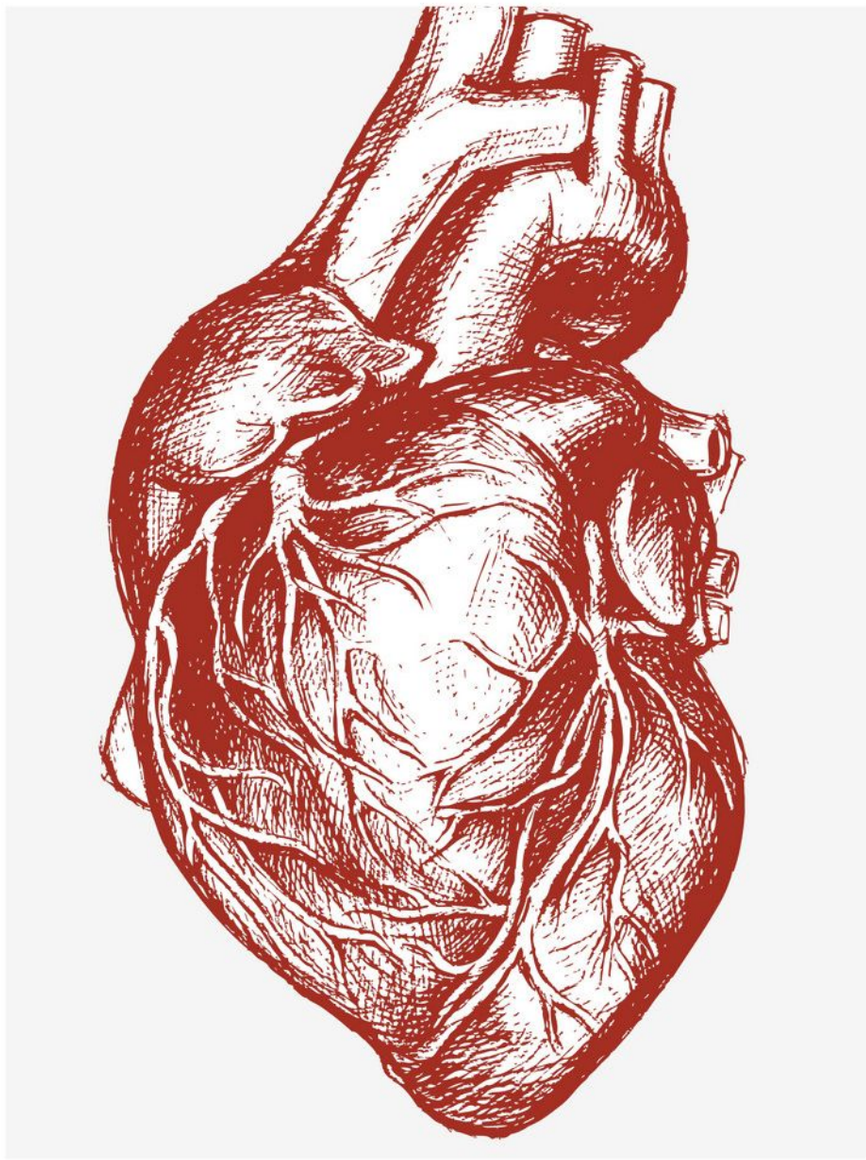
ГБОУ ВПО МГМСУ им. А.И.Евдокимова
СНК кафедры неотложной кардиологии
лечебного факультета

Монотерапия Тикагрелором против Двойной Антиагрегантной терапии после ЧКВ



Клюквина Дарья
7 курс, лечебный
факультет

Москва, 2019

Актуальность

Двойная антитромбоцитарная терапия, включающая в себя аспирин и ингибиторы рецепторов P2Y12 рекомендуются после ЧКВ в виде профилактики тромбоза стента и уменьшения рисков ишемических событий, включающих в себя острый инфаркт миокарда и инсульт.

Рекомендации

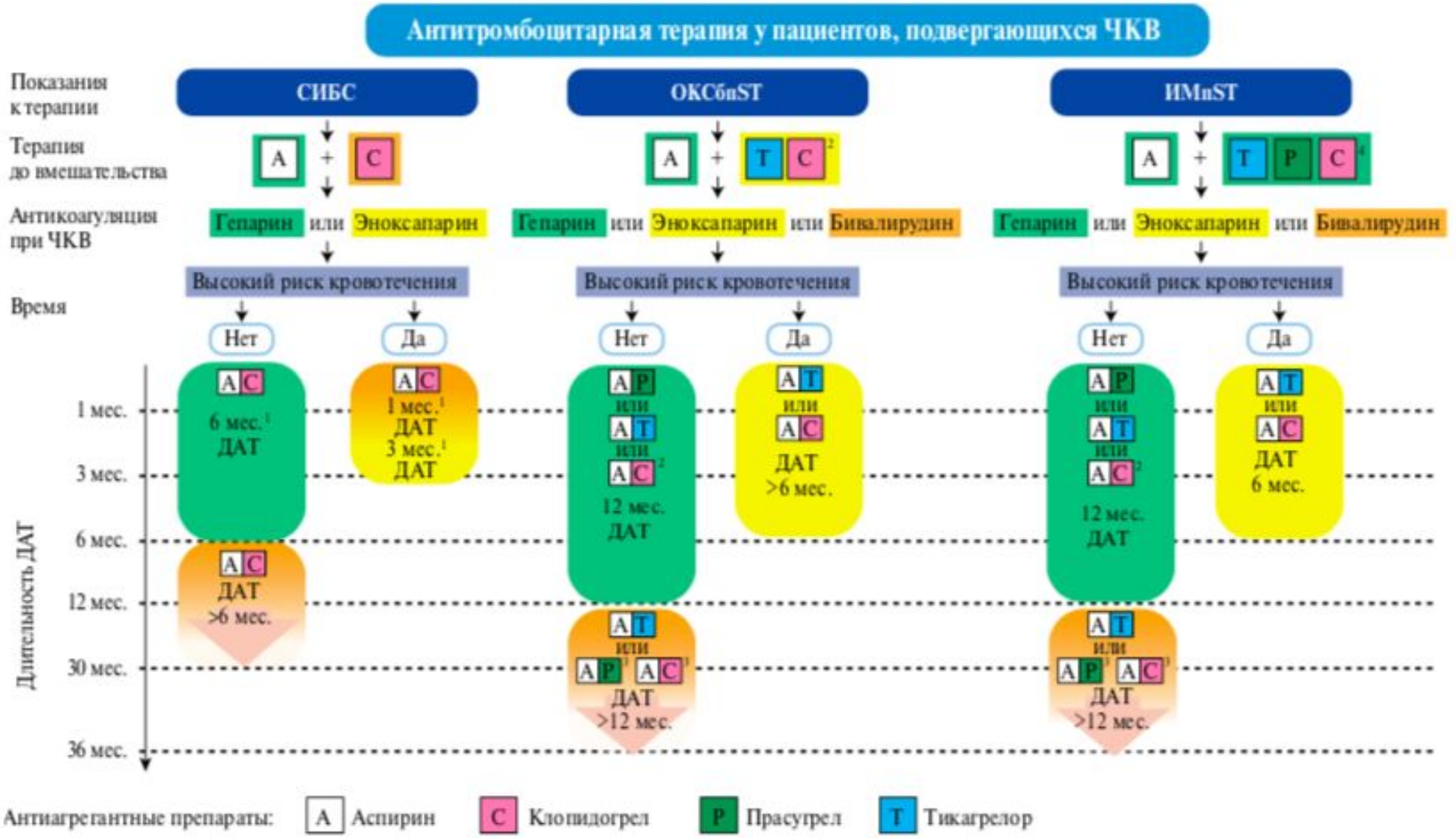


Рис. 10. Алгоритмы применения антитромботических препаратов у пациентов, подвергающихся ЧКВ.

Примечание: [1] — после ЧКВ с использованием баллона с лекарственным покрытием ДАТ следует проводить в течение 6 мес. (класс IIa), [2] — клопидогрел, если пациенту противопоказан прасугрел или тикагрелор или при снижении дозировки ДАТ (класс IIb), [3] — клопидогрел или прасугрел, если пациенту противопоказан тикагрелор, [4] — терапия перед ЧКВ (или самое позднее — во время ЧКВ) проводится клопидогрелем, если сильные ингибиторы $P2Y_{12}$ противопоказаны или недоступны (см. дополнительную табл. 4).

Высокий риск кровотечений оценивается как повышенный риск развития кровотечения на фоне ДАТ (например, ≥25 по шкале PRECISE-DAPT). Цветовая схема соотносится с классами рекомендаций ESC (зеленый — класс I; жёлтый — класс IIa и оранжевый — класс IIb).

Сокращения: ДАТ — двойная антиагрегантная терапия, ИМпST — инфаркт миокарда с подъёмом сегмента ST, ОКСбпST — острый коронарный синдром без подъёма сегмента ST, СИБС — стабильная ишемическая болезнь сердца, ЧКВ — чрескожное коронарное вмешательство.

Рекомендации ESC/EACTS по реваскуляризации миокарда 2018

Ticagrelor Alone Versus Dual Antiplatelet Therapy From 1 Month After Drug-Eluting Coronary Stenting

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Дизайн исследования

GLOBAL LEADERS: A Clinical Study Comparing Two Forms of Anti-platelet Therapy After Stent Implantation

Клиническое исследование

- 15991 участник
- Рандомизированное открытое параллельное исследование
- Дата начала исследования: 1 июля 2013г.
- Дата завершения исследования: 26 апреля 2018г.

GLOBAL LEADERS Adjudication Sub-Study [GLASSY]

- Ретроспективное исследование
- 7365 участников
- Начало анализа: 1 июня 2017г.

ЧКВ со стентированием

↓

1 месяц - двойная антиагрегантная терапия
(75 или 100 мг аспирина + 90 мг тикагрелора 2 р/дн)

23 месяца - тикагрелор 90мг 2 р/дн	11 месяцев - DABT (клопидогрель для СИБС, тикагрелор для ОКС)
	12 месяцев - аспирин

GLOBAL LEADERS: A Clinical Study Comparing Two Forms of Anti-platelet Therapy After Stent Implantation

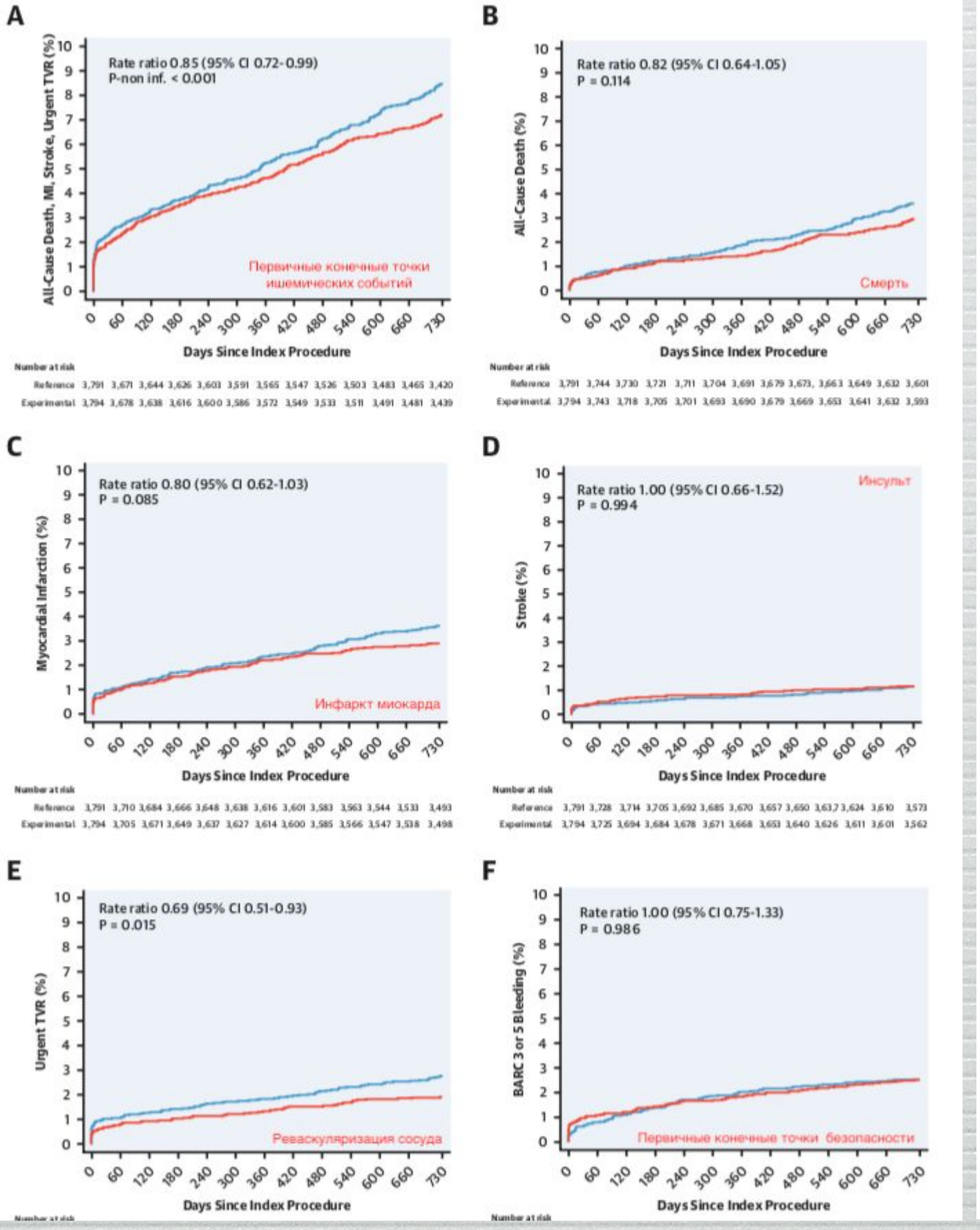
Характеристика участников исследования

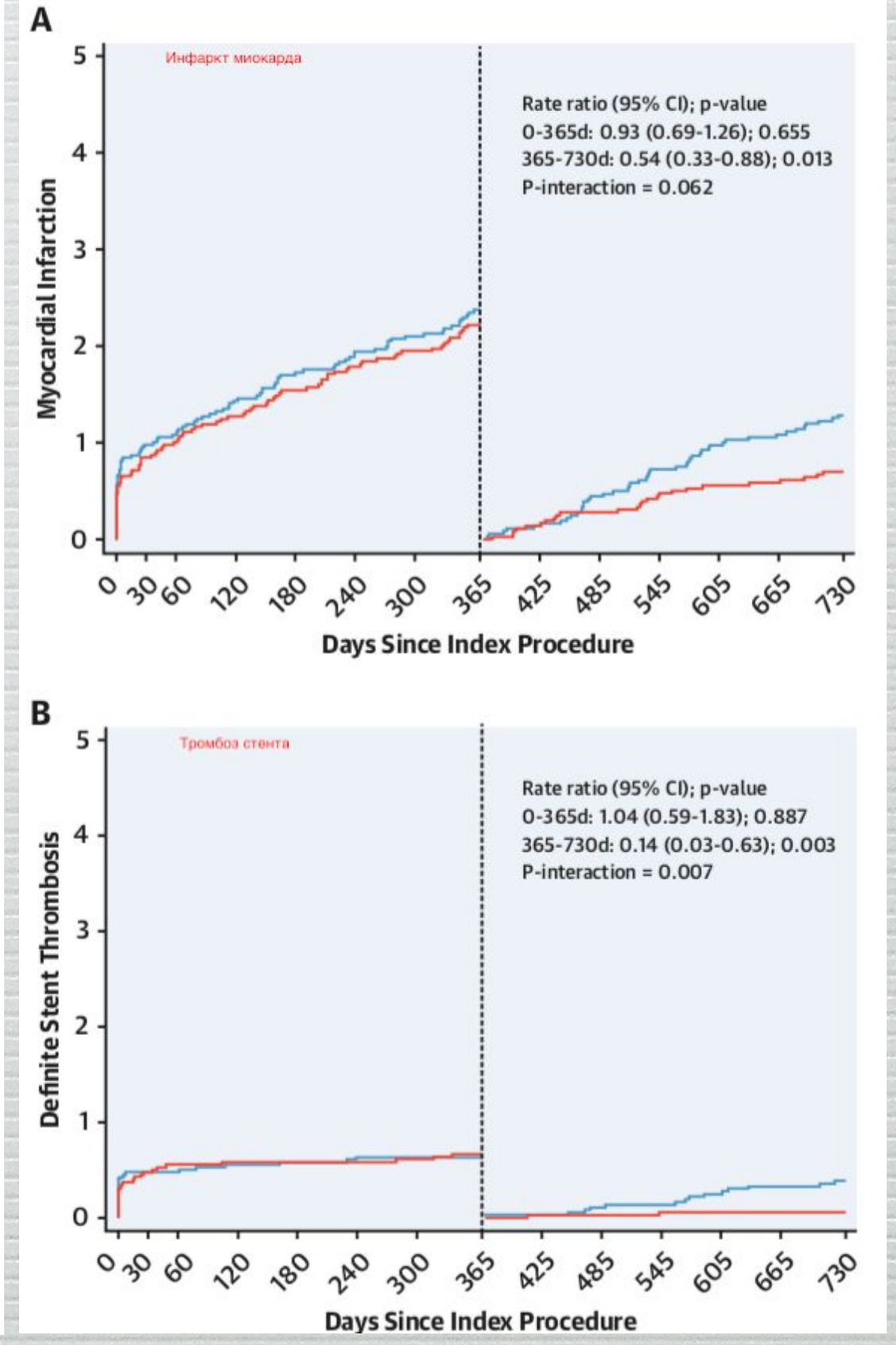
TABLE 1 Baseline Characteristics of Study Patients

	Experimental Intervention Group (n = 3,794)	Control Group (n = 3,791)
Age, yrs	64.9 ± 10.3	64.8 ± 10.3
Female	910 (24.0)	889 (23.5)
Body mass index, kg/m^2	28.0 ± 4.5	27.9 ± 4.5
Medical history		
Diabetes mellitus	923 (24.3)	899 (23.7)
Insulin-dependent diabetes mellitus	263 (6.9)	268 (7.1)
Hypertension	2,752 (72.5)	2,740 (72.3)
Hypercholesterolemia	2,402 (63.3)	2,476 (65.3)
Previous stroke	97 (2.6)	99 (2.6)
Current smoker	1,084 (28.6)	1,102 (29.1)
Previous myocardial infarction	869 (22.9)	893 (23.6)
Previous percutaneous coronary intervention	1,236 (32.6)	1,286 (33.9)
Previous coronary artery bypass grafting	204 (5.4)	239 (6.3)
Peripheral vascular disease	253 (6.7)	300 (7.9)
Chronic obstructive pulmonary disease	198 (5.2)	204 (5.4)
Previous major bleeding	26 (0.7)	22 (0.6)
Impaired renal function*	510 (13.4)	495 (13.1)
Clinical presentation		
Cardiac arrest	25 (0.7)	20 (0.5)
Killip class II to IV	91 (2.4)	66 (1.7)
Stable coronary artery disease	1,855 (48.9)	1,890 (49.9)
Acute coronary syndrome	1,939 (51.1)	1,901 (50.1)
Unstable angina	490 (12.9)	499 (13.2)
Non-ST-segment elevation myocardial infarction	760 (20.0)	737 (19.4)
ST-segment elevation myocardial infarction	689 (18.2)	665 (17.5)
Time from symptom onset to wire crossing lesion ≤12 h	578 (83.9)	572 (86.0)
LVEF pre-PCI, %	55.1 ± 11.8	55.3 ± 11.3
Multivessel treatment	540 (14.2)	558 (14.7)

GLOBAL LEADERS: A Clinical Study Comparing Two Forms of Anti-platelet Therapy After Stent Implantation

Обсуждение





GLOBAL LEADERS: A Clinical Study Comparing Two Forms of Anti-platelet Therapy After Stent Implantation

Результаты

TABLE 2 Adjudicated Clinical Outcomes at 2-Year Follow-Up

	Experimental Intervention Group (n = 3,794)	Control Group (n = 3,791)	Rate Ratio (95% CI)	p Value
All-cause death, MI, stroke, or urgent TVR*	271 (7.14)	319 (8.41)	0.85 (0.72–0.99)	0.047
All-cause death	111 (2.93)	136 (3.59)	0.82 (0.64–1.05)	0.114
Cardiovascular death	69 (1.82)	88 (2.32)	0.79 (0.57–1.08)	0.131
Undetermined cause	18 (0.47)	24 (0.63)	0.75 (0.41–1.39)	0.358
Noncardiovascular death	42 (1.11)	48 (1.27)	0.88 (0.58–1.33)	0.534
MI	108 (2.85)	135 (3.56)	0.80 (0.62–1.03)	0.085
Cardiovascular death or MI	171 (4.51)	205 (5.41)	0.83 (0.68–1.02)	0.081
Stroke	44 (1.16)	44 (1.16)	1.00 (0.66–1.52)	0.994
Urgent TVR	71 (1.87)	103 (2.72)	0.69 (0.51–0.93)	0.015
Definite, probable, or possible stent thrombosis	65 (1.71)	82 (2.16)	0.79 (0.57–1.10)	0.162
Definite or probable stent thrombosis	33 (0.87)	46 (1.21)	0.72 (0.46–1.12)	0.144
Definite stent thrombosis	27 (0.71)	38 (1.00)	0.71 (0.43–1.16)	0.173
Probable stent thrombosis	6 (0.16)	10 (0.26)	0.60 (0.22–1.65)	0.318
Possible stent thrombosis	32 (0.84)	38 (1.00)	0.84 (0.53–1.35)	0.479
BARC 3 or 5 bleeding†	94 (2.48)	94 (2.48)	1.00 (0.75–1.33)	0.986
BARC 1 bleeding	327 (8.62)	304 (8.02)	1.08 (0.92–1.26)	0.349
BARC 2 bleeding	244 (6.43)	239 (6.30)	1.02 (0.85–1.22)	0.821
BARC 3 bleeding	84 (2.21)	87 (2.29)	0.97 (0.72–1.31)	0.832
BARC 4 bleeding	5 (0.13)	7 (0.18)	0.71 (0.23–2.25)	0.564
BARC 5 bleeding	11 (0.29)	7 (0.18)	1.57 (0.61–4.06)	0.345
TIMI major bleeding	56 (1.48)	48 (1.27)	1.17 (0.80–1.72)	0.424
TIMI minor bleeding	26 (0.69)	36 (0.95)	0.72 (0.44–1.20)	0.206
TIMI other bleeding	540 (14.23)	523 (13.80)	1.03 (0.92–1.17)	0.588
TIMI CABG-related bleeding	4 (0.11)	7 (0.18)	0.57 (0.17–1.95)	0.366
GUSTO severe bleeding	42 (1.11)	23 (0.61)	1.83 (1.10–3.05)	0.018
GUSTO moderate bleeding	42 (1.11)	56 (1.48)	0.75 (0.50–1.12)	0.158
GUSTO mild bleeding	540 (14.23)	531 (14.01)	1.02 (0.90–1.15)	0.778

GLOBAL LEADERS: A Clinical Study Comparing Two Forms of Anti-platelet Therapy After Stent Implantation

Результаты

TABLE 2 Adjudicated Clinical Outcomes at 2-Year Follow-Up

	Experimental Intervention Group (n = 3,794)	Control Group (n = 3,791)	Rate Ratio (95% CI)	p Value
All-cause death, MI, stroke, or urgent TVR*	271 (7.14)	319 (8.41)	0.85 (0.72–0.99)	0.047
All-cause death	111 (2.93)	136 (3.59)	0.82 (0.64–1.05)	0.114
Cardiovascular death	69 (1.82)	88 (2.32)	0.79 (0.57–1.08)	0.131
Undetermined cause	18 (0.47)	24 (0.63)	0.75 (0.41–1.39)	0.358
Noncardiovascular death	42 (1.11)	48 (1.27)	0.88 (0.58–1.33)	0.534
MI	108 (2.85)	135 (3.56)	0.80 (0.62–1.03)	0.085
Cardiovascular death or MI	171 (4.51)	205 (5.41)	0.83 (0.68–1.02)	0.081
Stroke	44 (1.16)	44 (1.16)	1.00 (0.66–1.52)	0.994
Urgent TVR	71 (1.87)	103 (2.72)	0.69 (0.51–0.93)	0.015
Definite, probable, or possible stent thrombosis	65 (1.71)	82 (2.16)	0.79 (0.57–1.10)	0.162
Definite or probable stent thrombosis	33 (0.87)	46 (1.21)	0.72 (0.46–1.12)	0.144
Definite stent thrombosis	27 (0.71)	38 (1.00)	0.71 (0.43–1.16)	0.173
Probable stent thrombosis	6 (0.16)	10 (0.26)	0.60 (0.22–1.65)	0.318
Possible stent thrombosis	32 (0.84)	38 (1.00)	0.84 (0.53–1.35)	0.479
BARC 3 or 5 bleeding†	94 (2.48)	94 (2.48)	1.00 (0.75–1.33)	0.986
BARC 1 bleeding	327 (8.62)	304 (8.02)	1.08 (0.92–1.26)	0.349
BARC 2 bleeding	244 (6.43)	239 (6.30)	1.02 (0.85–1.22)	0.821
BARC 3 bleeding	84 (2.21)	87 (2.29)	0.97 (0.72–1.31)	0.832
BARC 4 bleeding	5 (0.13)	7 (0.18)	0.71 (0.23–2.25)	0.564
BARC 5 bleeding	11 (0.29)	7 (0.18)	1.57 (0.61–4.06)	0.345
TIMI major bleeding	56 (1.48)	48 (1.27)	1.17 (0.80–1.72)	0.424
TIMI minor bleeding	26 (0.69)	36 (0.95)	0.72 (0.44–1.20)	0.206
TIMI other bleeding	540 (14.23)	523 (13.80)	1.03 (0.92–1.17)	0.588
TIMI CABG-related bleeding	4 (0.11)	7 (0.18)	0.57 (0.17–1.95)	0.366
GUSTO severe bleeding	42 (1.11)	23 (0.61)	1.83 (1.10–3.05)	0.018
GUSTO moderate bleeding	42 (1.11)	56 (1.48)	0.75 (0.50–1.12)	0.158
GUSTO mild bleeding	540 (14.23)	531 (14.01)	1.02 (0.90–1.15)	0.778

GLOBAL LEADERS: A Clinical Study Comparing Two Forms of Anti-platelet Therapy After Stent Implantation

Результаты

TABLE 3 Adjudicated Clinical Outcomes at 30 Days and With Landmark From 30 Days to 1 Year and From 1 to 2 Years of Follow-Up

	Experimental Intervention Group (n = 3,794)	Control Group (n = 3,791)	Rate Ratio (95% CI)	p Value	Interaction p Value
At 30 days					
All-cause death, MI, stroke, or urgent TVR*	75 (1.98)	87 (2.29)	0.86 (0.63-1.17)	0.340	
All-cause death	19 (0.50)	21 (0.55)	0.90 (0.49-1.68)	0.751	
Cardiovascular death	19 (0.50)	20 (0.53)	0.95 (0.51-1.78)	0.872	
Undetermined cause	0 (0.00)	0 (0.00)			
Noncardiovascular death	0 (0.00)	1 (0.03)			
MI	32 (0.84)	37 (0.98)	0.86 (0.54-1.39)	0.545	
Cardiovascular death or MI	51 (1.34)	51 (1.35)	1.00 (0.68-1.48)	0.997	
Stroke	16 (0.42)	13 (0.34)	1.23 (0.59-2.56)	0.579	
Urgent TVR	26 (0.69)	39 (1.03)	0.66 (0.40-1.09)	0.105	
Definite, probable, or possible stent thrombosis	23 (0.61)	23 (0.61)	1.00 (0.56-1.78)	0.997	
Definite or probable stent thrombosis	23 (0.61)	23 (0.61)	1.00 (0.56-1.78)	0.997	
Definite stent thrombosis	18 (0.47)	18 (0.47)	1.00 (0.52-1.92)	0.998	
Probable stent thrombosis	5 (0.13)	5 (0.13)	1.00 (0.29-3.45)	0.999	
Possible stent thrombosis	0 (0.00)	0 (0.00)			
BARC 3 or 5 bleeding†	37 (0.98)	24 (0.63)	1.54 (0.92-2.58)	0.095	
BARC 1 bleeding	159 (4.19)	158 (4.17)	1.01 (0.81-1.26)	0.952	
BARC 2 bleeding	99 (2.61)	90 (2.37)	1.10 (0.83-1.47)	0.509	
BARC 3 bleeding	32 (0.84)	22 (0.58)	1.46 (0.85-2.51)	0.172	
BARC 4 bleeding	3 (0.08)	3 (0.08)	1.00 (0.20-4.96)	1.000	
BARC 5 bleeding	5 (0.13)	2 (0.05)	2.50 (0.48-12.90)	0.257	

Результаты

TABLE 3 Adjudicated Clinical Outcomes at 30 Days and With Landmark From 30 Days to 1 Year and From 1 to 2 Years of Follow-Up

	Experimental Intervention Group (n = 3,794)	Control Group (n = 3,791)	Rate Ratio (95% CI)	p Value	Interaction p Value
At 30 days					
All-cause death, MI, stroke, or urgent TVR*	75 (1.98)	87 (2.29)	0.86 (0.63-1.17)	0.340	
All-cause death	19 (0.50)	21 (0.55)	0.90 (0.49-1.68)	0.751	
Cardiovascular death	19 (0.50)	20 (0.53)	0.95 (0.51-1.78)	0.872	
Undetermined cause	0 (0.00)	0 (0.00)			
Noncardiovascular death	0 (0.00)	1 (0.03)			
MI	32 (0.84)	37 (0.98)	0.86 (0.54-1.39)	0.545	
Cardiovascular death or MI	51 (1.34)	51 (1.35)	1.00 (0.68-1.48)	0.997	
Stroke	16 (0.42)	13 (0.34)	1.23 (0.59-2.56)	0.579	
Urgent TVR	26 (0.69)	39 (1.03)	0.66 (0.40-1.09)	0.105	
Definite, probable, or possible stent thrombosis	23 (0.61)	23 (0.61)	1.00 (0.56-1.78)	0.997	
Definite or probable stent thrombosis	23 (0.61)	23 (0.61)	1.00 (0.56-1.78)	0.997	
Definite stent thrombosis	18 (0.47)	18 (0.47)	1.00 (0.52-1.92)	0.998	
Probable stent thrombosis	5 (0.13)	5 (0.13)	1.00 (0.29-3.45)	0.999	
Possible stent thrombosis	0 (0.00)	0 (0.00)			
BARC 3 or 5 bleeding†	37 (0.98)	24 (0.63)	1.54 (0.92-2.58)	0.095	
BARC 1 bleeding	159 (4.19)	158 (4.17)	1.01 (0.81-1.26)	0.952	
BARC 2 bleeding	99 (2.61)	90 (2.37)	1.10 (0.83-1.47)	0.509	
BARC 3 bleeding	32 (0.84)	22 (0.58)	1.46 (0.85-2.51)	0.172	
BARC 4 bleeding	3 (0.08)	3 (0.08)	1.00 (0.20-4.96)	1.000	
BARC 5 bleeding	5 (0.13)	2 (0.05)	2.50 (0.48-12.90)	0.257	

Результаты

TABLE 3 Adjudicated Clinical Outcomes at 30 Days and With Landmark From 30 Days to 1 Year and From 1 to 2 Years of Follow-Up

	Experimental Intervention Group (n = 3,794)	Control Group (n = 3,791)	Rate Ratio (95% CI)	p Value	Interaction p Value
At 1 yr					
All-cause death, MI, stroke, or urgent TVR*	175 (4.61)	199 (5.25)	0.88 (0.72-1.08)		0.213
All-cause death	54 (1.42)	71 (1.87)	0.76 (0.53-1.09)		0.131
Cardiovascular death	40 (1.05)	51 (1.35)	0.79 (0.52-1.19)		0.251
Undetermined cause	7 (0.18)	9 (0.24)	0.78 (0.29-.2.10)		0.622
Noncardiovascular death	14 (0.37)	20 (0.53)	0.70 (0-35-1.39)		0.307
MI	83 (2.19)	89 (2.35)	0.93 (0.69-1.26)		0.655
Cardiovascular death or MI	120 (3.16)	131 (3.46)	0.92 (0.72-1.18)		0.494
Stroke	32 (0.84)	28 (0.74)	1.14 (0.69-1.90)		0.602
Urgent TVR	50 (1.32)	69 (1.82)	0.72 (0.50-1.04)		0.080
Definite, probable, or possible stent thrombosis	44 (1.16)	50 (1.32)	0.88 (0.59-1.32)		0.538
Definite or probable stent thrombosis	31 (0.82)	32 (0.84)	0.97 (0.59-1.59)		0.899
Definite stent thrombosis	25 (0.66)	24 (0.63)	1.04 (0.59-1.83)		0.887
Probable stent thrombosis	6 (0.16)	9 (0.24)	0.67 (0.24-1.87)		0.439
Possible stent thrombosis	13 (0.34)	18 (0.47)	0.72 (0.35-1.48)		0.373
BARC 3 or 5 bleeding†	70 (1.85)	76 (2.00)	0.92 (0.67-1.28)		0.632
BARC 1 bleeding	281 (7.41)	288 (7.60)	0.98 (0.83-1.15)		0.782
BARC 2 bleeding	182 (4.80)	207 (5.46)	0.88 (0.72-1.07)		0.207
BARC 3 bleeding	64 (1.69)	73 (1.93)	0.88 (0.63-1.23)		0.452
BARC 4 bleeding	5 (0.13)	6 (0.16)	0.83 (0.25-2.73)		0.763
BARC 5 bleeding	6 (0.16)	3 (0.08)	2.00 (0.50-8.01)		0.317

Результаты

TABLE 3 Adjudicated Clinical Outcomes at 30 Days and With Landmark From 30 Days to 1 Year and From 1 to 2 Years of Follow-Up

	Experimental Intervention Group (n = 3,794)	Control Group (n = 3,791)	Rate Ratio (95% CI)	p Value	Interaction p Value
At 1 yr					
All-cause death, MI, stroke, or urgent TVR*	175 (4.61)	199 (5.25)	0.88 (0.72-1.08)		0.213
All-cause death	54 (1.42)	71 (1.87)	0.76 (0.53-1.09)		0.131
Cardiovascular death	40 (1.05)	51 (1.35)	0.79 (0.52-1.19)		0.251
Undetermined cause	7 (0.18)	9 (0.24)	0.78 (0.29-.2.10)		0.622
Noncardiovascular death	14 (0.37)	20 (0.53)	0.70 (0-35-1.39)		0.307
MI	83 (2.19)	89 (2.35)	0.93 (0.69-1.26)		0.655
Cardiovascular death or MI	120 (3.16)	131 (3.46)	0.92 (0.72-1.18)		0.494
Stroke	32 (0.84)	28 (0.74)	1.14 (0.69-1.90)		0.602
Urgent TVR	50 (1.32)	69 (1.82)	0.72 (0.50-1.04)		0.080
Definite, probable, or possible stent thrombosis	44 (1.16)	50 (1.32)	0.88 (0.59-1.32)		0.538
Definite or probable stent thrombosis	31 (0.82)	32 (0.84)	0.97 (0.59-1.59)		0.899
Definite stent thrombosis	25 (0.66)	24 (0.63)	1.04 (0.59-1.83)		0.887
Probable stent thrombosis	6 (0.16)	9 (0.24)	0.67 (0.24-1.87)		0.439
Possible stent thrombosis	13 (0.34)	18 (0.47)	0.72 (0.35-1.48)		0.373
BARC 3 or 5 bleeding†	70 (1.85)	76 (2.00)	0.92 (0.67-1.28)		0.632
BARC 1 bleeding	281 (7.41)	288 (7.60)	0.98 (0.83-1.15)		0.782
BARC 2 bleeding	182 (4.80)	207 (5.46)	0.88 (0.72-1.07)		0.207
BARC 3 bleeding	64 (1.69)	73 (1.93)	0.88 (0.63-1.23)		0.452
BARC 4 bleeding	5 (0.13)	6 (0.16)	0.83 (0.25-2.73)		0.763
BARC 5 bleeding	6 (0.16)	3 (0.08)	2.00 (0.50-8.01)		0.317

Результаты

	Experimental Intervention Group (n = 3,794)	Control Group (n = 3,791)	Rate Ratio (95% CI)	p Value	Interaction p Value
From 1 to 2 yrs					
All-cause death, MI, stroke, or urgent TVR*	96 (2.69)	120 (3.37)	0.80 (0.61-1.04)	0.098	0.574
All-cause death	57 (1.55)	65 (1.76)	0.88 (0.62-1.25)	0.472	0.580
Cardiovascular death	29 (0.79)	37 (1.00)	0.78 (0.48-1.28)	0.327	0.998
Undetermined cause	11 (0.30)	15 (0.41)	0.73 (0.34-1.60)	0.435	0.925
Noncardiovascular death	28 (0.76)	28 (0.76)	1.00 (0-59-1.69)	0.995	0.418
Cardiovascular death or MI	51 (1.41)	74 (2.05)	0.69 (0.48-0.98)	0.039	0.196
MI	25 (0.69)	46 (1.27)	0.54 (0.33-0.88)	0.013	0.062
Stroke	12 (0.33)	16 (0.44)	0.75 (0.36-1.59)	0.453	0.361
Urgent TVR	21 (0.58)	34 (0.94)	0.62 (0.36-1.06)	0.077	0.629
Definite, probable, or possible stent thrombosis	21 (0.57)	32 (0.87)	0.66 (0.38-1.14)	0.132	0.400
Definite or probable stent thrombosis	2 (0.05)	14 (0.38)	0.14 (0.03-0.63)	0.003	0.008
Definite stent thrombosis	2 (0.05)	14 (0.38)	0.14 (0.03-0.63)	0.003	0.007
Probable stent thrombosis	0 (0.00)	1 (0.03)			
Possible stent thrombosis	19 (0.51)	20 (0.54)	0.95 (0.51-1.78)	0.876	0.574
BARC 3 or 5 bleeding†	24 (0.66)	18 (0.50)	1.34 (0.72-2.46)	0.352	0.295
BARC 1 bleeding	46 (1.35)	16 (0.47)	2.89 (1.63-5.10)	<0.001	<0.001
BARC 2 bleeding	62 (1.76)	32 (0.92)	1.93 (1.26-2.96)	0.002	0.001
BARC 3 bleeding	20 (0.55)	14 (0.39)	1.43 (0.72-2.83)	0.302	0.208
BARC 4 bleeding	0 (0.00)	1 (0.03)			
BARC 5 bleeding	5 (0.14)	4 (0.11)	1.25 (0.34-4.66)	0.737	0.629

GLOBAL LEADERS: A Clinical Study Comparing Two Forms of Anti-platelet Therapy After Stent Implantation

Результаты

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Заключение

Результаты исследования показали, что монотерапия тикагрелором после 1 месяца DAPT не уступает традиционной DAPT в профилактике всех причин смерти в течение 2 лет после стентирования.

Кроме того, по сравнению с обычным лечением это не повысило риск развития сильных кровотечений.

Ожидаются результаты дальнейших крупных рандомизированных исследований.

Спасибо за внимание!