



Des études, des études et encore des études !

Dr. Jean Buithieu, cardiologue interniste,
Hôpital Royal Victoria - MUHC

Dr. Marc Jolicœur, cardiologue, Institut de
Cardiologie de Montréal, Université de
Montréal





Conflit intérêt (Marc Jolicoeur)

**Research Grants (significant):
AstraZeneca,
Boston Scientific, Philips**



**Dr. Jolicoeur is supported by
research grants from the FRSQ and
the CIHR**

**Fonds de la recherche
en santé**

Québec 

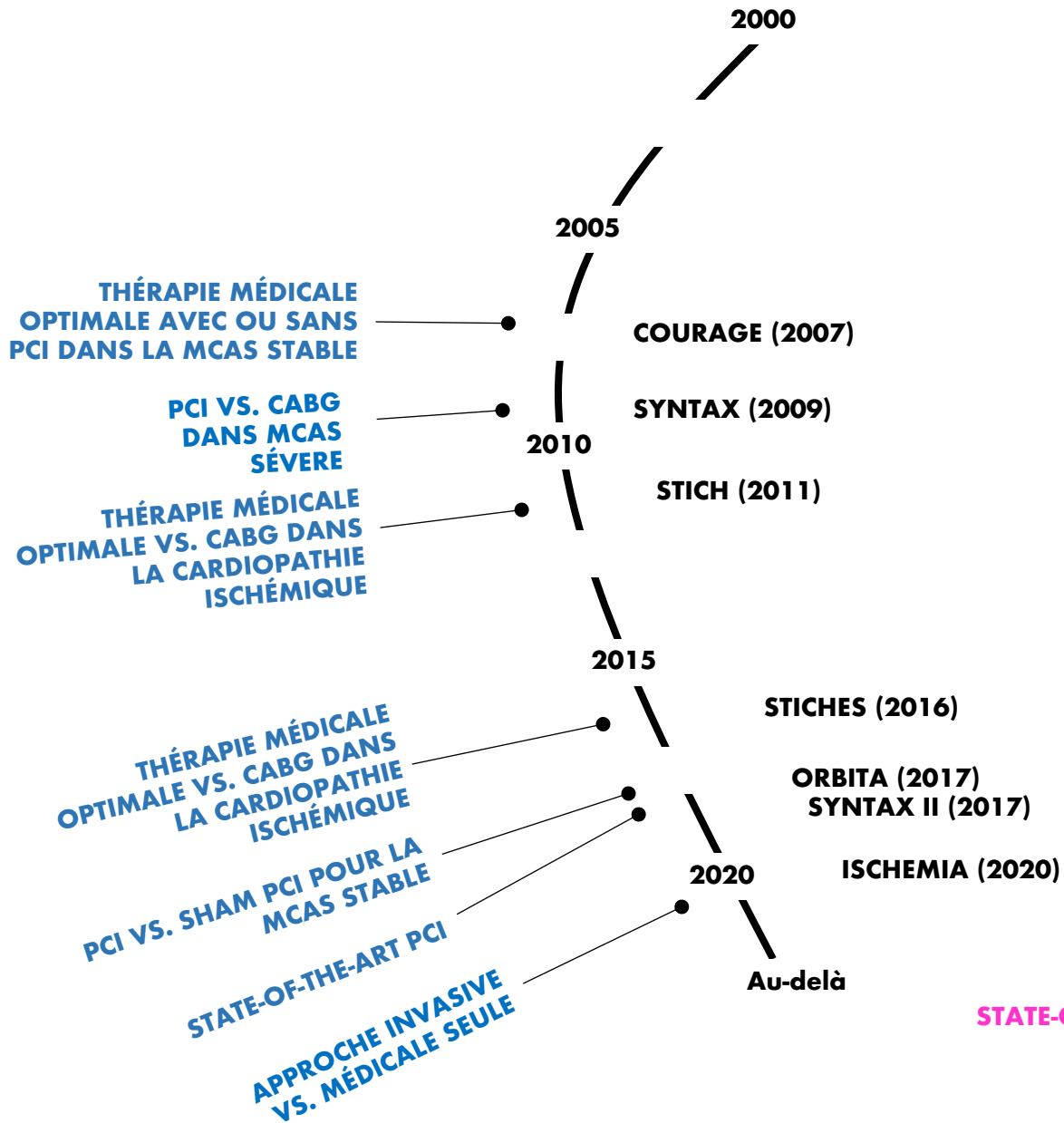


CIHR IRSC
Canadian Institutes of Health Research
Instituts de recherche en santé du Canada

Objectifs

- Réviser les faits marquants en MCAS au cours des 20 dernières années.
- Connaître les avenues diagnostiques et thérapeutiques futures possibles en MCAS au cours des 20 prochaines années.

-
- **La revascularisation des syndromes ischémiques stables semble intuitive mais des incongruences émergent**
 - **Pourtant, il demeure incertain si la stratification par ischémie et viabilité sont fiables sur le plan pronostique**
 - **Ou si même la revascularisation (par angioplastie) améliore les symptômes**



STATE-OF-THE-ART REVASCULARIZATION

COURAGE

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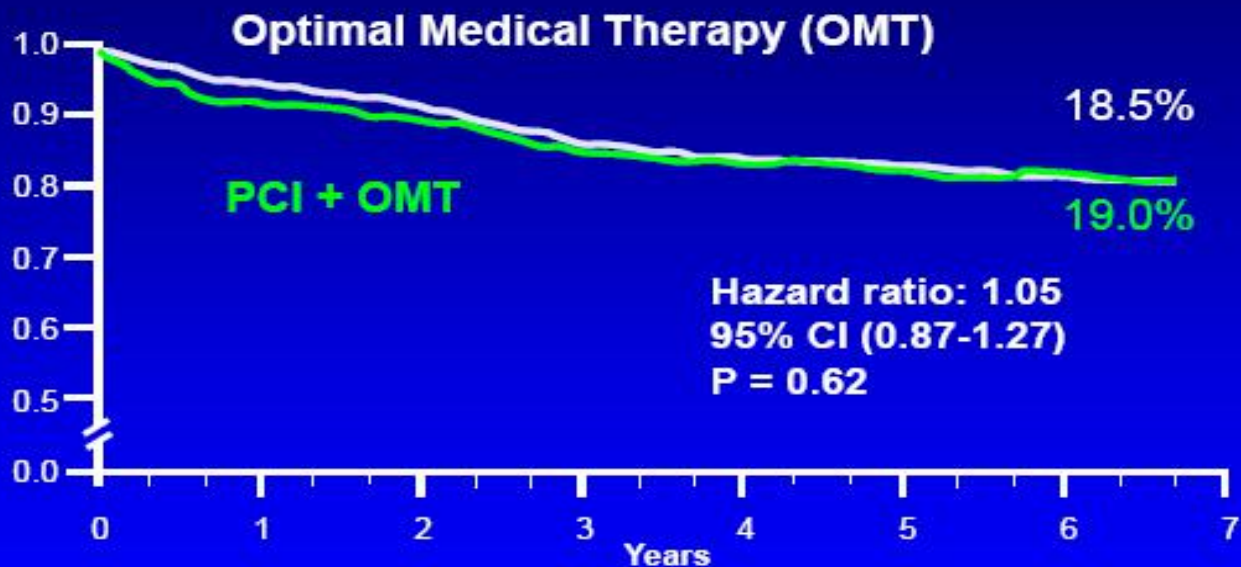
Optimal Medical Therapy with or without PCI
for Stable Coronary Disease

William E. Boden, M.D., Robert A. O'Rourke, M.D., Koon K. Teo, M.B., B.Ch., Ph.D., Pamela M. Hartigan, Ph.D., David J. Maron, M.D., William J. Kostuk, M.D., Merril Knudtson, M.D., Marcin Dada, M.D., Paul Casperson, Ph.D., Crystal L. Harris, Pharm.D., Bernard R. Chaitman, M.D., Leslee Shaw, Ph.D., Gilbert Gosselin, M.D., Shah Nawaz, M.D., Lawrence M. Title, M.D., Gerald Gau, M.D., Alvin S. Blaustein, M.D., David C. Booth, M.D., Eric R. Bates, M.D., John A. Spertus, M.D., M.P.H., Daniel S. Berman, M.D., G.B. John Mancini, M.D., and William S. Weintraub, M.D., for the COURAGE Trial Research Group*

Déterminer si l'ajout de l'ICP au traitement médical optimal, lorsqu'il est utilisé comme stratégie de prise en charge initiale, réduit le risque de décès ou d'infarctus du myocarde chez les patients atteints de MCAS vs. le traitement médical optimal seul



PCI Did Not Reduce Death or MI

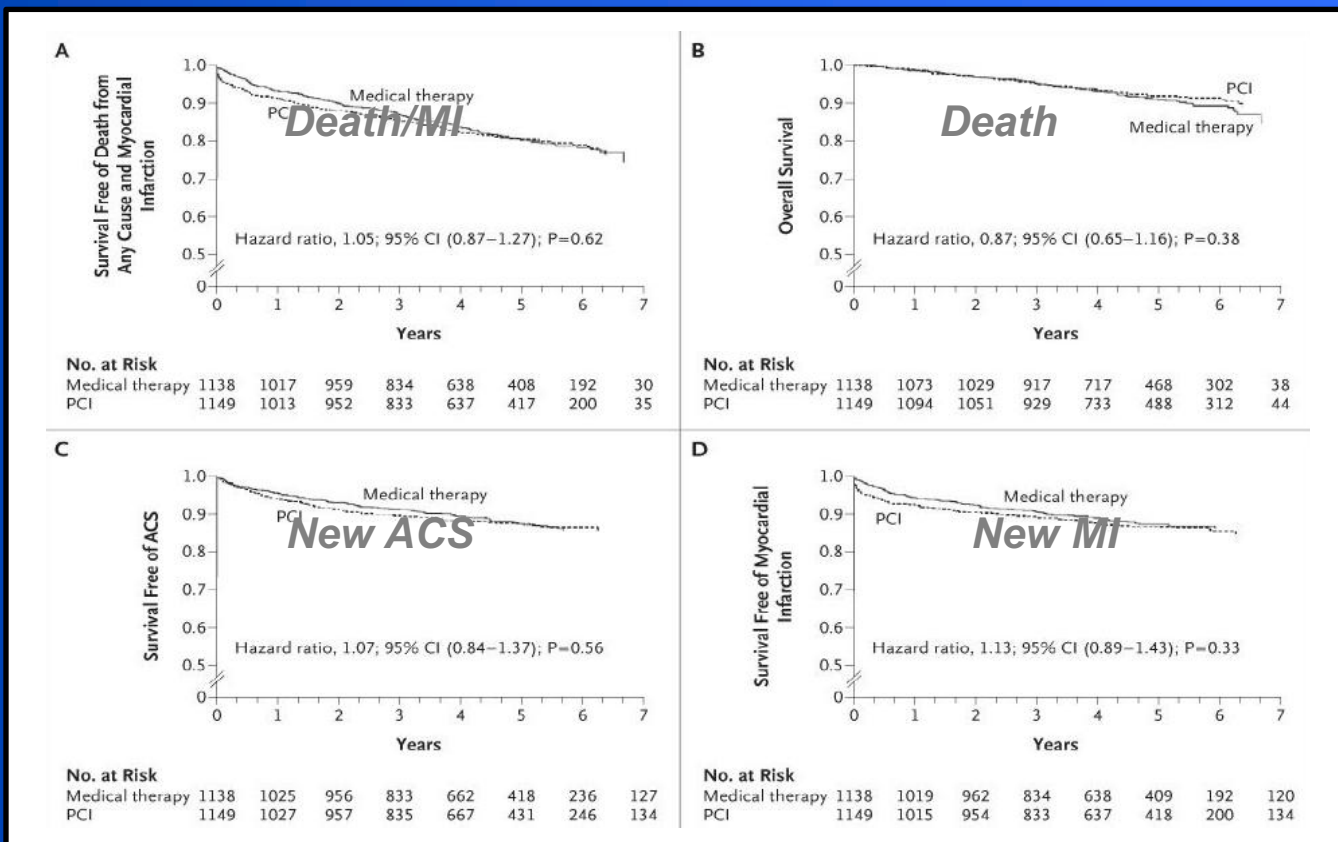


Number at Risk

	0	1	2	3	4	5	6	7
Medical Therapy	1138	1017	959	834	638	408	192	30
PCI	1149	1013	952	833	637	417	200	35

COURAGE: Points d'aboutissement primaire et secondaire

En comparaison au traitement médical seul, la PCI n'apporte aucun avantage supplémentaire sur les mortality/IM, Mortalité, IM ou de SCA



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Effect of PCI on Quality of Life in Patients with Stable Coronary Disease

William S. Weintraub, M.D., John A. Spertus, M.D., M.P.H., Paul Kolm, Ph.D., David J. Maron, M.D., Zefeng Zhang, M.D., Ph.D., Claudine Jurkowitz, M.D., M.P.H., Wei Zhang, M.S., Pamela M. Hartigan, Ph.D., Cheryl Lewis, R.N., Emir Veledar, Ph.D., Jim Bowen, B.S., Sandra B. Dunbar, D.S.N., Christi Deaton, Ph.D., Stanley Kaufman, M.D., Robert A. O'Rourke, M.D., Ron Goeree, M.S., Paul G. Barnett, Ph.D., Koon K. Teo, M.D., and William E. Boden, M.D., for the COURAGE Trial Research Group*

CONCLUSIONS

Among patients with stable angina, both those treated with PCI and those treated with optimal medical therapy alone had marked improvements in health status during follow-up. The PCI group had small, but significant, incremental benefits that disappeared by 36 months. (ClinicalTrials.gov number, NCT00007657.)

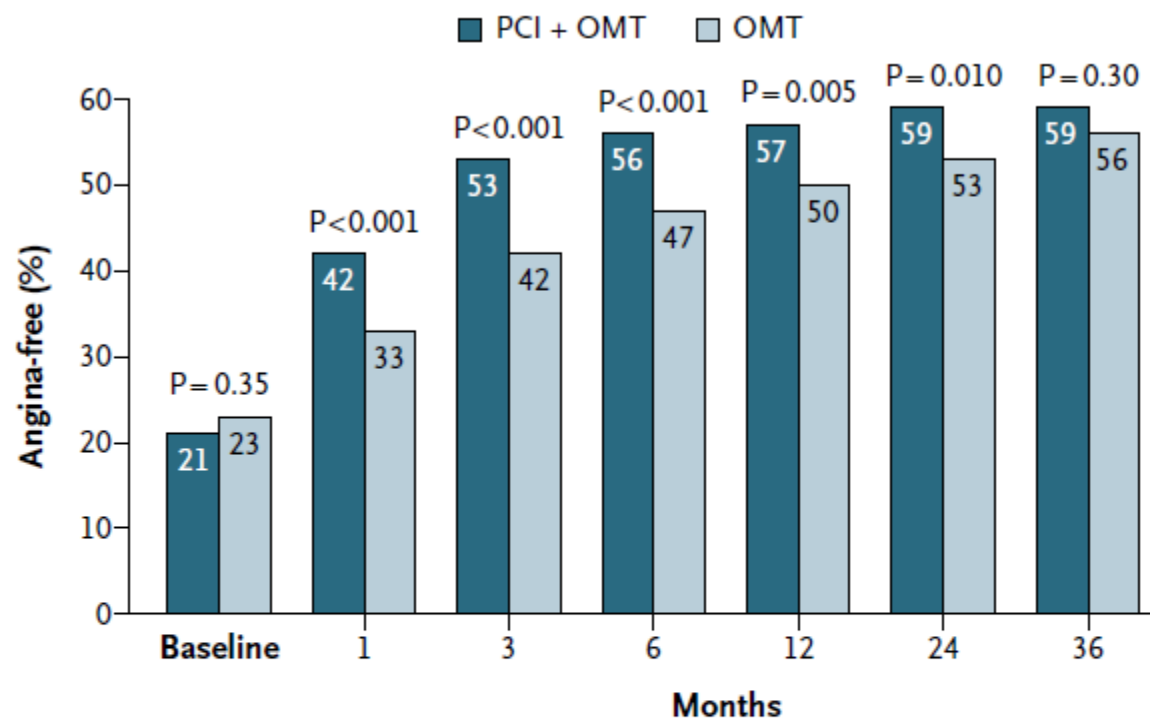
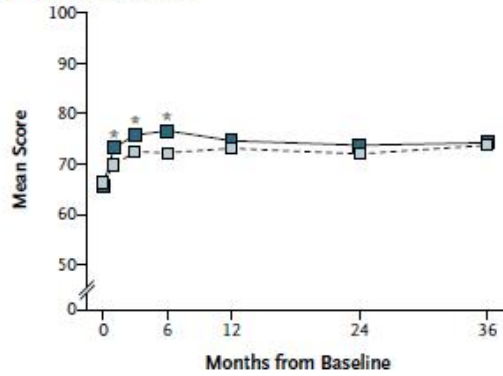


Figure 1. Freedom from Angina over Time as Assessed with the Angina-Frequency Scale of the Seattle Angina Questionnaire, According to Treatment Group.

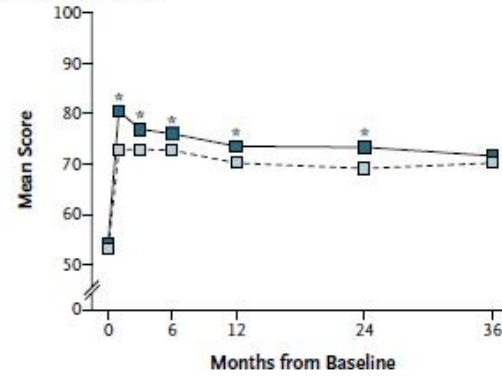
OMT denotes optimal medical therapy, and PCI percutaneous coronary intervention.

■ PCI + OMT □ OMT

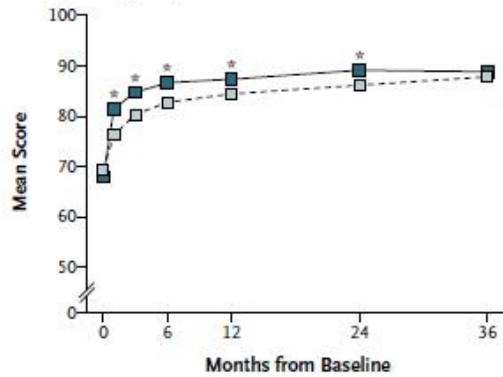
A Physical Limitation



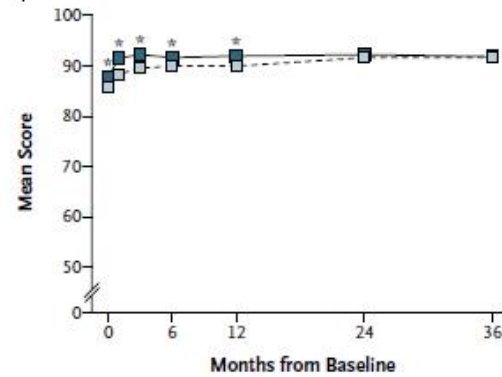
B Angina Stability



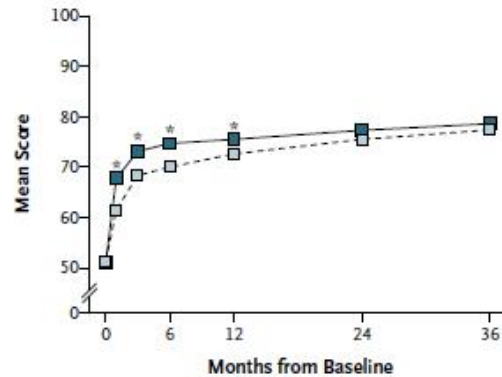
C Angina Frequency



D Treatment Satisfaction



E Quality of Life

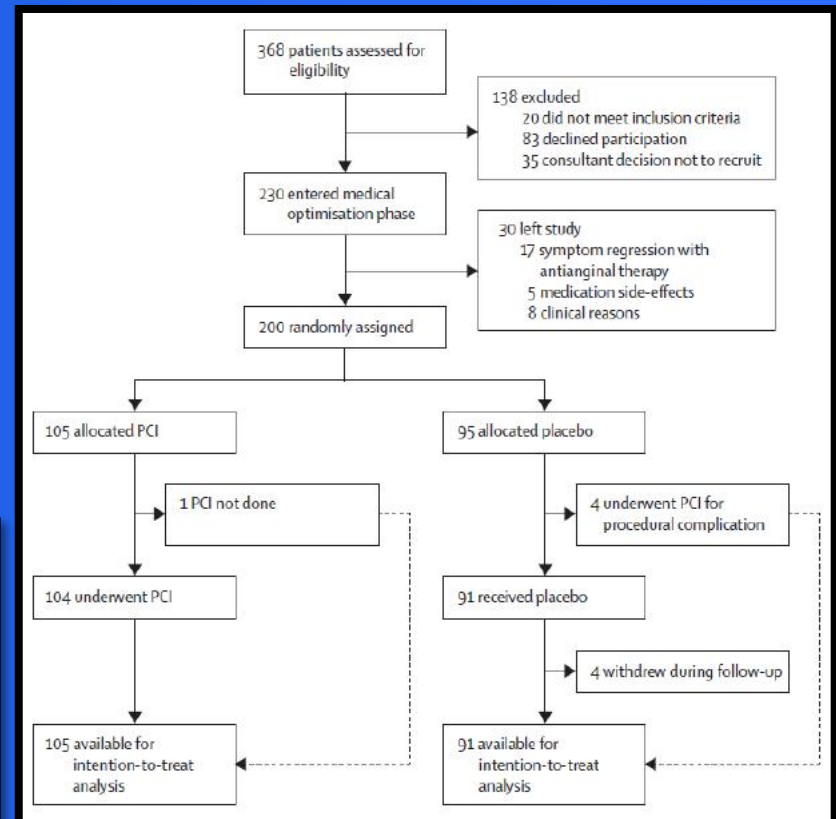
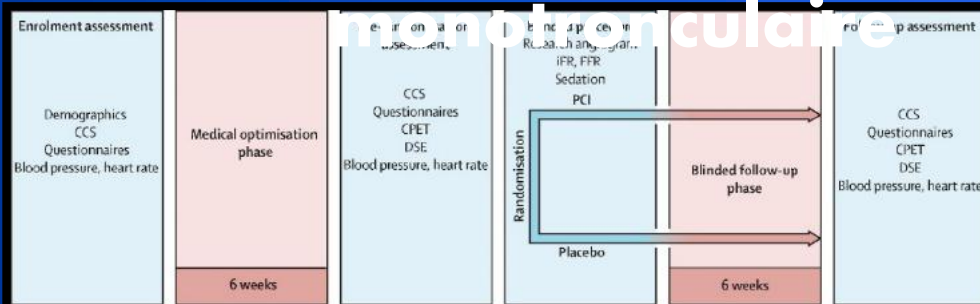


Percutaneous coronary intervention in stable angina (ORBITA): a double-blind, randomised controlled trial



Rasha Al-Lamee, David Thompson, Hakim-Moulay Dehbi, Sayan Sen, Kare Tang, John Davies, Thomas Keeble, Michael Mielewczik, Raffi Kaprielian, Iqbal S Malik, Sukhjinder S Nijjer, Ricardo Petraco, Christopher Cook, Yousif Ahmad, James Howard, Christopher Baker, Andrew Sharp, Robert Gerber, Suneel Talwar, Ravi Assomull, Jamil Mayet, Roland Wensel, David Collier, Matthew Shun-Shin, Simon A Thom, Justin E Davies, Darrel P Francis, on behalf of the ORBITA investigators*

- 1^{ER} essai avec groupe témoin placebo en double-aveugle comparant PCI à intervention factice chez patients avec MCAS et lésion > 70%



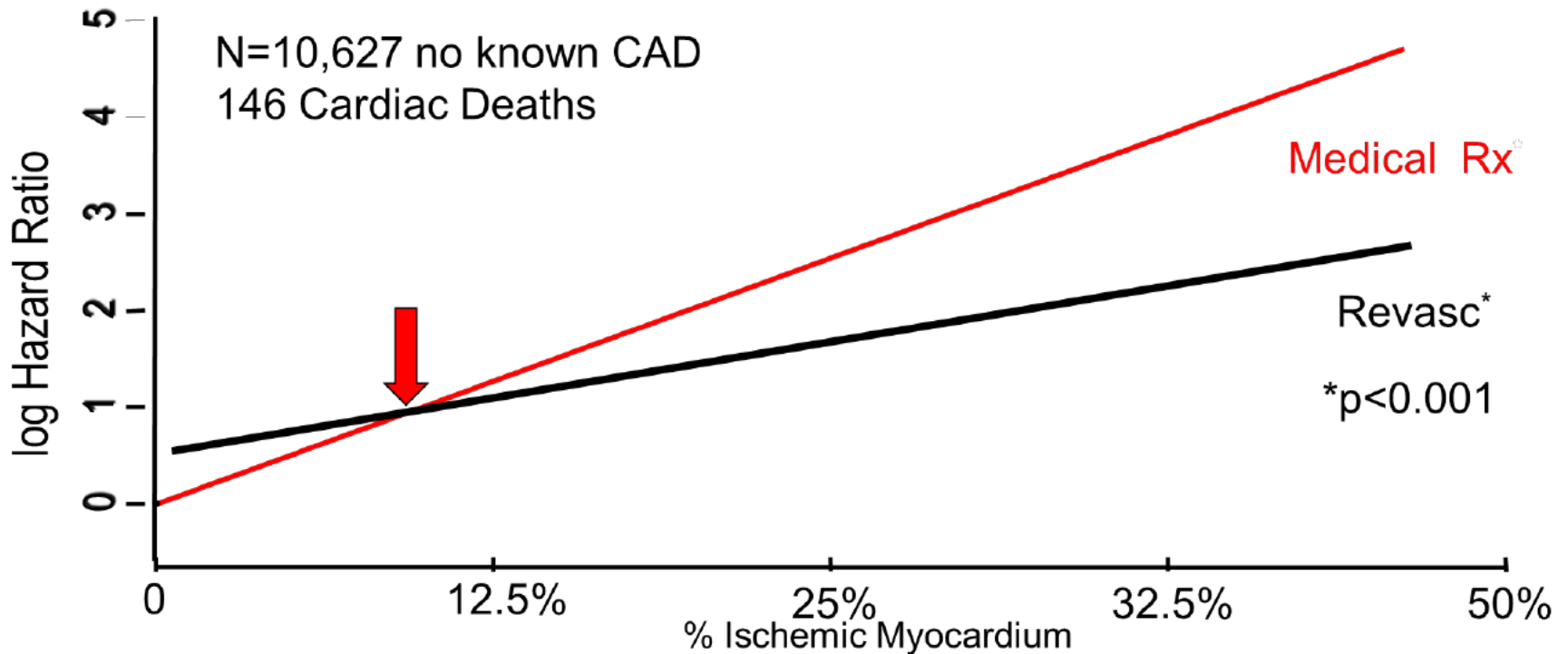
	PCI	Placebo
Exercise time (s)		
Patients assessed	104	90
Pre-randomisation	528.0 (178.7)	490.0 (195.0)
Follow-up	556.3 (178.7)	501.8 (190.9)
Increment (pre-randomisation to follow-up)	28.4 (95% CI 11.6 to 45.1)	11.8 (95% CI -7.8 to 31.3)
Difference in increment between groups	16.6 (95% CI -8.9 to 42.0)	..
p value	0.200	..
SAQ-angina frequency		
Patients assessed	103	90
Pre-randomisation	63.2 (20.4)	60.0 (25.1)
Follow-up	74.4 (21.4)	67.7 (22.1)
Increment (prerandomisation to follow-up)	11.2 (20.3; 95% CI 7.2 to 15.1)	7.7 (22.7; 95% CI 2.9 to 12.4)
Difference in increment between groups	3.5 (95% CI -2.6 to 9.6)	..
p value	0.260	..

**MAIS POUR QUEL SYNDROME
ISCHÉMIQUE STABLE FAUT-IL
RÉSERVER LA REVASCULARISATION
ALORS?**



Art: Antoine Tava; « Screaming heart »

Données observationnelles: Revascularisation associée à une mortalité moindre seulement si charge ischémique >10% à l'imagerie médicale



Une charge ischémique sévère signifie une augmentation des risques de mourir, soit d'arythmies ou encore d'infarctus/SCA



ISCHEMIA

**International Study Of Comparative Health Effectiveness
With Medical And Invasive Approaches (ISCHEMIA):**

Primary Report of Clinical Outcomes

Funded by the National Heart, Lung, and Blood Institute

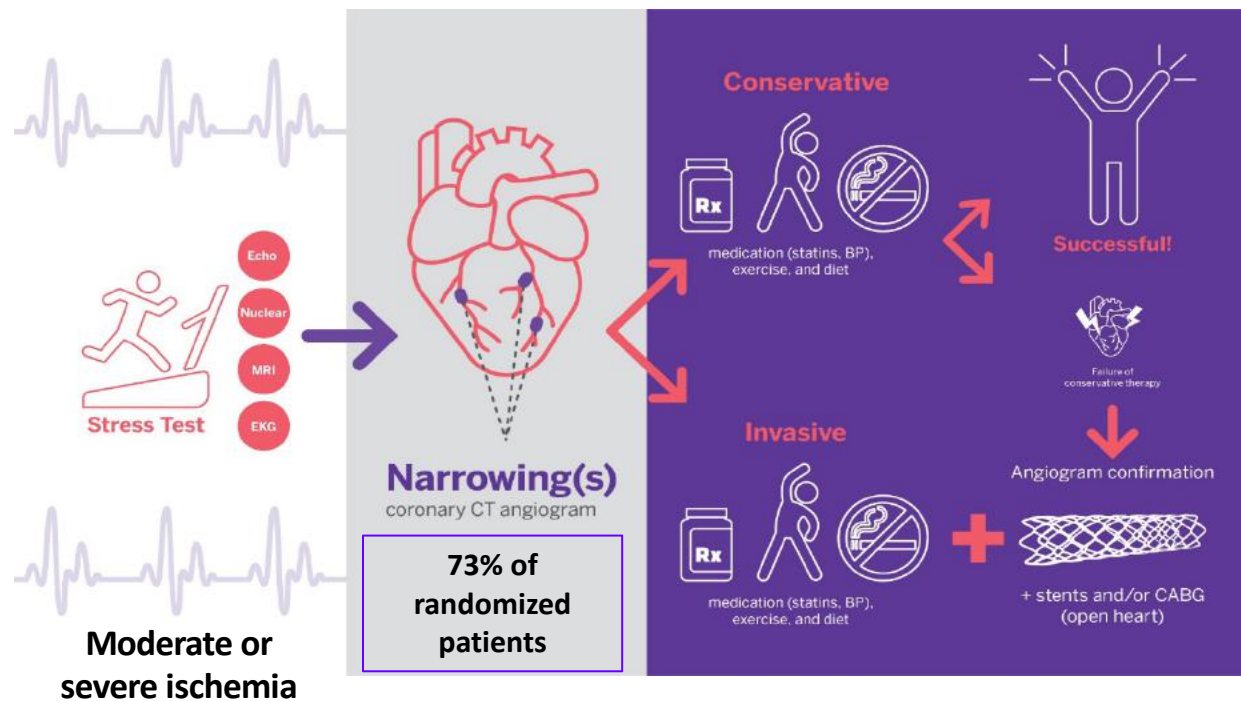
Judith S. Hochman, MD

NYU School of Medicine

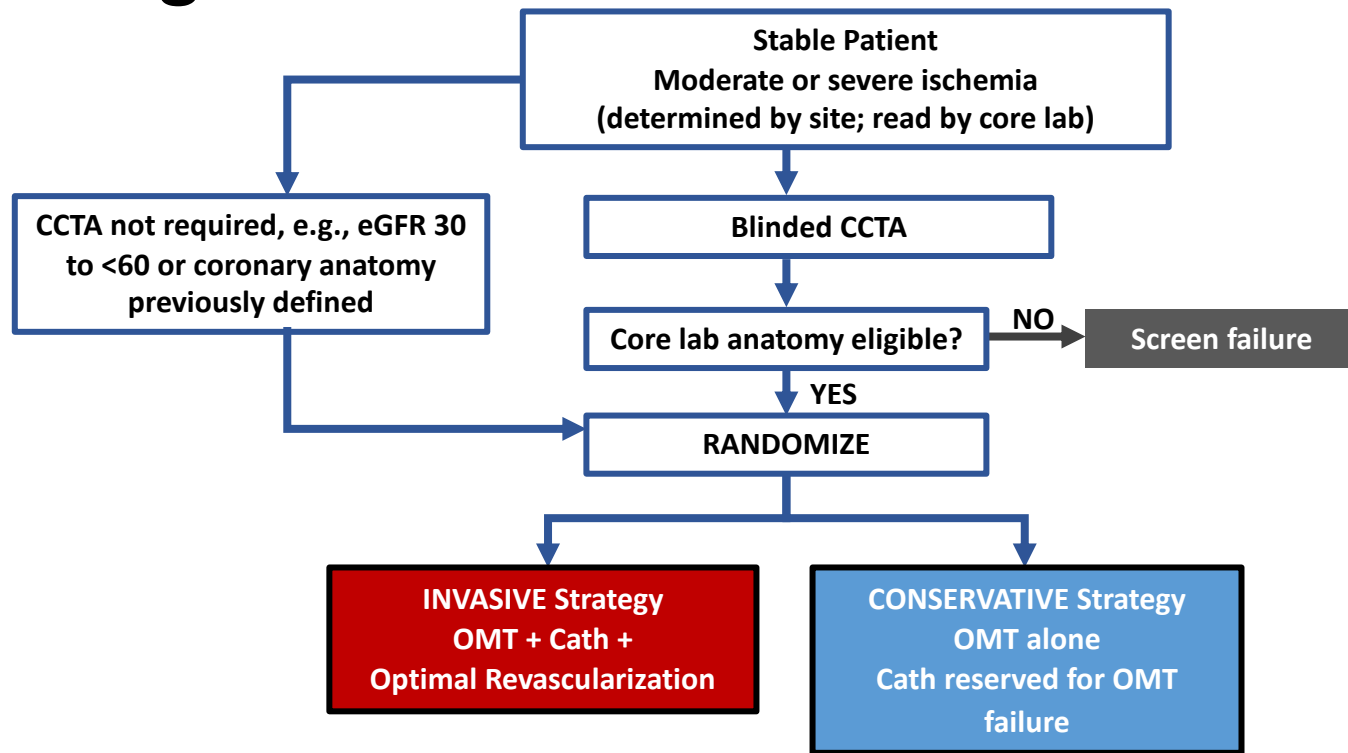
On behalf of the ISCHEMIA Research Group

ISCHEMIA – Question de recherche

- **Y a-t-il une bénéfice à la coronarographie ± revascularisation , chez des patients avec syndrome ischémique stable et démontrant une ischémique modérée ou sévère à l'imagerie?**



Study Design



Maron DJ, et al. American Heart Journal. 2018; 201:124-135.

Eligibility Criteria

Clinical and Stress Test Eligibility Criteria

Inclusion Criteria

- Age ≥ 21 years
- Moderate or severe ischemia*
 - Nuclear $\geq 10\%$ LV ischemia (summed difference score ≥ 7)
 - Echo ≥ 3 segments stress-induced moderate or severe hypokinesis, or akinesis
 - CMR
 - Perfusion: $\geq 12\%$ myocardium ischemic, and/or
 - Wall motion: $\geq 3/16$ segments with stress-induced severe hypokinesis or akinesis
 - Exercise Tolerance Testing (ETT) ≥ 1.5 mm ST depression in ≥ 2 leads or ≥ 2 mm ST depression in single lead at < 7 METS, with angina

Major Exclusion Criteria

- NYHA Class III-IV HF
- Unacceptable angina despite medical therapy
- EF $< 35\%$
- ACS within 2 months
- PCI or CABG within 1 year
- eGFR < 30 mL/min or on dialysis



CCTA Eligibility Criteria

Inclusion Criteria

- $\geq 50\%$ stenosis in a major epicardial vessel (stress imaging participants)
- $\geq 70\%$ stenosis in a proximal or mid vessel (ETT participants)

Major Exclusion Criteria

- $\geq 50\%$ stenosis in unprotected left main

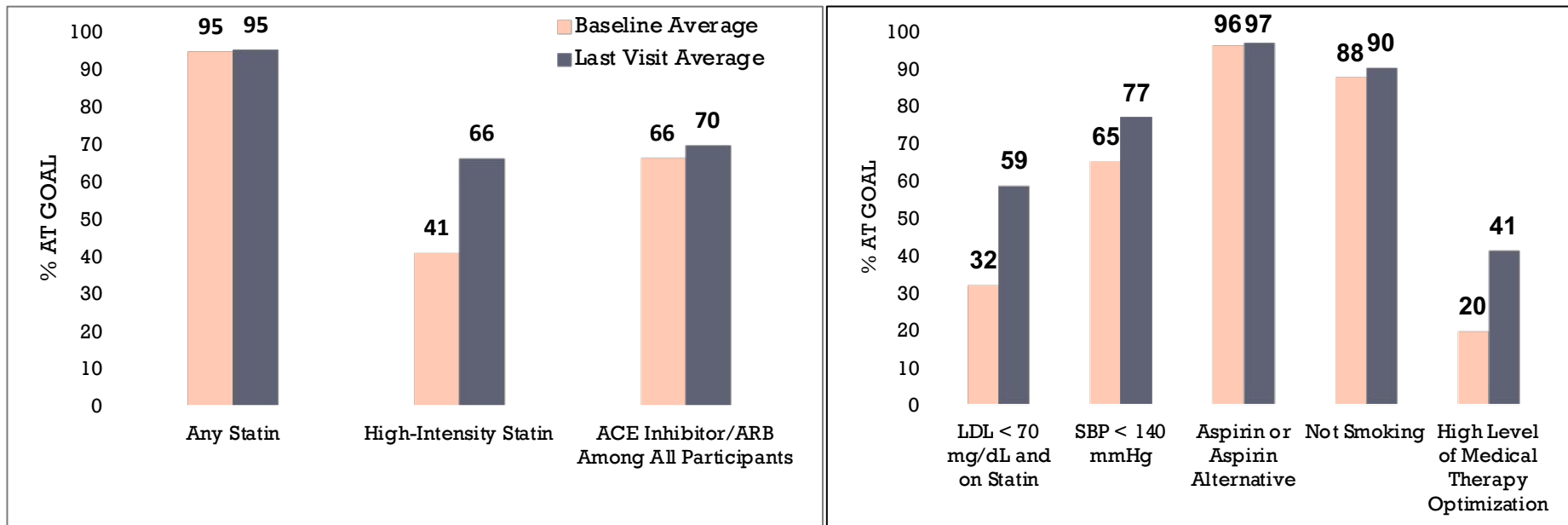
**Ischemia eligibility determined by sites. All stress tests interpreted at core labs.*

Maron DJ, et al. American Heart Journal. 2018; 201:124-135.

Risk Factor Management

Baseline vs last visit

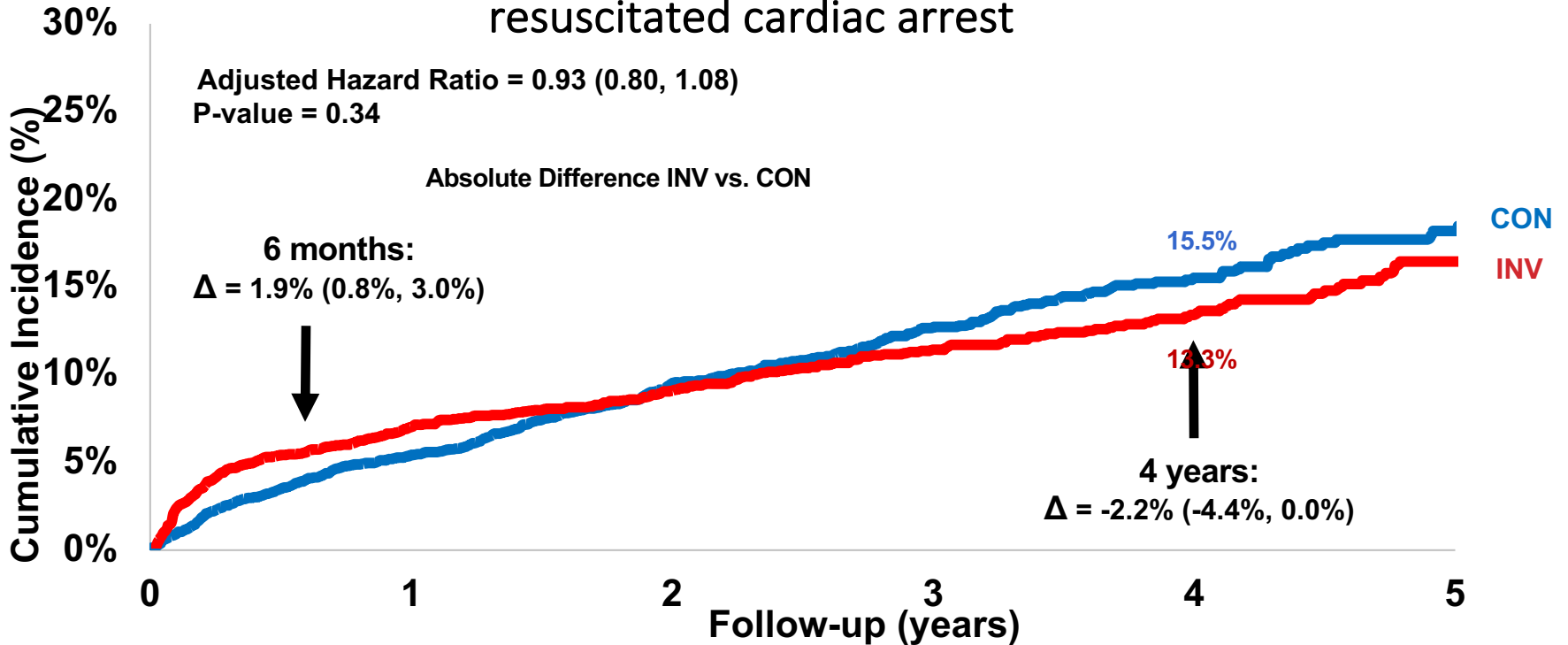
No between group differences INV vs CON



High Level of Medical Therapy Optimization is defined as a participant meeting all of the following goals: LDL < 70 mg/dL and on any statin, systolic blood pressure < 140 mm/Hg, on aspirin or other antiplatelet or anticoagulant, and not smoking. High level of medical therapy optimization is missing if any of the individual goals are missing.



Primary Outcome: CV Death, MI, hospitalization for UA, HF or resuscitated cardiac arrest

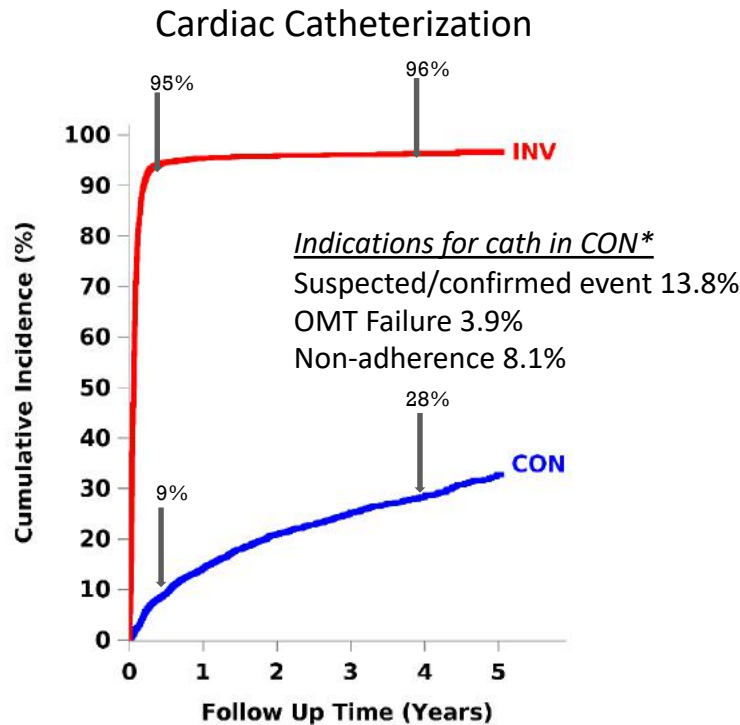


Subjects at Risk

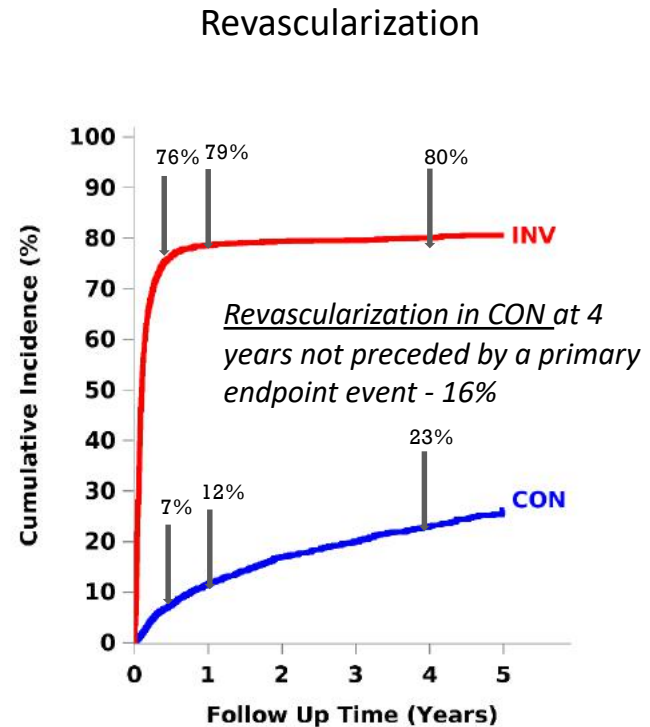
	0	1	2	3	4	5
CON	2591	2431	1907	1300	733	293
INV	2588	2364	1908	1291	730	271



Cardiac Catheterization and Revascularization



CON 2591 2186 1646 1087 601 232
 INV 2588 111 79 50 20 4

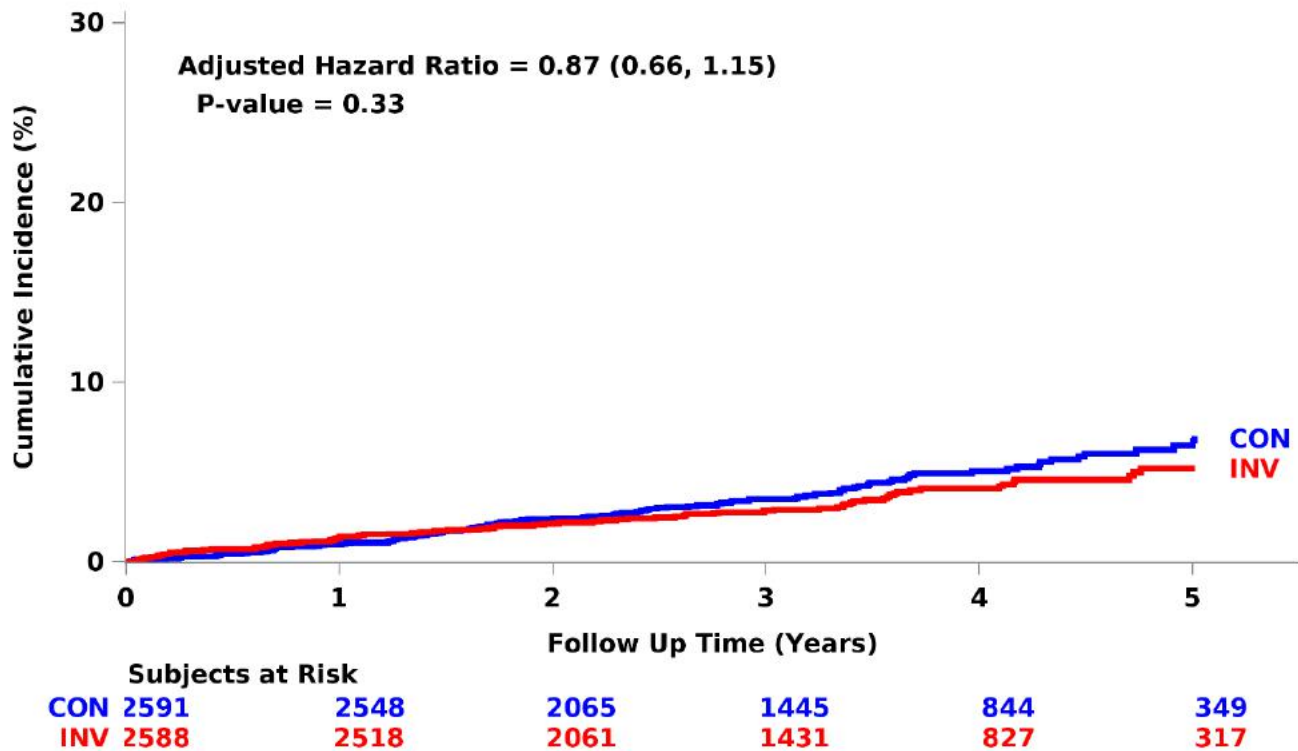


CON 2591 2250 1721 1157 642 254
 INV 2588 523 410 289 155 54

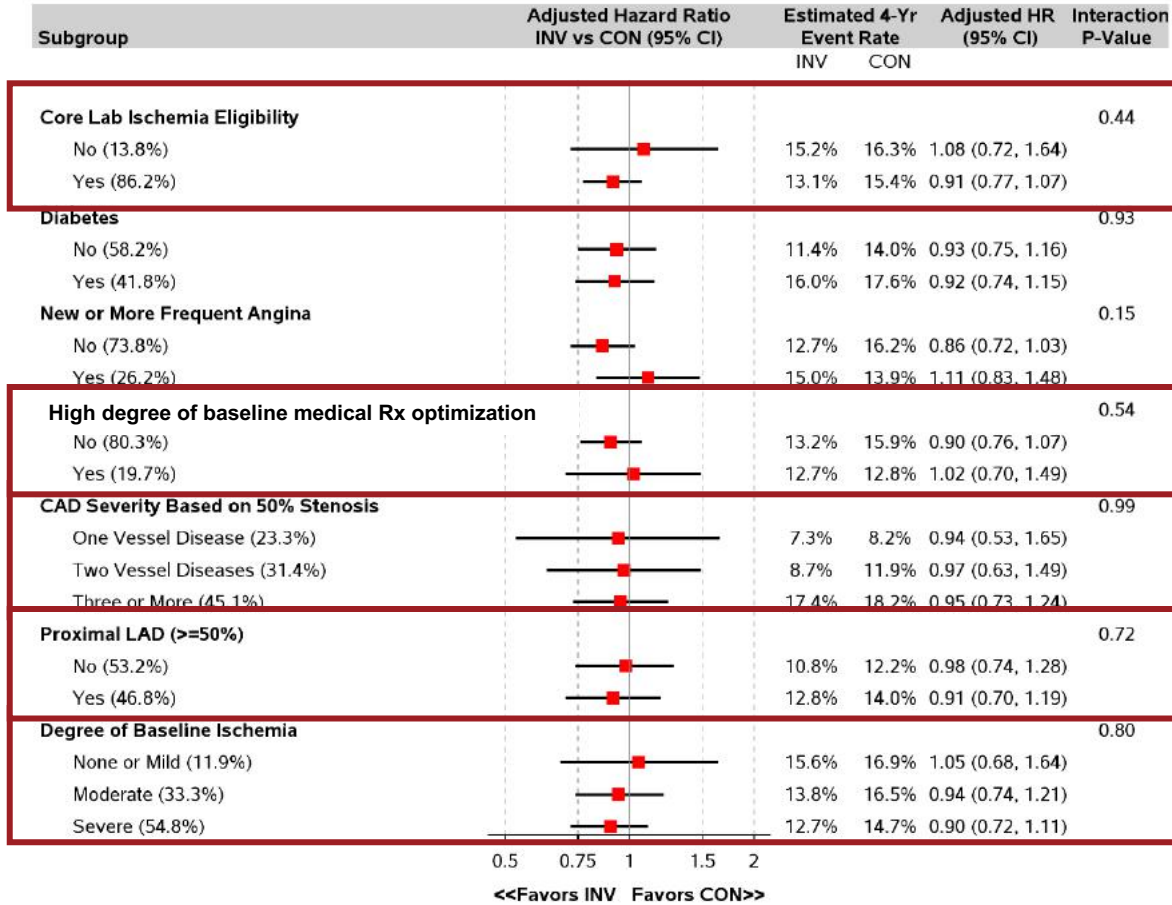
*Indications for Cath are percentages of CON patients whereas cumulative event rate shown at 4 years reflects censoring and the rate at that time point.



Cardiovascular Death



Primary endpoint
 Pre-specified Important Subgroups
There was no heterogeneity of treatment effect



N=3739 for Prox LAD Y/N
 N=2982 for # diseased vessels



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Coronary-Artery Bypass Surgery in Patients with Ischemic
Cardiomyopathy

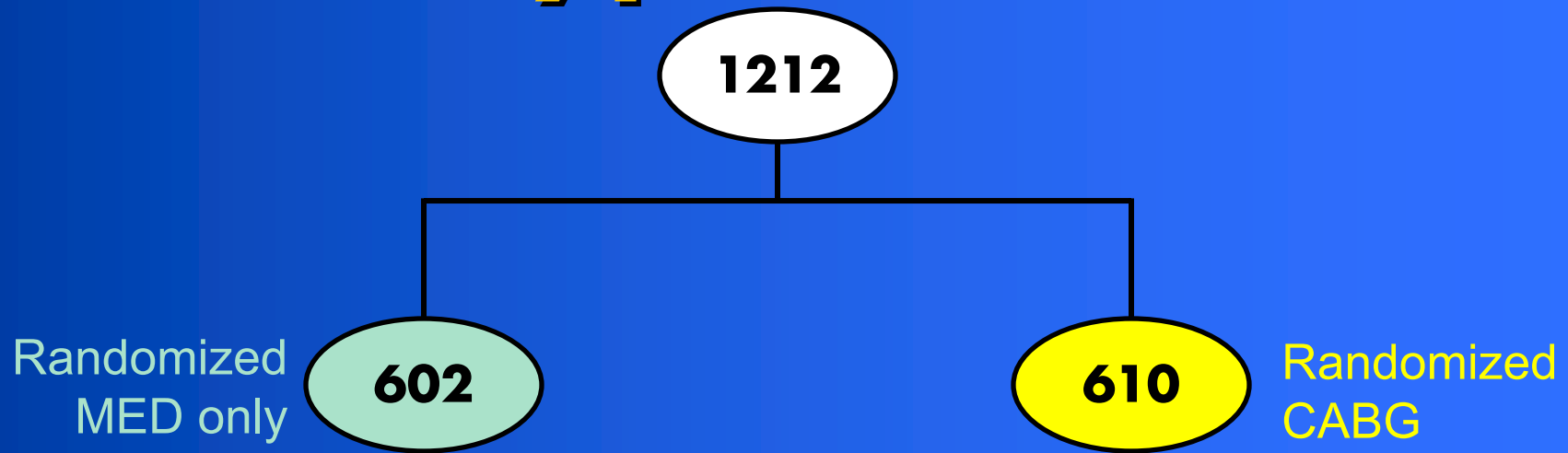
Eric J. Velazquez, M.D., Kerry L. Lee, Ph.D., Robert H. Jones, M.D., Hussein R. Al-Khalidi, Ph.D.,
James A. Hill, M.D., Julio A. Panza, M.D., Robert E. Michler, M.D., Robert O. Bonow, M.D., Torsten Doenst, M.D.,
Mark C. Petrie, M.D., Jae K. Oh, M.D., Lilin She, Ph.D., Vanessa L. Moore, A.A.S., Patrice Desvigne-Nickens, M.D.,
George Sopko, M.D., M.P.H., and Jean L. Rouleau, M.D., for the STICHES Investigators*

Chez les patients atteints de cardiopathie ischémique (FEVG<35%) avec une MCAS significative amenable a revascularisation, les pontages + MED invasif réduiront la mortalité totale vs. MED invasif seule.

STICH

Revascularization

Hypothesis



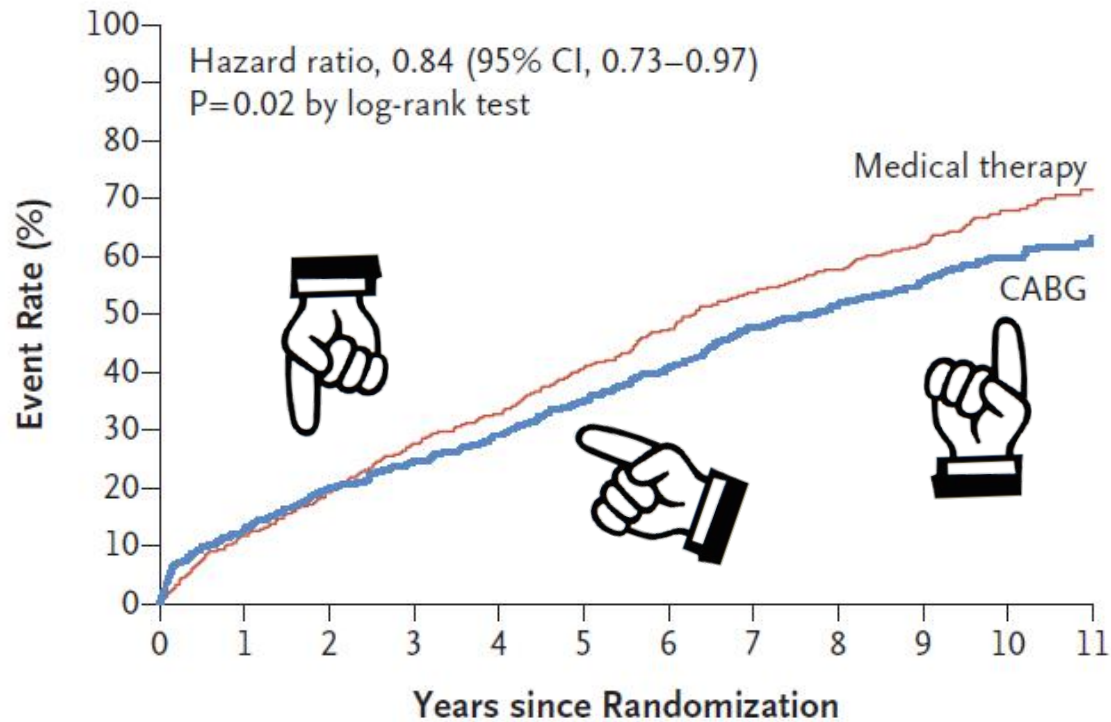
- 99 clinical sites in 22 countries
- Enrollment: July 2002 – May 2007

Medical Therapy

	MED (N=602)		CABG (N=610)	
Medication, %	Baseline	Latest Follow-up	Baseline	Latest Follow-up
Aspirin	85	84	80	84
Aspirin or warfarin	91	93	84	92
ACE inhibitor or ARB	88	89	91	89
Beta-blocker	88	90	83	90
Statin	83	87	79	90
K ⁺ sparing diuretic	46	53	46	54
ICD	2	19	2	15

STICHES

A Death from Any Cause (Primary Outcome)

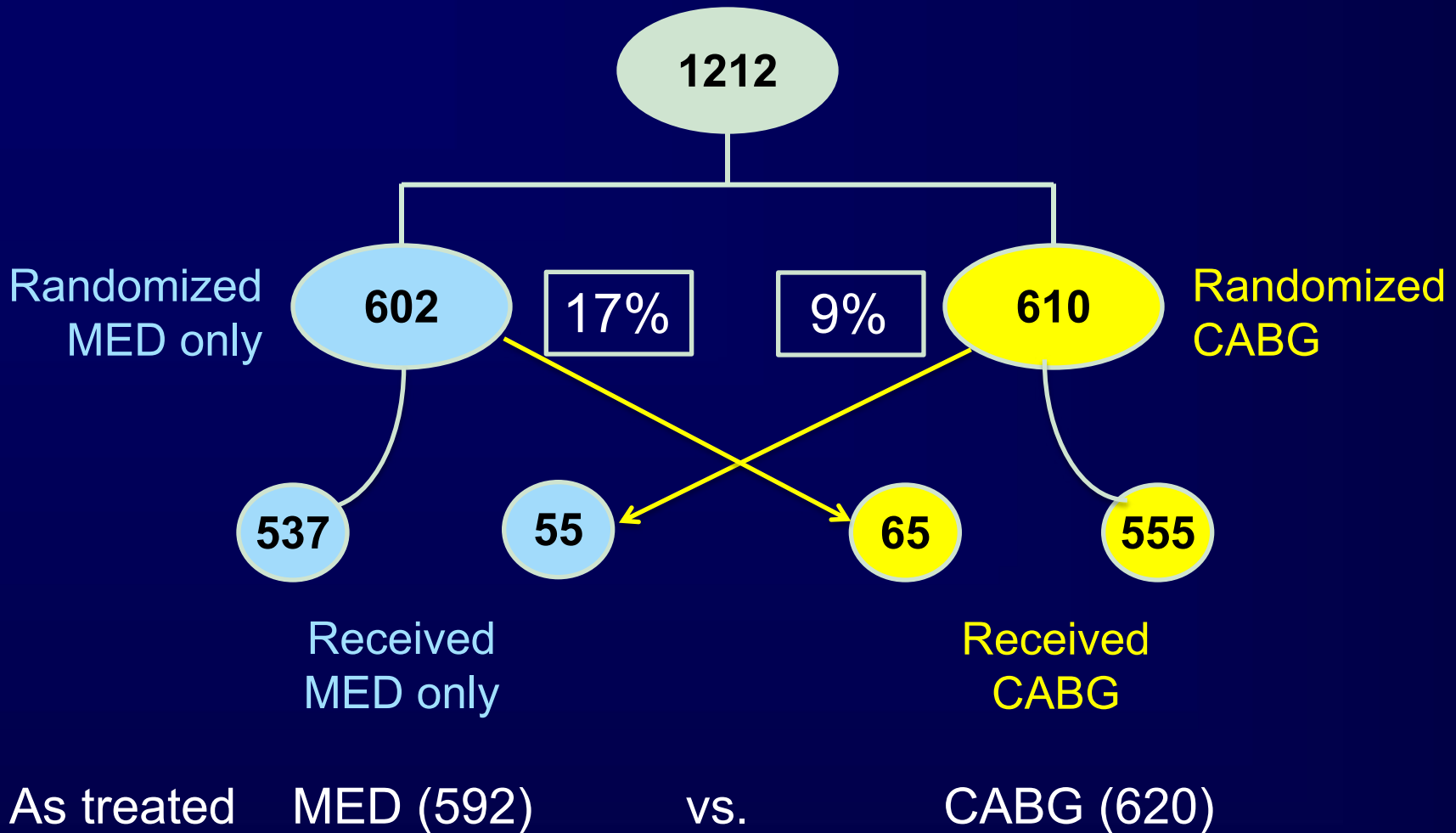


No. at Risk

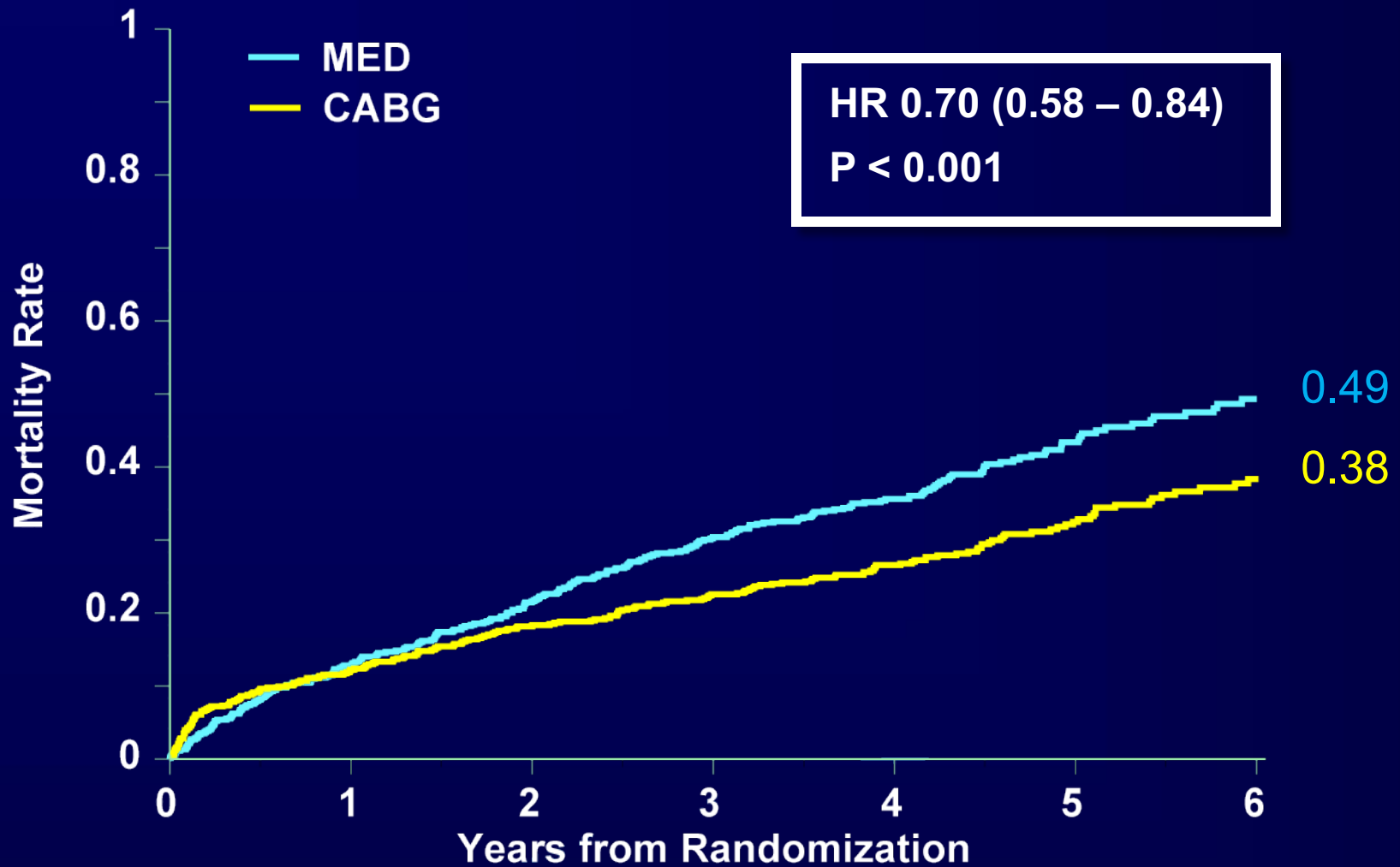
Medical therapy	602	532	487	435	404	357	315	274	248	164	82	37
CABG	610	532	487	460	432	392	356	312	286	205	103	42

STICH Revascularization Hypothesis

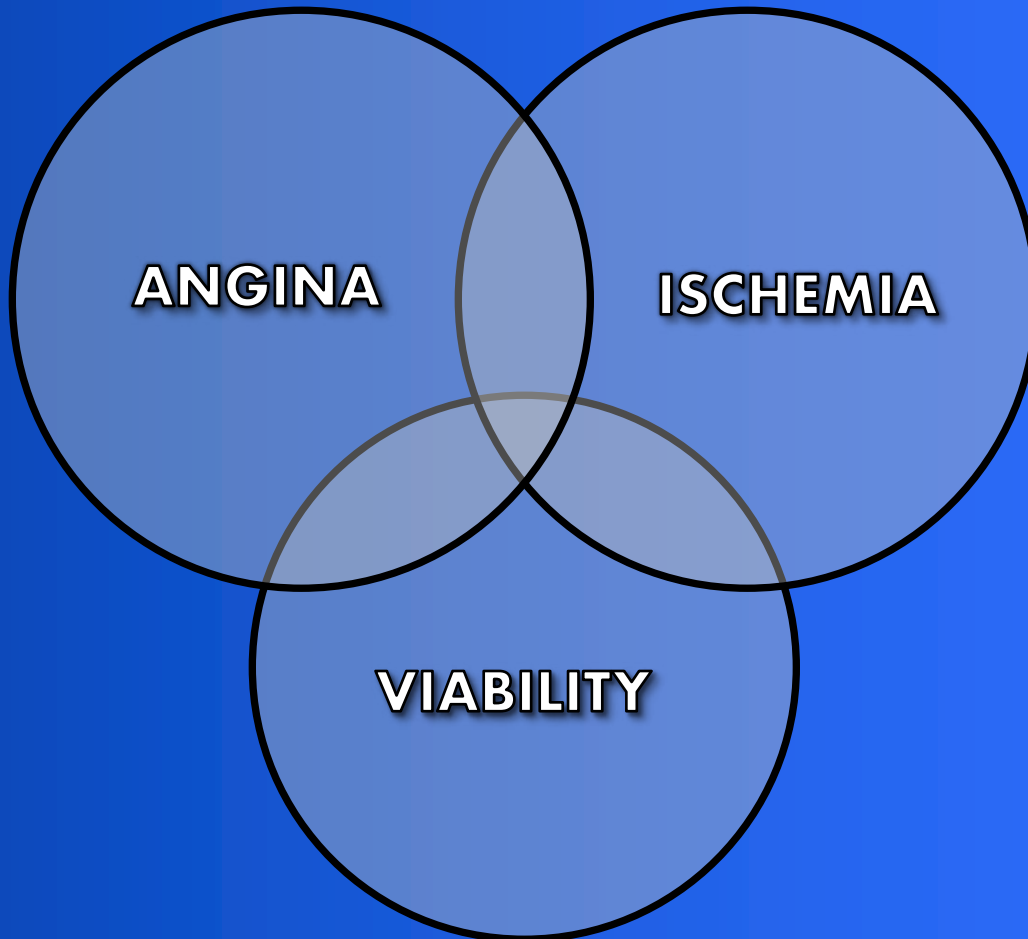
Treatment As Received



All-Cause Mortality — As Treated



MED	592	516	464	412	297	146	74
CABG	620	548	509	482	355	182	97



CHF

IHD

CABG

PCI



Recommendations for revascularization in CHF



CABG or PCI is indicated for HF patients on GDMT with **angina** and suitable coronary anatomy, especially significant left main stenosis or left main equivalent



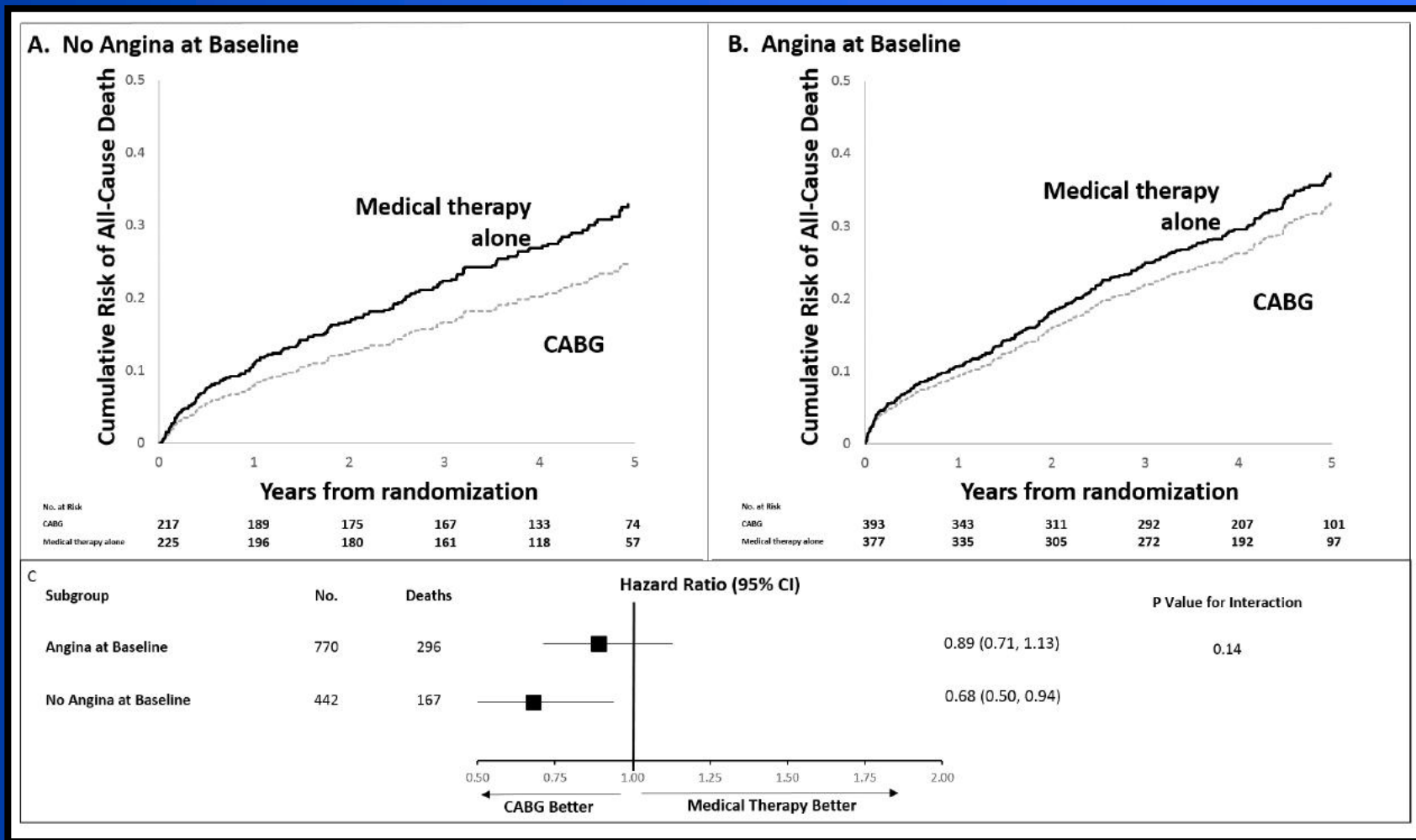
CABG or medical therapy is reasonable to improve morbidity and mortality for patients

with **severe LV dysfunction** (EF <35%), HF, and significant CAD



CABG may be considered in patients with ischemic heart disease, severe LV systolic dysfunction, and operable coronary anatomy whether or not viable myocardium is present

Figure 2. Adjusted Kaplan-Meier Analysis of the Probability of All-Cause Death According to Angina Status and Treatment Arm

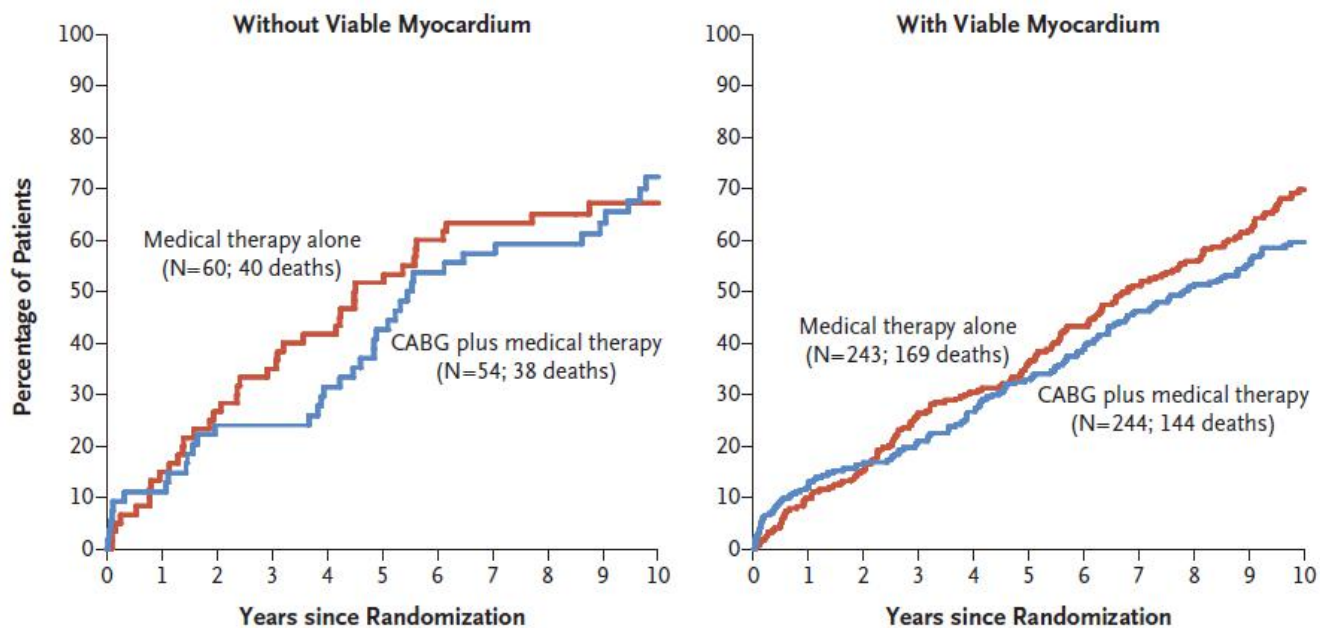


ORIGINAL ARTICLE

Myocardial Viability and Long-Term Outcomes in Ischemic Cardiomyopathy

Julio A. Panza, M.D., Alicia M. Ellis, Ph.D., Hussein R. Al-Khalidi, Ph.D.,
Thomas A. Holly, M.D., Daniel S. Berman, M.D., Jae K. Oh, M.D.,
Gerald M. Pohost, M.D., George Sopko, M.D., Lukasz Chrzanowski, M.D.,
Daniel B. Mark, M.D., Tomasz Kukulski, M.D., Liliana E. Favalaro, M.D.,
Gerald Maurer, M.D., Pedro S. Farsky, M.D., Ru-San Tan, M.D.,
Federico M. Asch, M.D., Eric J. Velazquez, M.D., Jean L. Rouleau, M.D.,
Kerry L. Lee, Ph.D., and Robert O. Bonow, M.D.

B Death from Any Cause, According to Myocardial Viability Status



No. at Risk

	0	1	2	3	4	5	6	7	8	9	10		0	1	2	3	4	5	6	7	8	9	10
Medical therapy alone	60	51	44	39	35	29	24	22	21	14	11		243	219	206	179	169	155	137	117	106	79	48
CABG plus medical therapy	54	48	41	41	37	31	25	23	22	17	11		244	213	203	193	179	161	146	128	116	94	58

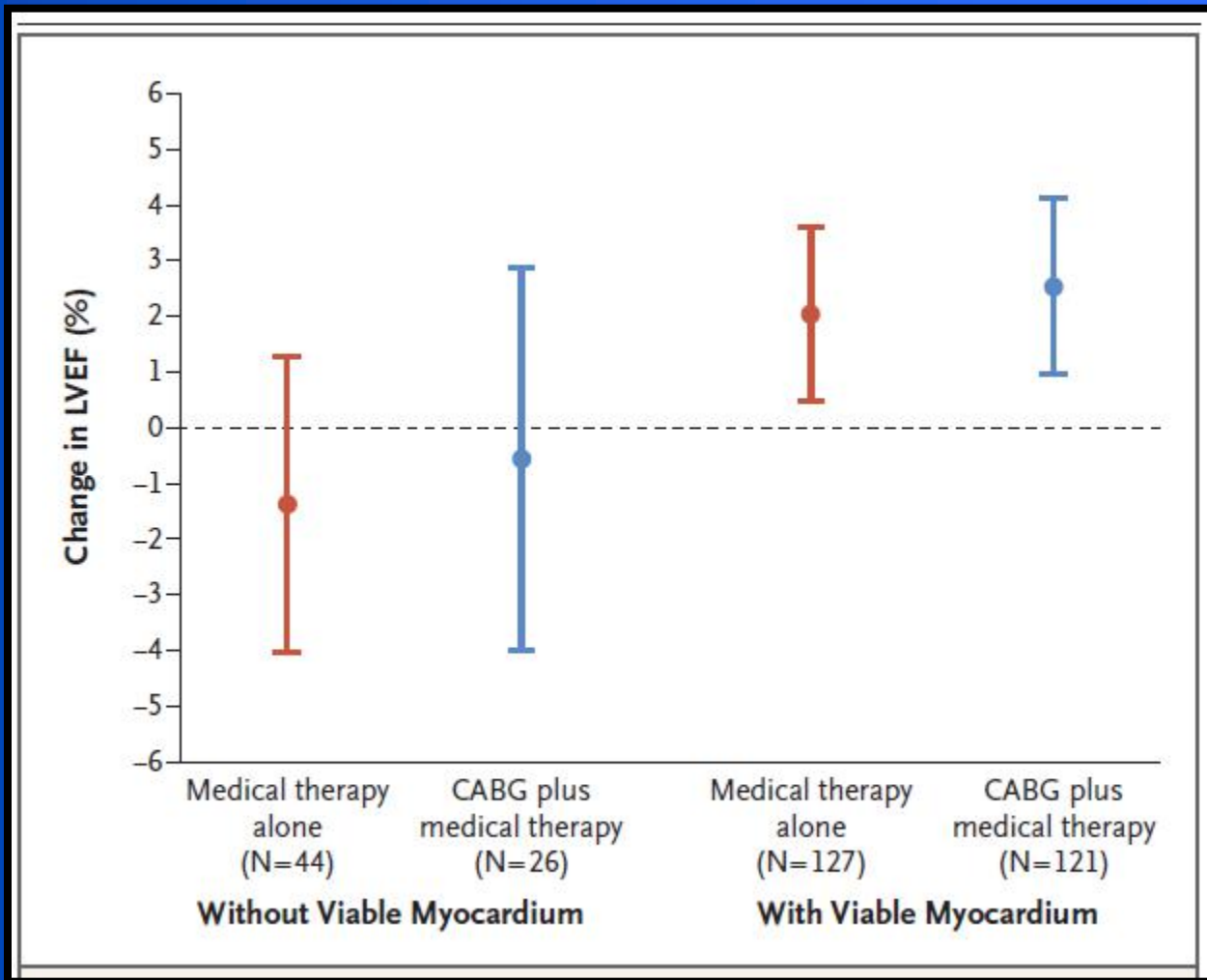
C Interaction between Treatment Assignment and Myocardial Viability Status

Subgroup	No. of Patients	No. of Deaths	Medical Therapy Alone 10-yr Kaplan-Meier Incidence (%)	CABG plus Medical Therapy 10-yr Kaplan-Meier Incidence (%)	Adjusted Hazard Ratio (95% CI)	P Value for Interaction
Without viable myocardium	114	78	67.2	72.3	0.81 (0.50–1.31)	0.34
With viable myocardium	487	313	69.8	59.6	0.70 (0.56–0.88)	

0.25 0.50 1.00 2.00

CABG plus Medical Therapy Better

Medical Therapy Alone Better



La viabilité cardiaque marque le pronostic, mais ne marque pas la réponse à la revascularisation!



ESC

European Society
of Cardiology

European Heart Journal (2017) 38, 3124–3134

doi:10.1093/eurheartj/ehx512

FASTTRACK CLINICAL RESEARCH
ESC Late Breaking Science in PCI 1

Interventional cardiology

Clinical outcomes of state-of-the-art percutaneous coronary revascularization in patients with *de novo* three vessel disease: 1-year results of the SYNTAX II study

Javier Escaned¹, Carlos Collet², Nicola Ryan¹, Giovanni Luigi De Maria³, Simon Walsh⁴, Manel Sabate⁵, Justin Davies⁶, Maciej Lesiak⁷, Raul Moreno⁸, Ignacio Cruz-Gonzalez⁹, Stephan P. Hoole¹⁰, Nick Ej West¹⁰, J. J. Piek², Azfar Zaman¹¹, Farzin Fath-Ordoubadi¹², Rodney H. Stables¹³, Clare Appleby¹³, Nicolas van Mieghem¹⁴, Robert Jm. van Geuns¹⁴, Neal Uren¹⁵, Javier Zueco¹⁶, Pawel Buszman¹⁷, Andres Iñiguez¹⁸, Javier Goicolea¹⁹, David Hildick-Smith²⁰, Andrzej Ochala²¹, Dariusz Dudek²², Colm Hanratty⁴, Rafael Cavalcante¹⁴, Arie Pieter Kappetein¹⁴, David P. Taggart³, Gerrit-Anne van Es^{23,24}, Marie-Angèle Morel²³, Ton de Vries²³, Yoshinobu Onuma^{14,23}, Vasim Farooq¹², Patrick W. Serruys^{6*}, and Adrian P. Banning³

SYNTAX-II historical trial

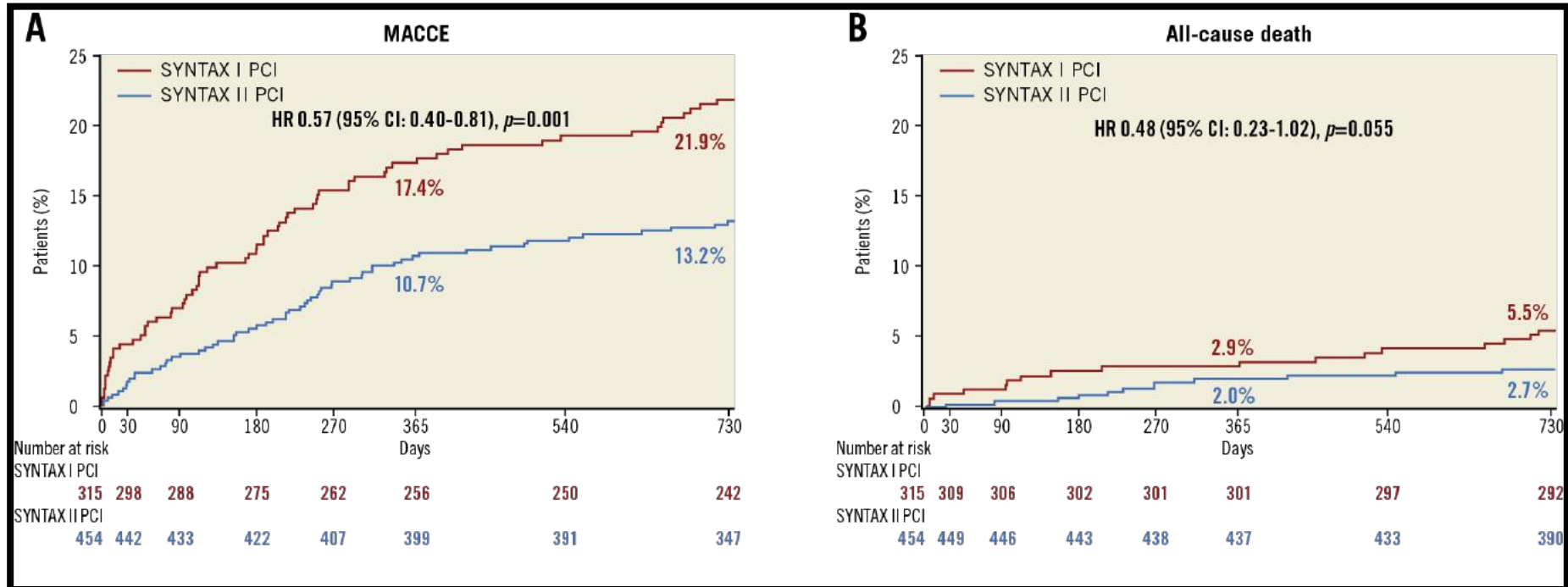
- **The SYNTAX II study is a multicenter, all-comers, open-label, single arm study that investigated the impact of a contemporary PCI strategy on clinical outcomes in patients with 3VD**
- **The rate of all-cause death, cerebrovascular event, MI and any revascularisation]) was compared to a predefined PCI cohort from the original SYNTAX-I trial selected on the basis of equipoise 4-year mortality between CABG and PCI.**
- **As an exploratory endpoint, comparisons were made with the historical CABG cohort of the original SYNTAX-I trial.**

Table 1 Baseline clinical characteristics

	SYNTAX II (n = 454)	SYNTAX I PCI arm (n = 315)	P-value
Age (years)	66.7±9.7 (454)	66.7±9.1 (315)	0.99
Male	93.2% (423/454)	93.0% (293/315)	0.93
Body mass index (kg/m ²)	28.9±4.7 (449)	28.2±4.4 (315)	0.032
Diabetes mellitus type I or II	30.3% (135/446)	29.2% (92/315)	0.75
Insulin treated	8.5% (38/446)	10.5% (33/315)	0.36
Oral medication	19.5% (87/446)	16.8% (53/315)	0.35
Diet only	2.0% (9/446)	1.9% (6/315)	0.91
Current smoker	14.7% (64/435)	17.8% (56/315)	0.26
Previous MI	12.5% (56/447)	28.7% (89/310)	<0.001
Previous stroke	5.6% (25/449)	1.9% (6/315)	0.010
Hypertension	77.0% (344/447)	73.4% (229/312)	0.26
Hyperlipidaemia	77.3% (341/441)	74.4% (232/312)	0.35
Creatinine clearance (ml/min)	82.0±26.9 (454)	87.3±28.5 (315)	0.008
Ejection fraction (%)	58.1±8.3 (454)	61.8±11.3 (315)	<0.001
Peripheral vascular disease	7.7% (35/454)	9.5% (30/315)	0.37
COPD	10.8% (49/454)	12.7% (40/315)	0.42
Clinical presentation			<0.001
Silent ischaemia	5.5% (30/449)	13.3% (42/315)	
Stable angina	68.8% (309/449)	61.6% (194/315)	
Unstable angina	25.6% (115/449)	25.1% (79/315)	
Anatomic SYNTAX Score	20.3±6.4 (454)	22.8±8.7 (315)	<0.001
SYNTAX Score II PCI	30.2±8.6 (454)	30.6±8.7 (315)	0.528
Predicted 4-year mortality PCI (%)	8.9±8.8% (454)	9.2±8.7% (315)	0.64
SYNTAX Score II CABG	29.1±10.4 (454)	29.1±9.6 (315)	1.0
Predicted 4-year mortality CABG (%)	9.0±9.3 (454)	8.5±8.1 (315)	0.44

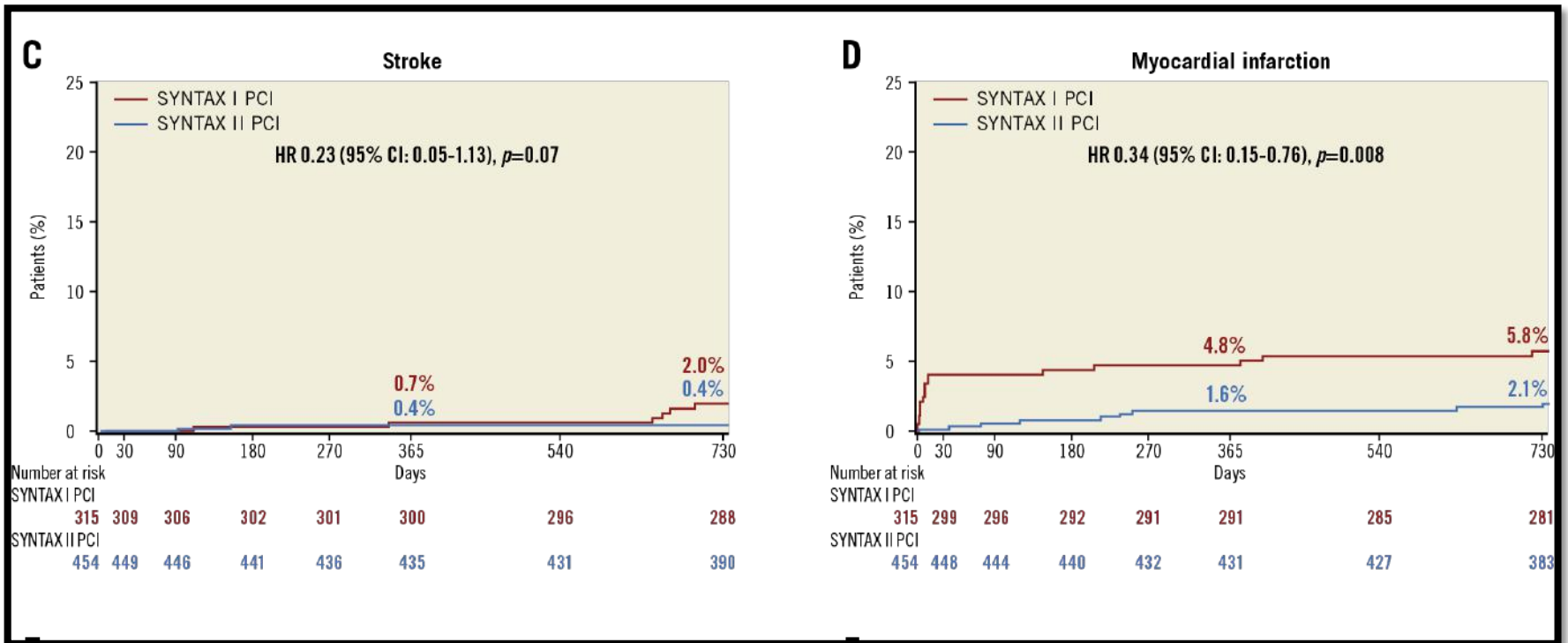
MI, myocardial infarction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft; COPD, chronic obstructive pulmonary disease.

Two-year clinical outcomes among the study patients, compared with the SYNTAX-I PCI cohort.

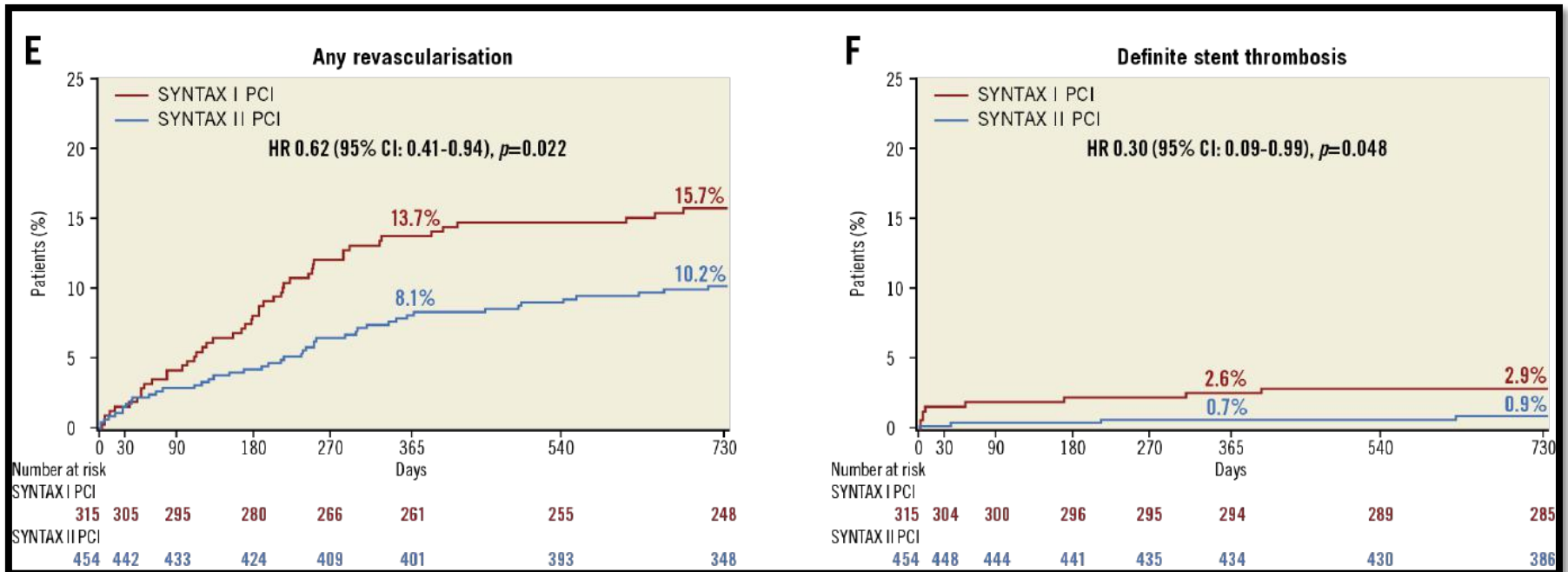


For the primary endpoint, a sensitivity analysis using inverse propensity score weighting (IPTW) and multivariate Cox proportional hazard regression model were performed

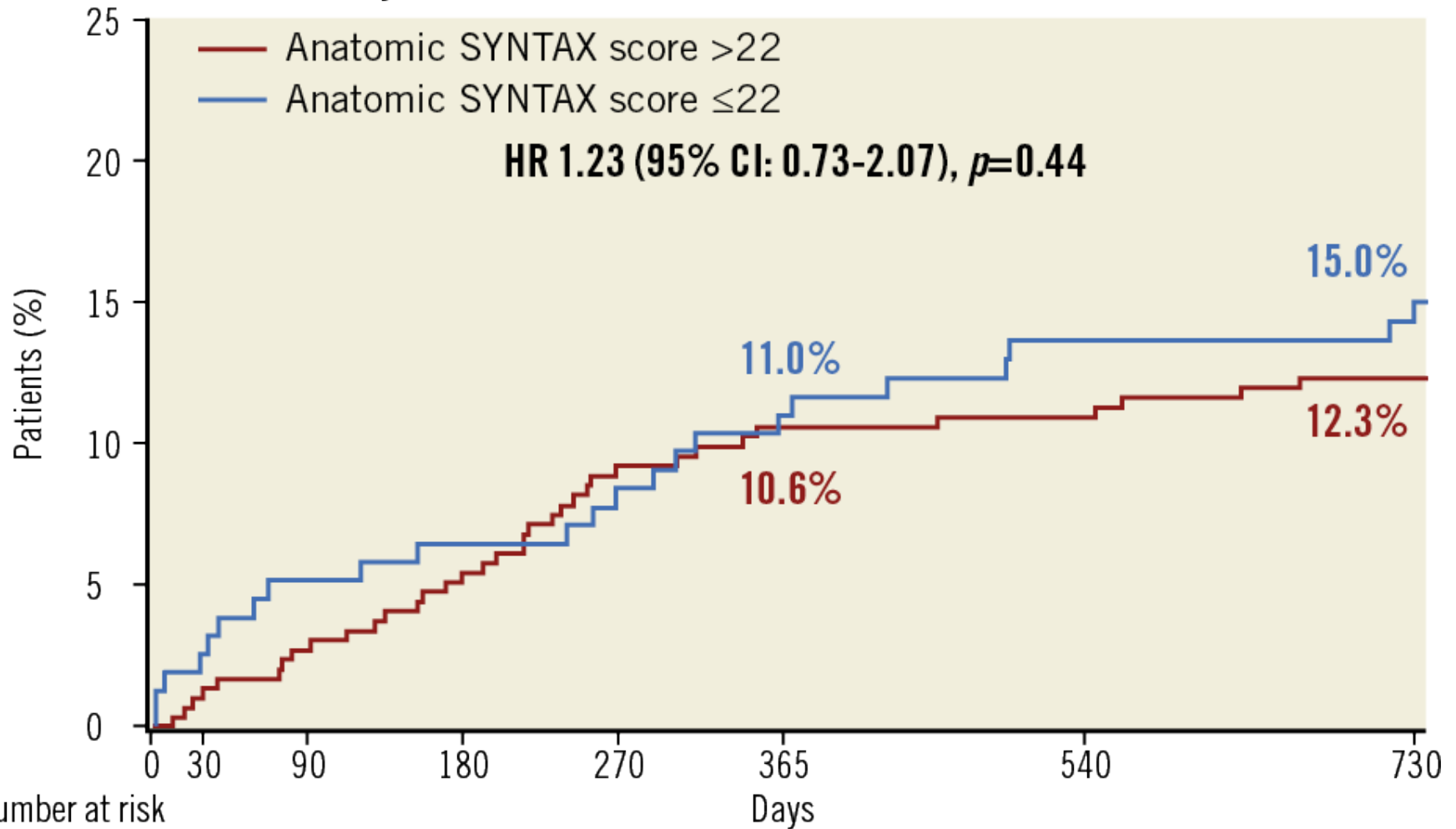
Two-year clinical outcomes among the study patients, compared with the SYNTAX-I PCI cohort.



Two-year clinical outcomes among the study patients, compared with the SYNTAX-I PCI cohort.



Major adverse cardiac or cerebrovascular events



Number at risk

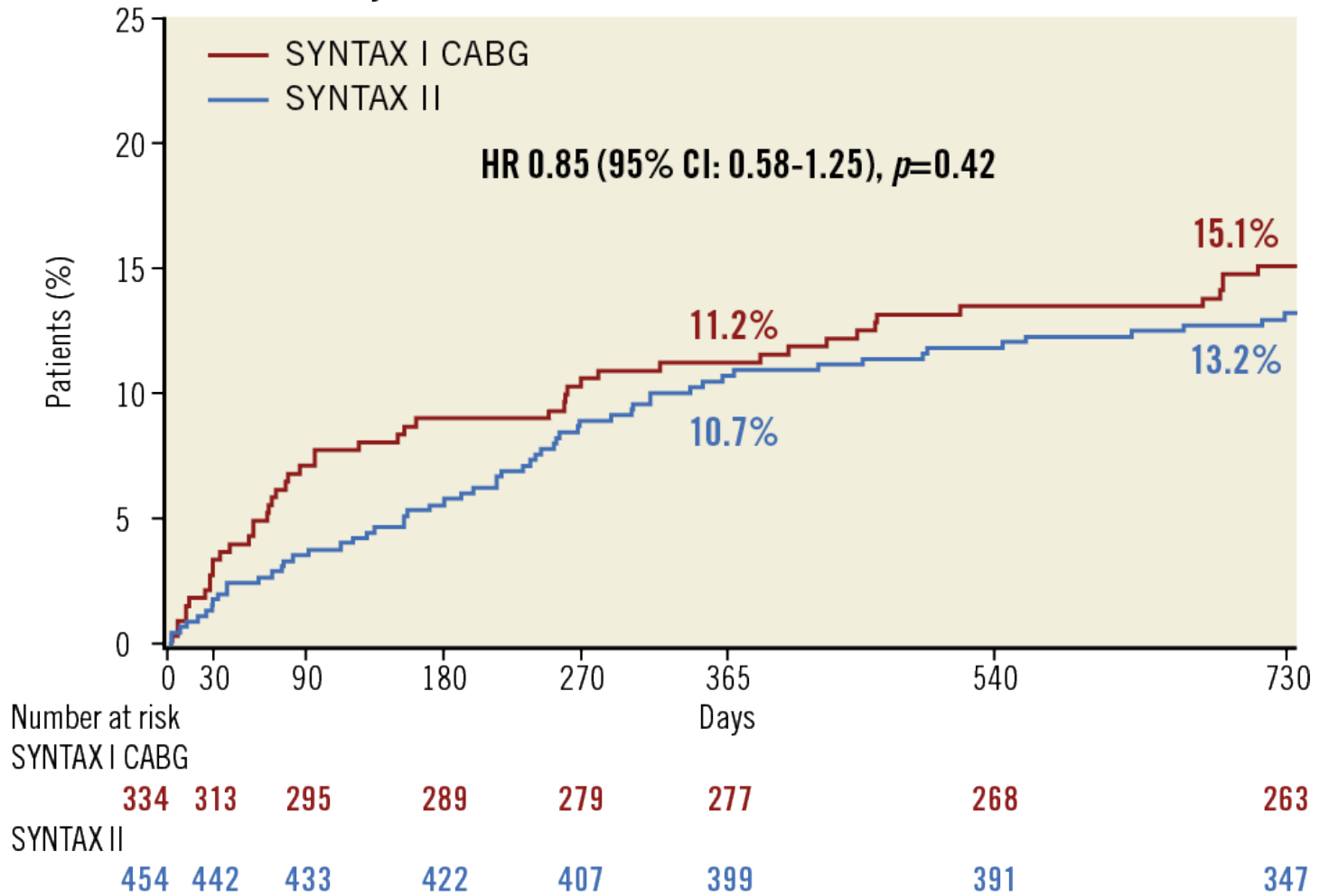
Anatomic SYNTAX score >22

156 151 147 144 141 137 132 118

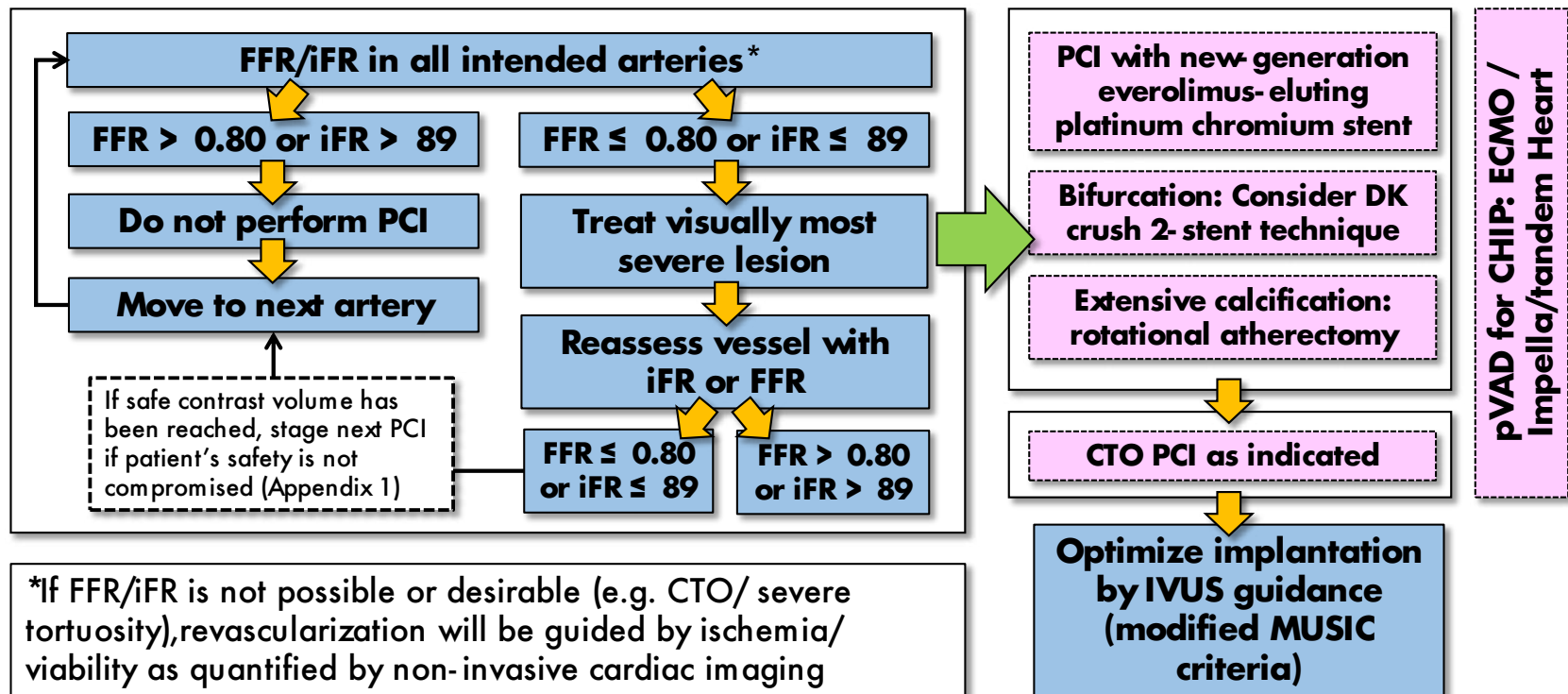
Anatomic SYNTAX score ≤22

298 291 286 278 266 262 259 229

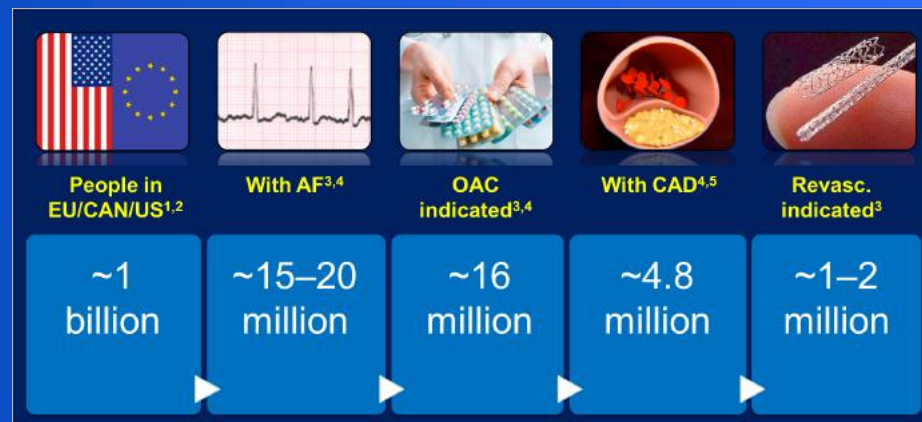
Major adverse cardiac or cerebrovascular events



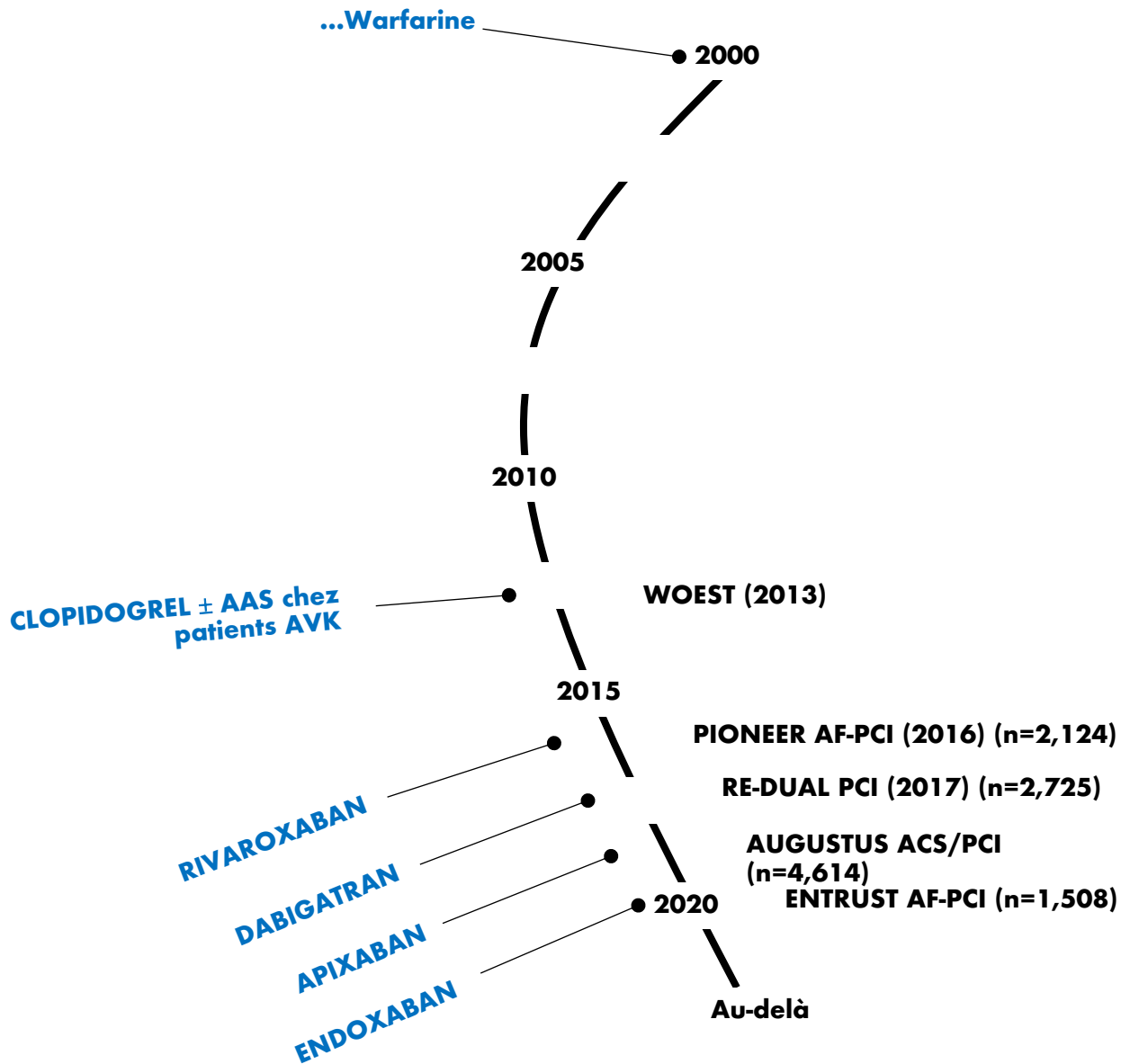
State-of-the-Art PCI for the STICH 3.0 Trial



- **Champ relativement récent qui débute avec l'étude WOEST (AAS+clopi vs. clopi seul chez patients anticoagulés avec warfarine) et qui montre une ↓ surprise des saignement et des événements ischémique avec l'arrêt de l'AAS. avec ou sans AAS**



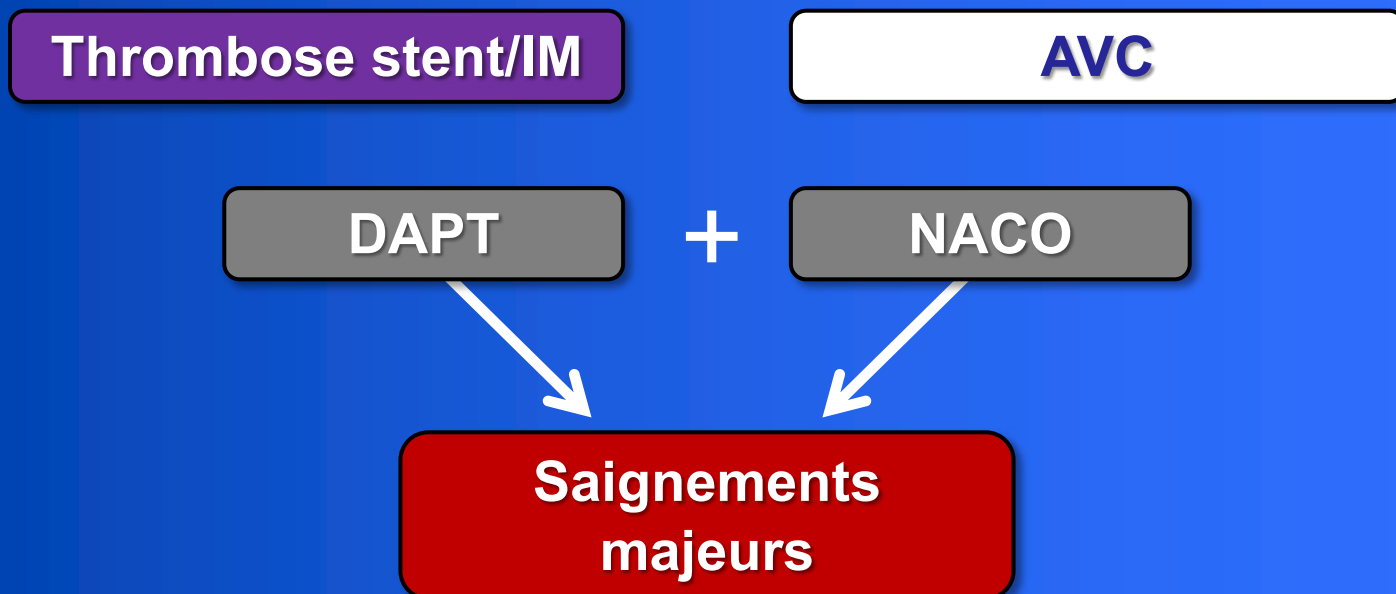
1. US population. Available at: www.census.gov/popclock. Accessed Aug 2019; 2. EU population. Available at: europa.eu/european-union/about-eu/figures/living_en. Accessed Aug 2019; 3. Capodanno D, Angiolillo DJ. *Circ Cardiovasc Interv* 2014;7:113–24; 4. Capodanno D, et al. *J Am Coll Cardiol* 2019;74:83–99; 5. Verheugt FWA, et al. *J Am Coll Cardiol* 2019. pii: S0735-1097(19)35400-2.



1. Gibson CM, et al. N Engl J Med 2016;375:2423–34; 2. Cannon CP, et al. N Engl J Med 2017;377:1513–24; 3. Lopes RD, et al. N Engl J Med 2019;380:1509–24; 4. Vranckx P, et al. Am Heart J 2018;196:105–12; 5. NCT02866175

PCI + endoprothèse chez patients avec FA et risque AVC élevé

Le problème: vous ne pouvez tout prévenir simultanément



Bewildering number of strategies in the ACS patient with atrial fibrillation

■ ASA dose:	None	Low	High				2	1+8 = 9
■ ASA duration (mos):	1	3	6	12			4	ASA
■ Thienopyridine:	None	Clop	Ticlid	Pras	Ticag		4	1+16 = 17
■ Thienopyridine duration (mos):	1	3	6	12			4	Thieno
■ AC:	None	Warf	Dabi	Riva	Apix	Edox	5	1+10 = 11
■ AC INR/dose:	Low	High					2	ACs

Permutations of single, dual or triple therapy as *Early Initial Therapy (0, 1, 3, 6 mos)* following ACS: $9 \times 17 \times 11 = 1,683$

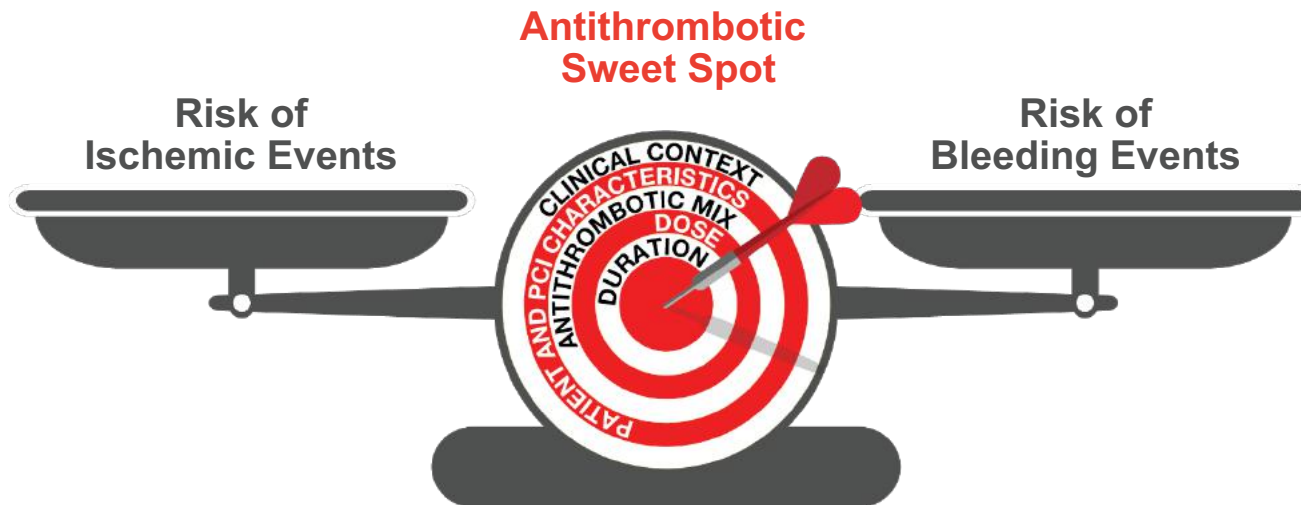
Permutations of single or dual therapy *Late After Early Therapy (0, 1, 3, 6 mos)* following ACS: **1,683**

Total Permutations *throughout one year: 2.8 million*

AC, anticoagulant; Apix, apixaban; ASA, acetylsalicylic acid; Clop, clopidogrel; Dabi, dabigatran; Edox, edoxaban; INR, international normalised ratio; mos, months; Pras, prasugrel; Riva, rivaroxaban; Ticag, ticagrelor; Warf, warfarin.
Slide by C. Michael Gibson, M.S., M.D.

1. Data adapted from Gibson CM. J Am Coll Cardiol 2017;69:172-5.

Trouver la bonne combinaison!

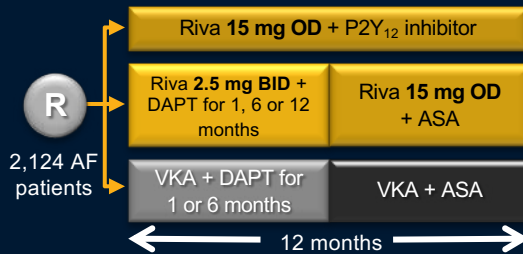


The right combination of antithrombotic agents at the right dose and duration to reduce ischemic events as much as possible at a minimal cost of bleeding

NOAC AF-PCI clinical studies

PIONEER AF-PCI – Rivaroxaban¹

Primary endpoint:
TIMI major, minor bleeding or bleeding requiring medical attention (for 12 months)



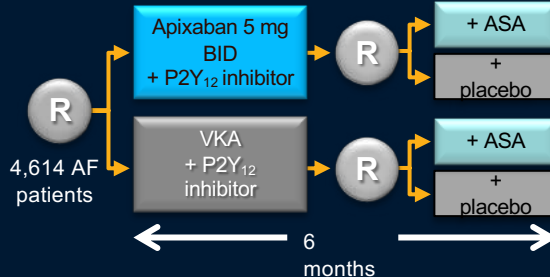
RE-DUAL AF-PCI – Dabigatran²

Primary endpoint:
Time to first major or CRNM bleeding (ISTH)



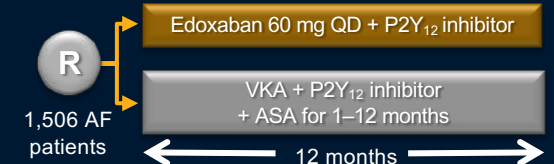
AUGUSTUS AF-PCI – Apixaban³

2x2 Factorial design
Primary endpoint:
ISTH major bleeding or CRNM bleeding



ENTRUST AF-PCI – Edoxaban⁴

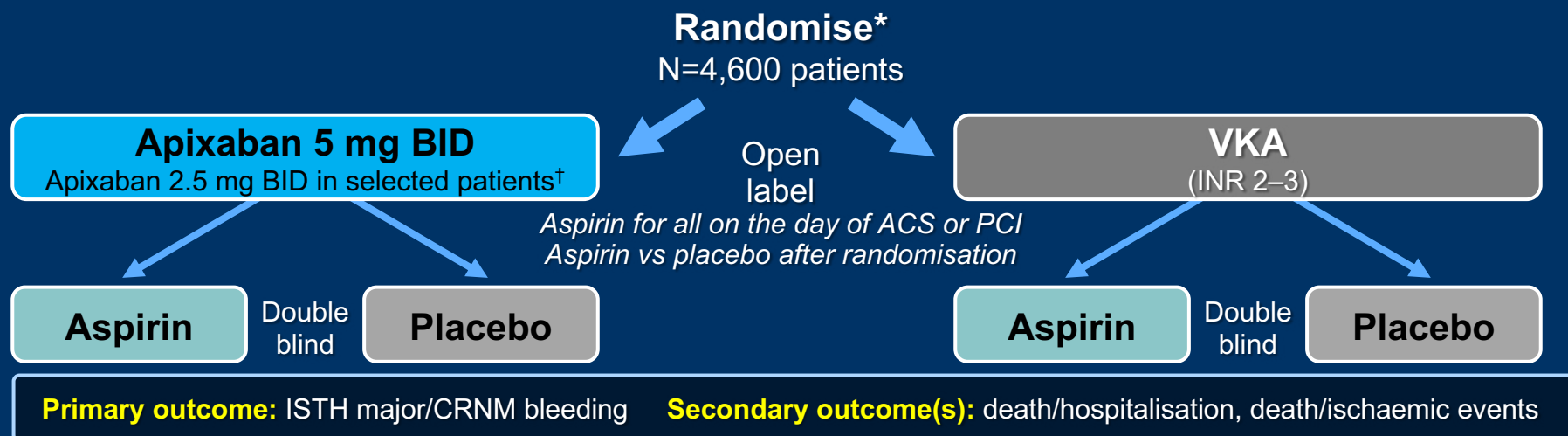
Primary endpoint:
ISTH major and CRNM bleeding



Aucun de ces RCTs n'a été conçu pour évaluer l'efficacité

1. Gibson CM, et al. N Engl J Med 2016;375:2423–34; 2. Cannon CP, et al. N Engl J Med 2017;377:1513–24;
3. Lopes RD, et al. N Engl J Med 2019;380:1509–24; 4. Vranckx P, et al. Lancet 2019;394:1335–43.

AUGUSTUS: Trial design



INCLUSION

- AF (prior, persistent, >6 hours); physician decision for OAC
- ACS or PCI; planned P2Y₁₂ inhibitor for ≥6 months

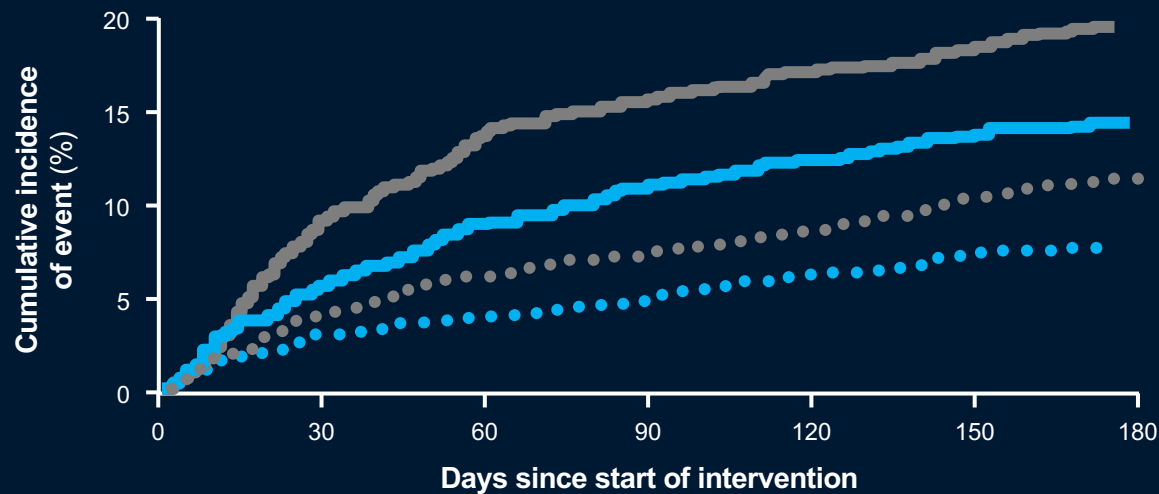
EXCLUSION

- Contraindication to DAPT
- Other conditions that require OAC (such as prosthetic valves or moderate or severe mitral stenosis), severe renal insufficiency, and history of intracranial haemorrhage
- Recent or planned CABG, coagulopathy or ongoing bleeding, contraindication to VKA, apixaban, all P2Y₁₂ inhibitors, or aspirin

*Randomisation was not sequential; at enrolment, eligible patients were randomised simultaneously to apixaban or VKA and to aspirin or aspirin placebo; [†]2.5 mg BID used in patients with ≥2 of the following criteria: age ≥80 years, weight ≤60 kg, or serum creatinine ≥1.5 mg/dL (133 μmol/L).

Lopes RD, et al. Am Heart J 2018;200:17–23.

Saignements majeurs



Number at risk:

Apixaban and aspirin	1,145	1,036	975	937	903	880	485
Apixaban and placebo	1,143	1,075	1,044	1,007	975	947	536
VKA and aspirin	1,123	962	881	838	800	776	467
VKA and placebo	1,126	1,007	947	917	883	851	528

AUGUSTUS was not powered to compare individual primary outcomes for apixaban + placebo vs VKA + aspirin

1. Lopes RD, et al. N Engl J Med 2019;380:1509–24;
2. Lopes RD, et al. N Engl J Med 2019;380:1509–24. Suppl appendix.

Ischemic outcomes

Apixaban vs VKA

Endpoint	Apixaban (N=2,306)	VKA (N=2,308)	HR (95% CI)
Death/ischaemic events (%)	6.7	7.1	0.93 (0.75, 1.16)
Death (%)	3.3	3.2	1.03 (0.75, 1.42)
CV death (%)	2.5	2.3	1.05 (0.72, 1.52)
Stroke (%)	0.6	1.1	0.50 (0.26, 0.97)
Myocardial infarction (%)	3.1	3.5	0.89 (0.65, 1.23)
Definite or probable stent thrombosis (%)	0.6	0.8	0.77 (0.38, 1.56)
Urgent revascularisation (%)	1.7	1.9	0.90 (0.59, 1.38)
Hospitalisation (%)	22.5	26.3	0.83 (0.74, 0.93)



Lopes RD, et al. N Engl J Med 2019;380:1509–24.

Ischemic outcomes

Aspirin vs placebo

Endpoint	Aspirin (N=2,307)	Placebo (N=2,307)	HR (95% CI)
Death/ischaemic events (%)	6.5	7.3	0.89 (0.71, 1.11)
Death (%)	3.1	3.4	0.91 (0.66, 1.26)
CV death (%)	2.3	2.5	0.92 (0.63, 1.33)
Stroke (%)	0.9	0.8	1.06 (0.56, 1.98)
Myocardial infarction (%)	2.9	3.6	0.81 (0.59, 1.12)
Definite or probable stent thrombosis (%)	0.5	0.9	0.52 (0.25, 1.08)
Urgent revascularisation (%)	1.6	2.0	0.79 (0.51, 1.21)
Hospitalisation (%)	25.4	23.4	1.10 (0.98, 1.24)



Lopes RD, et al. N Engl J Med 2019;380:1509–24.

JAMA Cardiology | **Brief Report**

Optimal Antithrombotic Regimens for Patients With Atrial Fibrillation Undergoing Percutaneous Coronary Intervention An Updated Network Meta-analysis

Renato D. Lopes, MD, PhD; Hwanhee Hong, PhD; Ralf E. Harskamp, MD, PhD; Deepak L. Bhatt, MD, MPH; Roxana Mehran, MD; Christopher P. Cannon, MD; Christopher B. Granger, MD; Freek W. A. Verheugt, MD, PhD; Jianghao Li, MS; Jurriën M. ten Berg, MD, PhD; Nikolaus Sarafoff, MD; Pascal Vranckx, MD; Andreas Goette, MD; C. Michael Gibson, MD; John H. Alexander, MD, MHS

 [Supplemental content](#)

IMPORTANCE Antithrombotic treatment in patients with atrial fibrillation (AF) and percutaneous coronary intervention (PCI) presents a balancing act with regard to bleeding and ischemic risks.

OBJECTIVES To evaluate the safety and efficacy of 4 antithrombotic regimens by conducting an up-to-date network meta-analysis and to identify the optimal treatment for patients with AF undergoing PCI.

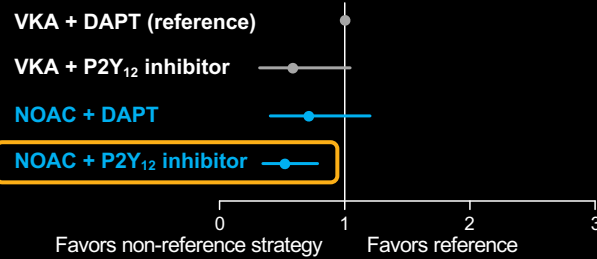
DATA SOURCES Online computerized database (MEDLINE).

STUDY SELECTION Five randomized studies were included (N = 11 542; WOEST, PIONEER AF-PCI, RE-DUAL PCI, AUGUSTUS, ENTRUST-AF PCI).

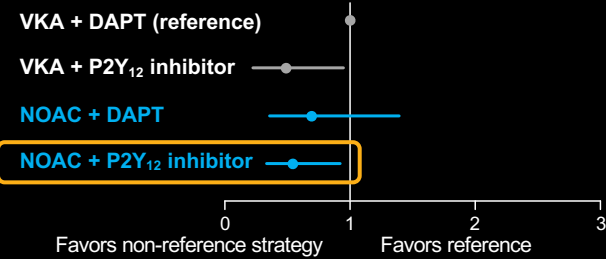
Together with

Métaanalyse (~ 12,000 participants) Patients avec FA traités par PCI/stent

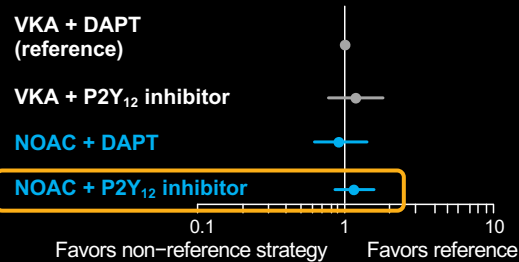
TIMI major bleeding



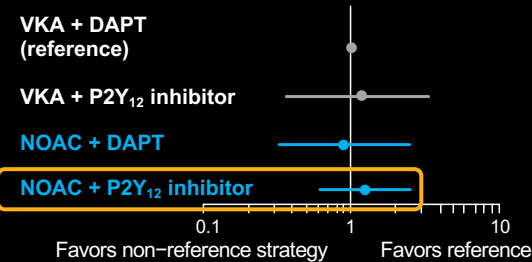
Trial-defined primary bleeding outcome



Myocardial infarction



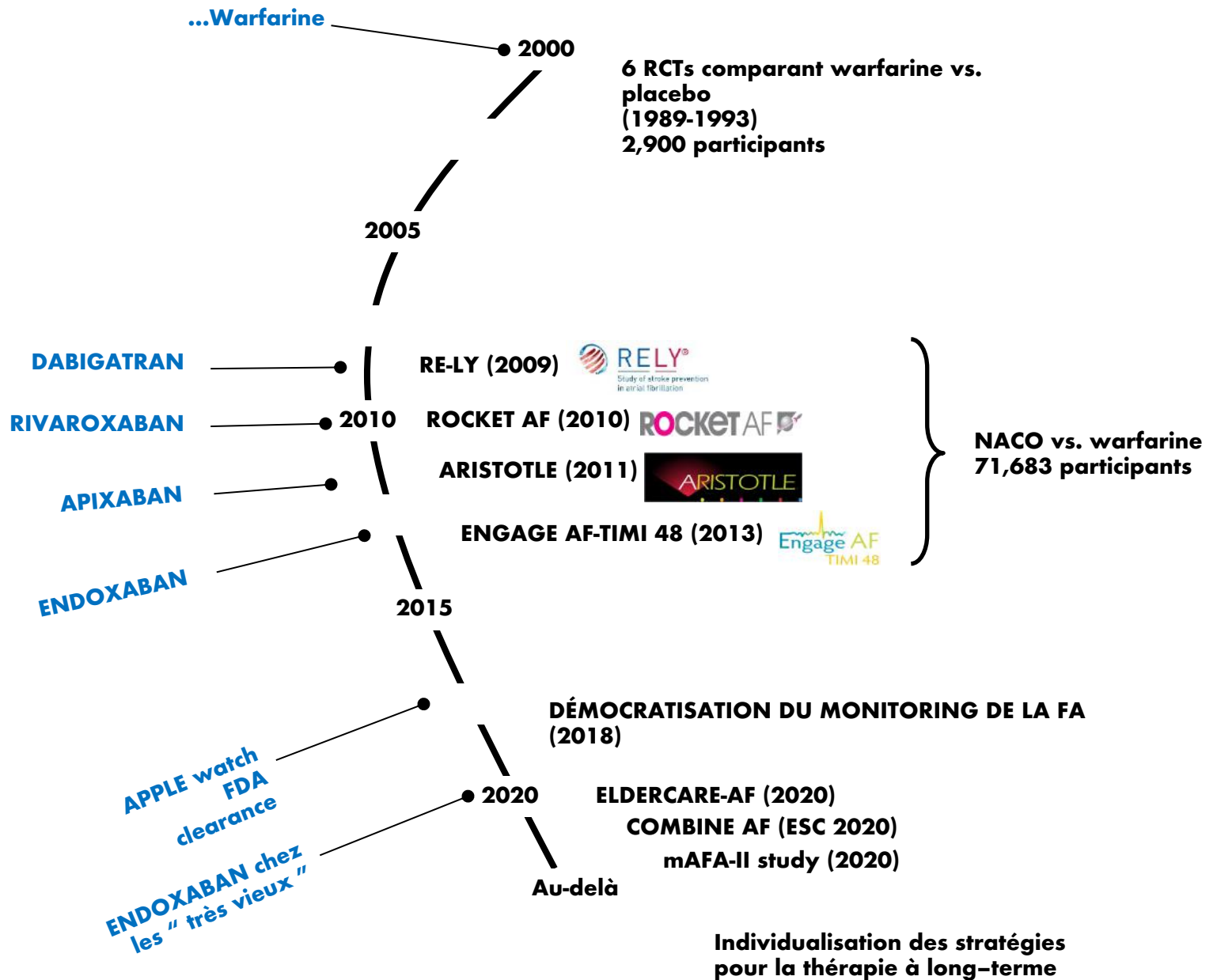
Stent thrombosis



Data show odds ratio (95% CI)

1. Lopes RD, et al. JAMA Cardiol 2020;5:582-9.

-
- **Les 20 dernières années auront assisté à l'émergence des nouveaux anticoagulants oraux**
 - **... et un profilage en fonction du risque de saignement**
 - **Les technologies digitales auront permis la démocratisation du dépistage de la FA asymptomatique.**



Les essais de phase III

	RELY	ROCKET	ARISTOTLE	ENGAGE-AF
Sample size	18,113	14,266	18,201	21,150
New treatment	Dabigatran 110mg BID Dabigatran 150mg BID	Rivaroxaban 20mg QD	Apixaban 5mg BID	Edoxaban 30mg QD Edoxaban 60mg QD
Design	Non-inferiority PROBE	Non-inferiority Double-blind	Non-inferiority Double-blind	Non-inferiority Double-blind
Patients	AF + CHADS2 \geq 1	AF + CHADS2 \geq 2	AF + CHADS2 \geq 1	AF + CHADS2 \geq 2
Renal Exclusion	CrCl < 30 ml/min	CrCl < 30 ml/min	CrCl < 25 ml/min	CrCl < 30 ml/min
Primary outcome	Stroke (ischemic or hemorrhagic) or systemic embolism	Stroke (ischemic or hemorrhagic) or systemic embolism	Stroke (ischemic or hemorrhagic) or systemic embolism	Stroke (ischemic or hemorrhagic) or systemic embolism
Safety outcome	Primary: Major Bleeding Secondary: Major Bleeding + CRNM	Primary: Major Bleeding Secondary: Major Bleeding + CRNM	Primary: Major Bleeding Secondary: Major Bleeding + CRNM	Primary: Major Bleeding Secondary: Major Bleeding + CRNM

Connolly S et al NEJM 2009; Patel M et al NEJM 2011; Granger C et al NEJM 2011; ENGAGE- AF Study Investigators. AHJ 2010

Les anticoagulants oraux

	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Mechanism of action	Selective direct FIIa inhibitor	Selective direct FXa inhibitor	Selective direct FXa inhibitor	Selective direct FXa inhibitor
Bioavailability	Oral prodrug with poor oral bioavailability (6.5%)	Good oral bioavailability	Good oral bioavailability	Good oral bioavailability
T_{1/2}	12 - 17 hours	6 - 9 hours	12 hours	9 - 11 hours
Dosing	Twice daily	Once or twice daily	Twice daily	Once or twice daily
Time action	1 - 4 hrs post-dose for max. inhibition	1 - 4 hrs post-dose for max. inhibition	1 - 4 hrs post-dose for max. inhibition	1 - 4 hrs post-dose for max. inhibition
Platelet aggregation	No direct effect	No direct effect	No direct effect	No direct effect
Elimination	80% renal	35% renal	25% renal	50% renal

Anticogulation orale et prévention des AVC

Warfarine vs.
contrôle ou placebo

Réduction risqué relatif
(95% CI)

RCTs

AFASAK I (1990)

SPAF I (1991)

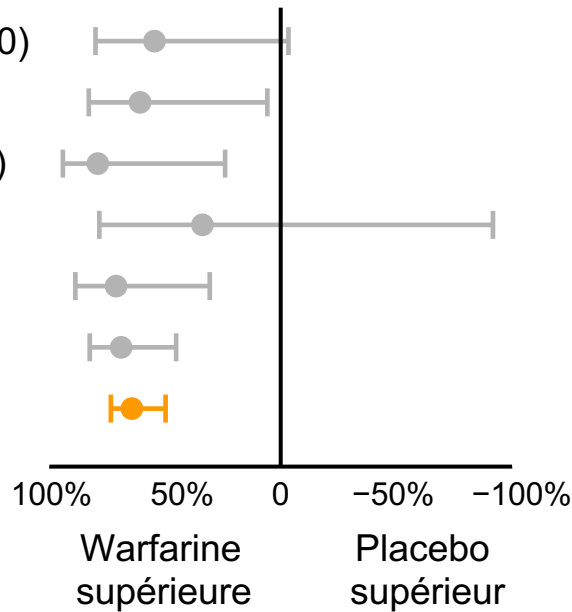
BAATAF (1990)

CAFA (1991)

SPINAF (1992)

EAFI (1993)

Méta-analyse



RRR 64%

**Warfarin vs. Placebo or Control
(6 trials, total n=2,900)**

Hart R, et al. Ann Intern Med. 2007;146:857-867.

NACO vs.
warfarine

Réduction risque relatif
(95% CI)

RCTs

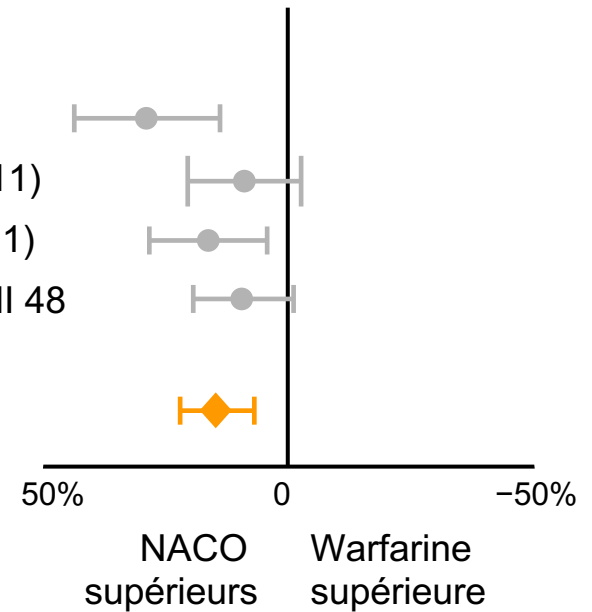
RE-LY (2009)

ROCKET AF (2011)

ARISTOTLE (2011)

ENGAGE AF-TIMI 48
(2013)

Méta-analyse



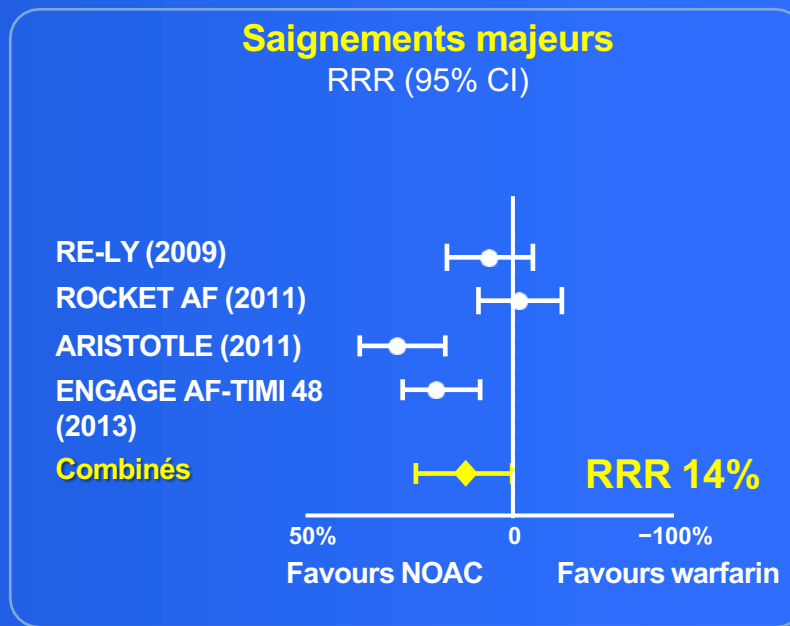
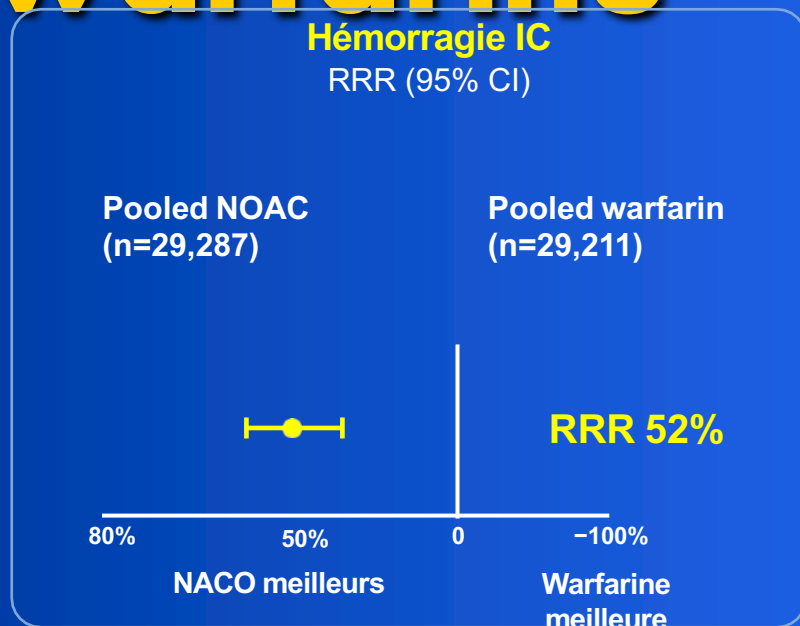
RRR 19%

**NOAC vs. Warfarin
(4 trials, total n=71,683)**

Ruff C, et al. Lancet. 2014;383:955-962.

Saignements: NACOs vs. warfarine

4 RCTs, total n=71,682



Head-to-head trials do not exist and direct comparisons between agents cannot be made. This analysis compared NOACs with warfarin in randomised studies

Adapted from Ruff C, et al. Lancet 2014;383:955-62.

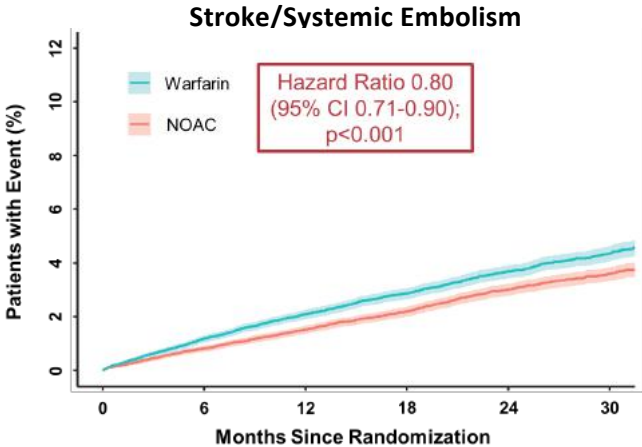
Non-Vitamin K Antagonist Oral Anticoagulants Versus Warfarin in Atrial Fibrillation

Individual Patient Data from the Pivotal Randomized
Trials



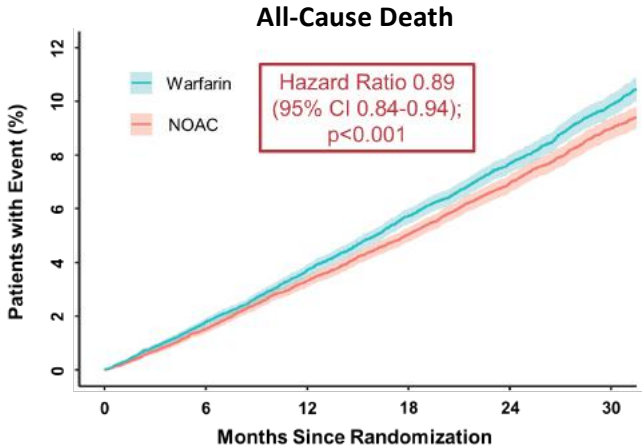
(A Collaboration between Multiple institutions to Better Investigate Non-vitamin K antagonist
oral anticoagulant use in Atrial Fibrillation)

Kaplan-Meier Curves



Number at Risk (number of events)

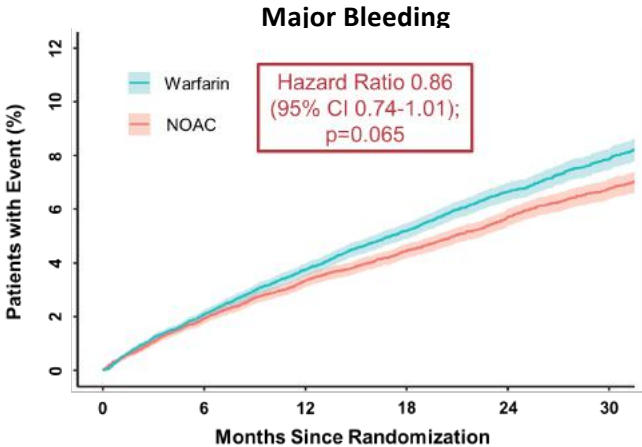
	0	6	12	18	24	30
Warfarin	29229 (0)	28027 (336)	27051 (591)	21654 (786)	15324 (944)	8870 (1031)
NOAC	29312 (0)	28256 (231)	27328 (431)	21907 (602)	15595 (761)	9027 (837)



Number at Risk (number of events)

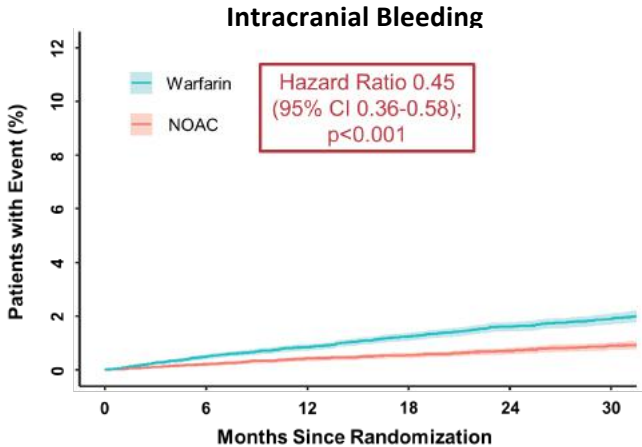
	0	6	12	18	24	30
Warfarin	29229 (0)	28302 (512)	27476 (1067)	22120 (1587)	15735 (1987)	9139 (2289)
NOAC	29312 (0)	28462 (442)	27654 (956)	22276 (1404)	15951 (1794)	9271 (2080)

Kaplan-Meier Curves



Number at Risk (number of events)

Warfarin	29187 (0)	25639 (572)	23562 (992)	18382 (1311)	12618 (1555)	7009 (1686)
NOAC	29270 (0)	25375 (521)	23456 (877)	18258 (1117)	12577 (1321)	7050 (1434)



Number at Risk (number of events)

Warfarin	29187 (0)	25900 (132)	23995 (219)	18854 (306)	13037 (369)	7299 (398)
NOAC	29270 (0)	25624 (55)	23863 (107)	18685 (133)	12986 (159)	7317 (179)

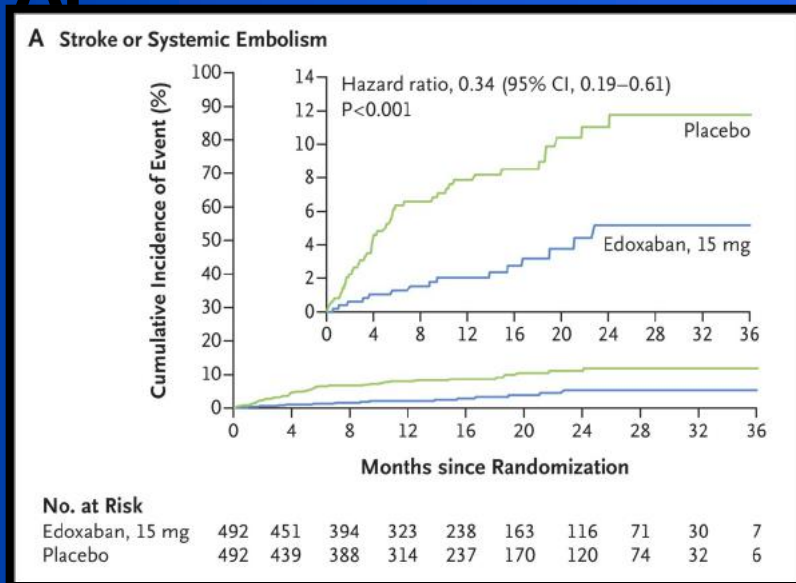
ELDERCARE-AF

Low-Dose Edoxaban in Very Elderly Patients with AF

- **Les patients âgés (> 80ans) atteints de FAC qui n'étaient pas des candidats appropriés pour des doses standard d'anticoagulants oraux en raison d'un risque élevé de saignement ont été assignés à edoxaban 15 mg die vs. placebo.**
- **Un total de 984 participants Japonais furent randomisés (1:1) à edoxaban 15 mg (492 patients) ou placebo (492 patients).**
 - **Un total 303 participants ont abandonnés (158 retrait de consentement, 135 décès et 10 autres raisons)**
- **FA non-valvulaire, pointage CHADS2 \geq 2**
- **Faible clairance de la créatinine (15 à 30 ml/m);**
- **Antécédents d'hémorragie organe cible ou gastro-intestinal;**
- **Petit poids corporel (\leq 45 kg),**
- **Utilisation continue d'un AINS, ou d'un antiplaquettaire.**

ELDERCARE-AF

Low-Dose Edoxaban in Very Elderly Patients with AF



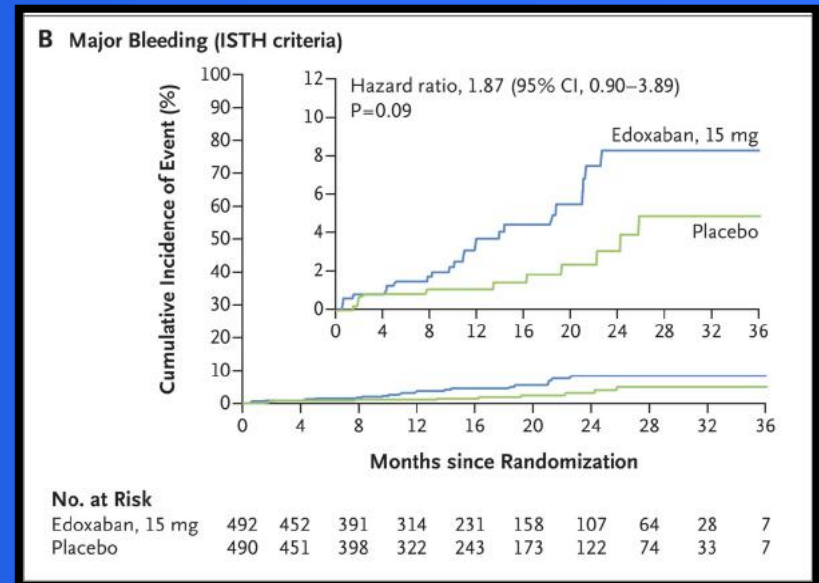
Taux annualisé d'AVC ou d'embolie systémique

Édoxaban = 2,3%

Placebo = 6,7%

(HR = 0.34 [0.19 – 0.61] ; p < 0,001)

Mortalité = 9.9%



Taux annualisé de saignements majeurs

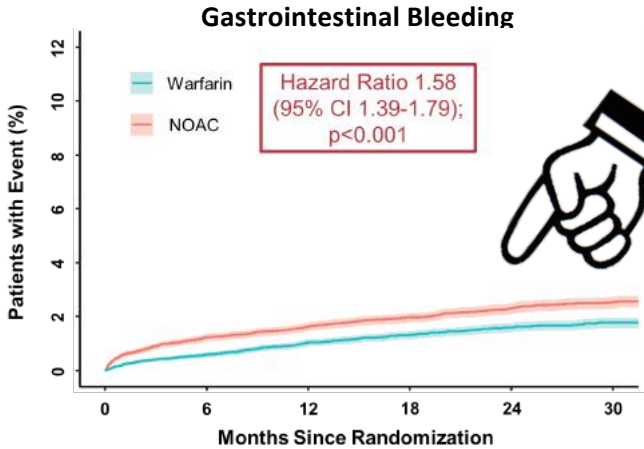
Édoxaban = 3,3%

Placebo = 1.8%

(HR = 1.87 [0.90 – 3.89]; p = 0,09)

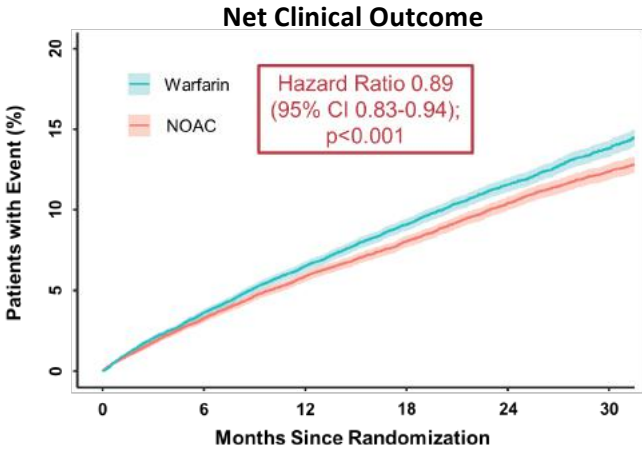
Mortalité = 10.2%

Kaplan-Meier Curves



Number at Risk (number of events)

Warfarin	29187 (0)	25792 (160)	23804 (269)	18677 (330)	12906 (377)	7226 (395)
NOAC	29270 (0)	25393 (335)	23577 (436)	18413 (508)	12791 (564)	7206 (588)



Number at Risk (number of events)

Warfarin	29187 (0)	25567 (999)	23446 (1744)	18260 (2327)	12504 (2758)	6946 (3012)
NOAC	29270 (0)	25323 (890)	23378 (1555)	18178 (2040)	12502 (2445)	6996 (2666)

Net clinical outcome = composite stroke, systemic embolism, major bleeding, all-cause death

2016 ESC Guidelines: Patients at high-risk of gastrointestinal bleeding

	Class	Level
In patients at high-risk of gastrointestinal bleeding, a VKA or another NOAC preparation should be preferred over dabigatran 150 mg twice daily, rivaroxaban 20 mg once daily, or edoxaban 60 mg once daily.	Ila	B

ORIGINAL ARTICLE

Large-Scale Assessment of a Smartwatch to Identify Atrial Fibrillation

Marco V. Perez, M.D., Kenneth W. Mahaffey, M.D., Haley Hedlin, Ph.D., John S. Rumsfeld, M.D., Ph.D., Ariadna Garcia, M.S., Todd Ferris, M.D., Vidhya Balasubramanian, M.S., Andrea M. Russo, M.D., Amol Rajmane, M.D., Lauren Cheung, M.D., Grace Hung, M.S., Justin Lee, M.P.H., Peter Kowey, M.D., Nisha Talati, M.B.A., Divya Nag, Santosh E. Gummidipundi, M.S., Alexis Beatty, M.D., M.A.S., Mellanie True Hills, B.S., Sumbul Desai, M.D., Christopher B. Granger, M.D., Manisha Desai, Ph.D., and Mintu P. Turakhia, M.D., M.A.S., for the Apple Heart Study Investigators*

APPLE HEART STUDY

La probabilité de recevoir une notification de pouls irrégulier était faible (0.52%). Parmi ceux ayant reçu une telle notification, 84% étaient concordantes avec FA et 34% représentaient de la FA lors de lectures ultérieures.

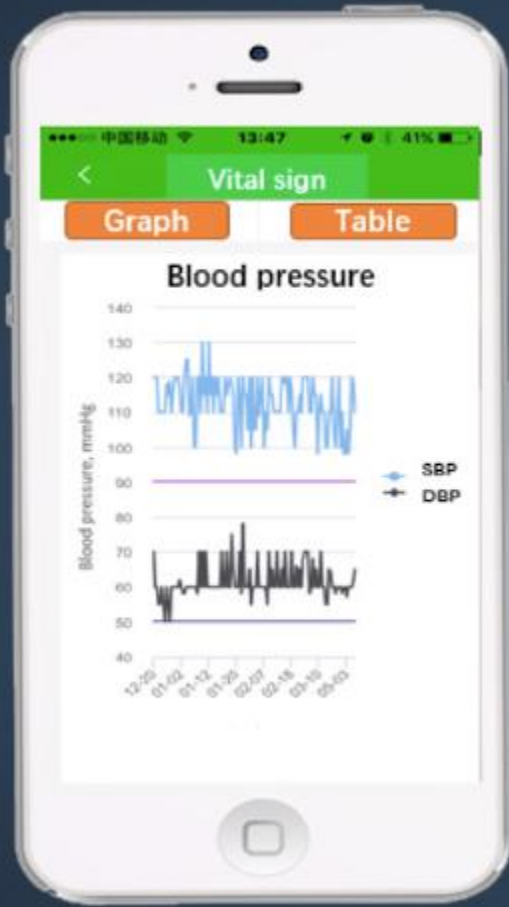
Mobile Health (mHealth) technology for improved screening, patient involvement and optimising integrated care in atrial fibrillation: The mAFA (mAF-App) II randomised trial

Yutao Guo ✉, Deirdre A. Lane, Liming Wang, Yundai Chen, Gregory Y. H. Lip, On behalf of the mAF-App II Trial investigators

HUAWEI HEART STUDY (PRE-mAFA)

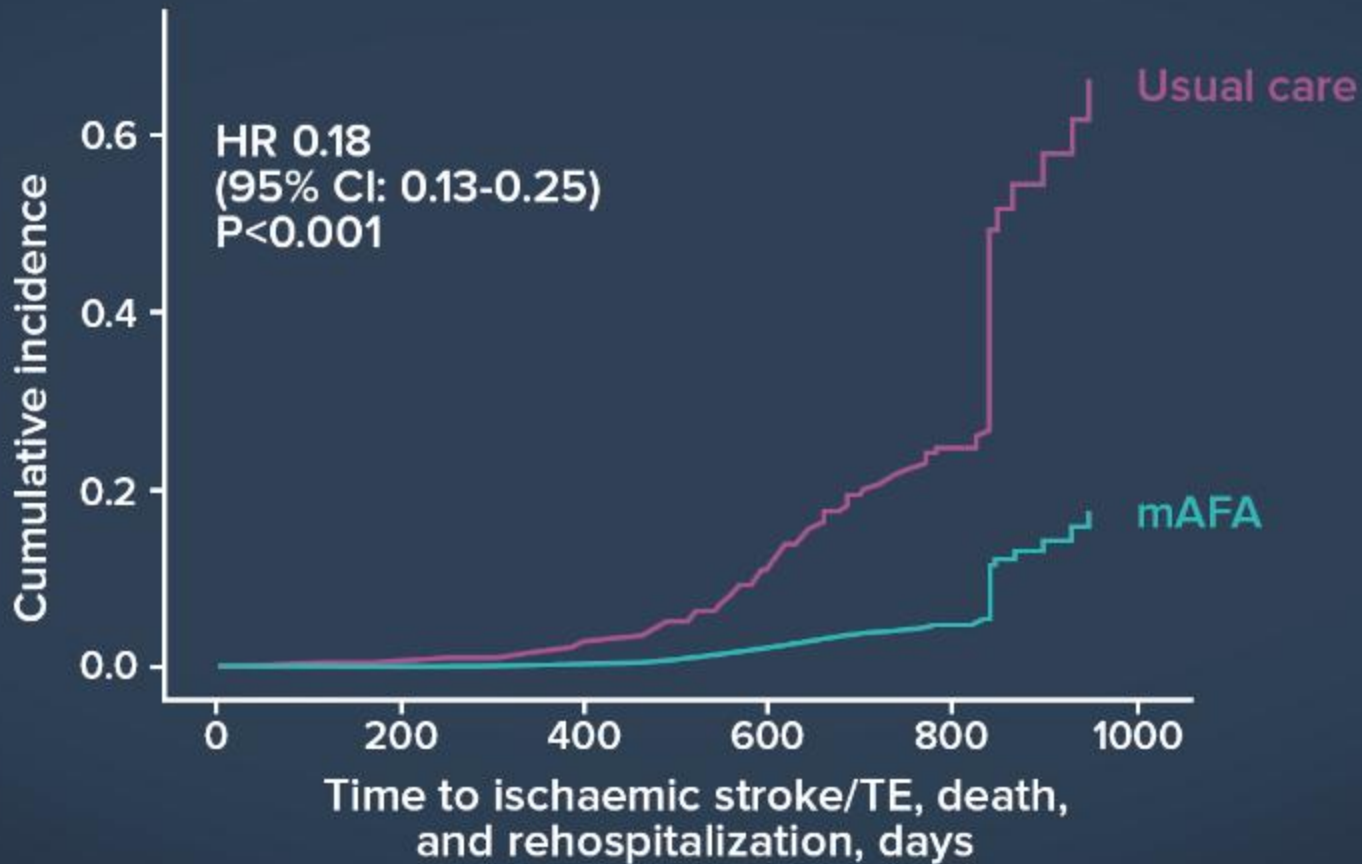


Sources: ESC and
Medscape



Date	SBP	DBP	PR	Weight
2016-12-20	120	70	66	67.0
2016-12-20	120	60	66	无
2016-12-28	120	60	66	67.0
2016-12-28	110	55	66	无
2016-12-28	110	55	66	无
2016-12-29	110	60	60	67.0
2016-12-29	110	55	54	无

mAFA VERSUS USUAL CARE



APPRAISE-2 Publication

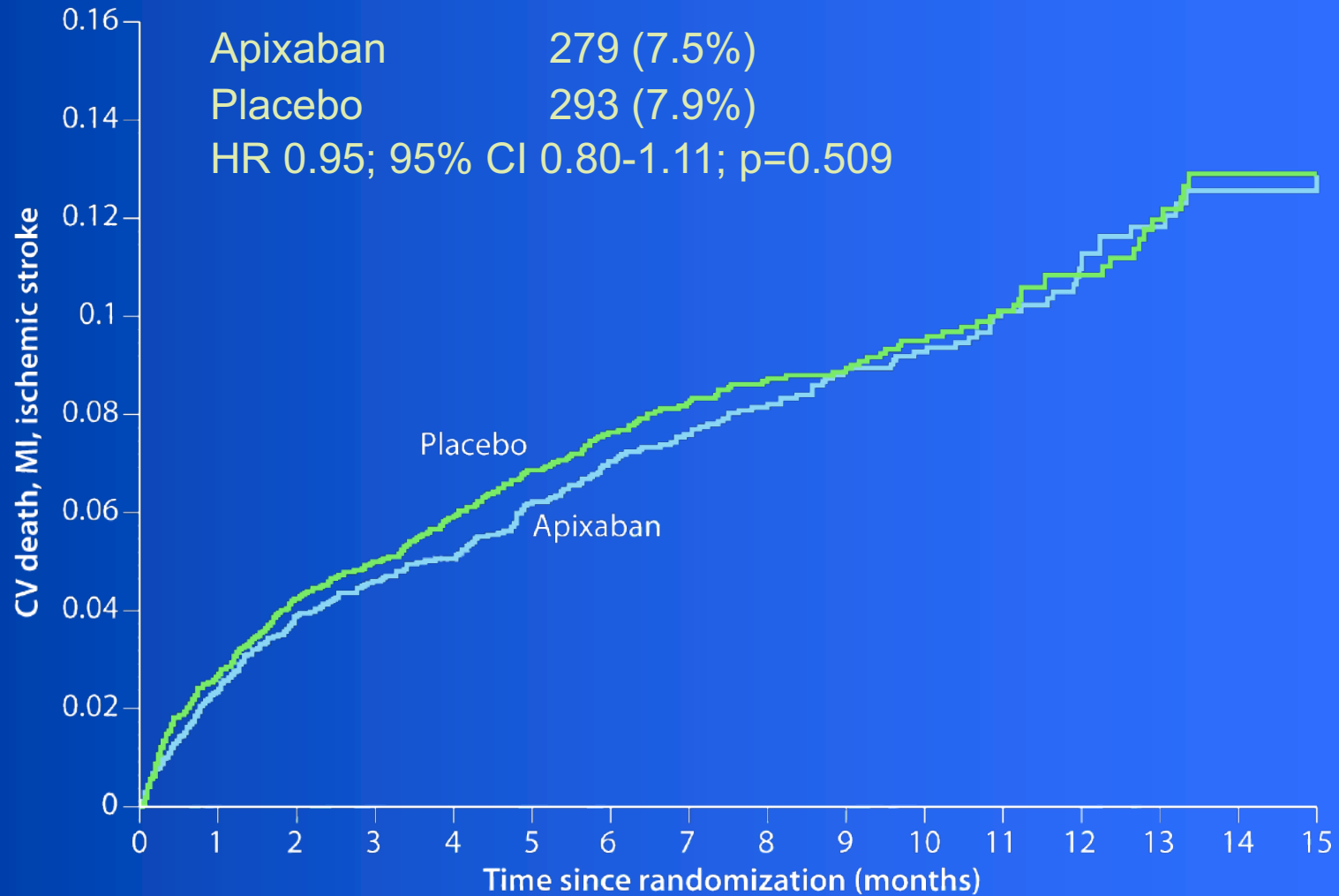
ORIGINAL ARTICLE

Apixaban with Antiplatelet Therapy after Acute Coronary Syndrome

John H. Alexander, M.D., M.H.S., Renato D. Lopes, M.D., Ph.D.,
Stefan James, M.D., Ph.D., Rakhi Kilaru, M.S., Yaohua He, M.D., Ph.D.,
Puneet Mohan, M.D., Ph.D., Deepak L. Bhatt, M.D., M.P.H., Shaun Goodman, M.D.,
Freek W. Verheugt, M.D., Ph.D., Marcus Flather, M.D., Kurt Huber, M.D.,
Danny Liaw, M.D., Ph.D., Steen E. Husted, M.D., Jose Lopez-Sendon, M.D.,
Raffaele De Caterina, M.D., Petr Jansky, M.D., Harald Darius, M.D.,
Dragos Vinereanu, M.D., Jan H. Cornel, M.D., Frank Cools, M.D., Dan Atar, M.D.,
Jose Luis Leiva-Pons, M.D., Matyas Keltai, M.D., Hisao Ogawa, M.D., Ph.D.,
Prem Pais, M.D., Alexander Parkhomenko, M.D., Witold Ruzyllo, M.D.,
Rafael Diaz, M.D., Harvey White, M.D., Mikhail Ruda, M.D., Margarida Geraldes, Ph.D.,
Jack Lawrence, M.D., Robert A. Harrington, M.D., and Lars Wallentin, M.D., Ph.D.,
for the APPRAISE-2 Investigators*

Primary Outcome

CV Death, MI, Ischemic Stroke



Apixaban 279 (7.5%)

Placebo 293 (7.9%)

HR 0.95; 95% CI 0.80-1.11; p=0.509

CV death, MI, ischemic stroke

Placebo

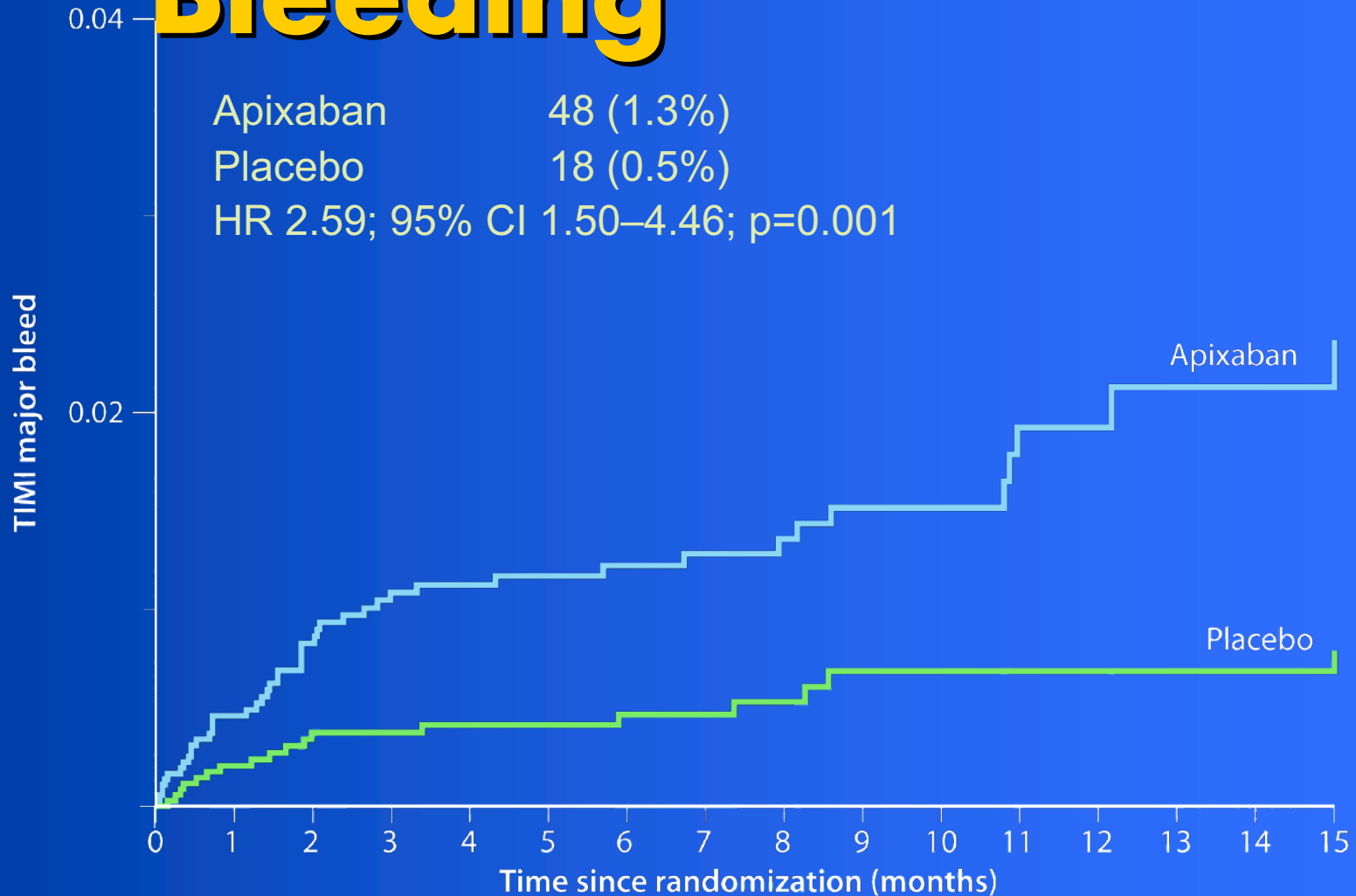
Apixaban

Time since randomization (months)

Apixaban	3705	3356	3048	2799	2552	2312	2025	1739	1525	1277	1021	797	561	390	254	154
Placebo	3687	3316	3014	2751	2537	2272	2030	1728	1495	1248	987	803	571	412	267	164

TIMI Major Bleeding

Apixaban 48 (1.3%)
 Placebo 18 (0.5%)
 HR 2.59; 95% CI 1.50–4.46; p=0.001



Apixaban	3672	3187	2815	2558	2264	2063	1794	1517	1326	1104	884	698	506	344	225	143
Placebo	3643	3178	2881	2600	2339	2133	1884	1573	1369	1137	905	734	532	380	240	151