Белялов

Персонализированное лечение

Врач общей практики
Подготовка по специальностям, психиатрии

Специалист, кардиолог
Подготовка по другим специальностям, психиатрии

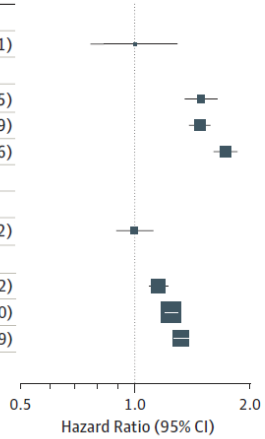
Коммерческая медицина

(Кардиоаритмологический центр)

Загрязнение воздуха и смертность

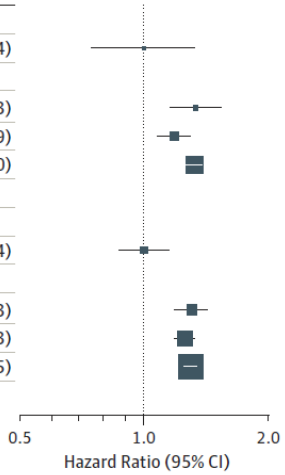
A Cooking fuel

	No. of Deaths	Mortality Rate per 100 000 Person-Years	Rate Difference per 100 000 Person-Years (95% CI)	Hazard Ratio (95% CI)
Cardiovascular mortality				
Always clean fuels	61	144	[Reference]	1.00 (0.77 to 1.31)
Solid fuels				
1-19 y use	522	254	110 (-4 to 224)	1.50 (1.36 to 1.65)
20-39 y use	980	239	95 (-9 to 199)	1.49 (1.39 to 1.59)
≥40 y use	1455	323	179 (74 to 284)	1.73 (1.61 to 1.86)
Trend: $\chi^2_1 = 18.1$ ($P < .001$)				
All-cause mortality				
Always clean fuels	361	391	[Reference]	1.00 (0.89 to 1.12)
Solid fuels				
1-19 y use	1632	640	249 (117 to 381)	1.16 (1.10 to 1.22)
20-39 y use	2987	690	299 (179 to 419)	1.25 (1.20 to 1.30)
≥40 y use	3336	837	446 (322 to 570)	1.33 (1.27 to 1.39)
Trend: $\chi^2_1 = 30.0$ ($P < .001$)				



B Heating fuel

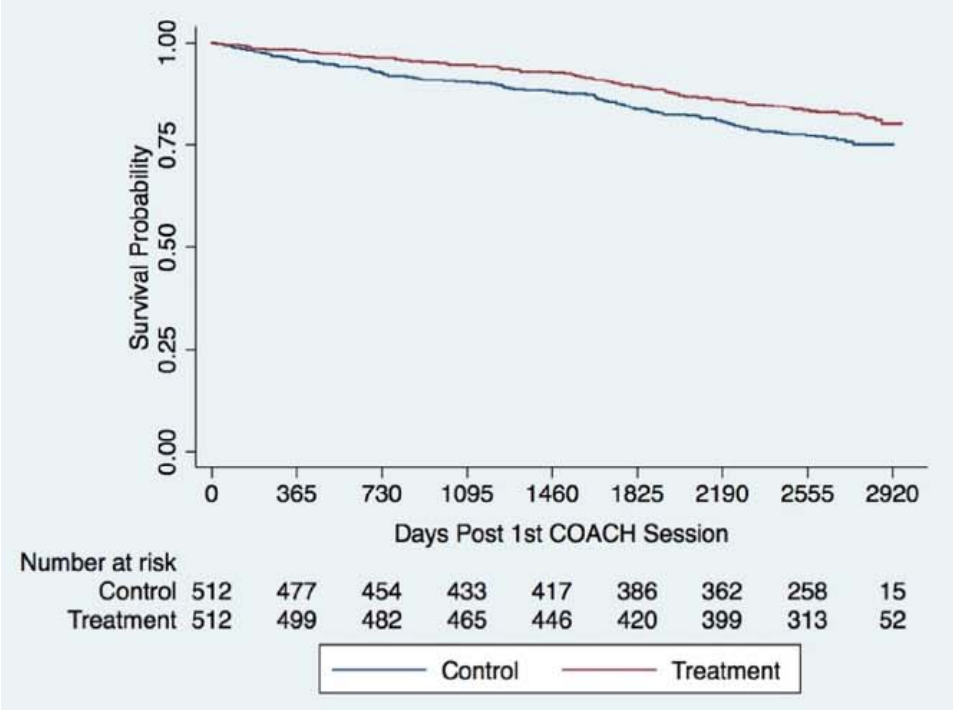
	No. of Deaths	Mortality Rate per 100 000 Person-Years	Rate Difference per 100 000 Person-Years (95% CI)	Hazard Ratio (95% CI)
Cardiovascular mortality				
Always clean fuels	101	172	[Reference]	1.00 (0.75 to 1.34)
Solid fuels				
1-19 y use	208	394	222 (35 to 409)	1.34 (1.16 to 1.53)
20-39 y use	509	317	145 (-25 to 315)	1.18 (1.08 to 1.29)
≥40 y use	3092	401	229 (62 to 396)	1.33 (1.26 to 1.40)
Trend: $\chi^2_1 = 8.4$ ($P = .004$)				
All-cause mortality				
Always clean fuels	468	773	[Reference]	1.00 (0.87 to 1.14)
Solid fuels				
1-19 y use	510	865	92 (-555 to 739)	1.31 (1.19 to 1.43)
20-39 y use	1439	799	26 (-614 to 666)	1.26 (1.19 to 1.33)
≥40 y use	6831	942	169 (-469 to 807)	1.30 (1.26 to 1.35)
Trend: $\chi^2_1 = 17.1$ ($P < .001$)				

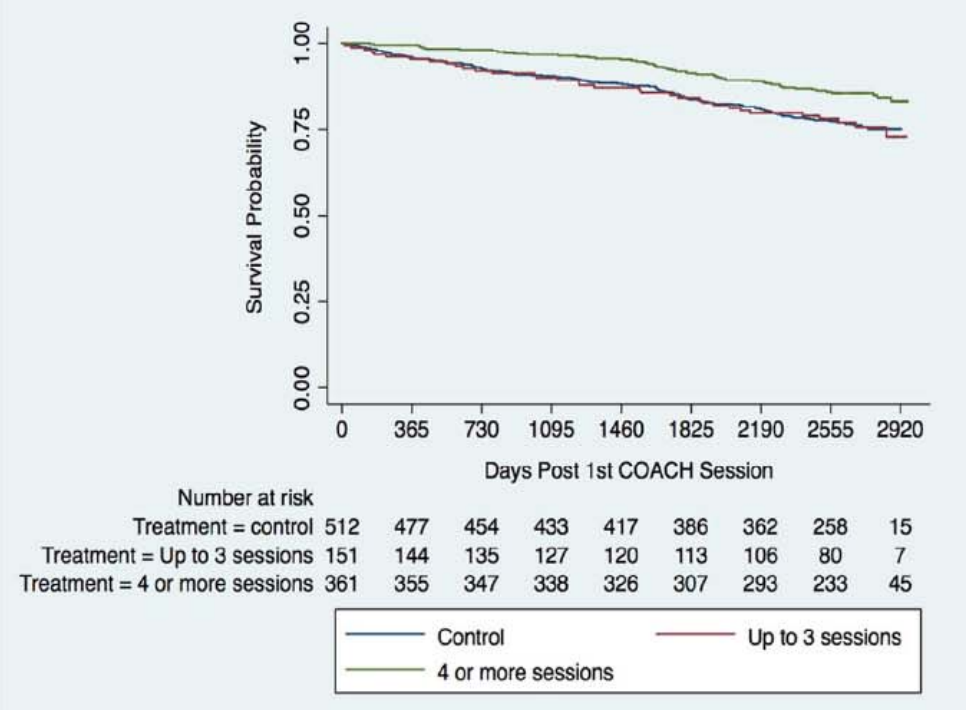


Дрова и уголь повысили сердечно-сосудистую смертность на 20-29%, общую смертность на 11-14%

Yu K, Qiu G, Chan K, et al. Association of Solid Fuel Use With Risk of Cardiovascular and All-Cause Mortality in Rural China. JAMA. 2018;319(13):1351–1361.

Обучение пациентов и смертность



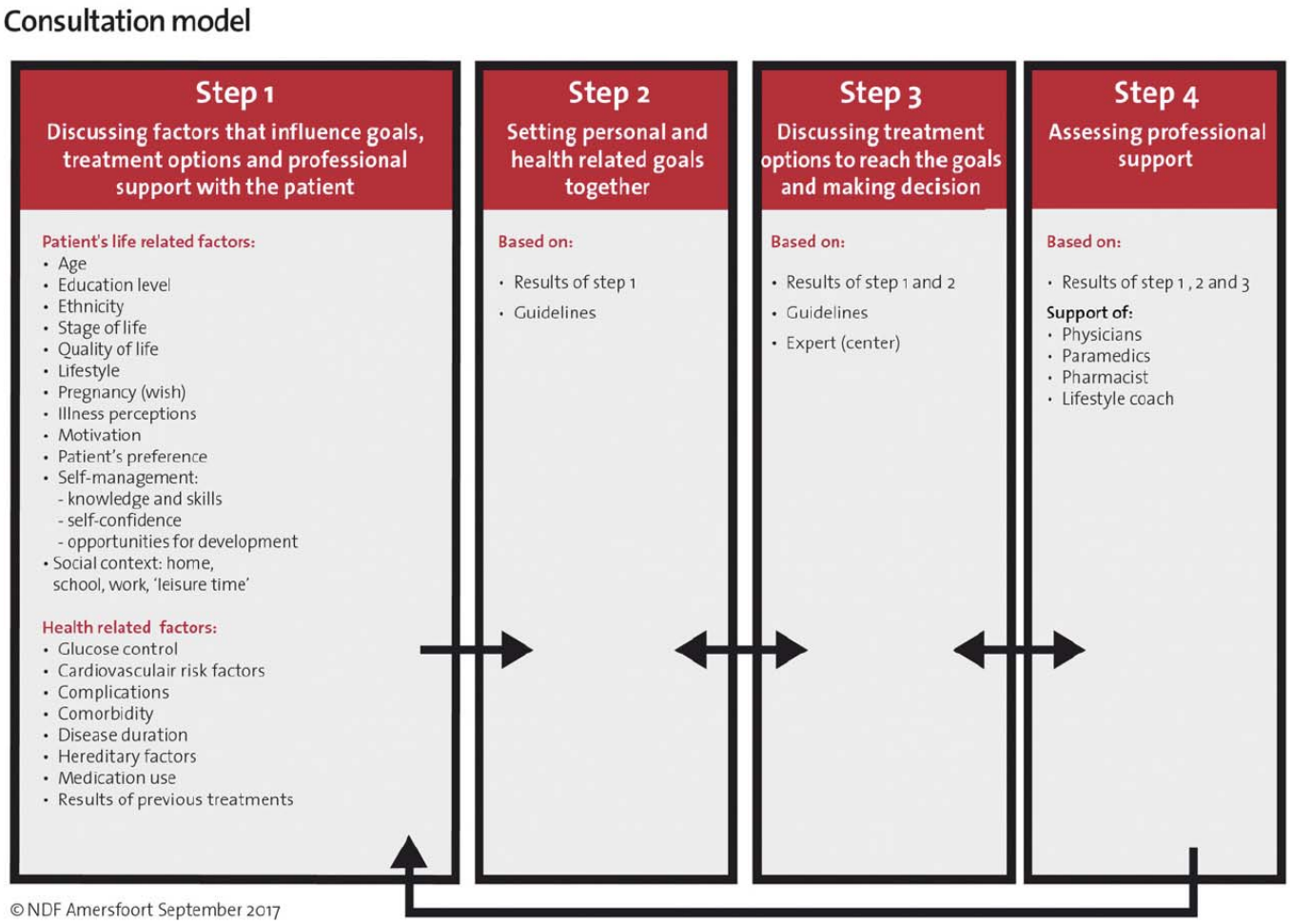


Обучение пациентов снизило смертность от ССЗ на 30%

COACH

Byrnes J, Elliott T, Vale MJ, Jelinek MV, Scuffham P. Coaching Patients Saves Lives and Money. Am J Med. 2018;131(4):415-421.e411.

Пациент-ориентированный подход при диабете



Модель применима в 72% случаев, >50% времени говорит пациент

Nationwide Dutch Study

Rutten G. et al. Implementation of a Structured Diabetes Consultation Model to Facilitate a Person-Centered Approach: Results From a Nationwide Dutch Study. Diabetes Care. 2018;41(4):688.

Классификация FORTA у стариков

Класс A (эффективные)

- Апиксабан, аспирин, бета-блокаторы (3 года после инфаркта миокарда), БРА, дигидропиридины, ИАПФ, клопидогрел (стент), метформин, статины.

Класс B (возможные)

- бета-блокаторы, варфарин, дигоксин, диуретики, иДПП-4, инсулины, клопидогрел, ривароксабан, статины (>85 лет).

Класс C (сомнительные)

- Амиодарон, бензодиазепины короткодействующие (алпразолам), верапамил, глимепирид, дабигатран, ивабрадин, ИОЗСН, миртазапин, моксонидин, пиоглитазон, пролонгированные нитраты, СИОЗС, спиронолактон, фибраты, эзетимиб.

Класс D (опасные)

- Агомелатин, антиаритмики I класса, бензодиазепины пролонгированные (диазепам, хлордиазепоксид), ИНГТ-2, НПВП, препараты сульфонилмочевины, соталол, трициклические антидепрессанты.

Выбор многоцелевых препаратов

	ИБС	АГ	ФП	СН	Диабет	ХБП	НЖБП	Цирроз
иАПФ, БРА	+	+++	+	+++	+	++		
аМКР	+	+	+	++		+/-		++
Бета-блокаторы	+++	++	++	+++				++
Ранолазин	++		+		+			-
Статины	+++		+		+/-	+	+	+
Метформин	+			+	+++	+	+	
Пиоглитазон	+	+	+	-	+++		+	
иНГТ-2	+	+		++	+++			

Болезни печени и дислипидемия

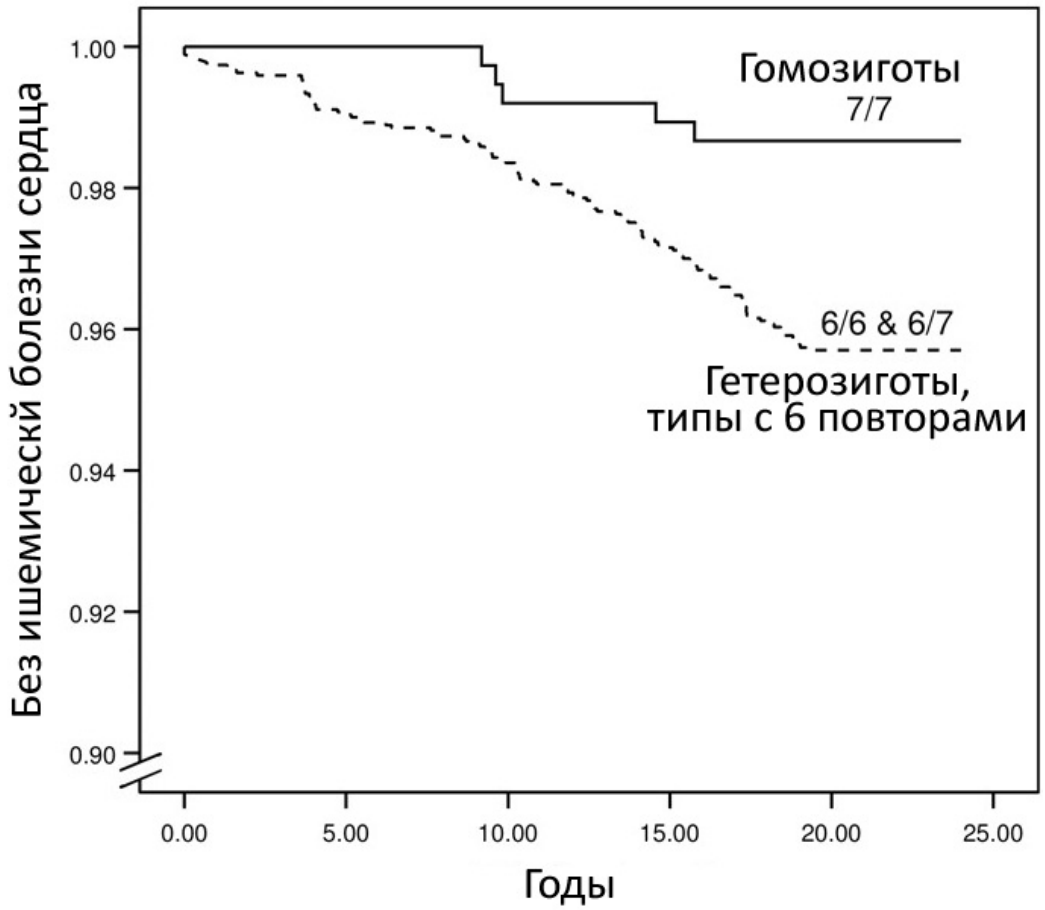
AUC при циррозе ≠ фармакокинетике
Реже поражения печени

Main pharmacokinetic characteristics of statins.

	Atorvastatin	Fluvastatin	Lovastatin	Pravastatin	Rosuvastatin	Simvastatin
Optimal time of dosing	Any time of day	Bed-time	With meals morning and evening	Bed-time	Any time of day	Evening
Absorption, %	30	98	31	37	50	65–85
t_{max}, h	2–4	0.5–1.5	2–4	0.9–16	3–4	1.3–2.4
$t_{1/2}$	11–30	0.5–2.3	2.5–3	0.8–3	20	1.9–3
Bioavaibility, %	12	10–35	<5	18	20	<5
Solubility	Lipophilic	Lipophilic	Lipophilic	Hydrophilic	Hydrophilic	Lipophilic
Protein binding, %	>98	>98	96–98.5	43–54	88	>95
Primary metabolic pathway	CYP3A4	CYP2C9	CYP3A4	Glucuronidation – CYP3A4	CYP2C9–CYP2C19	CYP3A4
Hepatic excretion, %	>70	>68	>70	46–66	90	78–97
Renal excretion, %	2	6	30	60	10	13

Björnsson E. Hepatotoxicity of statins and other lipid-lowering agents. Liver Int. 2017;37(2):173-178.

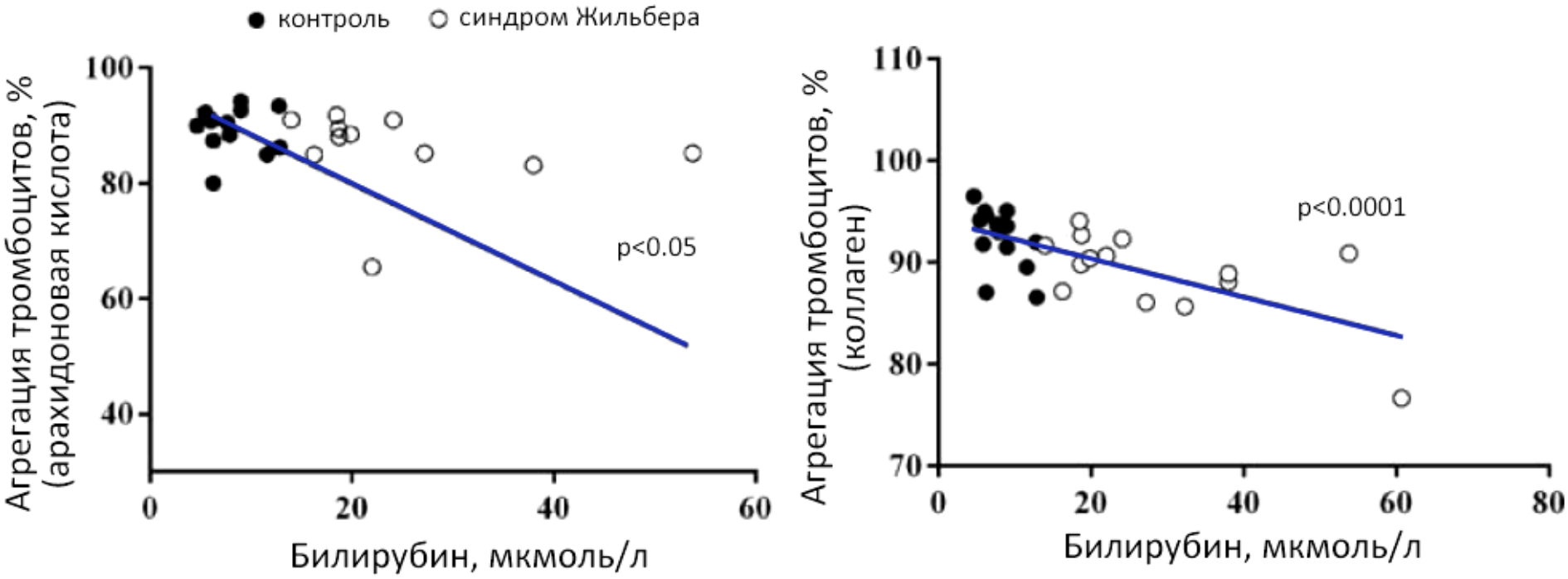
Синдром Жильбера и риск ИБС



Повышение билирубина ассоциируется со снижением риска ИБС

Lin JP, et al. Association Between the UGT1A1*28 Allele, Bilirubin Levels, and Coronary Heart Disease in the Framingham Heart Study. Circulation 2006;114:1476-81.

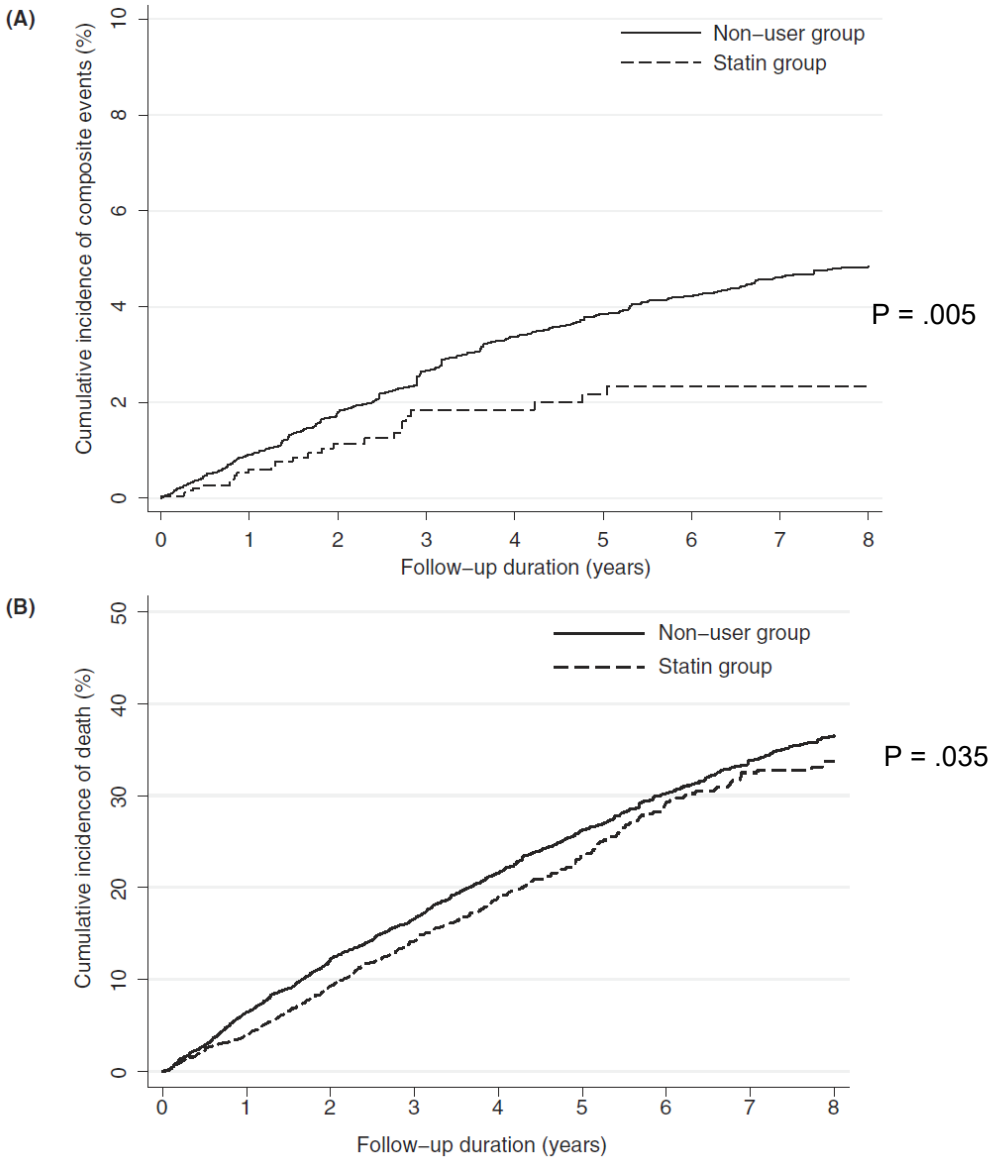
Синдром Жильбера и активность тромбоцитов



Повышение билирубина приводит к снижению агрегации тромбоцитов

Kundur AR, et al. Bilirubin, platelet activation and heart disease: a missing link to cardiovascular protection in Gilbert's syndrome? Atherosclerosis. 2015;239(1):73-84.

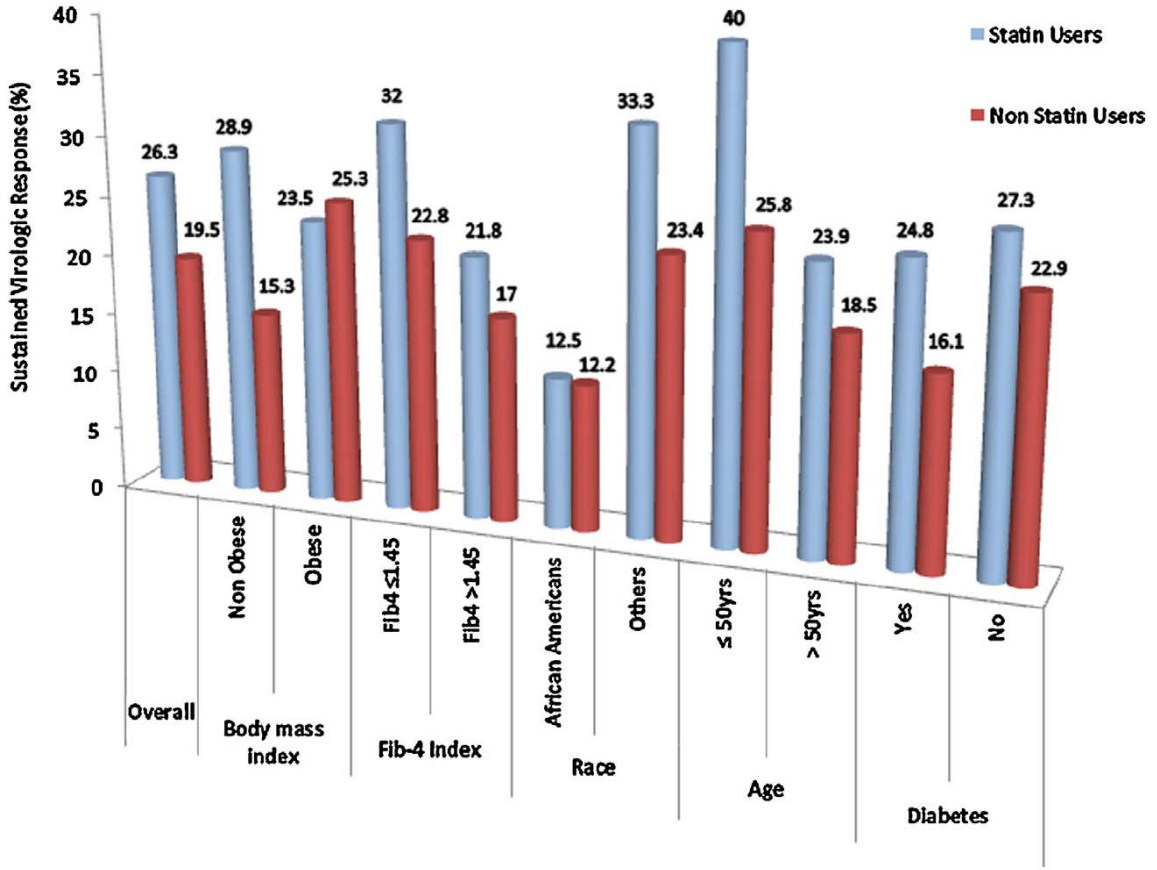
Статины и хронический вирусный гепатит



Статины снизили риск декомпенсации печени и смерти

Wong JC-T, et al. Statins reduce the risk of liver decompensation and death in chronic viral hepatitis: a propensity score weighted landmark analysis. Aliment Pharmacol Ther. 2017;46:1001–1010.

Статины и противовирусная терапия



Статины повышают частоту вирологического ответа на противовирусную терапию гепатита С

Pandya P, Rzouq F, Oni O. Sustained virologic response and other potential genotype-specific roles of statins among patients with hepatitis C-related chronic liver diseases. Clin Res Hepatol Gastroenterol. 2015;39(5):555-65.

Статины и хронические болезни печени

Прогрессирование фиброза

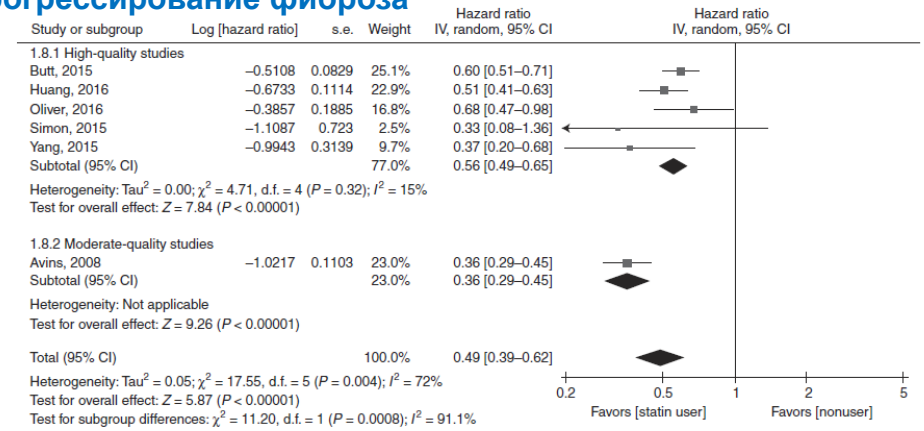


Figure 3. Forest plot to evaluate role of statins in fibrosis progression with subgroup analysis based on quality of studies.

Декомпенсации цирроза

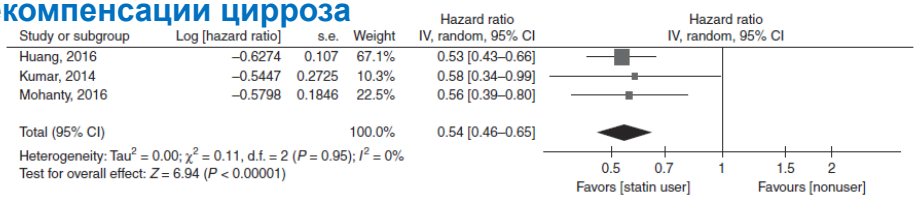


Figure 4. Forest plot to evaluate role of statins in decompensation of cirrhosis.

Смертность

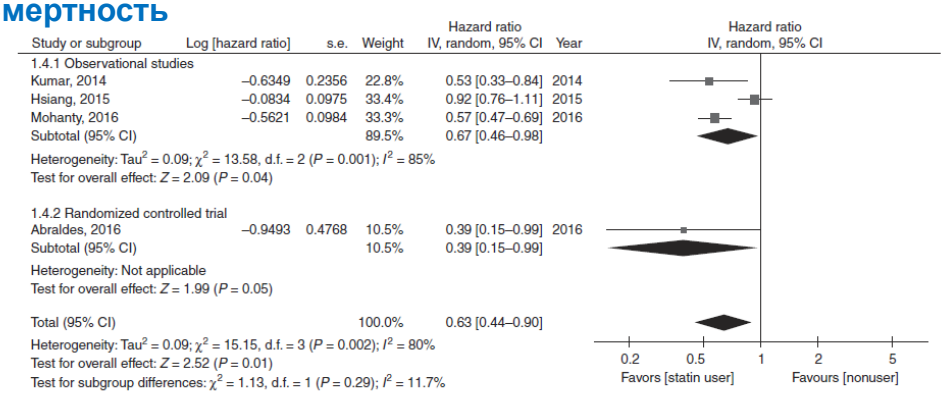


Figure 5. Forest plot to evaluate role of statins in mortality in chronic liver disease patients.

Статины снизили риск прогрессирования фиброза, декомпенсации цирроза и смертность

Метаанализы

Kamal S, et al. Beneficial Effects of Statins on the Rates of Hepatic Fibrosis, Hepatic Decompensation, and Mortality in Chronic Liver Disease: A Systematic Review and Meta-Analysis. Am J Gastroenterol. 2017;112(10):1495-1505.

Kim R. et al. Statin Use and Risk of Cirrhosis and Related Complications in Patients With Chronic Liver Diseases: A Systematic Review and Meta-analysis. Clin Gastroenterol Hepatol. 2017;15(10):1521-1530.e8.

Статины и НЖБП

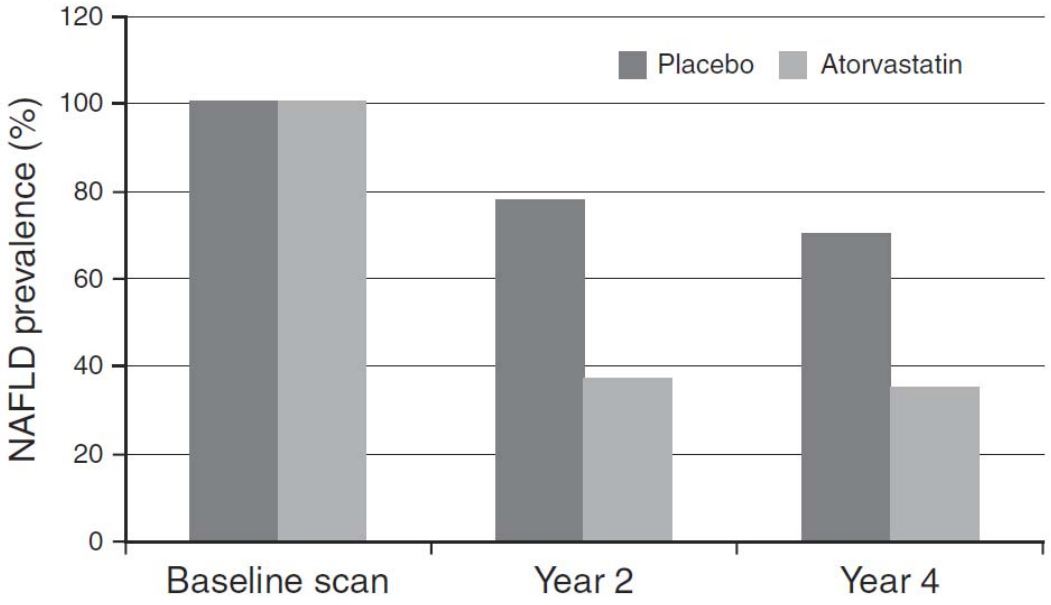
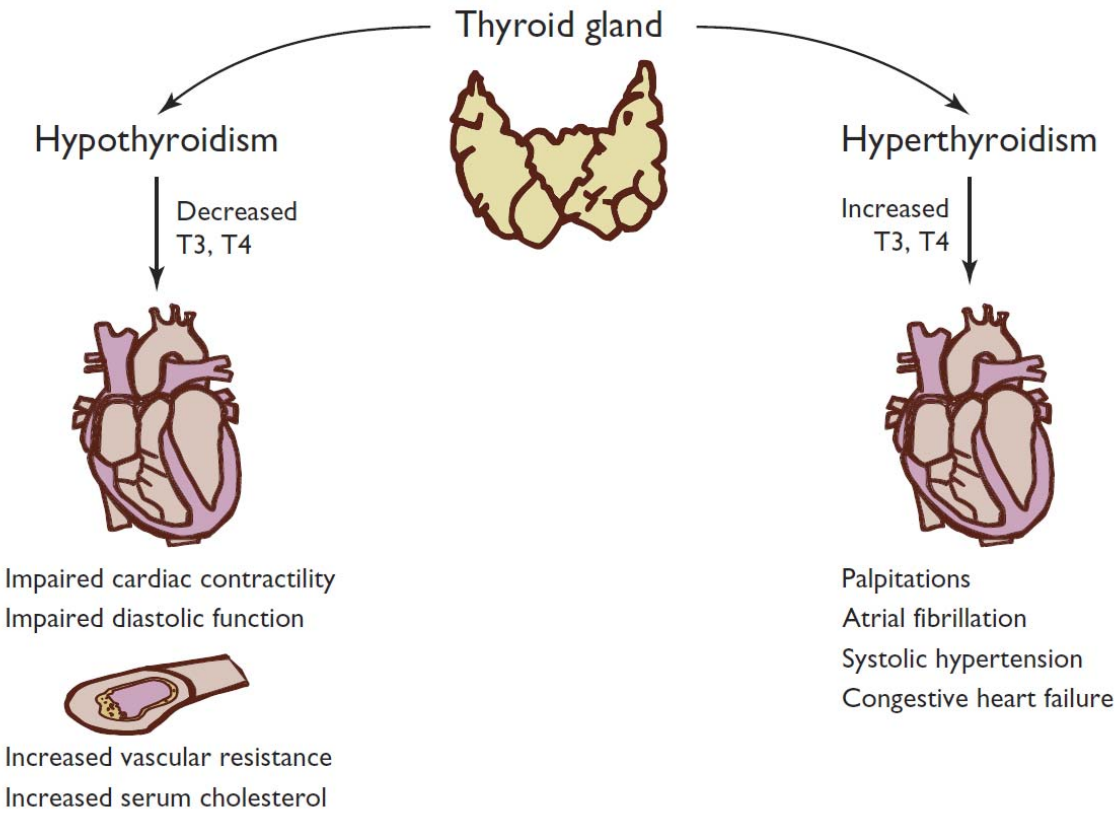


Figure 1. Bar graph showing the prevalence of nonalcoholic fatty liver disease (NAFLD) at baseline at and the 2nd and final computed tomography (CT) scans.

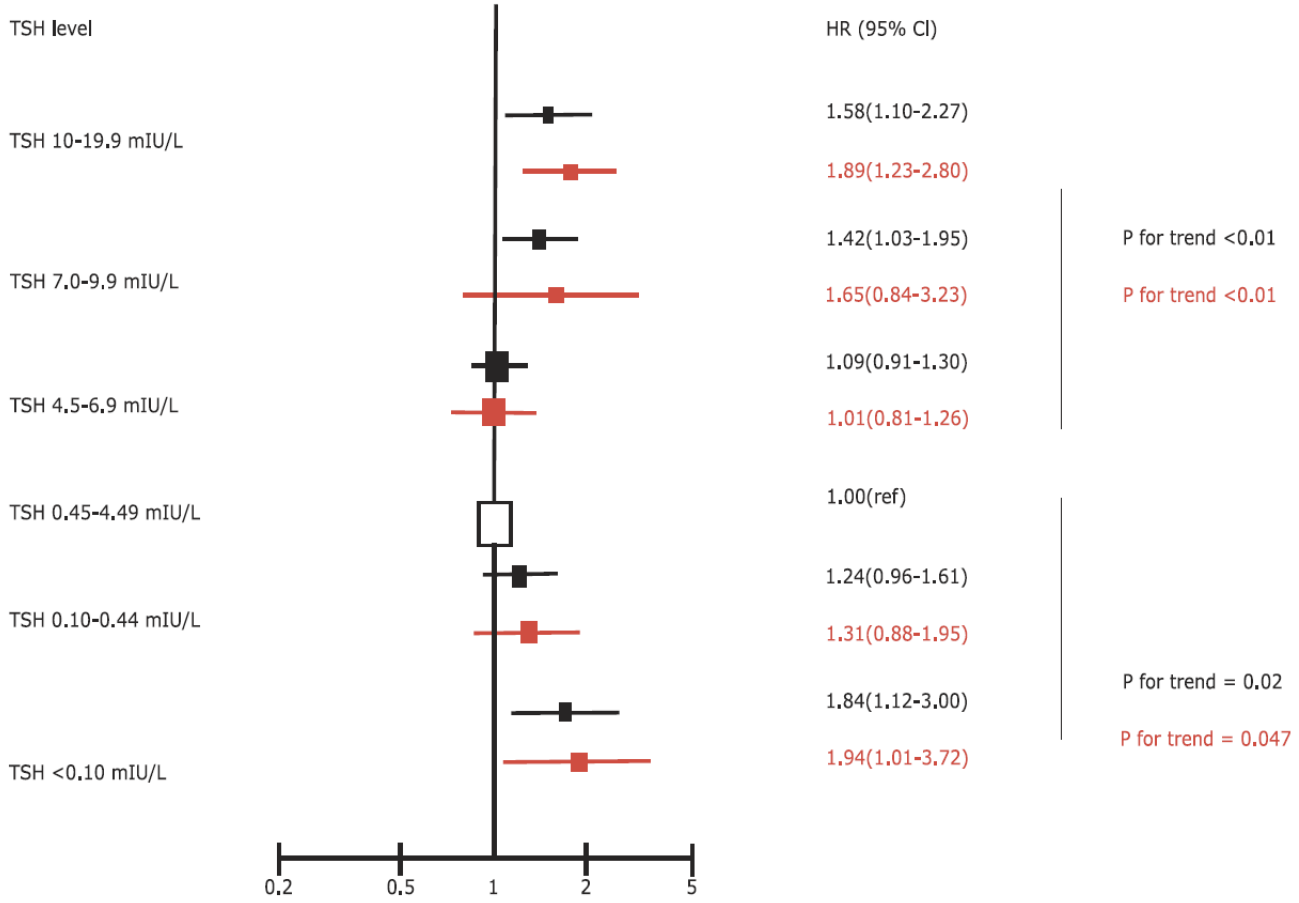
Статины уменьшают риск неалкогольной жировой болезни печени

Foster T, Budoff M, Saab S, et al. Atorvastatin and Antioxidants for the Treatment of Nonalcoholic Fatty Liver Disease: The St Francis Heart Study Randomized Clinical Trial. American Journal of Gastroenterology. 2011;106(1):71-7.

Дисфункции щитовидной железы и болезни сердца



Риски смерти от ИБС и СН при изменении ТТГ

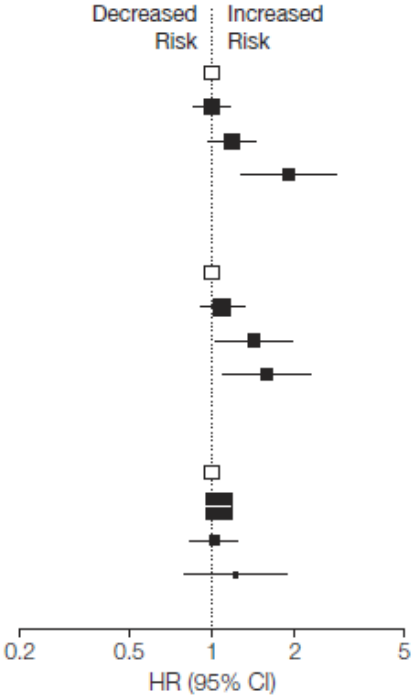


ИБС – черные, СН - красные

Floriani C, Gencer B, Collet T-H, Rodondi N. Subclinical thyroid dysfunction and cardiovascular diseases: 2016 update. Eur Heart J. 2018;39(7):503-507.

Субклинический гипотиреоз и риск ИБС

CHD Events by TSH Level, mIU/L[b]	No. of Events	No. of Participants	HR Ratio (95% CI)
0.5-4.49	4040	23957	1 [Reference]
4.5-6.9	264	1344	1.00 (0.86-1.18)
7.0-9.9	96	441	1.17 (0.96-1.43)
10-19.9	70	235	1.89 (1.28-2.80)
			P<.001 for trend
CHD Mortality by TSH Level, mIU/L[c]			
0.5-4.49	1958	50953	1 [Reference]
4.5-6.9	132	2363	1.09 (0.91-1.30)
7.0-9.9	50	652	1.42 (1.03-1.95)
10-19.9	28	333	1.58 (1.10-2.27)
			P = .005 for trend
Total Mortality by TSH Level, mIU/L[d]			
0.5-4.49	8749	51837	1 [Reference]
4.5-6.9	640	2431	1.06 (0.96-1.17)
7.0-9.9	170	672	1.02 (0.84-1.24)
10-19.9	105	347	1.22 (0.80-1.87)
			P = .39 for trend

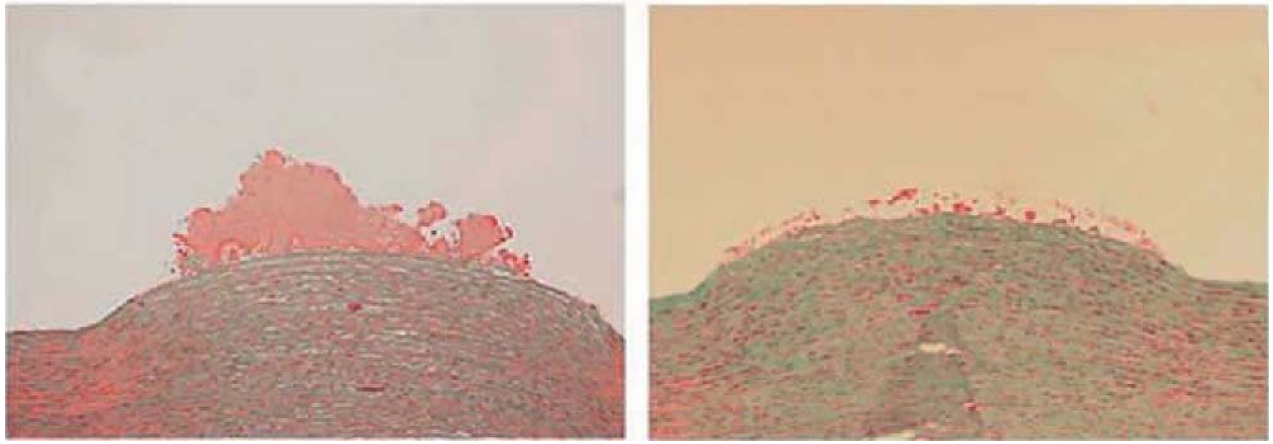


Rodondi N, et al. Subclinical Hypothyroidism and the Risk of Coronary Heart Disease and Mortality. JAMA 2010;304(12):1365-74.

Субклинический гипотиреоз и коронарный тромбоз

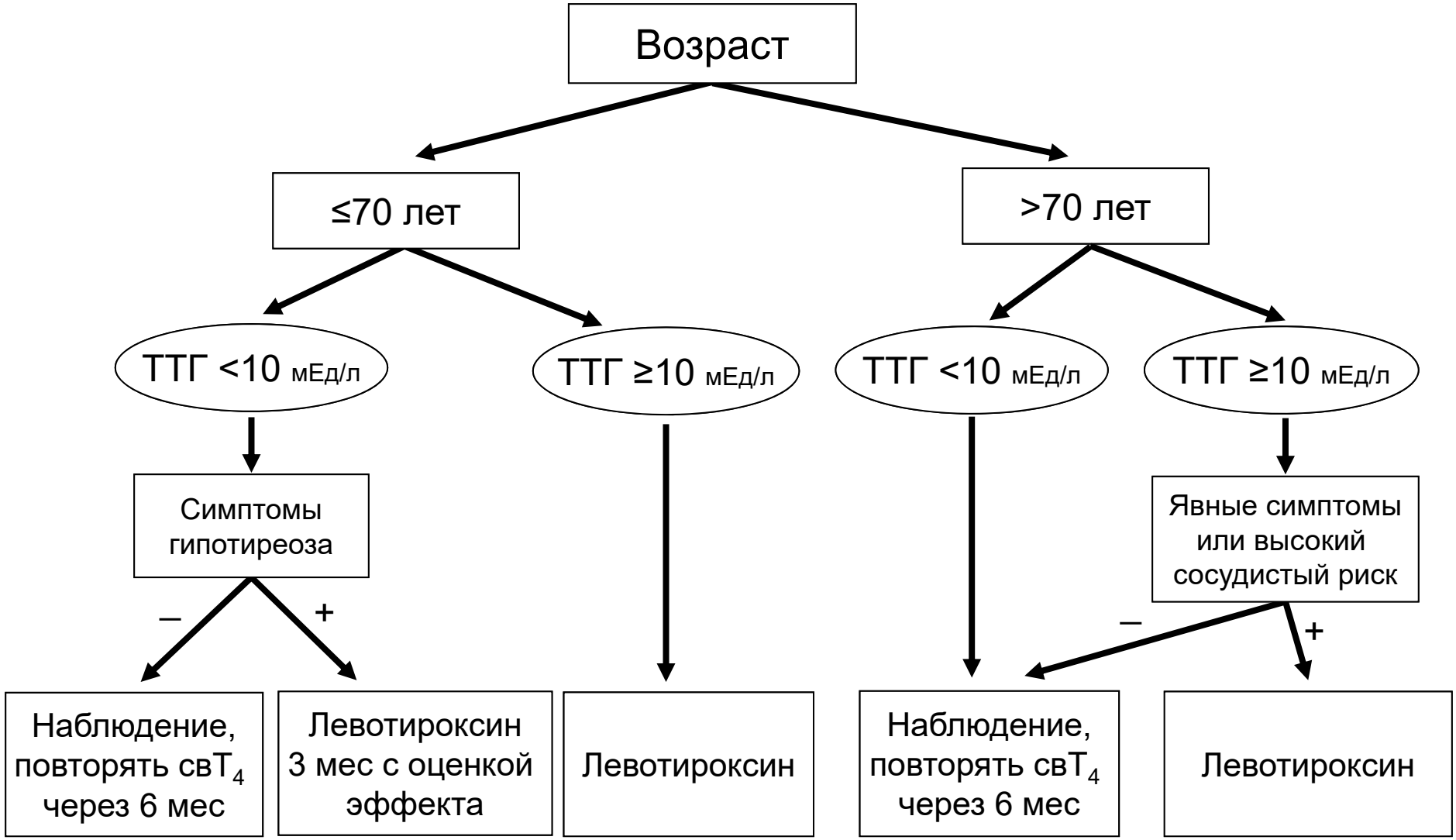
Субклинический гипотиреоз

Эутиреоз



Viswanathan G, et al. Blood Thrombogenicity Is Independently Associated With Serum TSH Levels in Post–Non-ST Elevation Acute Coronary Syndrome. The Journal of Clinical Endocrinology & Metabolism. 2014;6:E1050-E1054.

Ведение субклинического гипотиреоза (ETA)



Лечение субклинического гипотиреоза у пожилых

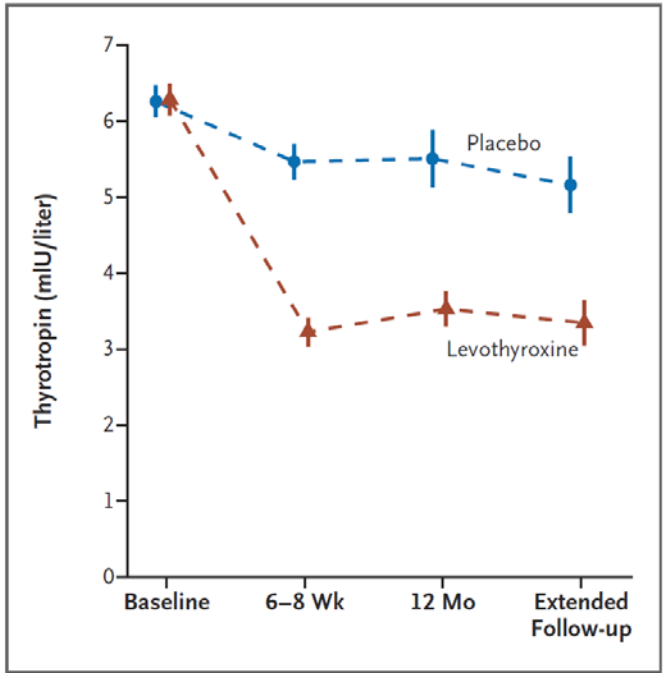


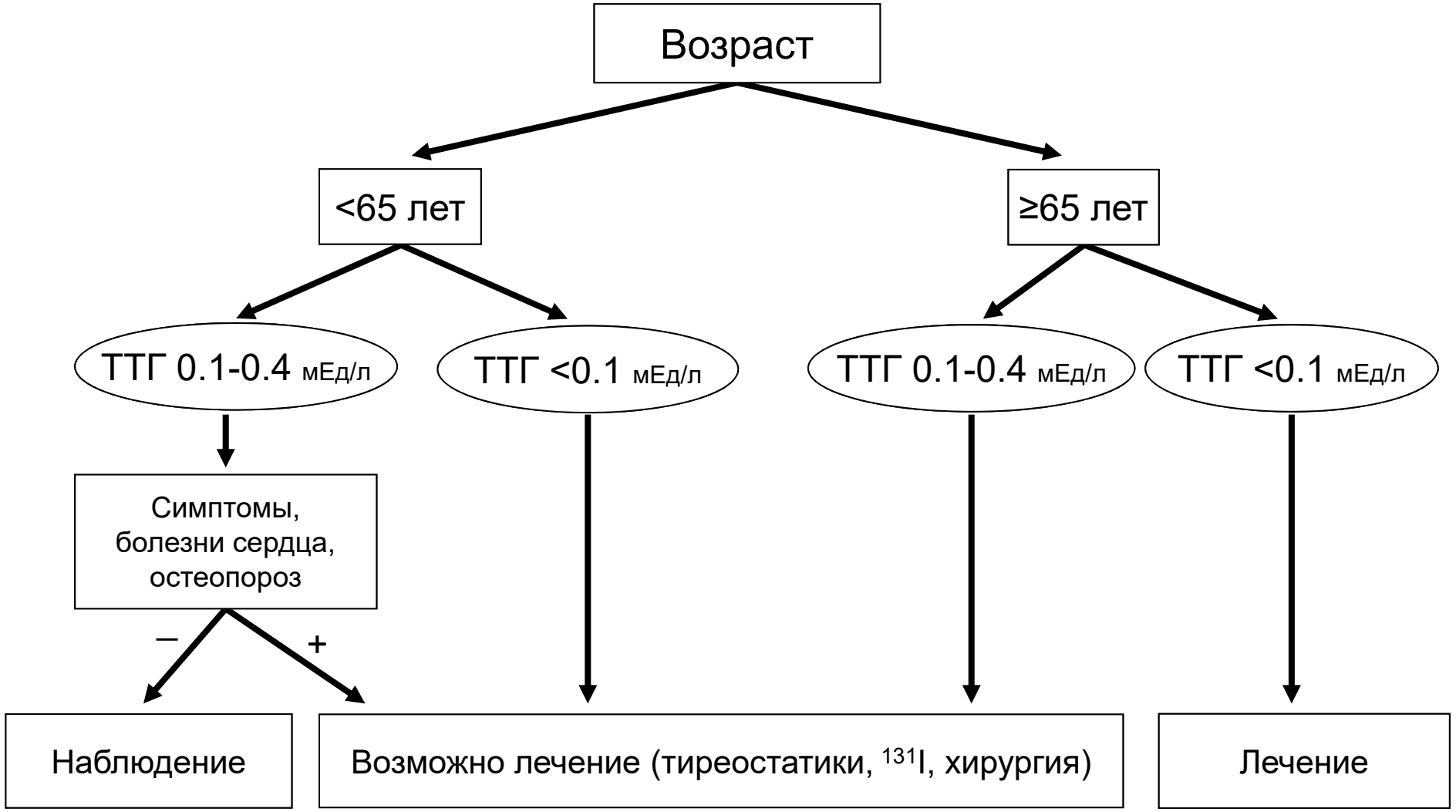
Table 3. Clinical Outcomes and Adverse Events.*

Variable	All Patients (N=737)	Placebo Group (N=369)	Levothyroxine Group (N=368)	Hazard Ratio (95% CI)
Clinical outcome				
Fatal or nonfatal cardiovascular event — no. (%)	38 (5.2)	20 (5.4)	18 (4.9)	0.89 (0.47–1.69)
Cardiovascular death — no. (%)	3 (0.4)	1 (0.3)	2 (0.5)	—
Death from any cause — no. (%)	15 (2.0)	5 (1.4)	10 (2.7)	1.91 (0.65–5.60)
Serious adverse event				
No. of patients with ≥1 serious adverse event	181 (24.6)	103 (27.9)	78 (21.2)	0.94 (0.88–1.00)†
No. of events	343	201	142	—
Adverse event of special interest				
New-onset atrial fibrillation — no. (%)	24 (3.3)	13 (3.5)	11 (3.0)	0.80 (0.35–1.80)
Heart failure — no. (%)	9 (1.2)	6 (1.6)	3 (0.8)	—
Fracture — no. (%)	17 (2.3)	8 (2.2)	9 (2.4)	1.06 (0.41–2.76)
New diagnosis of osteoporosis — no. (%)	7 (0.9)	4 (1.1)	3 (0.8)	—
Withdrawal				
Permanent discontinuation of trial regimen — no. (%)	160 (21.7)	79 (21.4)	81 (22.0)	1.06 (0.78–1.44)
Withdrawal from follow-up — no. (%)	41 (5.6)	22 (6.0)	19 (5.2)	0.84 (0.46–1.56)

Лечение левотироксином не приносит пользы после 70 лет

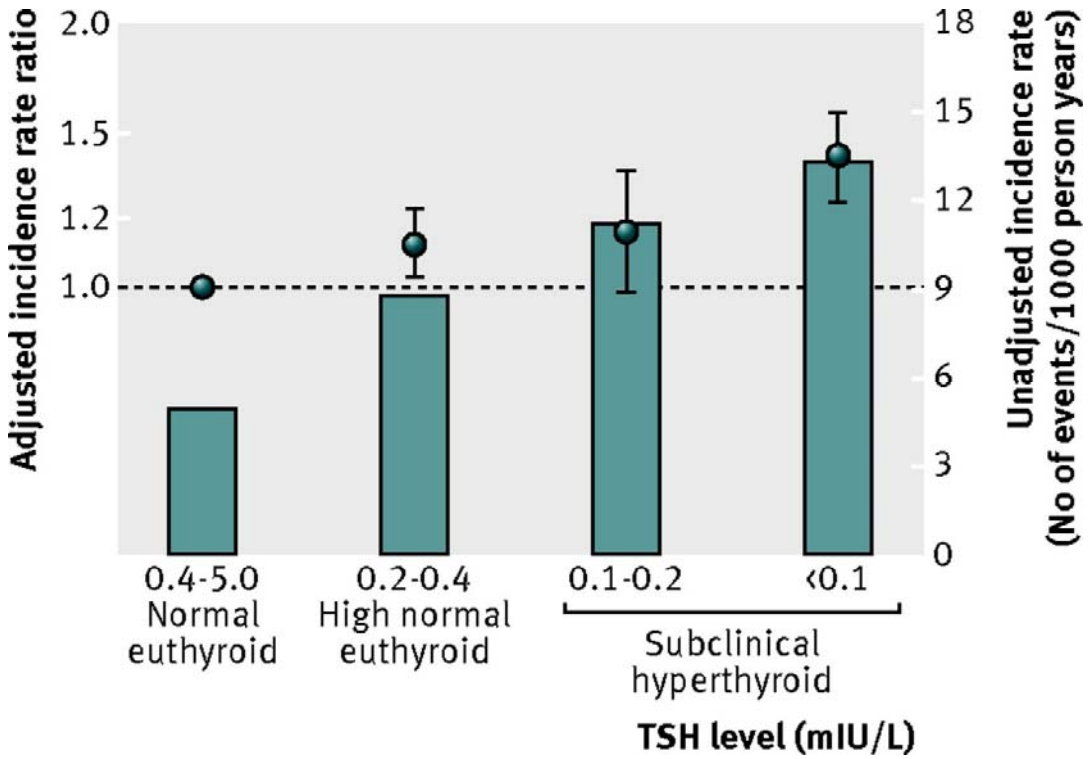
Stott DJ, Rodondi N, Kearney PM, et al. Thyroid Hormone Therapy for Older Adults with Subclinical Hypothyroidism. New Engl J Med. 2017;376(26):2534-2544.

Ведение субклинического гипертиреоза (ATA)



0.5–7% в год явный гипертиреоз
5–12% нормализация

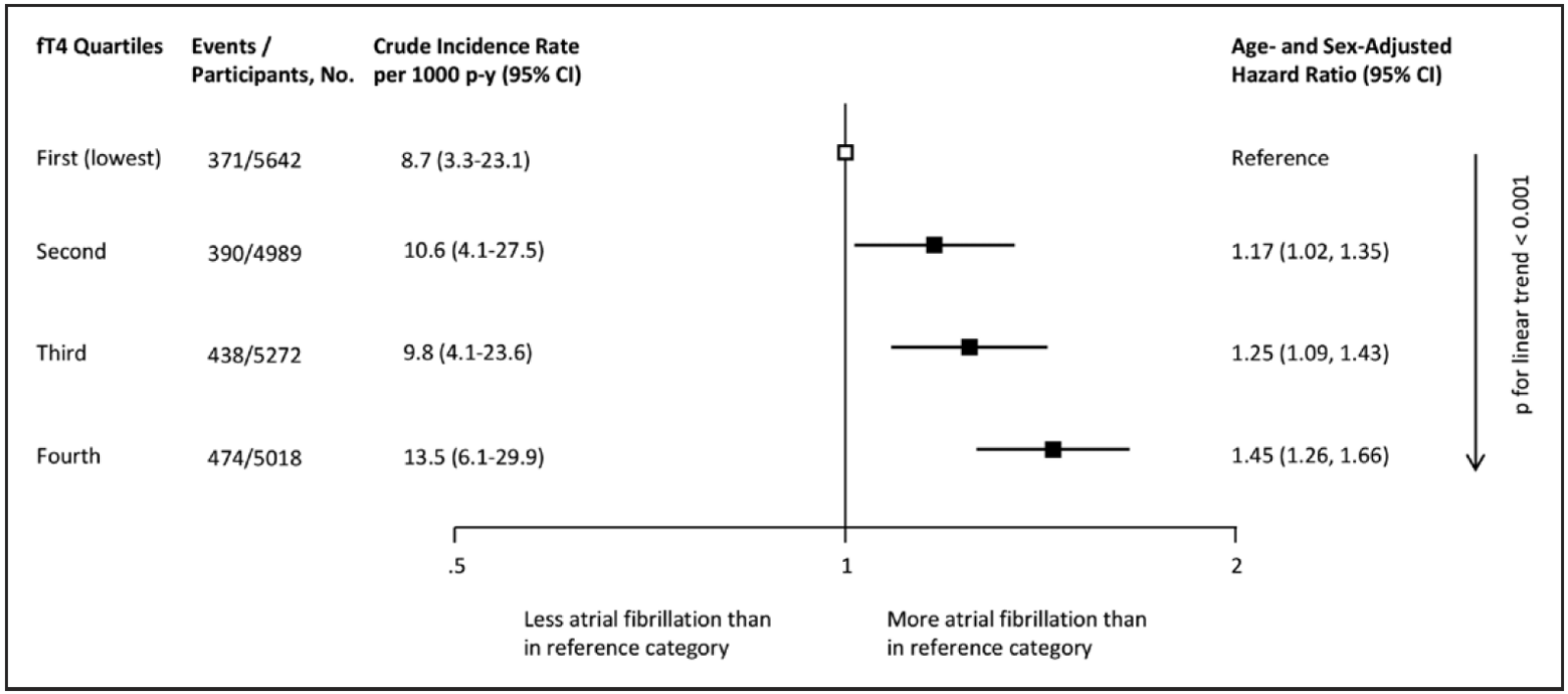
ФП и дисфункция щитовидной железы



У пациентов с ФП может быть полезным лечение субклинического гипертиреоза

Selmer C, Olesen JB, Hansen ML, et al. The spectrum of thyroid disease and risk of new onset atrial fibrillation: a large population cohort study. BMJ 2012;345:e7895

Уровень свободного T_4 и риск ФП



Увеличение свободного тироксина даже в «нормальном» диапазоне повышает риск ФП

Baumgartner C, da Costa BR, Collet T-H, et al. Thyroid Function Within the Normal Range, Subclinical Hypothyroidism, and the Risk of Atrial Fibrillation. Circulation. 2017;136(22):2100.

Риск тромбоэмболий при гипертиреозе

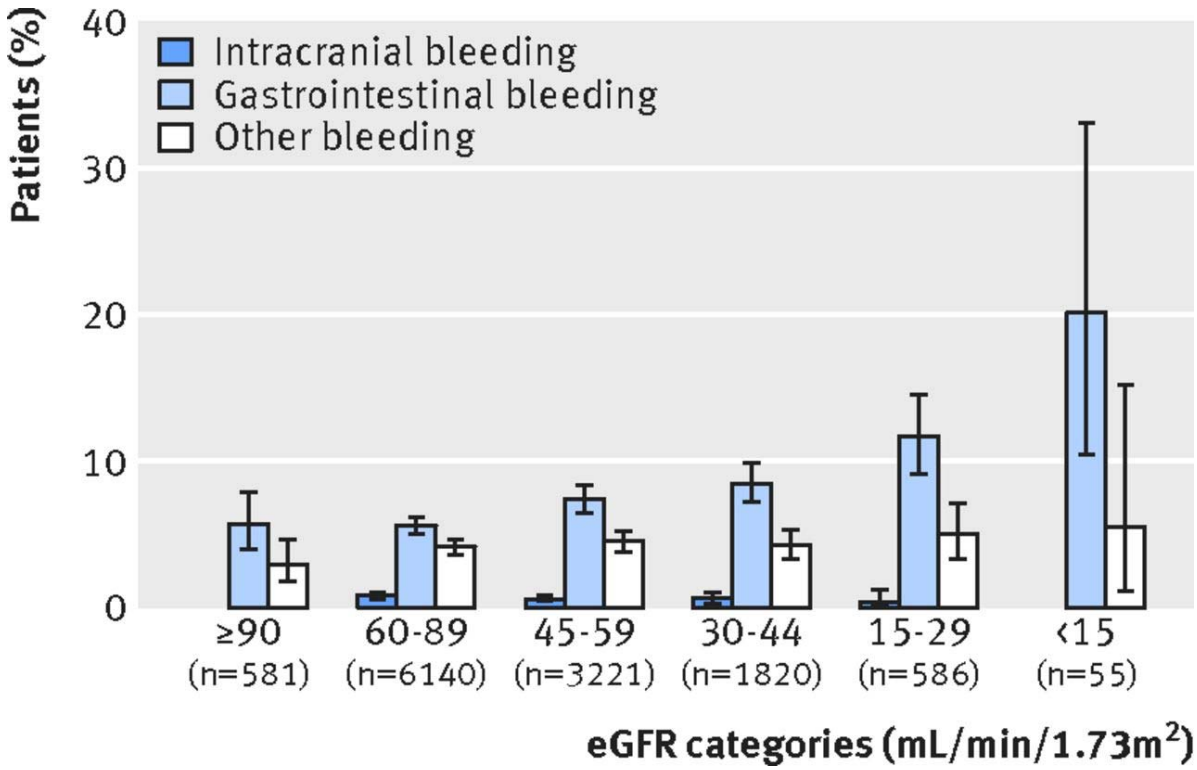
	SEC plus Low LAA velocities		Thrombogenic milieu	
	OR (95% CI)	*P -value*	*OR (95% CI)*	*P-value*
PSAP range				
More than 40 mmHg	1.791(0.461; 0.962)	0.400	0.677 (0.188; 2.441)	0.551
Free T4				
Above 2x ref range	0.716 (0.180; 2.857)	0.637	0.941 (0.247; 3.586)	0.929
Duration of thyrotoxicosis	**4.486 (1.146; 17.563)**	**0.031**	2.841 (0.757; 10.660)	0.122
> 12 months				
CHA_2DS_2-VASc risk	0.419 (0.103; 1.709)	0.225	0.650 (0.174; 2.435)	0.523
High ≥2				

Длительность гипертиреоза >12 мес (не CHA_2DS_2-VASc) увеличивает риск тромбообразования в предсердиях

de Souza M. et al. Is CHA2DS2-VASc appropriate for hyperthyroid patients with atrial fibrillation? Implications of adding a transesophageal echocardiography evaluation. Int J Card. 2017;228:919-925.

Дисфункция почек и фибрилляция предсердий

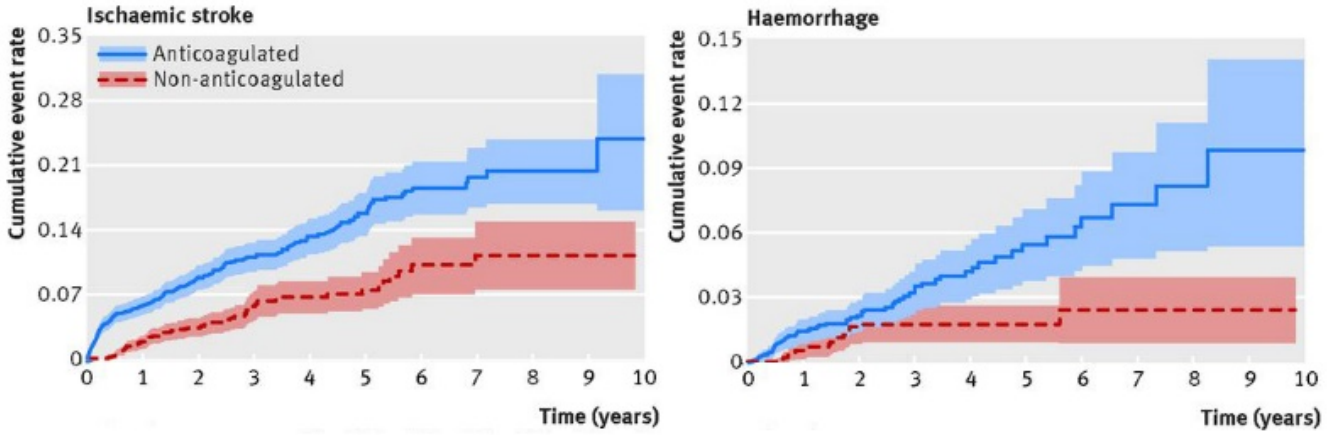
Риск кровотечений при ФП и дисфункции почек на варфарине



При снижении функции почек значительно возрастает частота гастроинтестинальных кровотечений

Jun M, et al. The association between kidney function and major bleeding in older adults with atrial fibrillation starting warfarin treatment: population based observational study. BMJ 2015;350.

Риск ишемического инсульта и кровотечений при дисфункции почек



2.73 million patients from 110 general practices across England and Wales.

У пациентов старше 65 лет с рСКФ <50 мл/мин/1.73 м^2 на антикоагулянтах увеличен риск инсультов и кровотечений (требуются индивидуальные решения)

Kumar S, et al. Ischaemic stroke, haemorrhage, and mortality in older patients with chronic kidney disease newly started on anticoagulation for atrial fibrillation: a population based study from UK primary care. BMJ. 2018;360.

НОАК и гастроинтестинальные кровотечения

Table 5. Stratified Analysis in Propensity Score Matched Apixaban vs Dabigatran Users

	Apixaban (n = 6542)		Dabigatran (n = 6542)		Apixaban vs dabigatran (n = 13,084)	
Variable	Events, n	IR	Events, n	IR	HR (95% CI)	*P* for interaction
Overall	33	1.38	121	2.73	0.39*** (0.27–0.58)	
Age						
18–64 y	2	0.34	7	0.73	0.38 (0.08–1.84)	.54
65–74 y	5	0.69	29	2.12	0.25** (0.10–0.65)	
≥75 y	26	2.43	85	4.06	0.45*** (0.29–0.71)	

NOTE. *P* value in the table is for interaction; **$P < .01$; ***$P < .001$ indicates significance for the HR.
IR, incidence rate per 100 person-years.

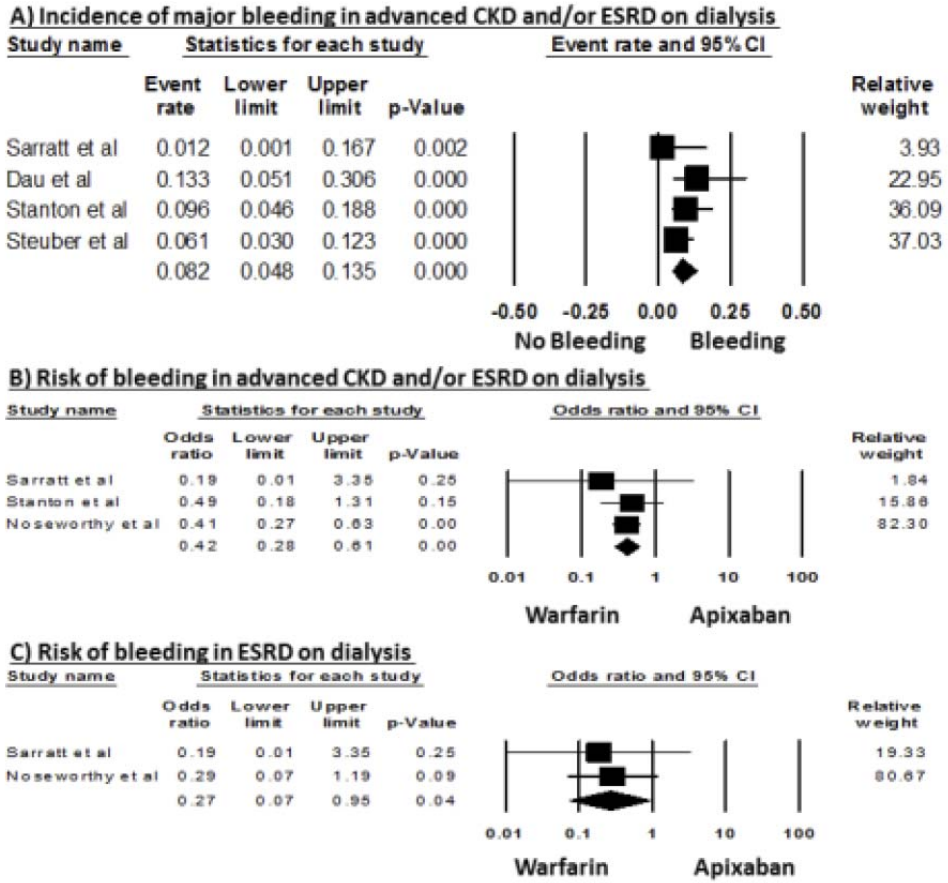
Table 6. Stratified Analysis in Propensity Score–Matched Apixaban vs Rivaroxaban Users

	Apixaban (n = 6565)		Rivaroxaban (n = 6565)		Apixaban vs rivaroxaban (n = 13,130)	
Variable	Events, n	IR	Events, n	IR	HR (95% CI)	*P* for interaction
Overall	32	1.34	116	3.54	0.33*** (0.22–0.49)	
Age						
18–64 y	2	0.34	6	0.81	0.38 (0.08–1.89)	.36
65–74 y	5	0.69	32	3.24	0.18*** (0.07–0.47)	
≥75 y	25	2.32	78	5.05	0.39*** (0.25–0.61)	

NOTE. *P* value in the table is for interaction; ***$P < .001$ indicates significance for the HR.
IR, incidence rate per 100 person-years.

Abraham NS, et al. Gastrointestinal Safety of Direct Oral Anticoagulants: A Large Population-Based Study. Gastroenterology. 2017;152(5):1014-1022.e1011.

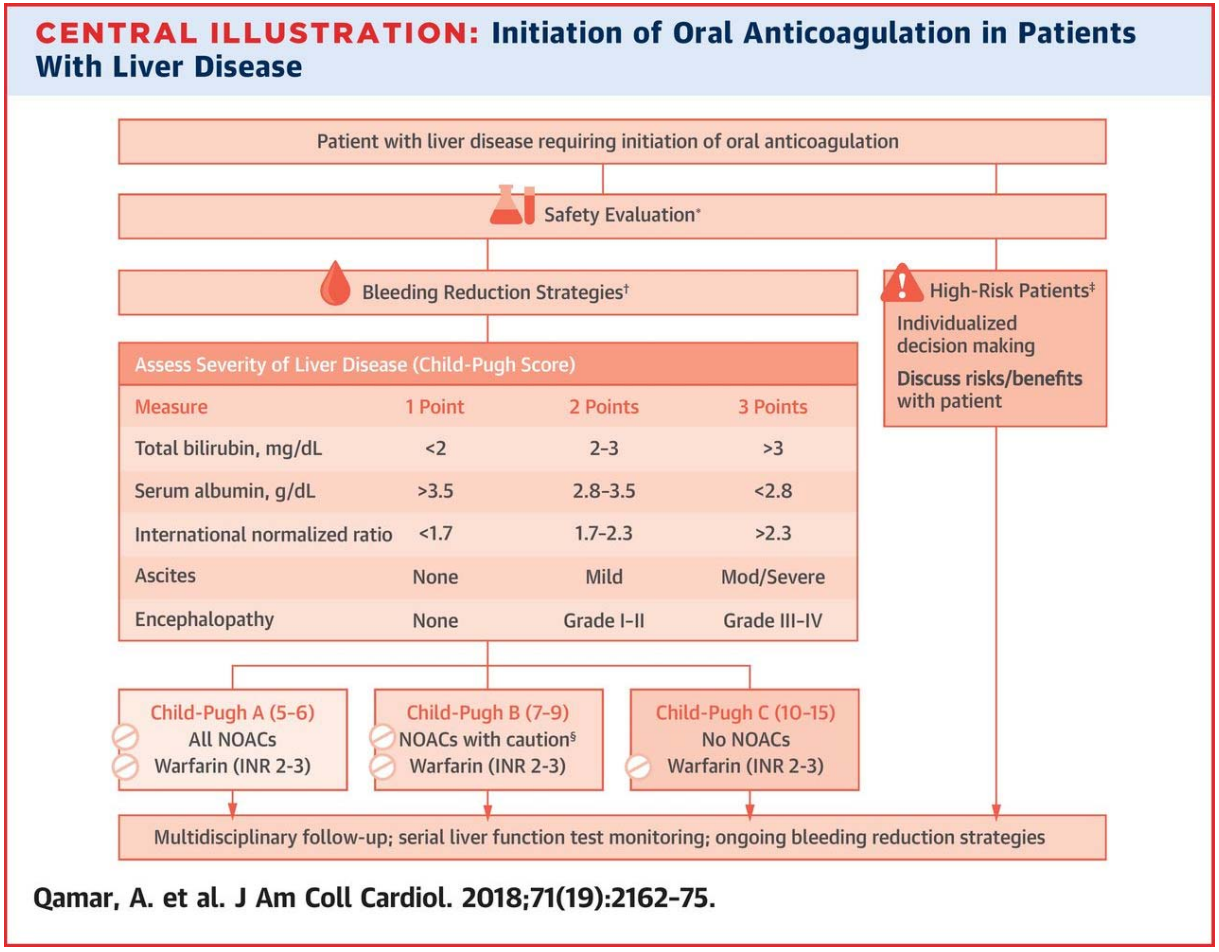
Апиксабан и терминальная ХБП



Метаанализ

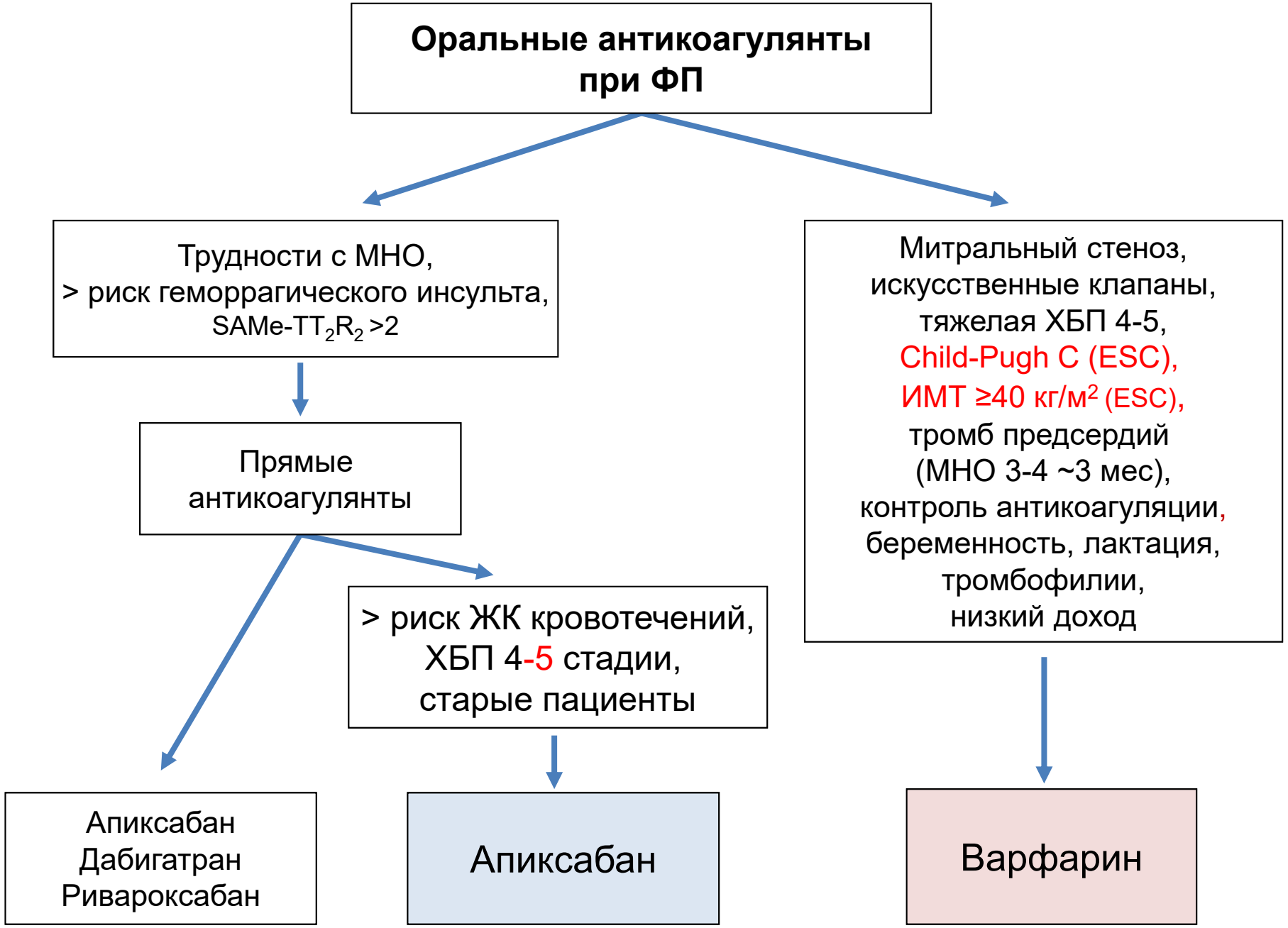
Chokesuwattanaskul R, et al. Safety and efficacy of apixaban versus warfarin in patients with end-stage renal disease: Meta-analysis. Pacing Clin Electrophysiol. 2018 Mar 25.

Антикоагулянты при болезни печени



Отсутствие контроля препятствует использованию прямых антикоагулянтов

Qamar A, Vaduganathan M, Greenberger N, et al. Oral Anticoagulation in Patients With Liver Disease. Journal of the American College of Cardiology. 2018;19:2162-2175.


Оральные антикоагулянты при ФП
Трудности с МНО, > риск геморрагического инсульта, SAMe-TT2R2 >2
Прямые антикоагулянты
Апиксабан Дабигатран Ривароксабан
> риск ЖК кровотечений, ХБП 4-5 стадии, старые пациенты
Апиксабан
Митральный стеноз, искусственные клапаны, тяжелая ХБП 4-5, Child-Pugh C (ESC), ИМТ ≥40 кг/м2 (ESC), тромб предсердий (МНО 3-4 ~3 мес), контроль антикоагуляции, беременность, лактация, тромбофилии, низкий доход
Варфарин

НПВП, ингибиторы протонной помпы и сердечно-сосудистый риск

НПВП и риск ИМ, инсульта

Table 4
Risk of stroke and acute myocardial infarction in relation to nonsteroidal anti-inflammatory drugs use among patients with rheumatoid arthritis, based on different lengths for case and control periods

	Case Period 1–14 days Control Period 15–28 days				Case Period 1–30 days Control Period 31–60 days				Case Period 1–30 days Control Period 61–90 days			
	Crude OR	(95%CI)	Adjusted OR*	(95%CI)	Crude OR	(95%CI)	Adjusted OR*	(95%CI)	Crude OR	(95%CI)	Adjusted OR*	(95%CI)
Stroke and AMI (n = 5921)												
Overall NSAIDs use	1.46†	(1.33–1.60)	1.44†	(1.30–1.59)	1.51†	(1.37–1.67)	1.41†	(1.27–1.56)	1.42†	(1.29–1.55)	1.30†	(1.18–1.44)
Selective NSAIDs	0.96	(0.79–1.15)	0.88	(0.72–1.09)	1.40†	(1.15–1.70)	1.20	(0.97–1.49)	1.43†	(1.18–1.74)	1.23	(0.99–1.52)
Nonselective NSAIDs	1.62†	(1.46–1.79)	1.54†	(1.39–1.72)	1.50†	(1.36–1.66)	1.41†	(1.27–1.57)	1.41†	(1.29–1.55)	1.31†	(1.19–1.45)
Stroke (n = 5001)												
Overall NSAIDs use	1.45†	(1.31–1.61)	1.45†	(1.29–1.62)	1.50†	(1.35–1.67)	1.43†	(1.28–1.60)	1.42†	(1.28–1.57)	1.32†	(1.19–1.48)
Selective NSAIDs	0.90	(0.73–1.11)	0.84	(0.67–1.06)	1.35†	(1.09–1.68)	1.20	(0.95–1.50)	1.38†	(1.12–1.71)	1.22	(0.97–1.53)
Nonselective NSAIDs	1.61†	(1.44–1.80)	1.56†	(1.39–1.75)	1.49†	(1.33–1.66)	1.42†	(1.27–1.59)	1.40†	(1.27–1.56)	1.31†	(1.18–1.46)
AMI (n = 920)												
Overall NSAIDs use	1.48†	(1.18–1.86)	1.45†	(1.11–1.90)	1.58†	(1.23–2.02)	1.31	(0.99–1.74)	1.39	(1.10–1.75)	1.17	(0.90–1.53)
Selective NSAIDs	1.19	(0.79–1.78)	1.22	(0.71–2.07)	1.65†	(1.02–2.69)	1.10	(0.62–1.96)	1.72†	(1.05–2.82)	1.12	(0.61–2.03)
Nonselective NSAIDs	1.63†	(1.27–2.10)	1.50†	(1.14–1.98)	1.58†	(1.23–2.02)	1.39†	(1.06–1.82)	1.45†	(1.15–1.83)	1.30†	(1.00–1.69)

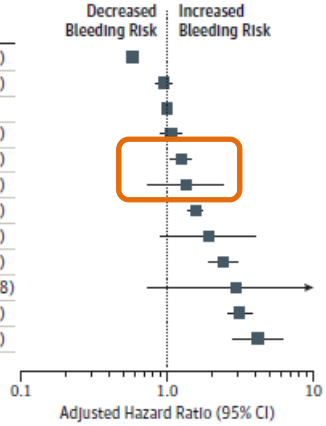
**Селективные НПВП не более опасны,
чем неселективные НПВП в отношении ССЗ**

Chen Y, Hsieh F, Chang C, et al. Effect on Risk of Stroke and Acute Myocardial Infarction of Nonselective Nonsteroidal Anti-Inflammatory Drugs in Patients With Rheumatoid Arthritis. American Journal of Cardiology. 2018;10:1271-1277.

НПВП + аспирин или клопидогрел

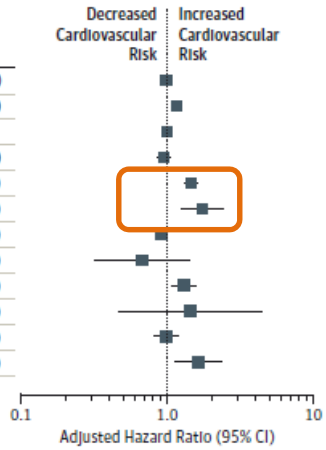
A Bleeding risk

	Events, No.	Sample Size, No.	Crude Rate (95% CI), Events per 100 Person-Years	Adjusted Hazard Ratio (95% CI)
Aspirin	2109	221458	1.5 (1.5-1.6)	0.58 (0.53-0.63)
Clopidogrel	258	35814	3.3 (2.9-3.7)	0.95 (0.83-1.09)
Clopidogrel + aspirin	1184	99468	3.3 (3.1-3.5)	1 [Reference]
Oral anticoagulants	175	24588	4.0 (3.5-4.7)	1.06 (0.90-1.25)
Aspirin + NSAID	176	57016	3.2 (2.8-3.8)	1.24 (1.05-1.47)
Clopidogrel + NSAID	11	3419	4.1 (2.3-7.3)	1.34 (0.74-2.42)
Oral anticoagulants + single antiplatelet	477	49504	5.2 (4.7-5.7)	1.56 (1.39-1.75)
Oral anticoagulants + NSAID	7	1478	7.2 (3.4-15.1)	1.92 (0.91-4.03)
Clopidogrel + aspirin + NSAID	83	14105	7.6 (6.2-9.5)	2.41 (1.93-3.01)
Triple therapy + NSAID	2	382	10.0 (2.5-39.9)	2.94 (0.73-11.78)
Triple therapy	116	8250	12.7 (10.6-15.2)	3.12 (2.57-3.78)
Oral anticoagulants + single antiplatelet + NSAID	26	2922	13.1 (8.9-19.3)	4.15 (2.81-6.13)



B Cardiovascular risk

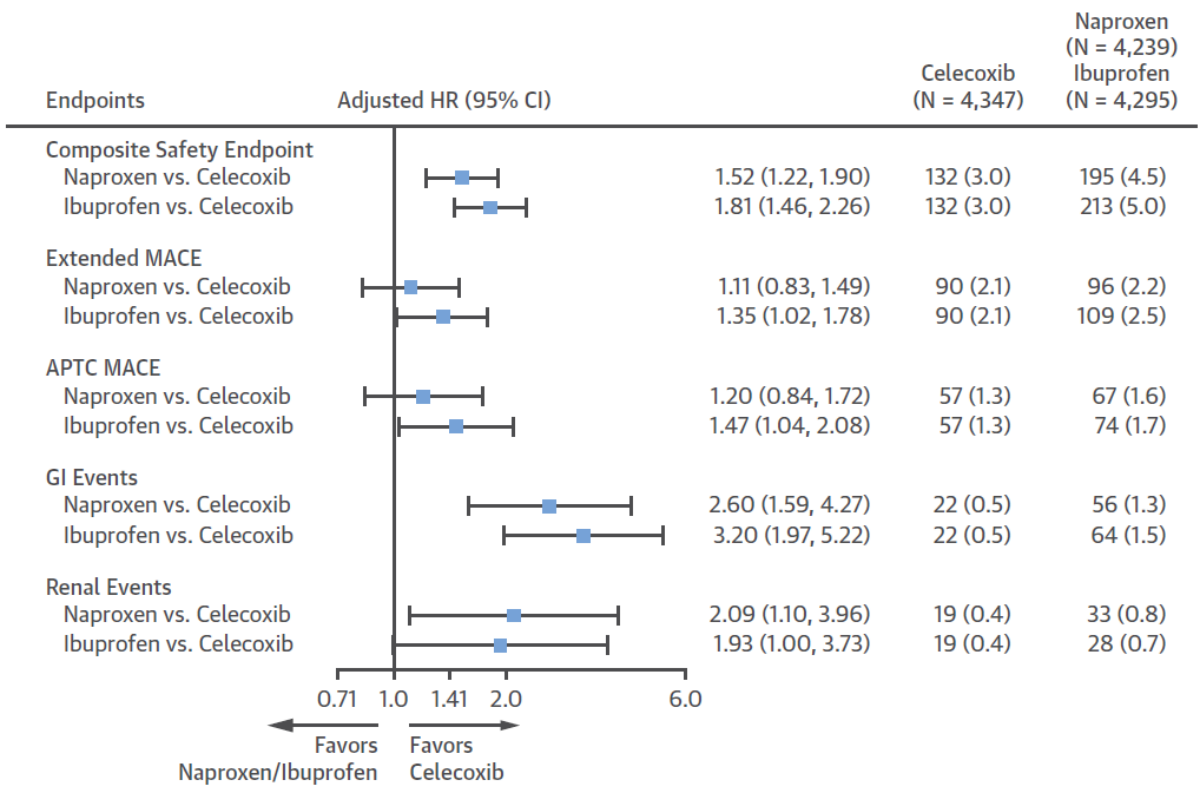
	Events, No.	Sample Size, No.	Crude Rate (95% CI), Events per 100 Person-Years	Adjusted Hazard Ratio (95% CI)
Aspirin	9194	209681	7.1 (6.9-7.2)	0.98 (0.94-1.03)
Clopidogrel	822	32494	11.6 (10.8-12.4)	1.16 (1.07-1.25)
Clopidogrel + aspirin	3229	90153	10.0 (9.7-10.4)	1 [Reference]
Oral anticoagulants	454	22979	11.2 (10.2-12.2)	0.94 (0.85-1.04)
Aspirin + NSAID	529	54076	10.3 (9.4-11.2)	1.46 (1.32-1.60)
Clopidogrel + NSAID	37	3073	15.4 (11.2-21.3)	1.75 (1.26-2.41)
Oral anticoagulants + single antiplatelet	822	45292	9.7 (9.0-10.3)	0.91 (0.84-1.00)
Oral anticoagulants + NSAID	7	1362	7.7 (3.7-16.2)	0.67 (0.32-1.41)
Clopidogrel + aspirin + NSAID	123	12608	12.7 (10.6-15.1)	1.30 (1.08-1.55)
Triple therapy + NSAID	3	324	18.8 (6.0-58.2)	1.44 (0.46-4.45)
Triple therapy	119	7213	14.9 (12.5-17.9)	0.98 (0.82-1.17)
Oral anticoagulants + single antiplatelet + NSAID	30	2722	16.0 (11.2-22.8)	1.62 (1.13-2.33)



Schjerning Olsen A, Gislason GH, McGettigan P, et al. Association of NSAID Use With Risk of Bleeding and Cardiovascular Events in Patients Receiving Antithrombotic Therapy After Myocardial Infarction. JAMA. 2015;313(8):805-814.

Аспирин + НПВП

FIGURE 1 Outcomes in Non-Aspirin Users on Naproxen or Ibuprofen Compared With Celecoxib



The number of events (percentage of total) is reported. APTC = Antiplatelet Trialists' Collaboration; CI = confidence interval; GI = gastrointestinal; HR = hazard ratio; MACE = major adverse cardiovascular event.

Целекоксиб безопаснее в сочетании с аспирином, чем неселективные НПВП

Reed G, et al. Effect of Aspirin Coadministration on the Safety of Celecoxib, Naproxen, or Ibuprofen. Journal of the American College of Cardiology. 2018;16:1741-1751.

Недостатки длительного лечения ИПП

Table 2. Absolute and Relative Risks for Adverse Effects Associate

Potential adverse effect	Relative risk
Chronic kidney disease[1]	10% to 20% increase
Dementia[2]	4% to 80% increase
Bone Fracture[3]	30% to 4-fold increase
Myocardial infarction	No association in RCTs
Small intestinal bacterial overgrowth	2-fold to 8-fold increase
Campylobacter or *Salmonella* infection	2-fold to 6-fold increase
Spontaneous bacterial peritonitis[4]	50% to 3-fold increase
Clostridium difficile infection[5]	No risk to 3-fold increase
Pneumonia	No association in RCTs
Micronutrient deficiencies[6]	60% to 70% increase
Gastrointestinal malignancies	No association in RCTs

ИПП могут вызывать различные неблагоприятные события, включая инфекции

Table 1. Summary of Evidence for Potential PPI-Associated Adverse Effects

Potential adverse effect	Types of studies	Threats to validity	Overall quality of evidence
Kidney disease	• Observational only	• Modest effect size • Residual confounding would bias towards harm • Absence of dose-response effect	Very low
Dementia	• Observational only	• Modest effect size • Residual confounding would bias towards harm	Very low
Bone fracture	• Observational only	• Inconsistent results • Modest effect size • Residual confounding would bias towards harm	Low or very low
Myocardial infarction	• Observational • RCT	• Results differ between RCTs and observational studies • Secondary analysis of RCT data • Modest effect size • Residual confounding would bias towards harm	Very low
Small intestinal bacterial overgrowth	• Observational • Crossover	• Sparse data • Residual confounding would bias towards harm • Protopathic bias	Low
Spontaneous bacterial peritonitis	• Observational only	• Modest effect size • Residual confounding would bias towards harm	Very low
Clostridium difficile infection	• Observational only	• Modest effect size • Residual confounding would bias towards harm	Low
Pneumonia	• Observational • RCT	• Results differ between RCTs and observational studies • Secondary analysis of RCT data • Modest effect size • Absence of dose-response effect • Residual confounding would bias towards harm • Protopathic bias	Very low
Micronutrient deficiencies	• Observational only	• Inconsistent results • Modest effect size • Absence of dose-response effect • Residual confounding would bias towards harm	Low or very low
Gastrointestinal malignancies	• Observational • RCT	• Results differ between RCTs and observational studies • RCTs use surrogate outcomes • Modest effect size • Residual confounding would bias towards harm • Confounding by indication and protopathic bias	Very low

AGA CLINICAL PRACTICE UPDATE: EXPERT REVIEWS

The Risks and Benefits of Long-term Use of Proton Pump Inhibitors: Expert Review and Best Practice Advice From the American Gastroenterological Association

ИПП и риск рака

Table 4 HRs and 95% CIs for the association between frequency and duration of PPIs use and risk of gastric cancer (propensity score adjustment with trimming)

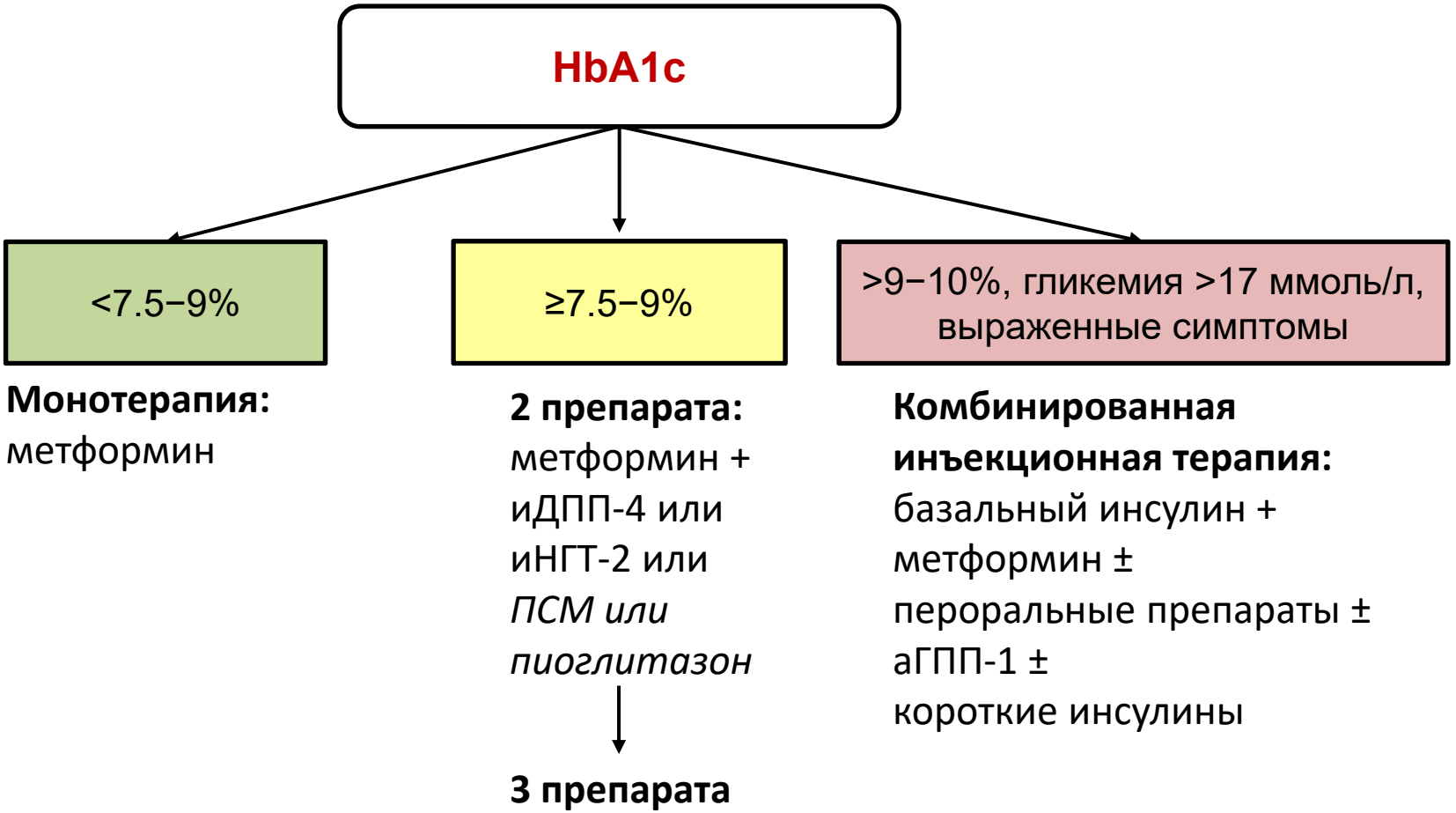
	Dose–-response relationship (n=57 057, GC=139)								
PPIs frequency	**HR**			**95% CI**			**p Value**		
Non-user (<weekly use)	Ref			–			–		
Weekly to <daily	2.43			1.37 to 4.31			0.002		
Daily	4.55			1.12 to 18.52			0.034		
PPIs frequency	PPIs use ≥1 year (n=50 932, GC=112)			PPIs use ≥2 years (n=49 462, GC=88)			PPIs use ≥3 years (n=48 511, GC=69)		
	HR	95% CI	p Value	HR	95% CI	p Value	HR	95% CI	p Value
Non-user (<weekly use)	Ref	–	–	Ref	–	–	Ref	–	–
Weekly to<daily	1.81	0.90–3.64	0.098	0.98	0.31–3.17	0.979	0.58	0.08–4.23	0.590
Daily	5.04	1.23–20.61	**0.024**	6.65	1.62–27.26	**0.009**	8.34	2.02–34.41	**0.004**

63 397 subjects, 153 (0.24%) developed GC during a median follow-up of 7.6 years

Cheung KS, et al Long-term proton pump inhibitors and risk of gastric cancer development after treatment for Helicobacter pylori: a population-based study. Gut 2018;67:28-35.

Диабет

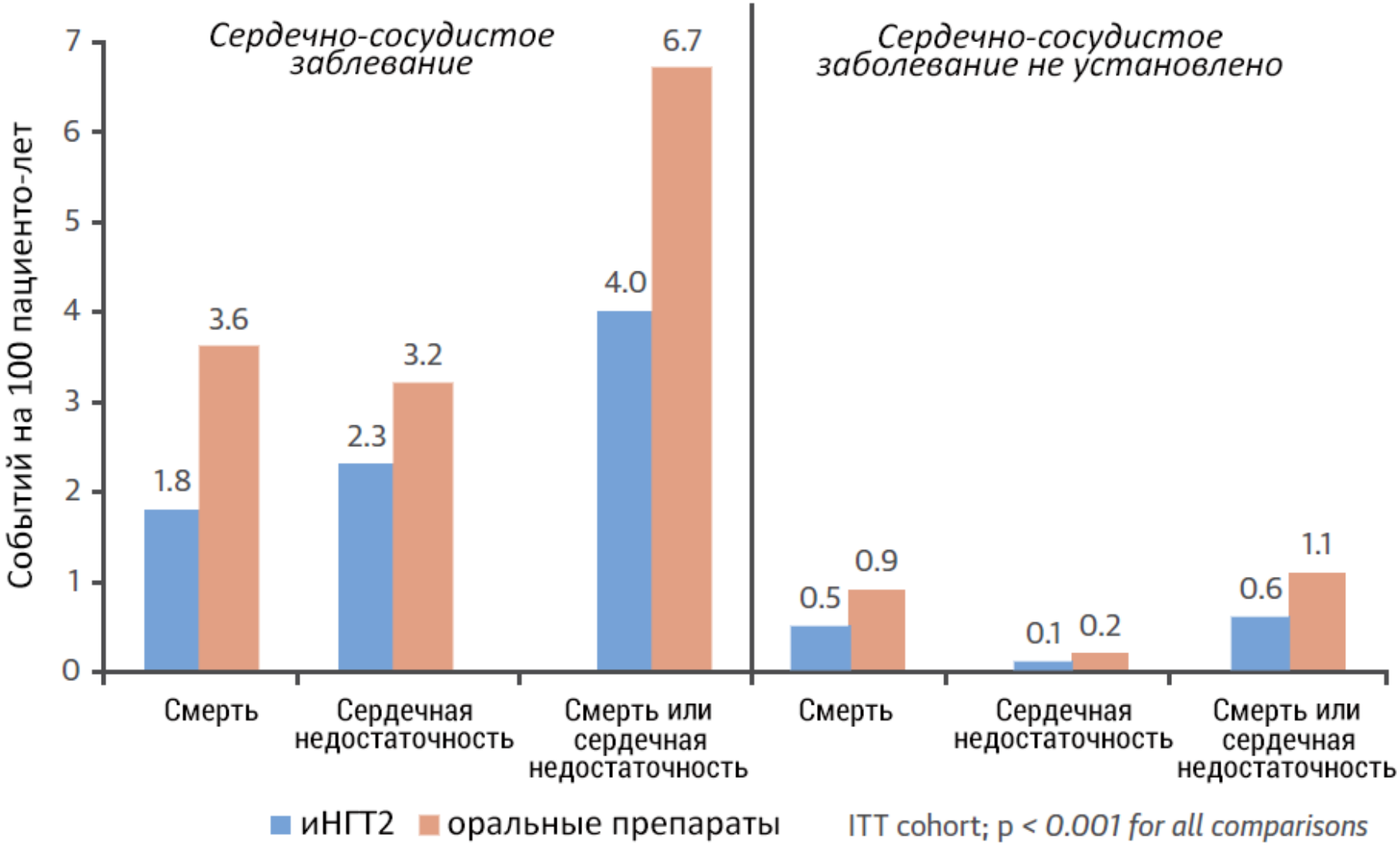
Выбор стартовой терапии



Интервал подбора дозы 3-6 мес

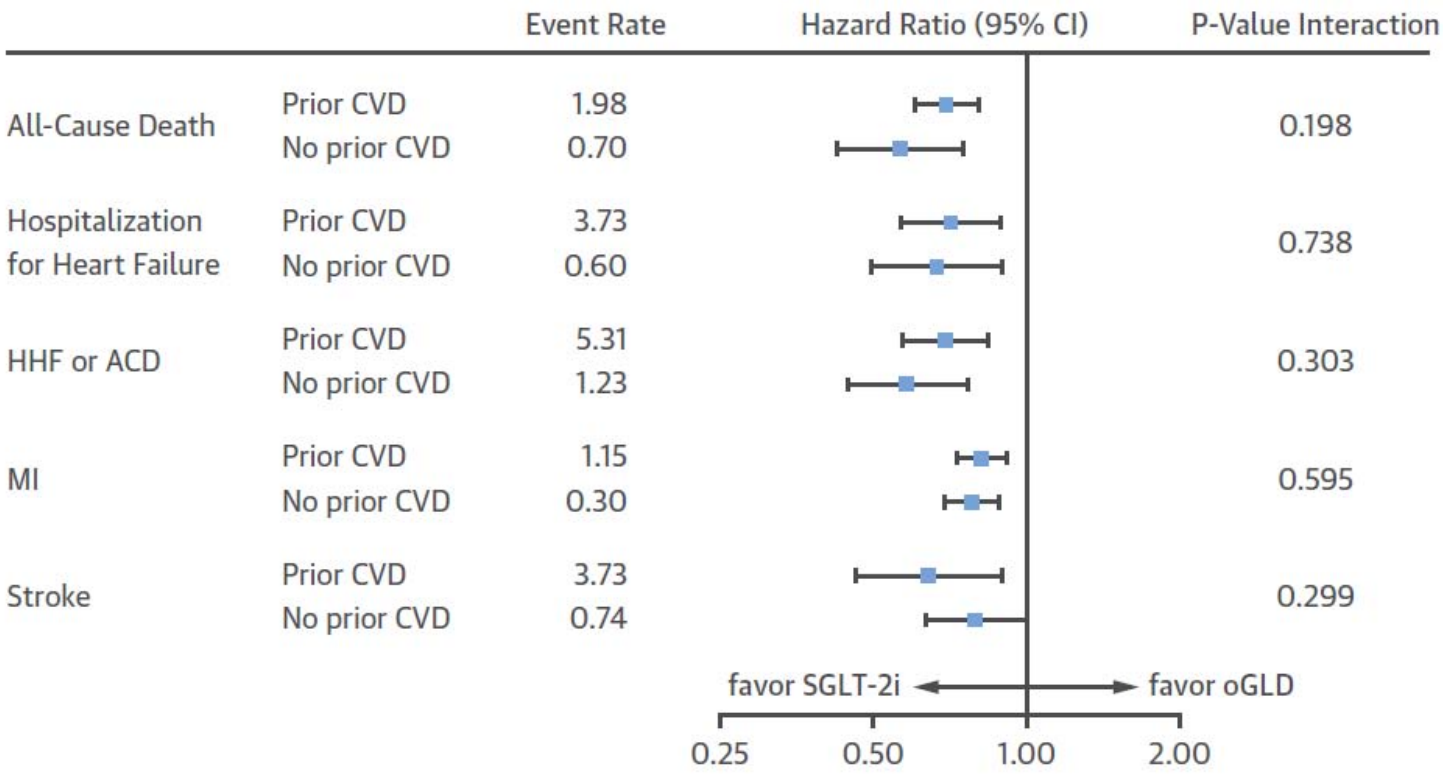
ADA, AACE/ACE

иНГТ-2 и сердечно-сосудистые риски



Cavender M, Norhammar A, Birkeland K, et al. SGLT-2 Inhibitors and Cardiovascular Risk. Journal of the American College of Cardiology. 2018;22:2497-2506.

иНГТ-2 и сердечно-сосудистые риски

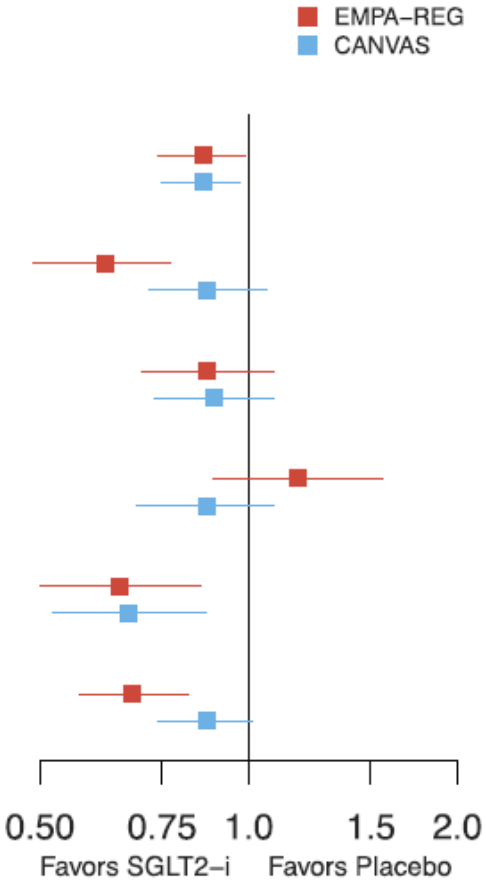


Ингибиторы натрий-глюкозного транспортера 2 снижают СС риски

Kosiborod M, Lam C, Kohsaka S, et al. Cardiovascular Events Associated With SGLT-2 Inhibitors Versus Other Glucose-Lowering Drugs. Journal of the American College of Cardiology. 2018;23:2628-2639.

иНГТ-2 и сердечно-сосудистые риски

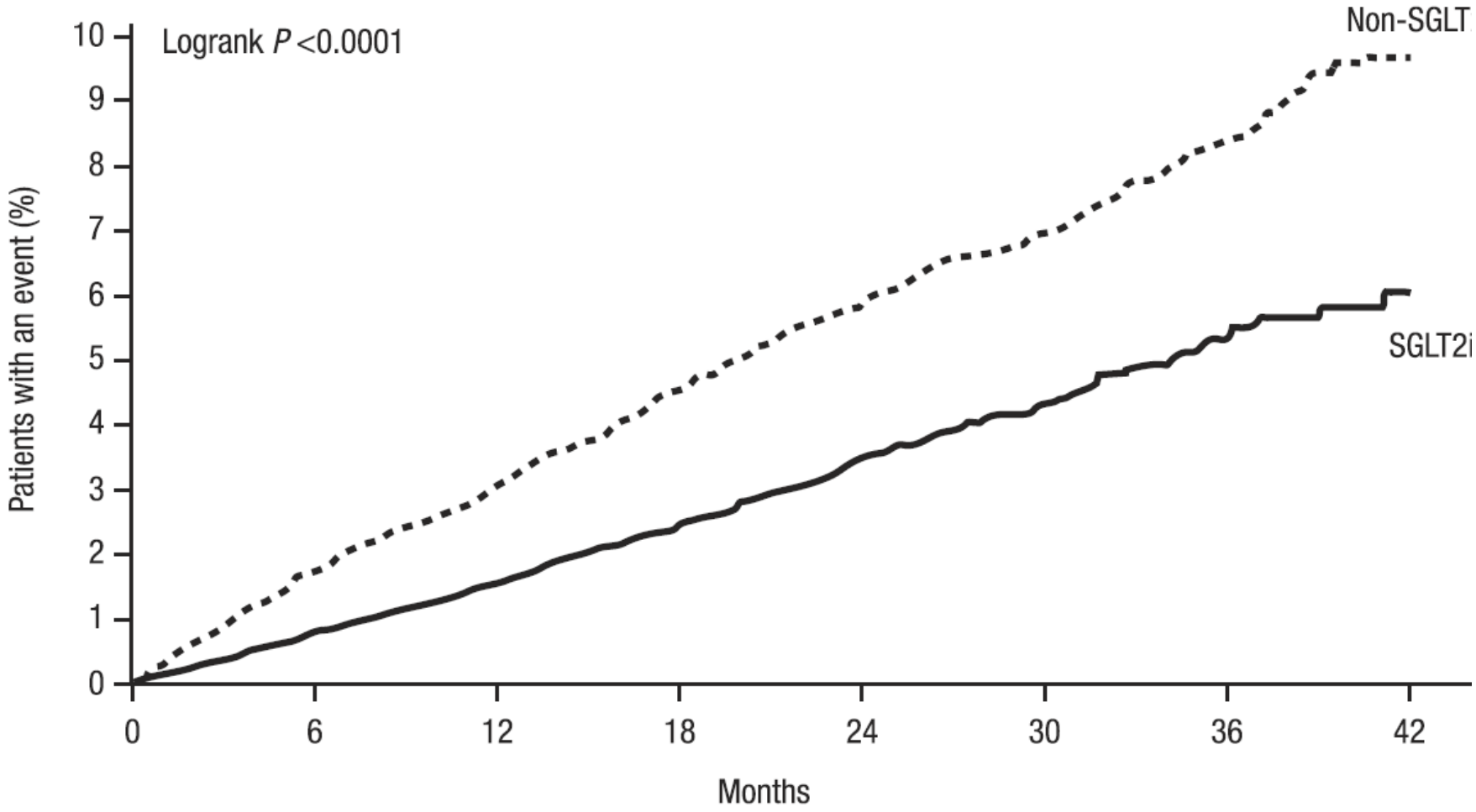
	Active Rate per 1000 patient-years	Placebo Rate per 1000 patient-years	Hazard Ratio (95% CI)
MACE-3	37.4	43.9	0.86 (0.74 – 0.99)
	26.9	31.5	0.86 (0.75 – 0.97)
CV Death	12.4	20.2	0.62 (0.49 – 0.77)
	11.6	12.8	0.87 (0.72 – 1.06)
Fatal and nonfatal MI	16.8	19.3	0.87 (0.70 – 1.09)
	11.2	12.6	0.89 (0.73 – 1.09)
Fatal and nonfatal stroke	12.3	10.5	1.18 (0.89 – 1.56)
	7.9	9.6	0.87 (0.69 – 1.09)
Heart failure hospitalization	19.4	14.5	0.65 (0.50 – 0.85)
	5.5	8.7	0.67 (0.52 – 0.87)
All cause mortality	19.4	28.6	0.68 (0.57 – 0.82)
	17.3	19.5	0.87 (0.74 – 1.01)



Ингибиторы натрий-глюкозного транспортера 2 снижают СС риски

Bethel MA, McMurray JJV. Class Effect for Sodium Glucose-Cotransporter-2 Inhibitors in Cardiovascular Outcomes. Circulation. 2018;137(12):1218.

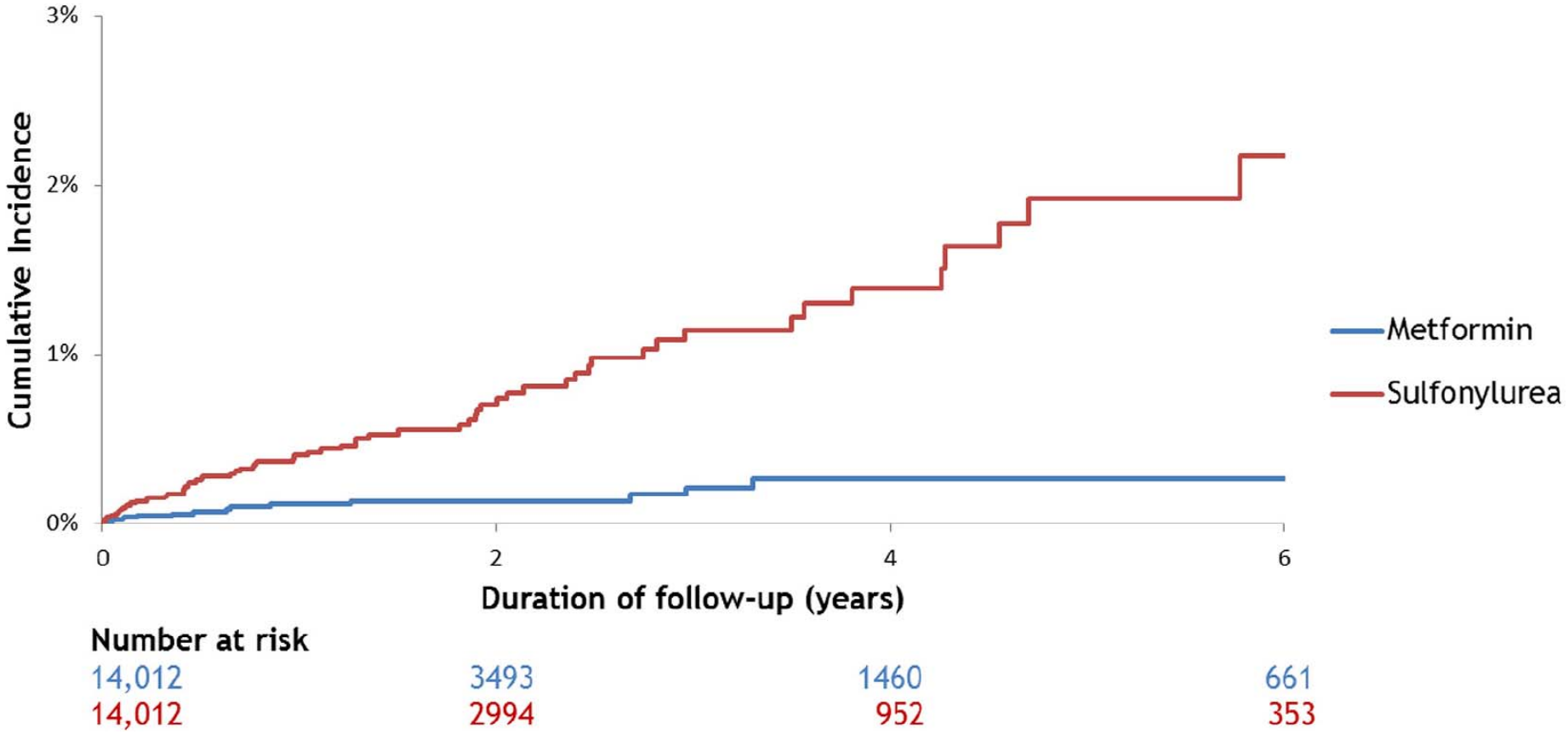
ИНГТ-2



EASEL

Udell J, Yuan Z, Rush T, et al. Cardiovascular Outcomes and Risks After Initiation of a Sodium Glucose Cotransporter 2 Inhibitor. Circulation. 2018;14:1450-1459.

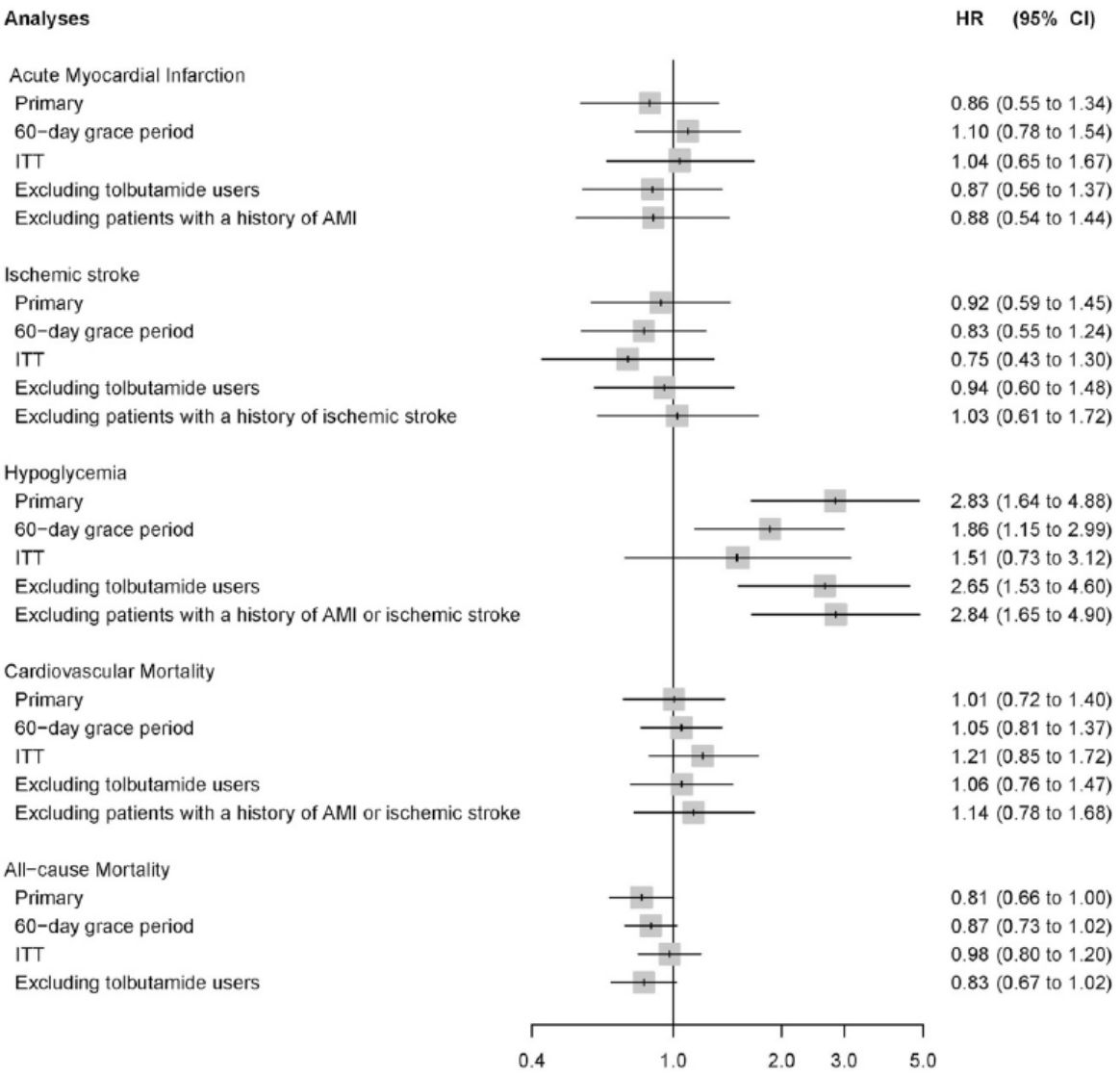
Риск гипогликемии у ПСМ



Гипогликемия у гликлазида и глимеприд реже, чем у глибенкламида

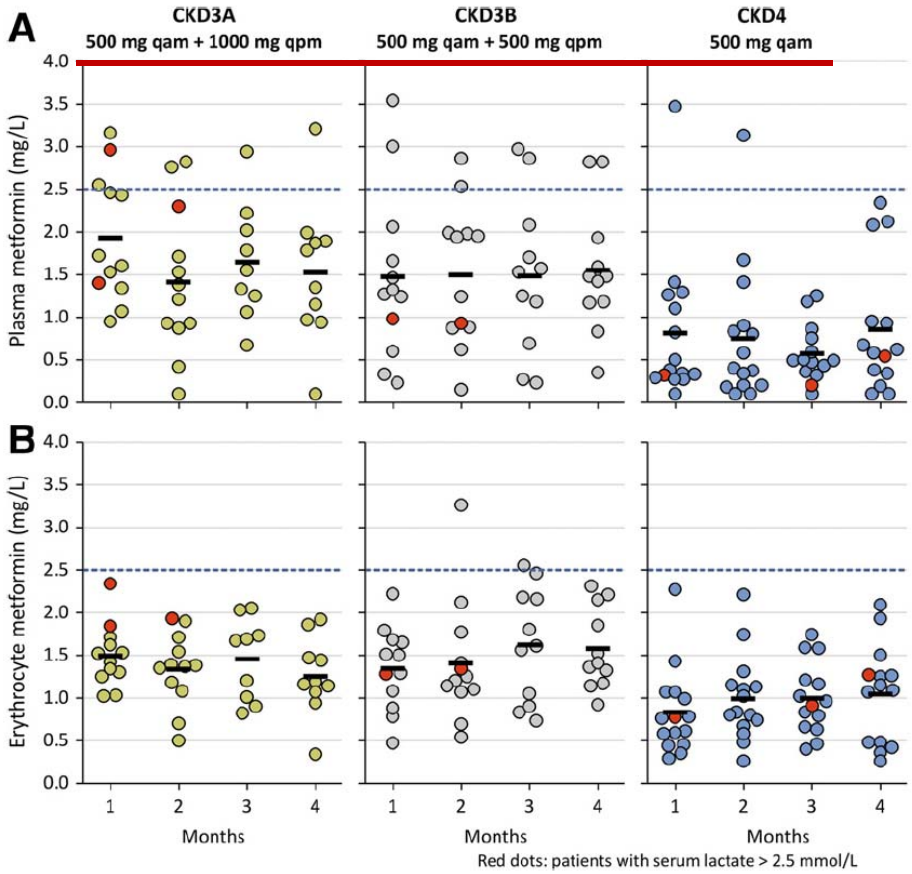
Yu O, Azoulay L, Yin H, et al. Sulfonylureas as Initial Treatment for Type 2 Diabetes and the Risk of Severe Hypoglycemia. Am J Med. 2018;131(3):317.e311-317.e322.

Длительно- и короткодействующие ПСМ



Douros A, Yin H, Yu O, et al. Pharmacologic Differences of Sulfonylureas and the Risk of Adverse Cardiovascular and Hypoglycemic Events. Diabetes Care. 2017;40(11):1506.

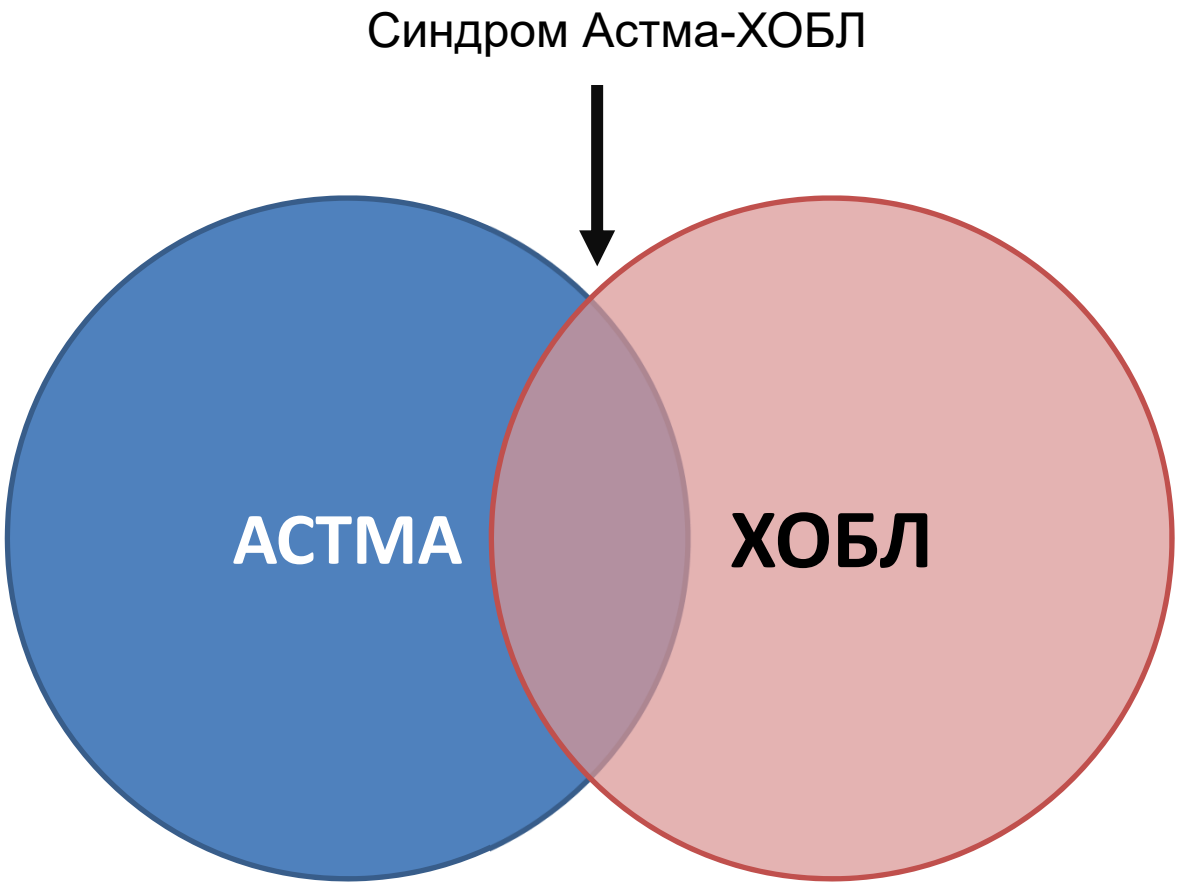
Метформин и дисфункция почек



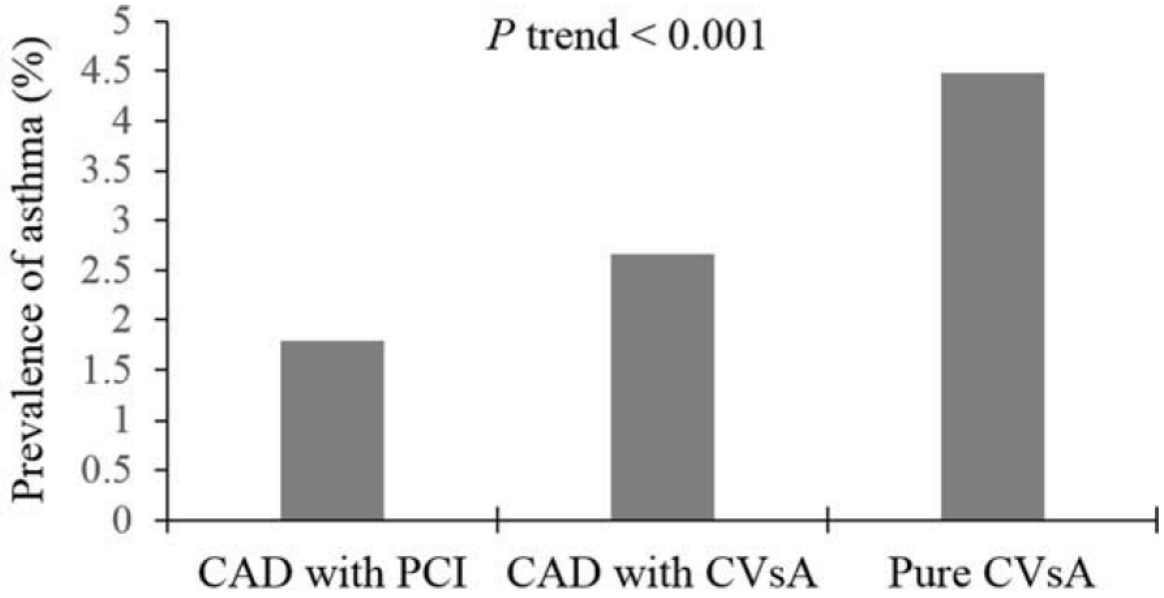
Метформин с коррекцией дозы безопасен при ХБП 3-4 стадий

Lalau J-D, Kajbaf F, Bennis Y, et al. Metformin Treatment in Patients With Type 2 Diabetes and Chronic Kidney Disease Stages 3A, 3B, or 4. Diabetes Care. 2018;41(3):547.

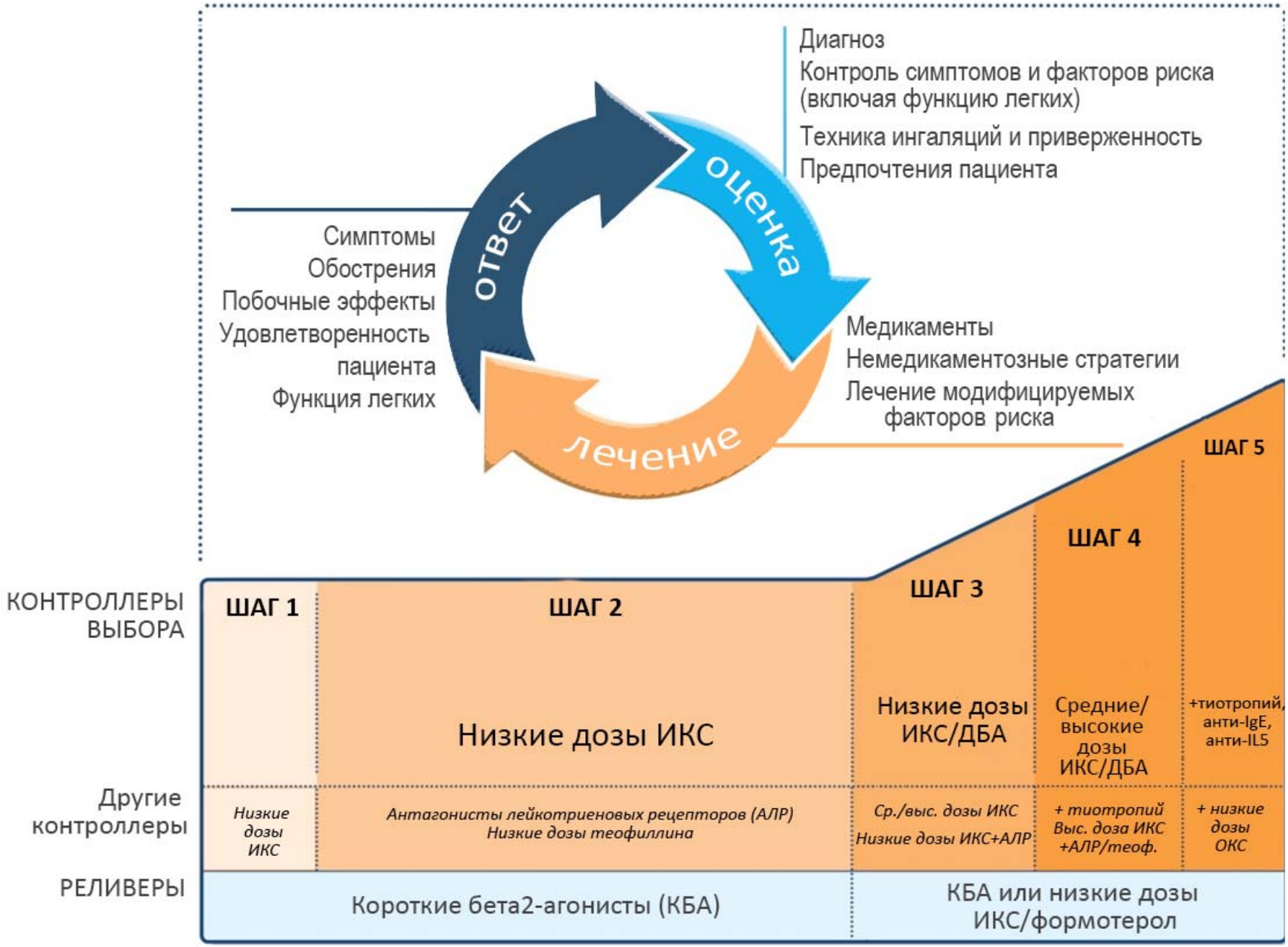
ИБС и бронхиальная астма


Синдром Астма-ХОБЛ
АСТМА
ХОБЛ

Астма и вазоспастическая стенокардия

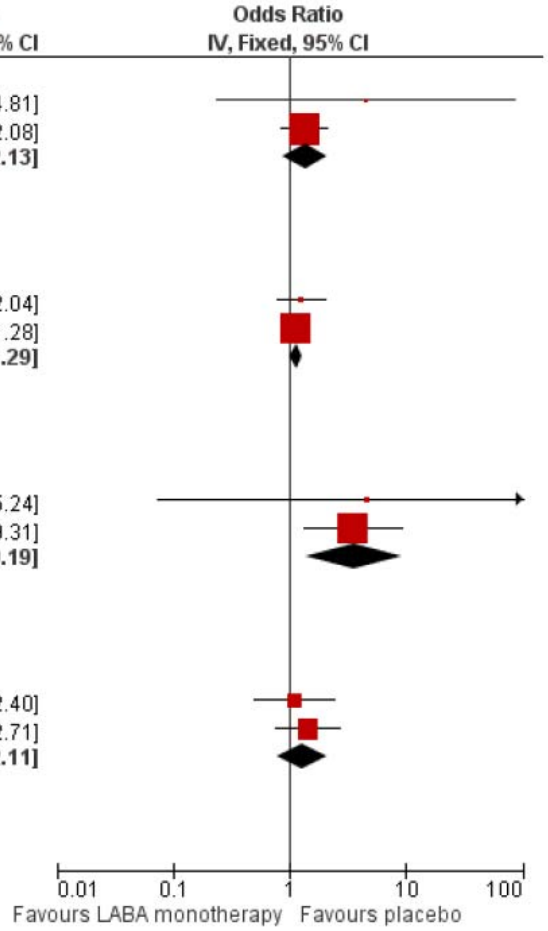


Hung M-J, Mao C-T, Hung M-Y, Chen T-H. Impact of Asthma on the Development of Coronary Vasospastic Angina: A Population-Based Cohort Study. Medicine. 2015;94(42):e1880.


Диагноз
Контроль симптомов и факторов риска (включая функцию легких)
Техника ингаляций и приверженность
Предпочтения пациента
оценка
Медикаменты
Немедикаментозные стратегии
Лечение модифицируемых факторов риска
лечение
Симптомы
Обострения
Побочные эффекты
Удовлетворенность пациента
Функция легких
ответ
КОНТРОЛЛЕРЫ ВЫБОРА
ШАГ 1
ШАГ 2
ШАГ 3
ШАГ 4
ШАГ 5
Низкие дозы ИКС
Низкие дозы ИКС/ДБА
Средние/ высокие дозы ИКС/ДБА
+тиотропий, анти-IgE, анти-IL5
Другие контроллеры
Низкие дозы ИКС
Антагонисты лейкотриеновых рецепторов (АЛР)
Низкие дозы теофиллина
Ср./выс. дозы ИКС
Низкие дозы ИКС+АЛР
+ тиотропий
Выс. доза ИКС +АЛР/теоф.
+ низкие дозы ОКС
РЕЛИВЕРЫ
Короткие бета2-агонисты (КБА)
КБА или низкие дозы ИКС/формотерол

Бронходилататоры без кортикостероидов

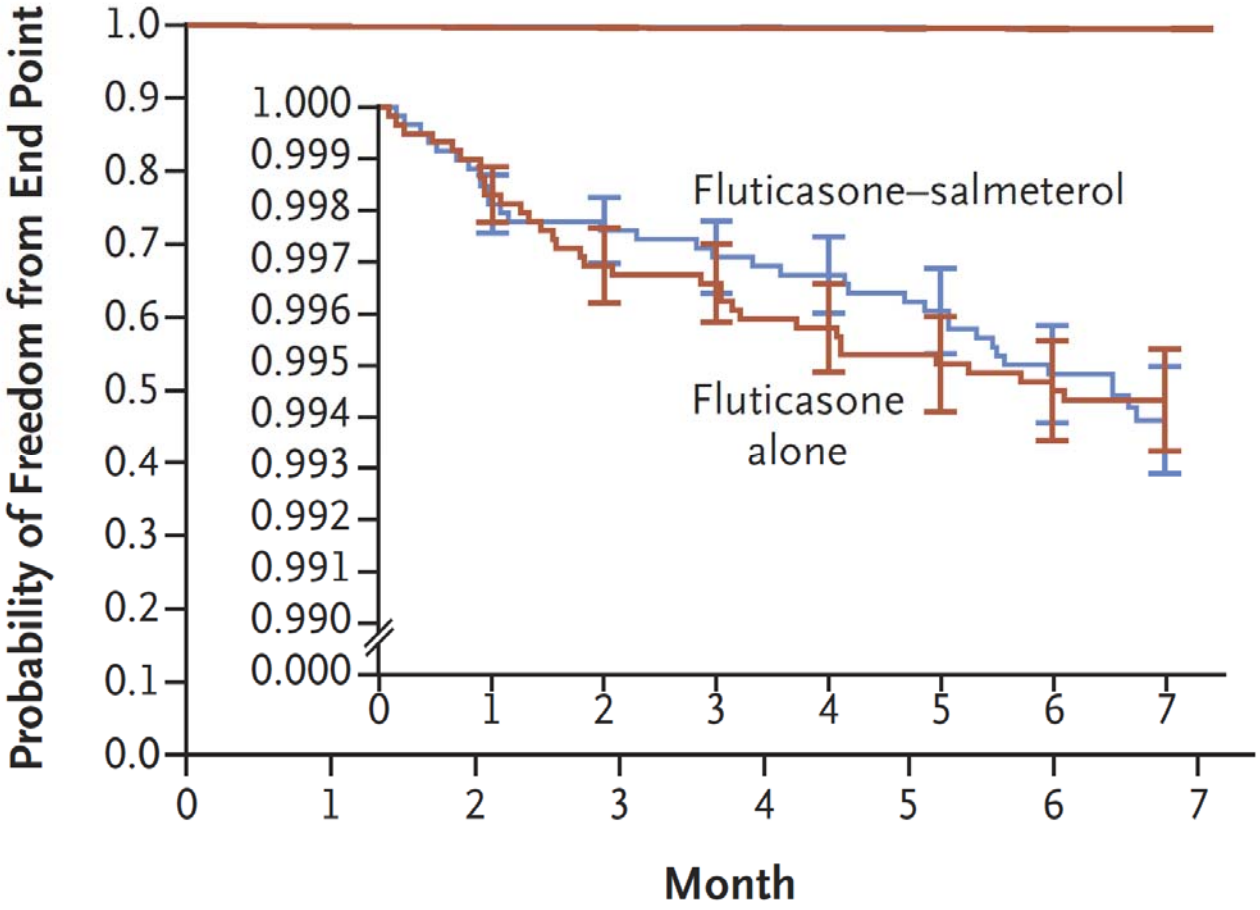
Study or Subgroup	log[Odds Ratio]	SE	LABA Total	Control Total	Weight	Odds Ratio IV, Fixed, 95% CI
Any death						
Formoterol Monotherapy	1.5012	1.4996	2924	1900	2.3%	4.49 [0.24, 84.81]
Salmeterol Monotherapy	0.2868	0.2282	14648	14480	97.7%	1.33 [0.85, 2.08]
Subtotal (95% CI)			**17572**	**16380**	**100.0%**	**1.37 [0.88, 2.13]**
Heterogeneity: Chi² = 0.64, df = 1 (P = 0.42); I² = 0%						
Test for overall effect: Z = 1.39 (P = 0.16)						
Any non-fatal SAE						
Formoterol Monotherapy	0.2318	0.2443	3401	2357	5.9%	1.26 [0.78, 2.04]
Salmeterol Monotherapy	0.1281	0.0614	15170	15026	94.1%	1.14 [1.01, 1.28]
Subtotal (95% CI)			**18571**	**17383**	**100.0%**	**1.14 [1.02, 1.29]**
Heterogeneity: Chi² = 0.17, df = 1 (P = 0.68); I² = 0%						
Test for overall effect: Z = 2.25 (P = 0.02)						
Asthma death						
Formoterol Monotherapy	1.5127	2.1126	2495	1690	5.3%	4.54 [0.07, 285.24]
Salmeterol Monotherapy	1.2509	0.5001	14648	14480	94.7%	3.49 [1.31, 9.31]
Subtotal (95% CI)			**17143**	**16170**	**100.0%**	**3.54 [1.36, 9.19]**
Heterogeneity: Chi² = 0.01, df = 1 (P = 0.90); I² = 0%						
Test for overall effect: Z = 2.60 (P = 0.009)						
Asthma non-fatal SAE						
Formoterol Monotherapy	0.0897	0.4006	2849	2022	39.9%	1.09 [0.50, 2.40]
Salmeterol Monotherapy	0.3552	0.3267	1994	1847	60.1%	1.43 [0.75, 2.71]
Subtotal (95% CI)			**4843**	**3869**	**100.0%**	**1.28 [0.78, 2.11]**
Heterogeneity: Chi² = 0.26, df = 1 (P = 0.61); I² = 0%						
Test for overall effect: Z = 0.98 (P = 0.33)						



Мета-анализ

Cates CJ, Wieland LS, Oleszczuk M, Kew KM. Safety of regular formoterol or salmeterol in adults with asthma: an overview of Cochrane reviews. Cochrane Database of Systematic Reviews 2014, Issue 2.

Бронходилататоры + кортикостероиды



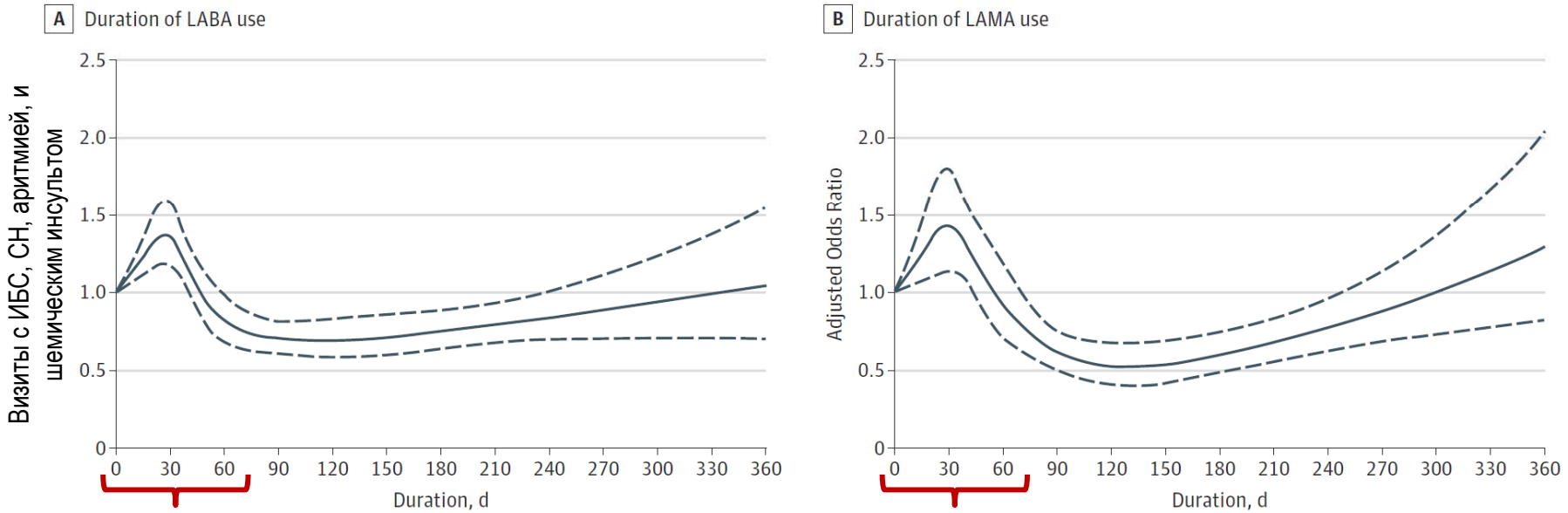
Безопасность бета$_2$-агонистов при ИБС не изучена.
Надежнее монотерапия ингаляционными кортикостероидами.

AUSTRI

Stempel DA, et al. Serious Asthma Events with Fluticasone plus Salmeterol versus Fluticasone Alone.
N Engl J Med. 2016;374(19):1822-30.

Бета$_2$-агонисты или холинолитики при ХОБЛ

Figure 1. Duration-Response Curves for the Adjusted Odds Ratios (95% CIs) of the Cardiovascular Risk as a Function of Duration of New LABA and New LAMA Therapy



Усилить лечение ССЗ

Усилить лечение ССЗ

Эффективность и риски холинолитиков и бета$_2$-агонистов близки

Wang M, et al. Association of Cardiovascular Risk With Inhaled Long-Acting Bronchodilators in Patients With Chronic Obstructive Pulmonary Disease. A Nested Case-Control Study. JAMA Intern Med. 2018;178(2):229–238.

Kew KM, Dias S, Cates CJ. Long-acting inhaled therapy (beta-agonists, anticholinergics and steroids) for COPD: a network meta-analysis. Cochrane Database of Systematic Reviews 2014, Issue 3. Art. No.: CD010844.