l'Essentiel de ESC 2018 PREVENTION INSUFFISANCE CARDIAQUE

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ESC 2018

- **Risk factors control in siabetes mellius**
- **Aspirin in primary prevention: ARRIVE & ASCEND**
- **Weight lowering drug lorcaserin and CV events : CAMELLIA**
- **Secondary prevention : EUROASPIRE V**
- **ESC/ESH guidelines for arterial hypertension**

- Rawshani A, NEJM 2018; 379:633

Risk factors mortality and cardiovascular outcomes in patients with Type 2 diabetes – F/U = 5.7 years

N = 271 174 matched with 1 356 870 Controls

Risk factors = HbA1c ; LDL CT ; Albuminuria ; Smoking ; BP

If All in normal range

Death HR = 1.06

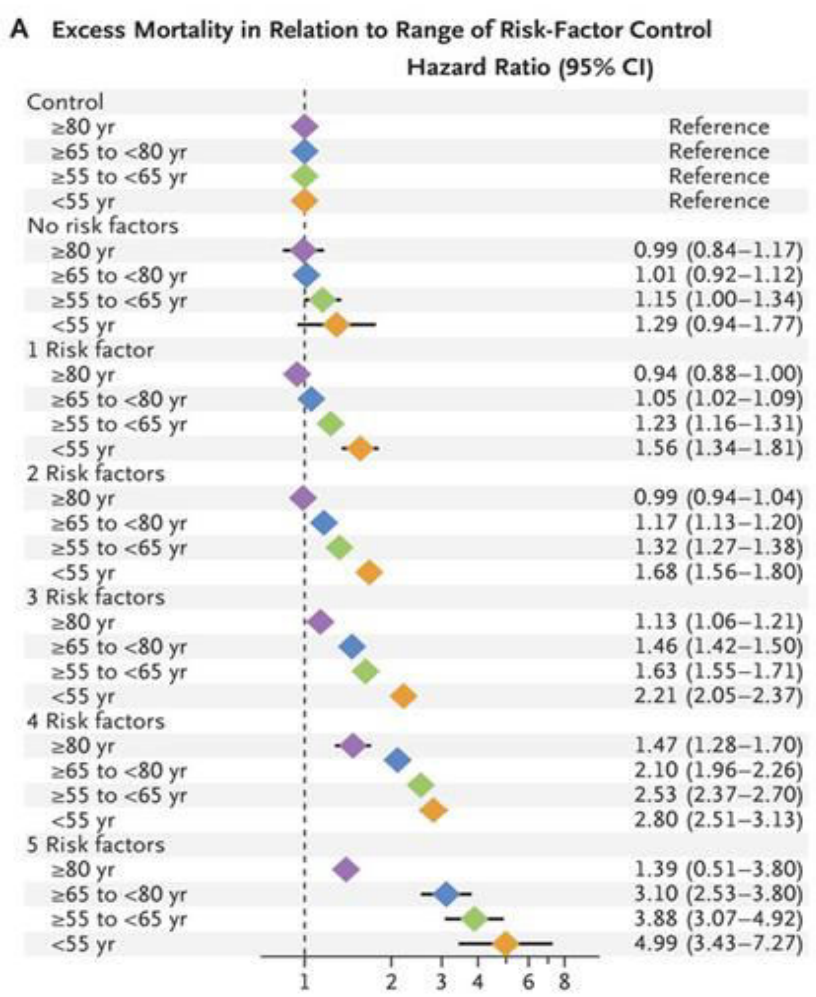
Myocardial infarction HR = 0.84

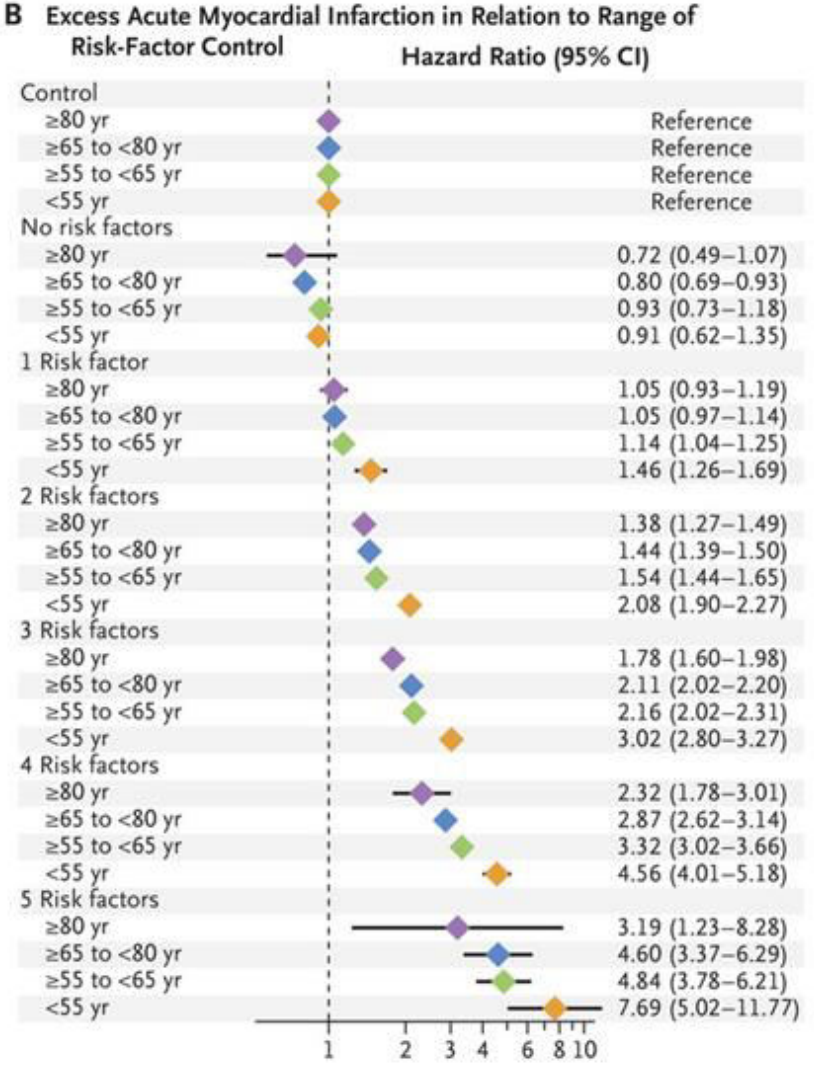
Stroke = 0.95

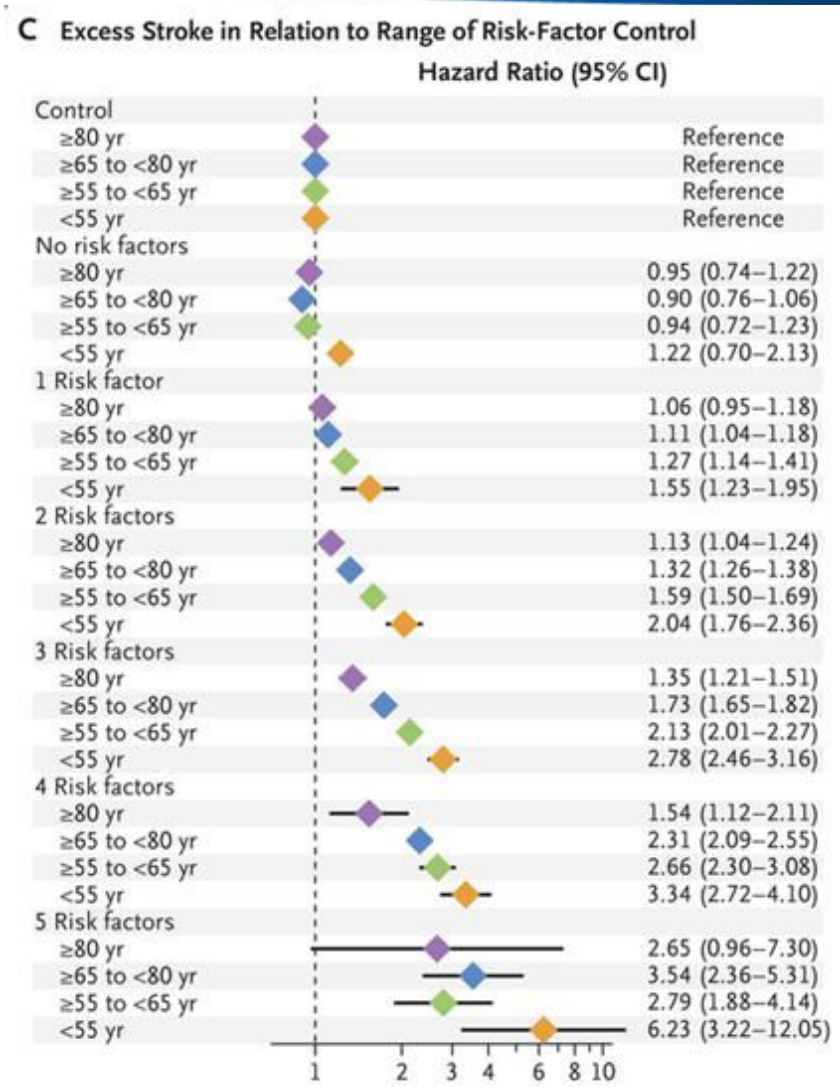
Hospit. Heart Failure = 1.45

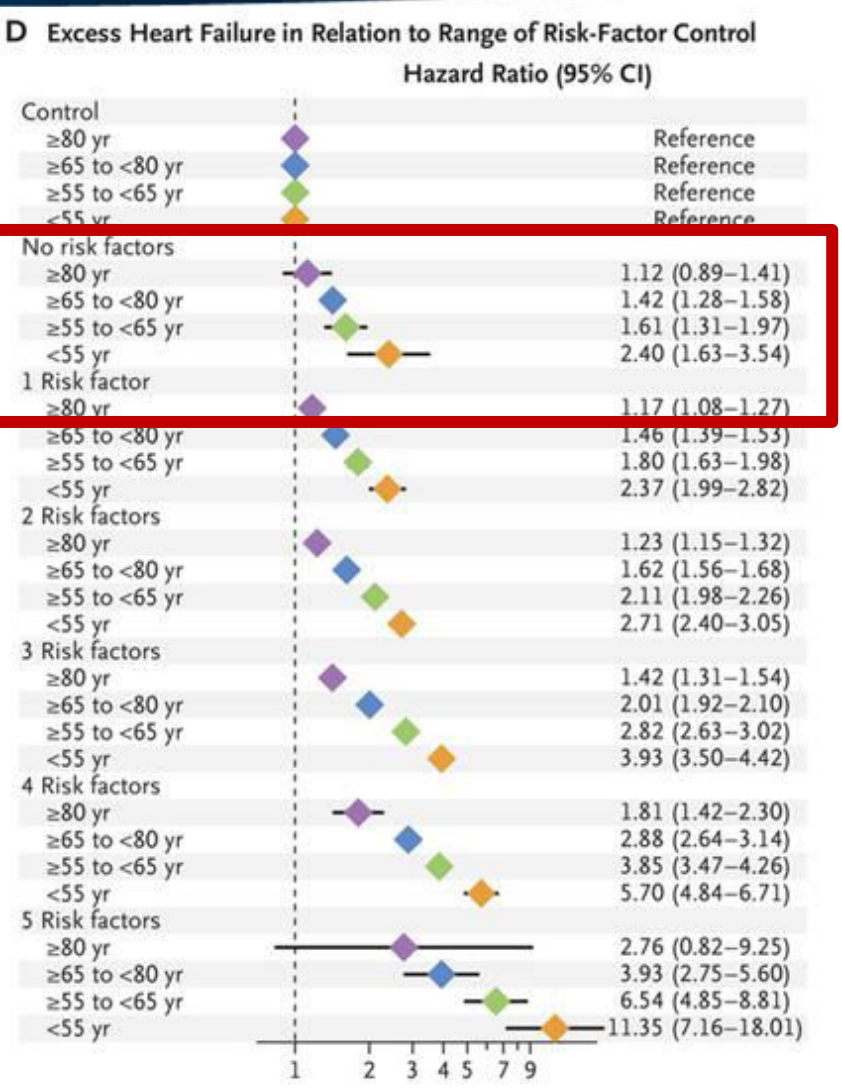
A Rawshani et al. N Engl J Med 2018; August 16th

Adjusted Hazard Ratios for Outcomes, According to Age Category and Number of Risk-Factor Variables outside Target Ranges, among Patients with Type 2 Diabetes, as Compared with Matched Controls.









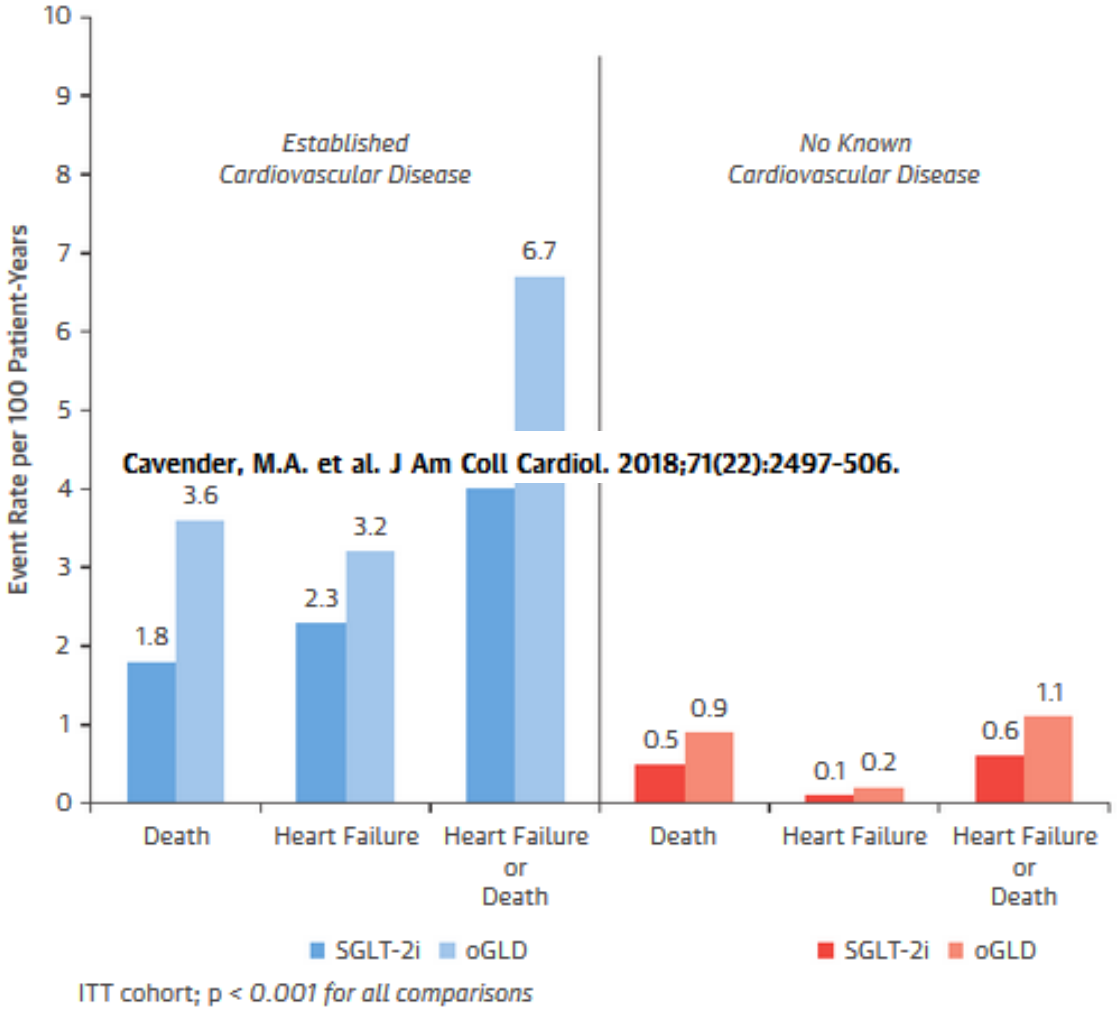
A Rawshani et al. N Engl J Med 2018;379:633-644.

CONCLUSION

Patients with Type 2 DM who have five risk factors variables within the target ranges have little / no excess risk of death, myocardial infarction or stroke, compared to the general population whereas the risk of HF is increased by # 45%.

CVD REAL

N=153078 SGLT2 I vs 153078 matched other Antidiabetic drugs

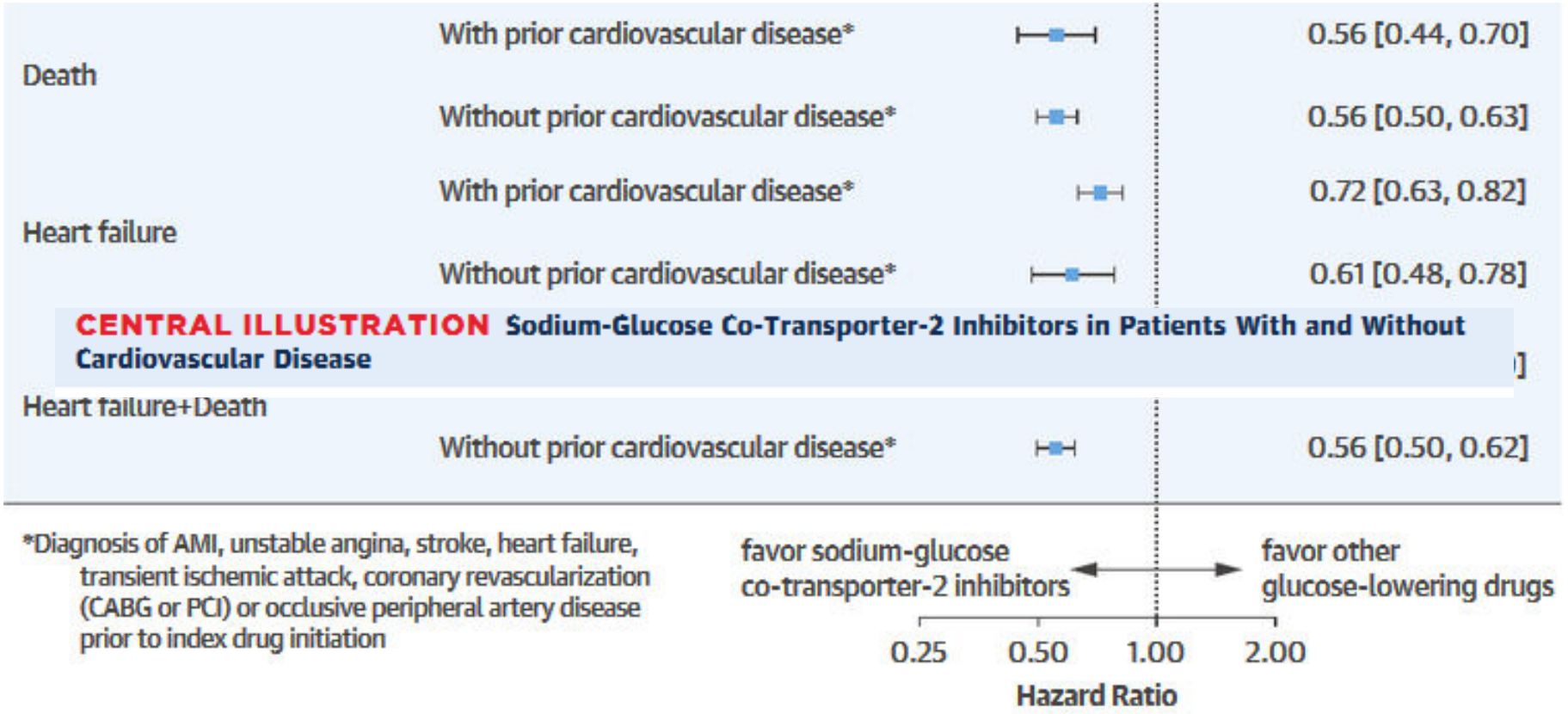


Cavender, M.A. et al. J Am Coll Cardiol. 2018;71(22):2497-506.

ITT cohort; p < *0.001 for all comparisons*

ITT = intention-to-treat; oGLD = other glucose-lowering drugs; SGLT-2i = sodium-glucose cotransporter-2 inhibitors.

Sodium-Glucose Co-Transporter-2 Inhibitors in Patients With and Without Cardiovascular Disease



Pooled adjusted hazard ratios from meta-analyses for death, heart failure, and heart failure or death in patients with and without cardiovascular disease at initiation of the index drug in the intention-to-treat cohort. AMI = acute myocardial infarction; CABG = coronary artery bypass graft; PCI = percutaneous coronary intervention.

Cavender, M.A. et al. J Am Coll Cardiol. 2018;71(22)! 2497-506

Ongoing trials SGLTi in heart failure/CKD

Etude	N	I.C.	Diabete	End Point	Fin
EMPEROR Reduced	2 850	FE altered	±	CVD / HFH	2020
EMPEROR Preserved	4 126	FE preserved	±	CVD / HFH	2020
DAPA HF	4 500	FE altered	±	CVD / HFH Urgent HF visit	2019
DERIVE	4 700	FE preserved	±	CVD / HFH Urgent HF visit	2021
EMPA Kidney	5 000	eGFR 20-45	±	ESRD	2022
DAPA CKD	4 000	eGFR 25-75	±	ESRD	2020
SOLOIST	4 000	decompensed HF EF> < 50%	+	CVD / HFH	2022

Use of aspirin to reduce risk of initial vascular events in patients at moderate risk of cardiovascular disease (ARRIVE): a randomised, double-blind, placebo-controlled trial

J Michael Gaziano, Carlos Brotons, Rosa Coppolecchia, Claudio Cricelli, Harald Darius, Philip B Gorelick, George Howard, Thomas A Pearson, Peter M Rothwell, Luis Miguel Ruilope, Michal Tendera, Gianni Tognoni; the ARRIVE Executive Committee

www.thelancet.com Published online August 26, 2018 http://dx.doi.org/10.1016/S0140-6736(18)31924-X

ARRIVE : The Context

- Role of Aspirin in primary prevention in people at moderate risk controversial.
- Increased risk of bleeding.

ARRIVE

N = 12 546 patients

- **Inclusion :**
  - ✓ **Male patients ≥ 60 years**
    2 → 4 risk factors
  - ✓ **Female patients ≥ 60 years**
    3+ risk factors
  - ✓ **No diabetes /documented CVD**
- **Risk estimate : 10 – 20% CAD at 10 years**

ARRIVE

- Primary endpoint = CV death / myocardial infarction / stroke / unstable angina / TIA.
- Bleeding events recorded.
- Enteric coated Aspirin 100 mg vs Placebo
- Follow up : 60 months

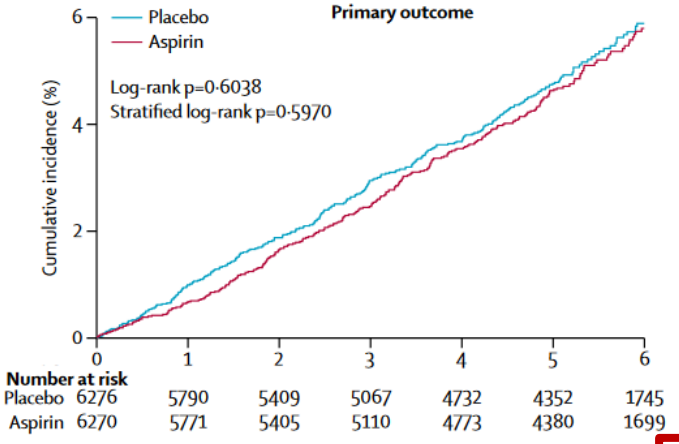
Efficacy endpoints in the intention-to-treat and per-protocol populations

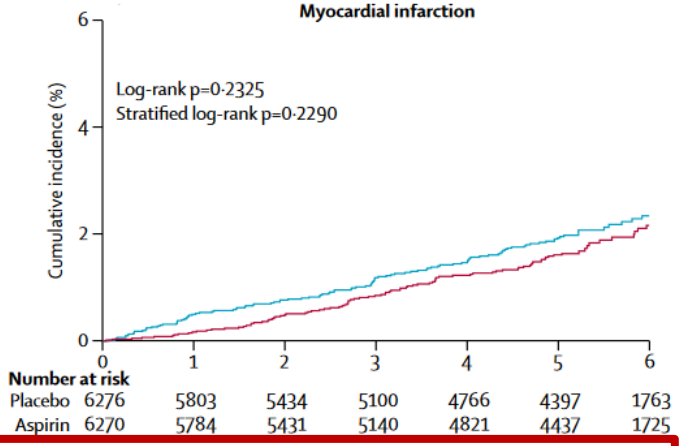
	Number of events in the intention-to-treat population			Number of events in the per-protocol population		
	Aspirin (n=6270)	Placebo (n=6276)	Hazard ratio (95% CI); p value	Aspirin (n=3790)	Placebo (n=3912)	Hazard ratio (95% CI); p value
Myocardial infarction, stroke, cardiovascular death, unstable angina, or transient ischaemic attack	269 (4·29%)	281 (4·48%)	0·96 (0·81–1·13); p=0·6038	129 (3·40%)	164 (4·19%)	0·81 (0·64–1·02); p=0·0756
Myocardial infarction, stroke, or cardiovascular death	208 (3·32%)	218 (3·47%)	0·95 (0·79–1·15); p=0·6190	103 (2·72%)	135 (3·45%)	0·79 (0·61–1·02); p=0·0661
Myocardial infarction*	95 (1·52%)	112 (1·78%)	0·85 (0·64–1·11); p=0·2325	37 (0·98%)	72 (1·84%)	0·53 (0·36–0·79); p=0·0014
Non-fatal myocardial infarction	88 (1·40%)	98 (1·56%)	0·90 (0·67–1·20); p=0·4562	32 (0·84%)	60 (1·53%)	0·55 (0·36–0·84); p=0·0056
Stroke*	75 (1·20%)	67 (1·07%)	1·12 (0·80–1·55); p=0·5072	40 (1·06%)	37 (0·95%)	1·12 (0·71–1·75); p=0·6291
Cardiovascular death	38 (0·61%)	39 (0·62%)	0·97 (0·62–1·52); p=0·9010	26 (0·69%)	26 (0·66%)	1·03 (0·60–1·77); p=0·9161
Unstable angina	20 (0·32%)	20 (0·32%)	1·00 (0·54–1·86); p=0·9979	8 (0·21%)	11 (0·28%)	0·75 (0·30–1·87); p=0·5380
Transient ischaemic attack	42 (0·67%)	45 (0·72%)	0·93 (0·61–1·42); p=0·7455	19 (0·50%)	19 (0·49%)	1·03 (0·55–1·95); p=0·9181
Any death	160 (2·55%)	161 (2·57%)	0·99 (0·80–1·24); p=0·9459	108 (2·85%)	101 (2·58%)	1·10 (0·84–1·45); p=0·4796

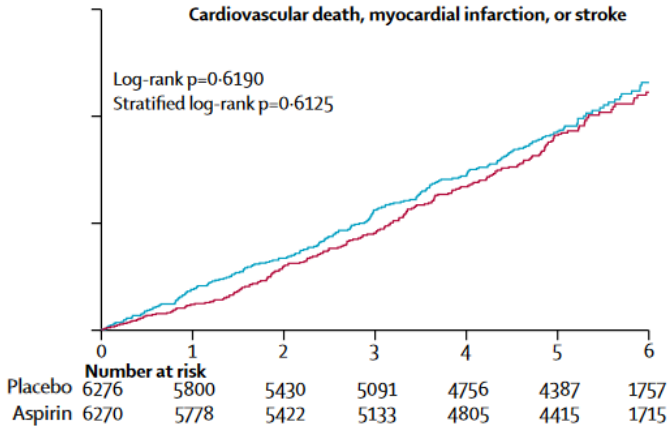
*Fatal or non-fatal.

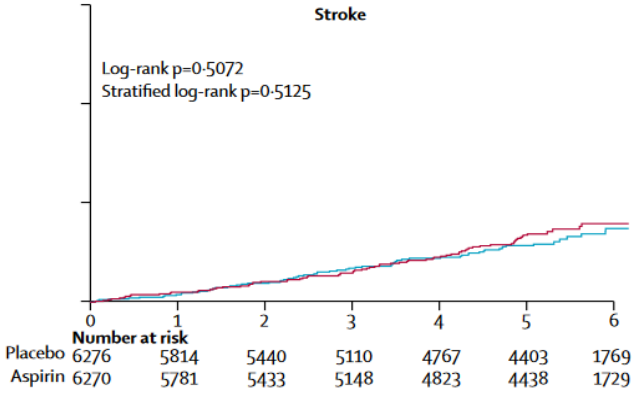
Gaziano JM et al, The Lancet, Published online August 26, 2018 http://dx.doi.org/10.1016/S0140-6736(18)31924-X

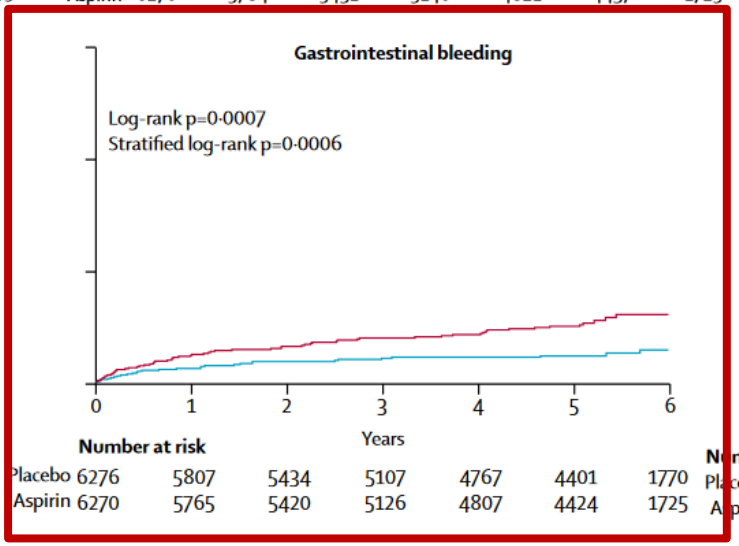
Kaplan-Meier cumulative incidence of primary outcome, original primary outcome, and components of the primary outcome (intention-to-treat population)

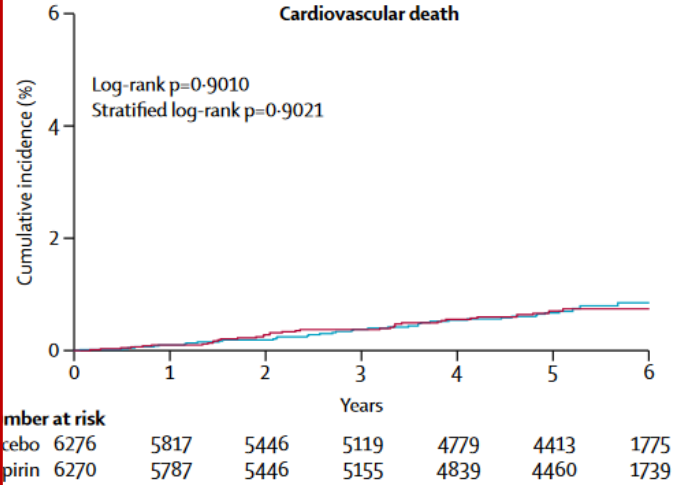












Gaziano JM et al, The Lancet, Published online August 26, 2018 http://dx.doi.org/10.1016/S0140-6736(18)31924-X

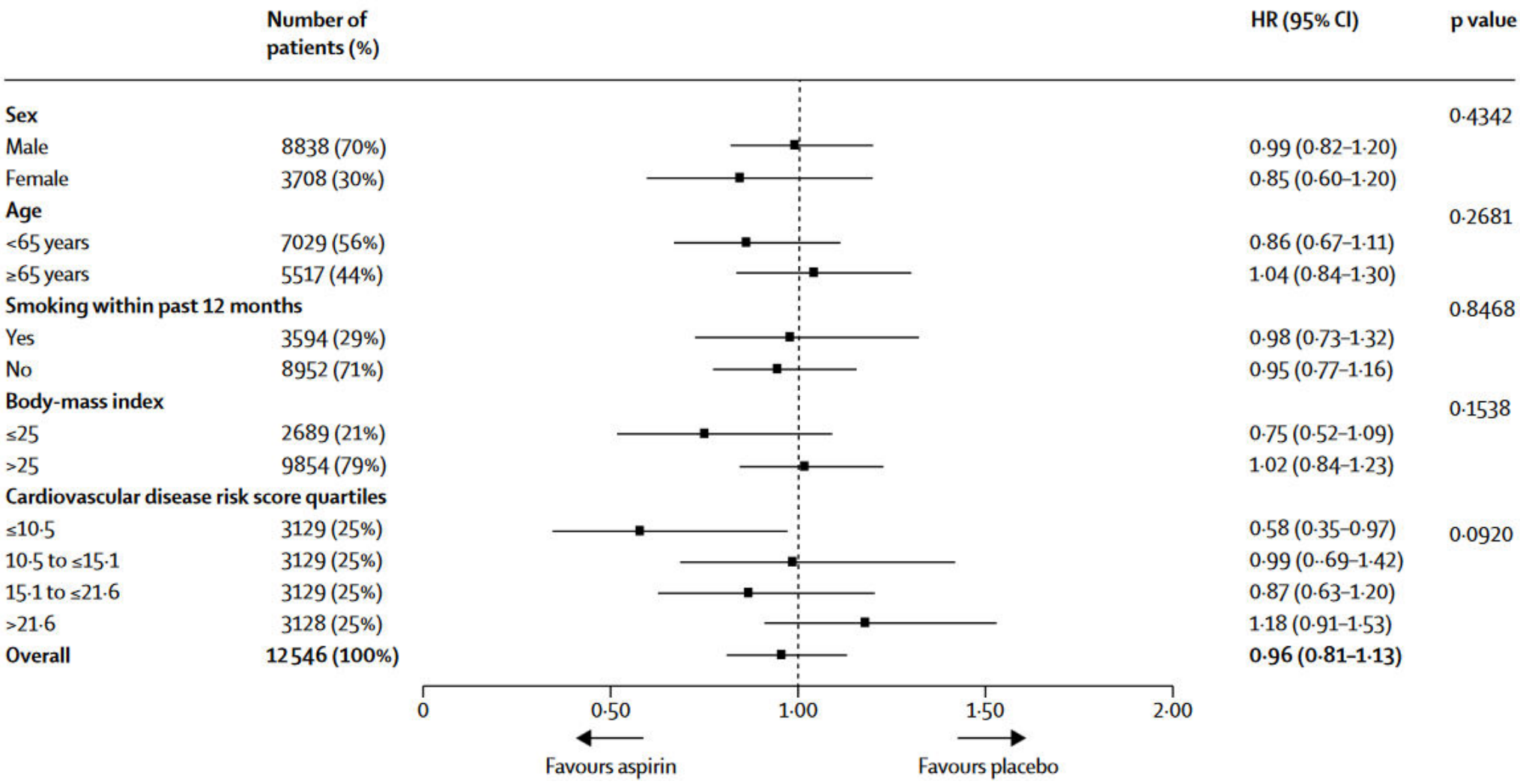
	Aspirin (n=6270)	Placebo (n=6276)
Total number of serious adverse events	1266 (20·19%)	1311 (20·89%)
Bleeding serious adverse events by severity		
Any gastrointestinal bleed	61 (0·97%)	29 (0·46%)
Severe gastrointestinal bleed	4 (0·06%)	2 (0·03%)
Moderate gastrointestinal bleed	15 (0·24%)	5 (0·08%)
Mild gastrointestinal bleed	42 (0·67%)	22 (0·35%)
Haemorrhagic stroke	8 (0·13%)	11 (0·18%)
Most common non-bleeding serious adverse events*		
Osteoarthritis	104 (1·66%)	103 (1·64%)
Coronary artery disease	46 (0·73%)	61 (0·97%)
Prostate cancer†	59 (0·94%)	44 (0·70%)
Acute myocardial infarction	43 (0·69%)	58 (0·92%)
Atrial fibrillation	37 (0·59%)	40 (0·64%)
Myocardial infarction	29 (0·46%)	38 (0·61%)
Inguinal hernia	35 (0·56%)	31 (0·49%)
Transient ischaemic attack	26 (0·41%)	30 (0·48%)
Pneumonia	26 (0·41%)	19 (0·30%)
Cholelithiasis	24 (0·38%)	17 (0·27%)
Chest pain	23 (0·37%)	19 (0·30%)
Angina pectoris	20 (0·32%)	14 (0·22%)
Benign prostatic hyperplasia†	10 (0·16%)	20 (0·32%)
Unstable angina	15 (0·24%)	19 (0·30%)
Pulmonary embolism	12 (0·19%)	16 (0·25%)
Colon cancer	14 (0·22%)	6 (0·10%)
Ankle fracture	13 (0·21%)	9 (0·14%)
Cholecystitis	13 (0·21%)	8 (0·13%)
Rotator cuff syndrome	6 (0·10%)	13 (0·21%)
Number of serious adverse events per participant		
One	873 (13·92%)	879 (14·01%)
Two	256 (4·08%)	281 (4·48%)
Three or more	137 (2·18%)	151 (2·41%)

Serious adverse events in the intention-to-treat population

*Data are number of participants with the serious adverse event. *At least 0·2% in any treatment group. †Male patients only*

Gaziano JM et al, The Lancet, Published online August 26, 2018 http://dx.doi.org/10.1016/S0140-6736(18)31924-X

Primary outcome by prespecified subgroups (intention-to-treat population) Hazard ratios are unstratified.



Gaziano JM et al, The Lancet, Published online August 26, 2018 http://dx.doi.org/10.1016/S0140-6736(18)31924-X

ARRIVE

CONCLUSION

- Patients at moderate CV risk w/o diabetes or evident CV disease do not benefit of Aspirin low dose.
- Substantial increase in gastro-intestinal bleeding events.

The NEW ENGLAND JOURNAL of MEDICINE

Effects of Aspirin for Primary Prevention in Persons with Diabetes Mellitus

The ASCEND Study Collaborative Group*

N Engl J Med, 2018 Aug 26. doi: 10.1056/NEJMoa1804988

ASCEND : THE CONTEXT

- Diabetes mellitus is associated with an increased risk of cardiovascular events.
- Aspirin beneficial in secondary prevention.
- Benefit in primary prevention?
- Excess bleeding has been reported.

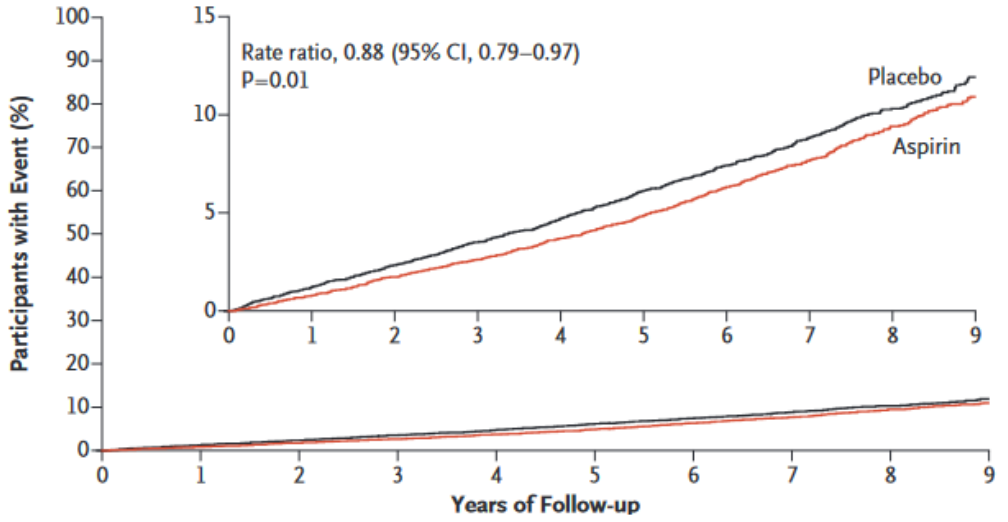
ASCEND

N = 15 480 patients

- Enteric coated aspirin 100 mg vs placebo.
- Most patients (# 95%) ; type 2 DM
- No evident cardiovascular disease.
- F/U 7.4 years
- Primary efficacy endpoint = CV death / myocardial infarction / stroke / TIA.
- Primary safety endpoint = major bleeding (intracranial / sight threatening bleeding / GI bleeding).

First Serious Vascular Event during Follow-up.

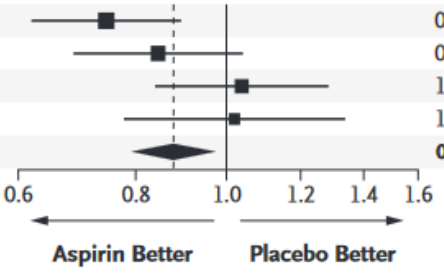
A. First Serious Vascular Event



No. at Risk										
Placebo	7740	7618	7486	7342	7188	7001	5771	3890	2200	1430
Aspirin	7740	7655	7536	7404	7252	7096	5825	3966	2222	1428
Cumulative benefit per 1000 participants in aspirin group		4±2	6±2	9±3	10±3	13±4	11±4	12±5	9±6	10±7

B. First Serious Vascular Event according to year of follow-up

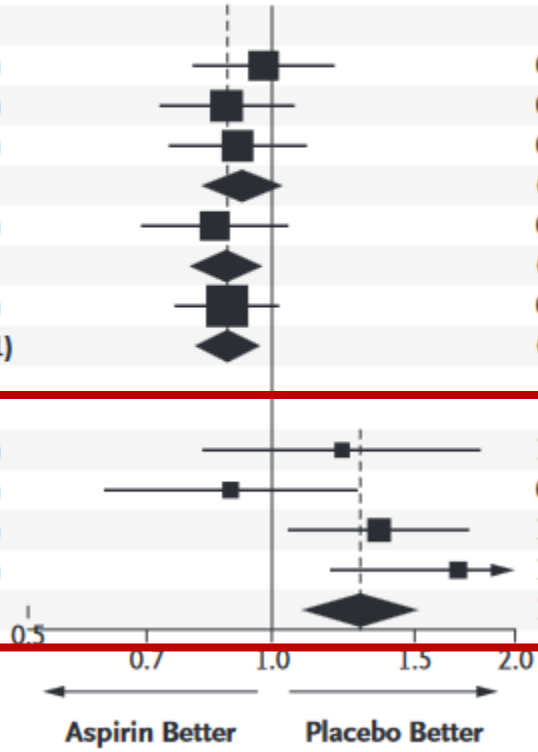
Year of First Event	Aspirin (N=7740)	Placebo (N=7740)	Rate Ratio (95% CI)	P Value
	no. of participants with event (%)			
<3	201 (2.6)	269 (3.5)	0.74 (0.62–0.89)	
3 to <5	169 (2.3)	198 (2.7)	0.85 (0.69–1.04)	
≥5 to <7	180 (2.5)	171 (2.4)	1.04 (0.84–1.28)	
7	108 (2.7)	105 (2.7)	1.02 (0.78–1.33)	
All	**658 (8.5)**	**743 (9.6)**	**0.88 (0.79–0.97)**	**0.01**



N Engl J Med, 2018 Aug 26. doi: 10.1056/NEJMoa1804988

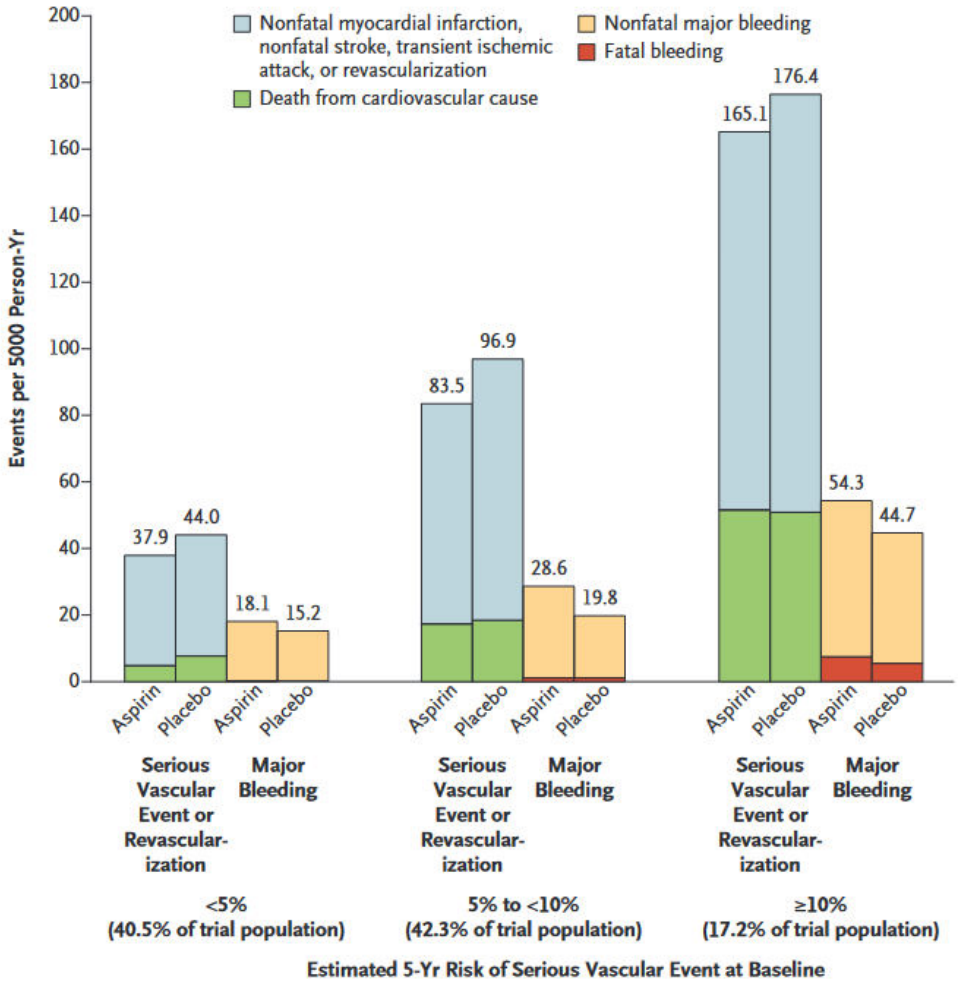
Effect of Assignment to Aspirin Group on Components of Serious Vascular Events, the Combined Outcome of Serious Vascular Event or Revascularization, and Major Bleeding and Its Components

Type of Event	Aspirin (N=7740)	Placebo (N=7740)	Rate Ratio (95% CI)	P Value
	no. of participants with event (%)			
Vascular Outcomes				
Nonfatal myocardial infarction	191 (2.5)	195 (2.5)	0.98 (0.80–1.19)	
Nonfatal presumed ischemic stroke	202 (2.6)	229 (3.0)	0.88 (0.73–1.06)	
Vascular death excluding intracranial hemorrhage	197 (2.5)	217 (2.8)	0.91 (0.75–1.10)	
Any serious vascular event excluding TIA	**542 (7.0)**	**587 (7.6)**	**0.92 (0.82–1.03)**	
TIA	168 (2.2)	197 (2.5)	0.85 (0.69–1.04)	
Any serious vascular event including TIA	**658 (8.5)**	**743 (9.6)**	**0.88 (0.79–0.97)**	**0.01**
Any arterial revascularization	340 (4.4)	384 (5.0)	0.88 (0.76–1.02)	
Any serious vascular event or revascularization	**833 (10.8)**	**936 (12.1)**	**0.88 (0.80–0.97)**	
Major Bleeding				
Intracranial hemorrhage	55 (0.7)	45 (0.6)	1.22 (0.82–1.81)	
Sight-threatening bleeding in eye	57 (0.7)	64 (0.8)	0.89 (0.62–1.27)	
Serious gastrointestinal bleeding	137 (1.8)	101 (1.3)	1.36 (1.05–1.75)	
Other major bleeding	74 (1.0)	43 (0.6)	1.70 (1.18–2.44)	
Any major bleeding	**314 (4.1)**	**245 (3.2)**	**1.29 (1.09–1.52)**	**0.003**



N Engl J Med, 2018 Aug 26. doi: 10.1056/NEJMoa1804988

Observed Absolute Effect of Assignment to Aspirin Group on Serious Vascular Events or Revascularization and on Major Bleeding, According to Vascular Risk



No. of Events per 5000 Person-Yr in Aspirin Group			
Serious vascular events avoided	5.7±3.7	11.2±5.4	4.9±12.9
Serious vascular events or revascularizations avoided	6.1±4.2	13.4±6.3	11.3±14.3
Major bleeding caused	2.8±2.6	8.9±3.2	9.6±7.5

N Engl J Med, 2018 Aug 26. doi: 10.1056/NEJMoa1804988

ASCEND

Conclusion

- Low dose Aspirin confers modest benefit on CV events in diabetes mellitus w/o evidence of CV disease.
- This benefit is offset by an increase in bleeding.
- Therefore, no indication of routine Aspirin low dose in primary prevention.

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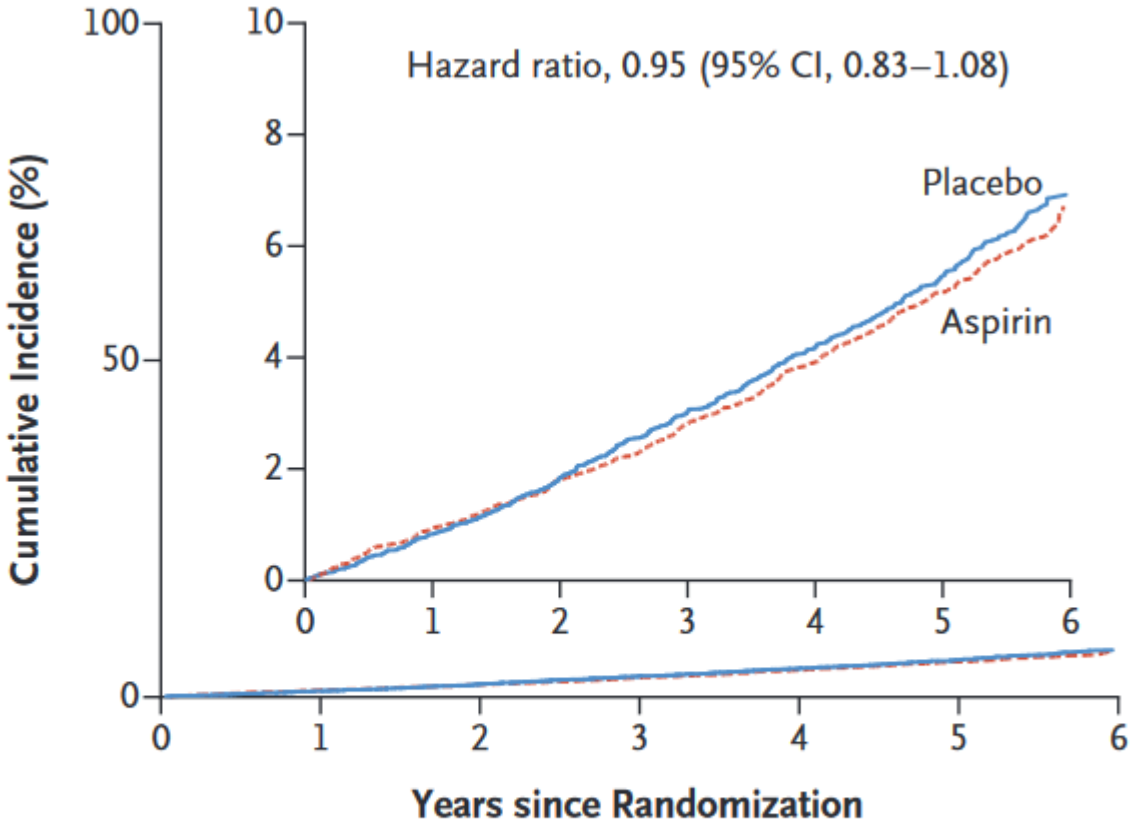
ORIGINAL ARTICLE

Effect of Aspirin on Cardiovascular Events and Bleeding in the Healthy Elderly

J.J. McNeil, R. Wolfe, R.L. Woods, A.M. Tonkin, G.A. Donnan, M.R. Nelson, C.M. Reid, J.E. Lockery, B. Kirpach, E. Storey, R.C. Shah, J.D. Williamson, K.L. Margolis, M.E. Ernst, W.P. Abhayaratna, N. Stocks, S.M. Fitzgerald, S.G. Orchard, R.E. Trevaks, L.J. Beilin, C.I. Johnston, J. Ryan, B. Radziszewska, M. Jelinek, M. Malik, C.B. Eaton, D. Brauer, G. Cloud, E.M. Wood, S.E. Mahady, S. Satterfield,* R. Grimm, and A.M. Murray, for the ASPREE Investigator Group†

McNeill JJ, N Engl J Med. 2018 Sep 16. doi: 10.1056/NEJMoa1805819

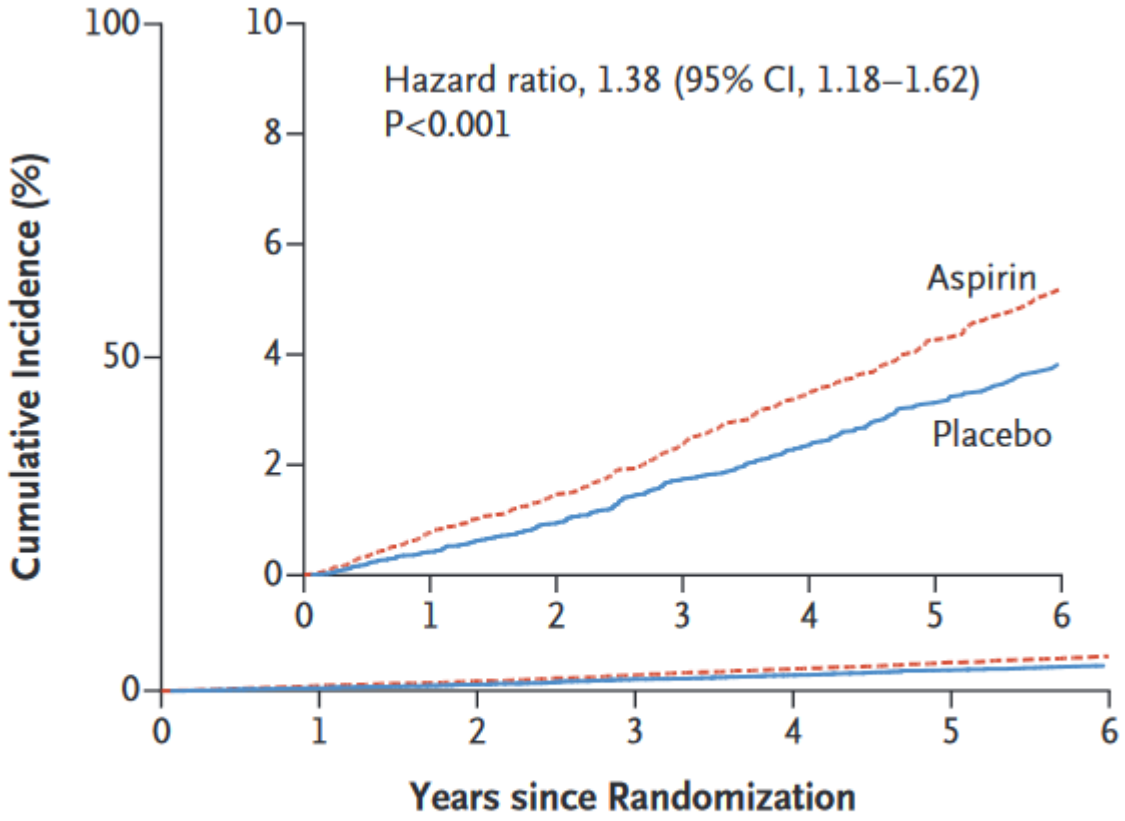
Cumulative Incidence of Cardiovascular Disease.



No. at Risk							
Aspirin	9525	9322	9068	7820	5827	3568	1234
Placebo	9589	9387	9119	7843	5839	3578	1223

McNeill JJ, N Engl J Med. 2018 Sep 16. doi: 10.1056/NEJMoa1805819

Cumulative Incidence of Major Hemorrhage.



No. at Risk							
Aspirin	9525	9337	9094	7833	5826	3574	1248
Placebo	9589	9424	9192	7930	5935	3632	1244

McNeill JJ, N Engl J Med. 2018 Sep 16. doi: 10.1056/NEJMoa1805819

The NEW ENGLAND JOURNAL of MEDICINE

Cardiovascular Safety of Lorcaserin in Overweight or Obese Patients

E.A. Bohula, S.D. Wiviott, D.K. McGuire, S.E. Inzucchi, J. Kuder, K.A. Im, C.L. Fanola, A. Qamar, C. Brown, A. Budaj, A. Garcia-Castillo, M. Gupta, L.A. Leiter, N.J. Weissman, H.D. White, T. Patel, B. Francis, W. Miao, C. Perdomo, S. Dhadda, M.P. Bonaca, C.T. Ruff, A.C. Keech, S.R. Smith, M.S. Sabatine, and B.M. Scirica, for the CAMELLIA–TIMI 61 Steering Committee and Investigators*

This article was published on August 26, 2018, at NEJM.org. DOI: 10.1056/NEJMoa1808721

CAMELLIA TIMI 61 : The Context

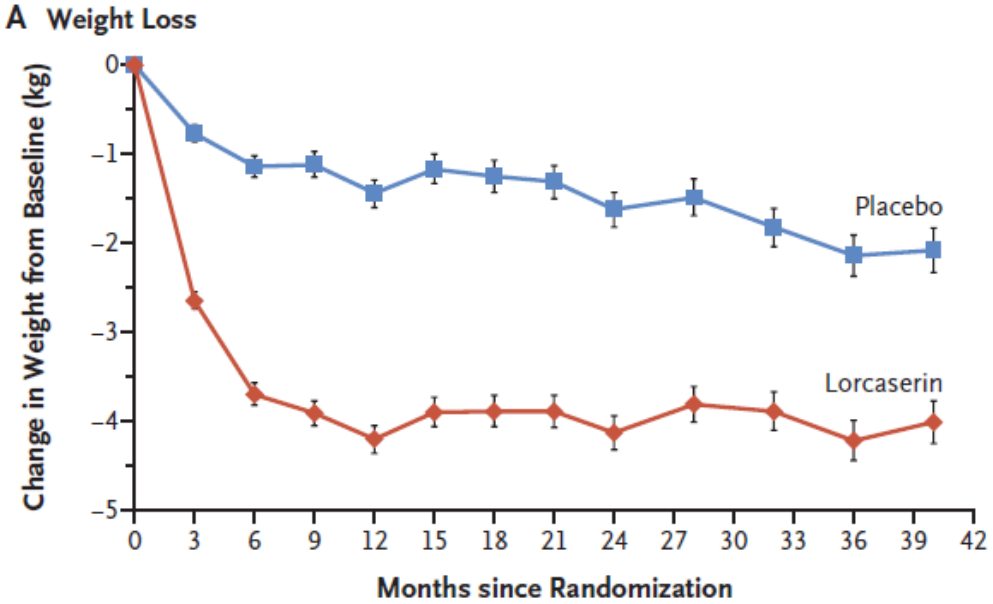
- Weight lowering pharmacologic agents have not shown cardio-vascular benefit.
- Cardio-vascular and neuro-psychiatric safety concerns.
- Lorcaserin is a selective agonist of the 5-hydroxytryptamin 2C serotonin receptor.

CAMELLIA TIMI 61

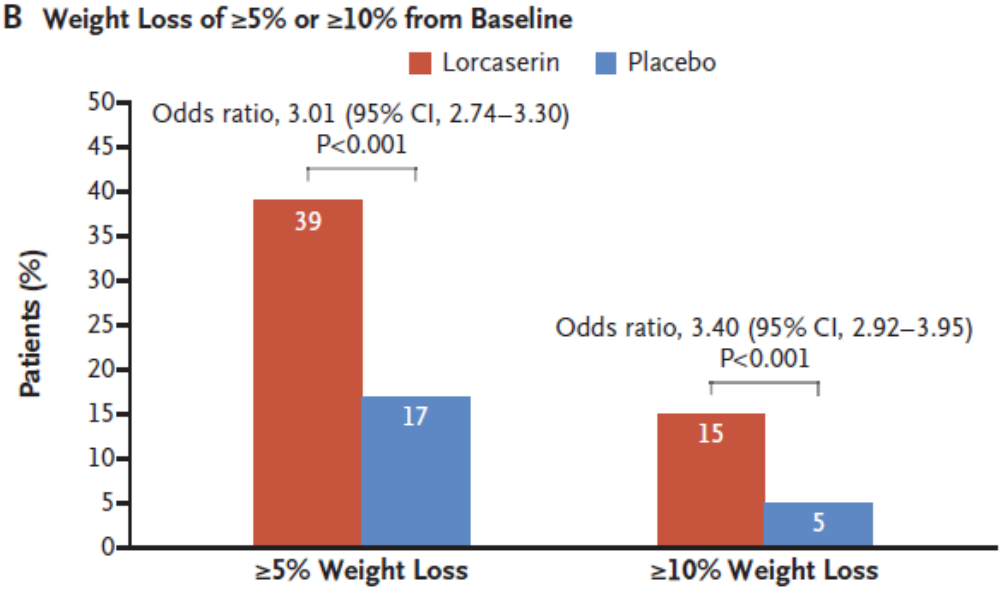
N = 12 000 patients

- Obese patients or overweight with BMI ≥ 27.
- With atherosclerotic disease or multiple risk factors.
- Lorcaserin 10 mg x 2/d or placebo.
- Primary safety endpoint : CV death / myocardial infarction / stroke.
- Primary efficacy endpoint : MACE + HF + stable angina or coronary revascularization.

Weight loss



Panel A shows the change in weight from baseline (as least-squares means) among patients in the lorcaserin group and the placebo group. I bars indicate 95% confidence intervals.

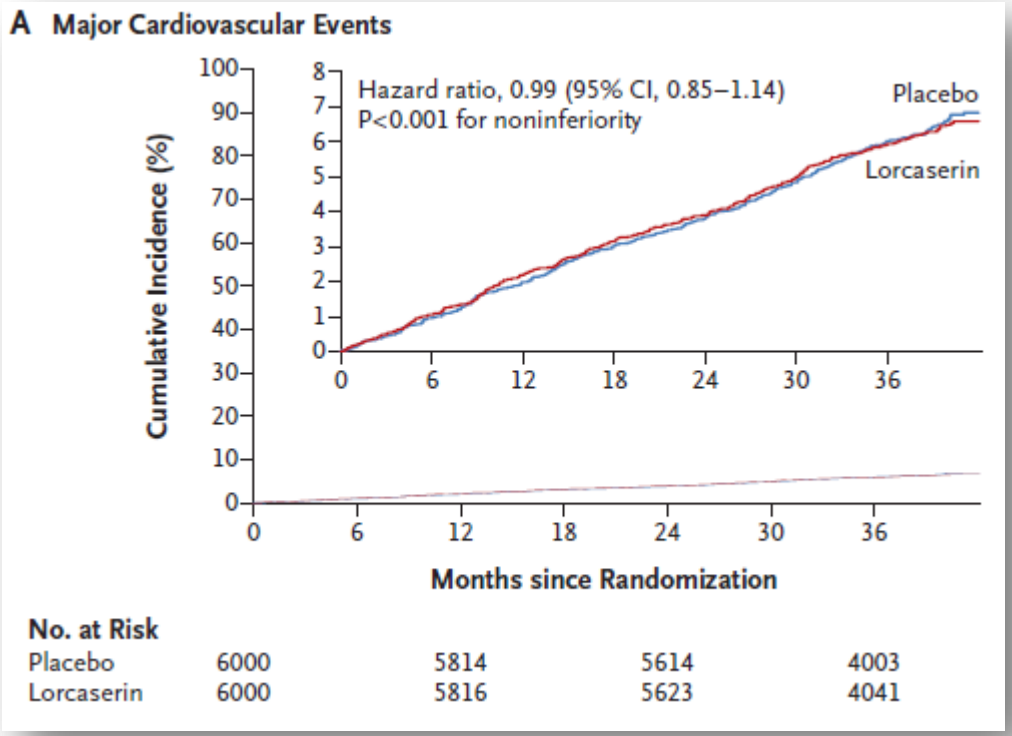


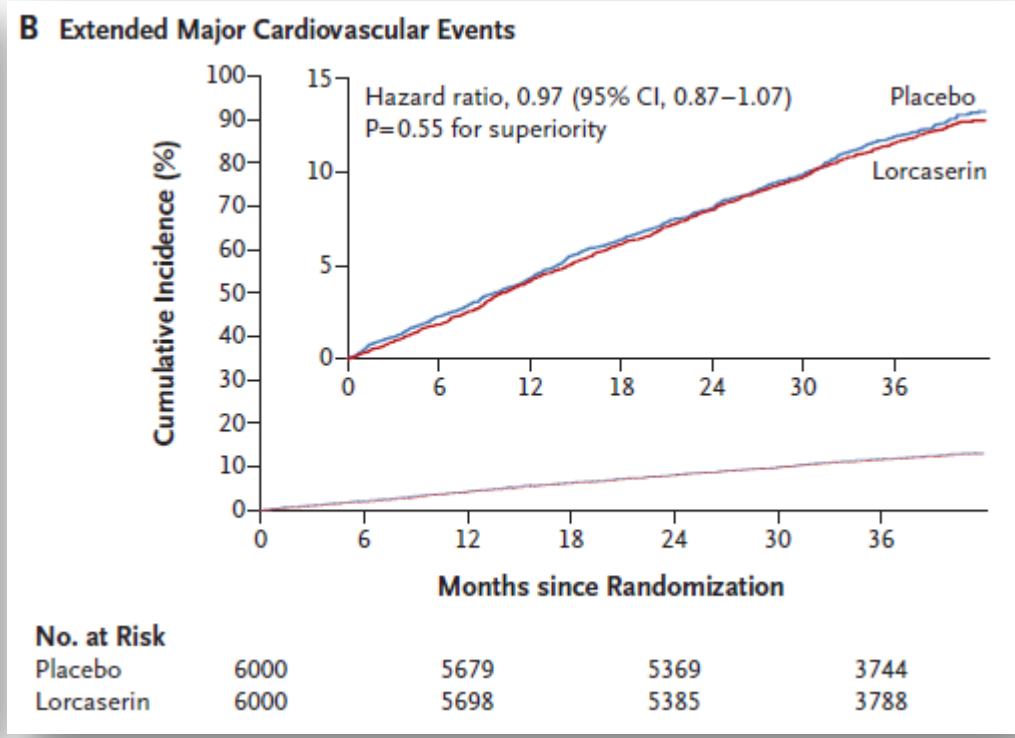
Panel B shows the percentage of patients with weight loss of at least 5% or at least 10% from baseline at 1 year in the lorcaserin group and the placebo group.

The analyses included all the patients for whom data regarding weight were available at baseline and at 1 year (5135 patients in the lorcaserin group and 5083 in the placebo group).

Bohula E.A. et al, NEJM, August 26, 2018. DOI: 10.1056/NEJMoa1808721

Major adverse cardiovascular outcomes





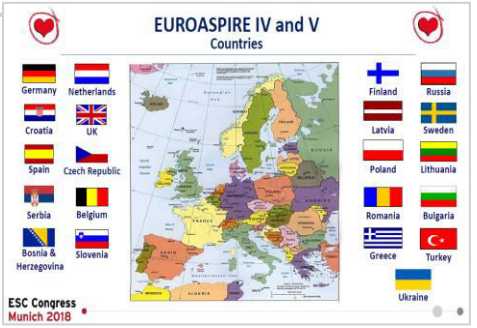
Bohula E.A. et al, NEJM, August 26, 2018. DOI: 10.1056/NEJMoa1808721

CAMELLIA TIMI 61

Conclusion

In a high risk population of overweight / obese patients, Lorcaserin facilitated weight loss w/o higher rate of CV events than that with placebo at 3.3 years of follow-up.

Trends in management of chronic heart disease patients EUROASPIRE

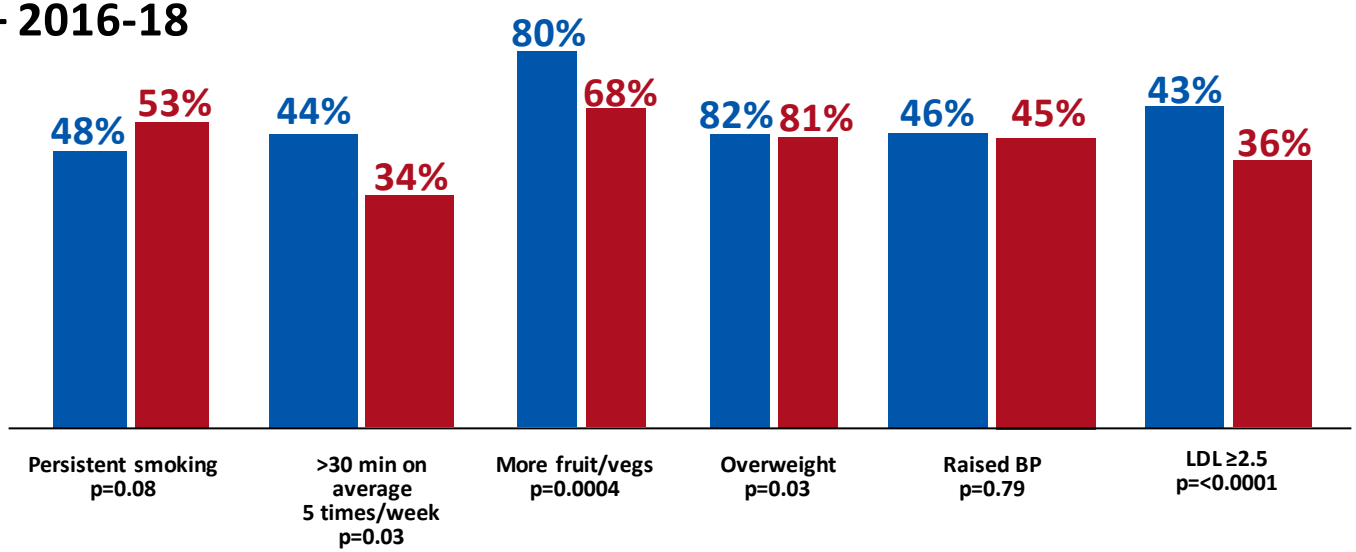


A comparison of EUROASPIRE IV and V surveys over 5 years in 21 countries

Patients with ACS or elective CABG/PCI 6mo-3yr prior

Euroaspire IV – 2012-15

Euroaspire V – 2016-18



Adverse lifestyle trends among European CHD patients are a major cause of concern

K. Kotseva (London, UK) 2974

Are beta blockers and calcium channel blockers beneficial on clinical outcomes in chronic ischaemic heart disease?

First-line anti-ischaemic agents use and long-term clinical outcomes in stable coronary artery disease. Insights from the CLARIFY registry

E. Sorbets, P.G. Steg, R. Young, N. Danchin, N. Greenlaw, I. Ford, M. Tendera, R. Ferrari, C. Reid, A. Parkhomenko, B. Merkely, J.C. Tardif, K.M. Fox, for the CLARIFY investigators

Emmanuel SORBETS, MD, PhD

25th August 2018

Available data on the prognostic effect of β-blockers and calcium antagonists in stable CAD

β-blockers:

. No RCT (or post-hoc)

. Metanalyses of old RCT in acute MI

. Recent observational studies with limitations

Lack of effects?

Calcium Antagonists:

. "Old" RCT

. Metanalyses of old RCT

. No large observational studies

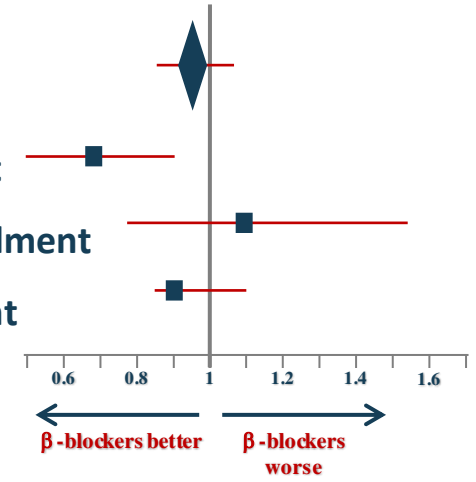
No prognostic effect

➥ Need for contemporary data

β-blockers and Calcium antagonists in CLARIFY

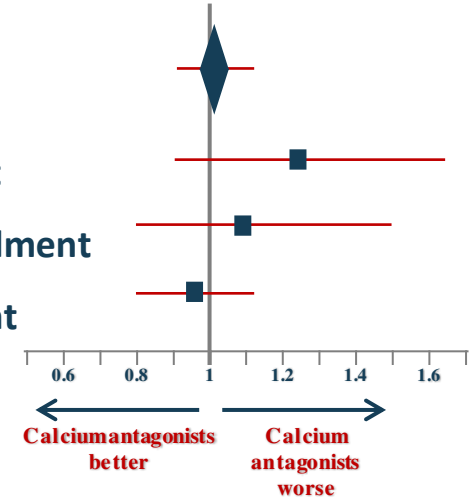
- **β-blockers use and all-cause mortality**

	HR	95% CI	P value
Overall	0.94	(0.84-1.06)	0.30
MI ≤ 1 year prior to enrollment	0.68	(0.50-0.91)	0.01
MI 1 to ≤ 3 years prior to enrollment	1.09	(0.76-1.56)	0.63
MI > 3 years prior to enrollment	0.91	(0.84-1.10)	0.33



- **Calcium Antagonists use and all-cause mortality**

	HR	95% CI	P value
Overall	1.02	(0.91-1.13)	0.76
MI ≤ 1 year prior to enrollment	1.24	(0.92-1.67)	0.16
MI 1 to ≤ 3 years prior to enrollment	1.09	(0.80-1.50)	0.58
MI > 3 years prior to enrollment	0.95	(0.80-1.13)	0.56

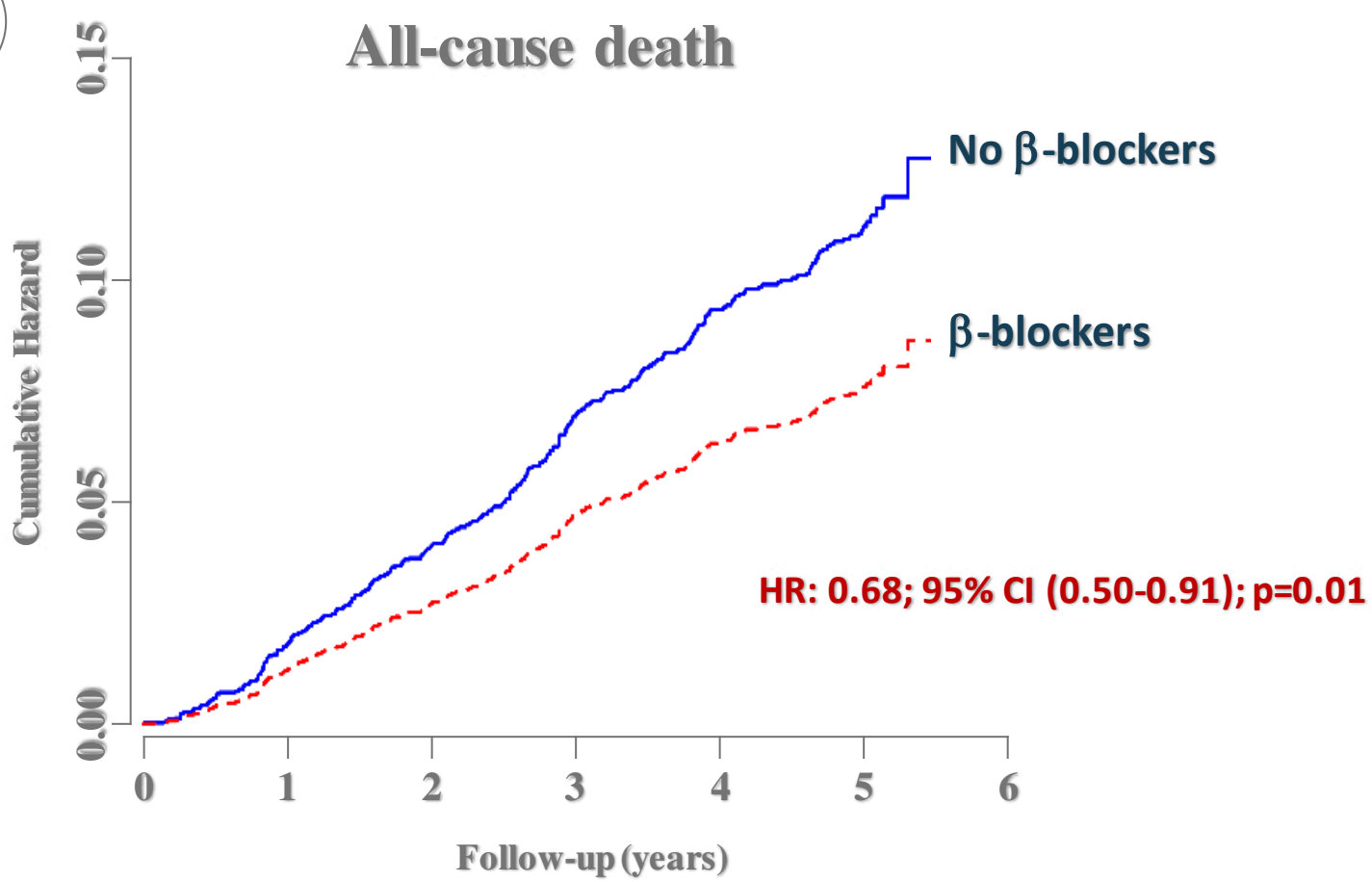


Survival analysis from Cox proportional hazards models
Multivariable adjustment for SBP, DBP, LVEF, histories of PCI, CABG, PAD, asthma/COPD and the REACH

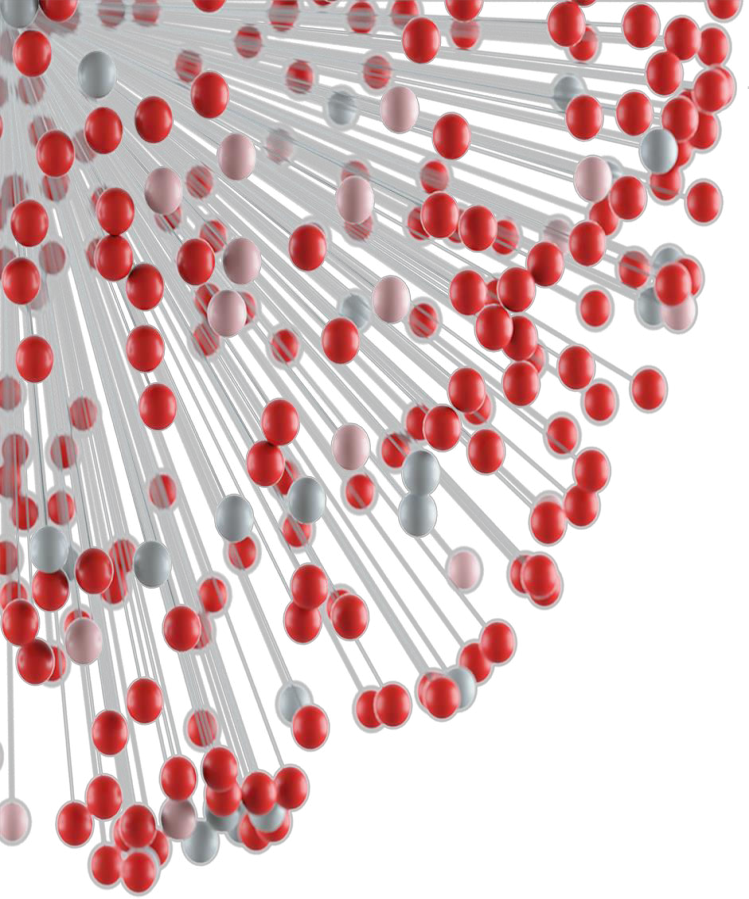
CLARIFY

Cumulative hazard of all-cause mortality according to β-blocker use at baseline in patients with previous MI ≤1 year prior to enrollment

MI ≤1 year prior to enrollment



Survival analysis from Cox proportional hazards models
Multivariable adjustment for SBP, DBP, LVEF, histories of PCI, CABG, PAD, asthma/COPD and the REACH



HEART FAILURE & CARDIOMYOPATHIES

Michel KOMAJDA

Hopital Saint Joseph Paris France

Conflicts of Interest

Lectures and grants: Servier Sanofi Novartis MSD

Contents

- **Devices and technology**
  - Telemonitoring again TIMHF 2
- **Diabetes mellitus**
  - Is insulin safe in HF?
  - Risk factors control and HF
- **Trials**
  - Commander HF : rivaroxaban in HFrEF in sinus rhythm
  - ATTR-ACT cardiac amyloidosis

HEART FAILURE & CARDIOMYOPATHIES

TIM-HFII TRIAL – REMOTE PATIENT MANAGEMENT IN HEART FAILURE

Friedrich Koehler

ESC Congress Munich 2018

Congress Highlights

Efficacy of telemedical interventional management in patients with heart failure (TIM-HF2): a randomised, controlled, parallel-group, unmasked trial

Friedrich Koehler, Kerstin Koehler, Oliver Deckwart, Sandra Prescher, Karl Wegscheider, Bridget-Anne Kirwan, Sebastian Winkler, Eik Vettorazzi, Leonhard Bruch, Michael Oeff, Christian Zugck, Gesine Doerr, Herbert Naegele, Stefan Störk, Christian Butter, Udo Sechtem, Christiane Angermann, Guntram Gola, Roland Prondzinsky, Frank Edelmann, Sebastian Spethmann, Sebastian M Schellong, P Christian Schulze, Johann Bauersachs, Brunhilde Wellge, Christoph Schoebel, Milos Tajsic, Henryk Dreger, Stefan D Anker, Karl Stangl**

Koehler F, et al. Lancet, 2018 Aug 24. pii: S0140-6736(18)31880-4. doi: 10.1016/S0140-6736(18)31880-4

TIMI HF2 : THE CONTEXT

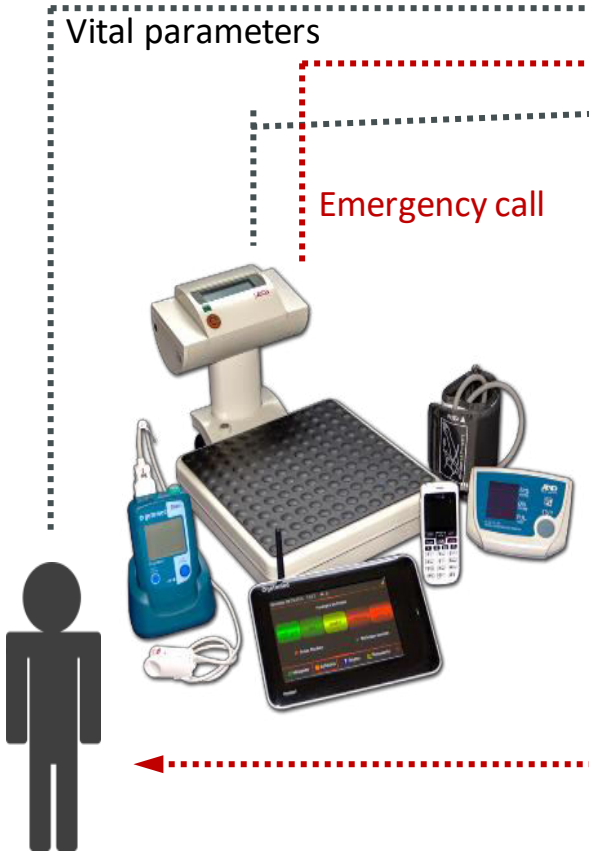
- Remote distance monitoring in HF shows inconsistent results.
- Post-hoc analysis of TIM HF suggests benefit in patients w/o depression.

TIMI HF2

N = 1 538 patients

- **NYHA Class II / III**
- **EF < 45% or > 45% + Diuretics**
- **Without depression**
- **Previous HF hospitalization within 12 months**

RPM Intervention used in TIM-HFII



TIM HF 2

- **Primary endpoint :**

  All cause death / percentage of days lost due to unplanned cardiovascular hospitalization

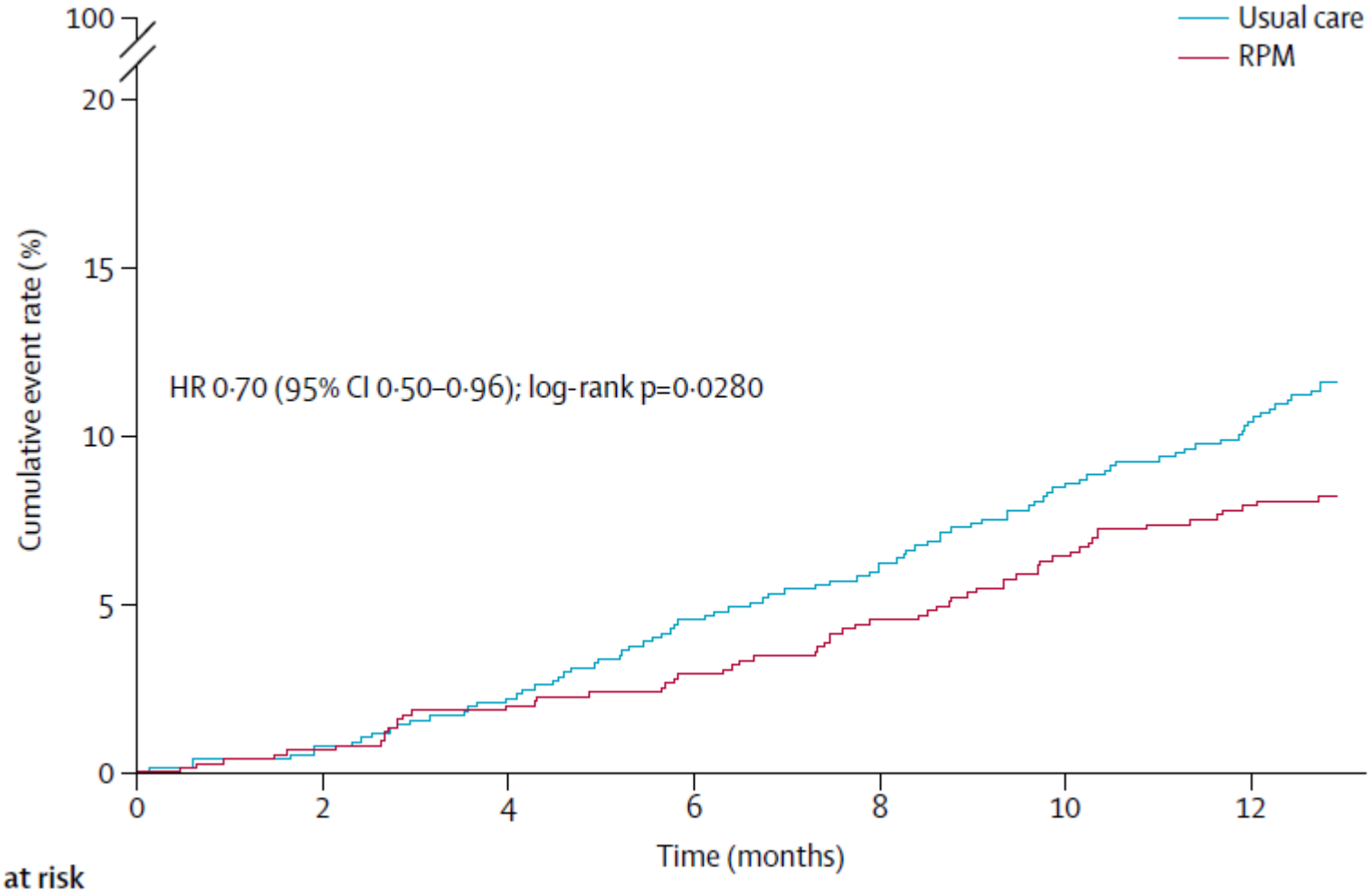
Primary and key secondary outcomes

	Remote patient management (n=765)		Usual care (n=773)		Ratio, remote patient management vs usual care (95% CI)	p value
	Number of patients with event	Weighted average (95% CI)	Number of patients with event	Weighted average (95% CI)		
Percentage of days lost due to unplanned cardiovascular hospitalisation or death of any cause	265 (35%)	4·88% (4·55–5·23)	290 (38%)	6·64% (6·19–7·13)	0·80* (0·65–1·00)	0·0460
Days lost per year	..	17·8 days (16·6–19·1)	..	24·2 days (22·6–26·0)	..	..
All-cause mortality†	61 (8%)	7·86 (6·14–10·10)	89 (12%)	11·34 (9·21–13·95)	0·70‡ (0·50–0·96)	0·0280
Cardiovascular mortality†	39 (5%)	5·04 (3·68–6·90)	59 (8%)	7·51 (5·82–9·70)	0·67‡ (0·45–1·01)	0·0560

*Ratio of the weighted average. †Measured during individual patient follow-up time plus 28 days after the last study visit, to a maximum of 393 days. ‡Hazard ratio.

Koehler F, et al. Lancet, 2018 Aug 24. pii: S0140-6736(18)31880-4. doi: 10.1016/S0140-6736(18)31880-4

Kaplan-Meier cumulative event curve for all-cause death



Number at risk

Usual care	773	767	756	738	716	697	681
RPM	765	755	737	724	709	688	673

Koehler F, et al. Lancet, 2018 Aug 24. pii: S0140-6736(18)31880-4. doi: 10.1016/S0140-6736(18)31880-4

Unplanned HF hospitalization

- **Secondary: % days lost due to unplanned HF hospitalisation: Ratio: 0.797 (0.67, 0.95), p=0.007**

TIM HF 2

- TIM HF 2 shows that in CHF w/o depression remote monitoring has positive results.
- A monitoring center 24 hours / 7 days is key for success.

HEART FAILURE & CARDIOMYOPATHIES

TREATMENT WITH INSULIN IS ASSOCIATED WITH WORSE OUTCOME IN PATIENTS WITH CHRONIC HEART FAILURE AND DIABETES

Franco Cosmi, Li Shen, Michela Magnoli, William T. Abraham, Inder S. Anand, John G. Cleland, Jay N. Cohn, Deborah Cosmi, Giorgia De Berardis, Kenneth Dickstein, Maria Grazia Franzosi, Lars Gullestad, Pardeep S. Jhund, John Kjekshus, Lars Køber, Vito Lepore, Giuseppe Lucisano, Aldo P. Maggioni, Serge Masson, John J.V. McMurray, Antonio Nicolucci, Vito Petrarolo, Fabio Robusto, Lidia Staszewsky, Luigi Tavazzi, Roberto Teli, Gianni Tognoni, John Wikstrand, and Roberto Latini

ESC Congress Munich 2018

Congress Highlights

Insulin, chronic heart failure, diabetes and outcomes

Val-HeFT

- 5010 patients
- 1276 (25.5%) with diabetes
- 440 (34.5%) taking insulin
- Follow-up: 1.96 years

ATMOSPHERE

- 7016 patients
- 1944 (27.7%) with diabetes
- 475 (24.4%) taking insulin
- Follow-up: 3.06 years

GISSI-HF

- 6975 patients
- 1974 (28.3%) with diabetes
- 542 (27.5%) taking insulin
- Follow-up: 3.87 years

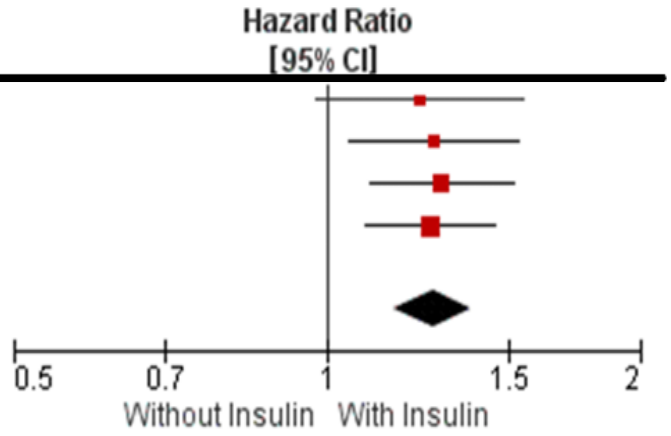
CORONA

- 5011 patients
- 1477 (29.5%) with diabetes
- 403 (27.3%) taking insulin
- Follow-up: 2.73 years

RESULTS: PROPENSITY SCORE

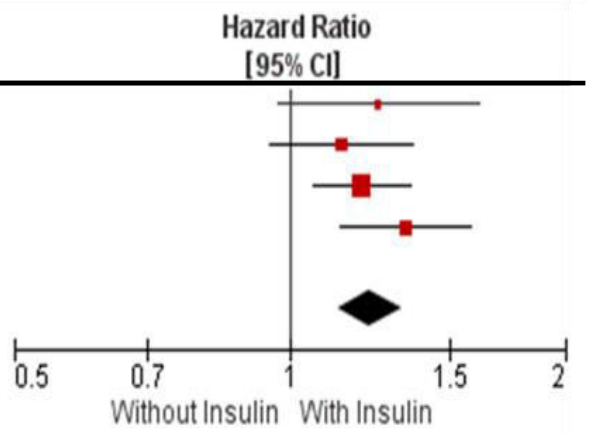
All-cause death

Study	Hazard Ratio [95% CI]
Val-HeFT	1.23 [0.98, 1.55]
CORONA	1.27 [1.05, 1.53]
GISSI-HF	1.29 [1.10, 1.51]
ATMOSPHERE	1.26 [1.09, 1.45]
Total (95% CI)	**1.27 [1.16, 1.38]**



Hospitalisation for HF

Study	Hazard Ratio [95% CI]
Val-HeFT	1.25 [0.97, 1.61]
CORONA	1.14 [0.95, 1.36]
GISSI-HF	1.20 [1.06, 1.35]
ATMOSPHERE	1.34 [1.14, 1.58]
Total (95% CI)	**1.23 [1.13, 1.33]**



REAL WORLD DATA

- **4 million subjects** of the Administrative Registry of Puglia Region in Italy

- **Insulin treatment was associated with a significantly higher risk of:**
  - **All cause death: OR=2.02 95%CI [1.87-2.19]**
  - **Hospitalisation for heart failure: OR 1.42 95%CI [1.32-1.53]**

HEART FAILURE & CARDIOMYOPATHIES

COMMANDER HF

Faiez Zannad

ESC Congress
Munich 2018

Congress
Highlights

The NEW ENGLAND JOURNAL of MEDICINE

Rivaroxaban in Patients with Heart Failure, Sinus Rhythm, and Coronary Disease

Faiez Zannad, M.D., Ph.D., Stefan D. Anker, M.D., Ph.D., William M. Byra, M.D., John G.F. Cleland, M.D., Min Fu, Ph.D., Mihai Gheorghiade, M.D.,* Carolyn S.P. Lam, M.D., Ph.D., Mandeep R. Mehra, M.D., James D. Neaton, Ph.D., Christopher C. Nessel, M.D., Theodore E. Spiro, M.D., Dirk J. van Veldhuisen, M.D., Ph.D., and Barry Greenberg, M.D., for the COMMANDER HF Investigators†

Zannad F et al, N Engl J Med, 2018 Aug 27. doi: 10.1056/NEJMoa1808848

COMMANDER HF : THE CONTEXT

- Heart failure is associated with a prothrombotic state.
- The benefit of anticoagulation in patients with HF in sinus rhythm is unknown.
- An increase in the risk of bleeding has been reported with Warfarin.

COMMANDER HF

- Is Rivaroxaban low dose (2.5 mg x 2/d) associated with improved outcomes in HFrEF in sinus rhythm of ischaemic origin?
- Is it safe?

COMMANDER HF

- N = 5 022 patients with HFrEF, coronary artery disease, elevated natriuretic peptides after an episode of decompensation within 21 days.
- F/U = 21 months.

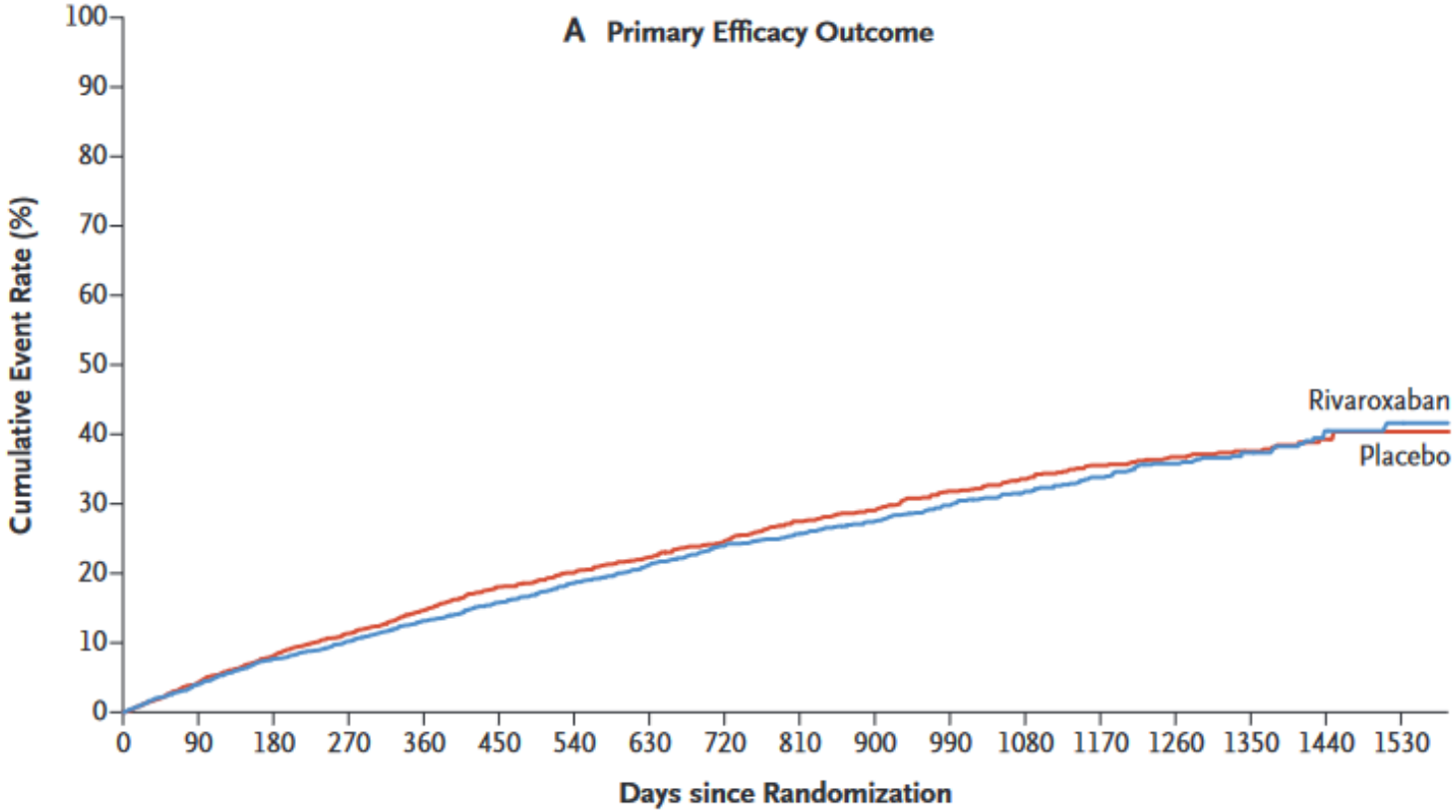
COMMANDER HF

- **Primary endpoint :**

  All cause death / myocardial infarction / stroke.

- **Safety endpoint :**

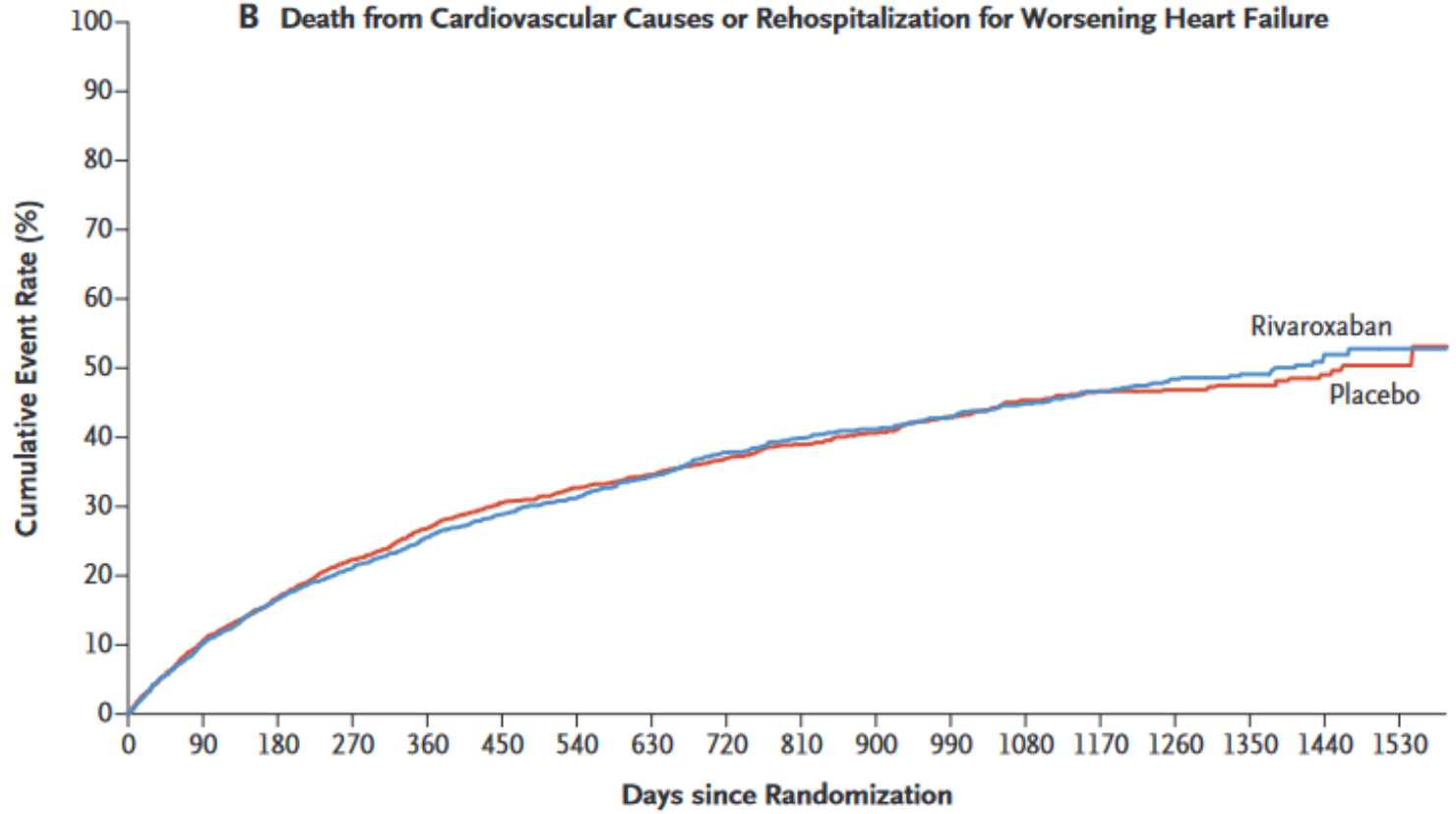
  Fatal bleeding / critical bleeding.



No. at Risk

Rivaroxaban	2507	2404	2308	2159	1883	1637	1384	1189	974	817	668	588	505	423	327	239	121	46
Placebo	2515	2407	2303	2145	1851	1589	1353	1169	960	804	661	582	502	426	330	236	127	43

Zannad F et al, N Engl J Med, 2018 Aug 27. doi: 10.1056/NEJMoa1808848



No. at Risk																		
Rivaroxaban	2507	2252	2077	1877	1585	1353	1145	971	773	650	531	475	406	341	259	184	94	29
Placebo	2515	2249	2075	1860	1557	1313	1100	946	766	644	532	473	403	346	267	187	96	36

Zannad F et al, N Engl J Med, 2018 Aug 27. doi: 10.1056/NEJMoa1808848

COMMANDER HF

Limitations

- No central adjudication of events.
- No electrocardiographic monitoring.
- Limited duration of follow up.

CONCLUSION

- Atherothrombotic events are uncommon in HF.
- New oral anticoagulants not routinely recommended in ischemic HF in sinus rhythm.

HEART FAILURE & CARDIOMYOPATHIES

ATTR-ACT TRIAL

Claudio Rapezzi

ESC Congress
Munich 2018

Congress
Highlights

The NEW ENGLAND JOURNAL of MEDICINE

Tafamidis Treatment for Patients with Transthyretin Amyloid Cardiomyopathy

Mathew S. Maurer, M.D., Jeffrey H. Schwartz, Ph.D., Balarama Gundapaneni, M.S., Perry M. Elliott, M.D., Giampaolo Merlini, M.D., Ph.D., Marcia Waddington-Cruz, M.D., Arnt V. Kristen, M.D., Martha Grogan, M.D., Ronald Witteles, M.D., Thibaud Damy, M.D., Ph.D., Brian M. Drachman, M.D., Sanjiv J. Shah, M.D., Mazen Hanna, M.D., Daniel P. Judge, M.D., Alexandra I. Barsdorf, Ph.D., Peter Huber, R.Ph., Terrell A. Patterson, Ph.D., Steven Riley, Pharm.D., Ph.D., Jennifer Schumacher, Ph.D., Michelle Stewart, Ph.D., Marla B. Sultan, M.D., M.B.A., and Claudio Rapezzi, M.D., for the ATTR-ACT Study Investigators*

Maurer MS, et al, New Engl J Med, 2018 Aug 27. doi: 10.1056/NEJMoa1805689

ATTR – ACT : THE CONTEXT

- Transthyretin amyloïd cardiomyopathy is caused by deposition of misfold transthyretin proteins in the myocardium.
- Restrictive cardiomyopathy associated with poor prognosis.
- No treatment has been shown to improve outcomes in this condition.

ATTR – ACT

- 2 categories of TTR cardiac amyloïdosis :
  - ✓ Wild type
  - ✓ Autosomal dominant
- Tafamidis binds to transthyretin thyroxin binding sites and limits cardiac deposition.

ATTR – ACT

N = 441 patients

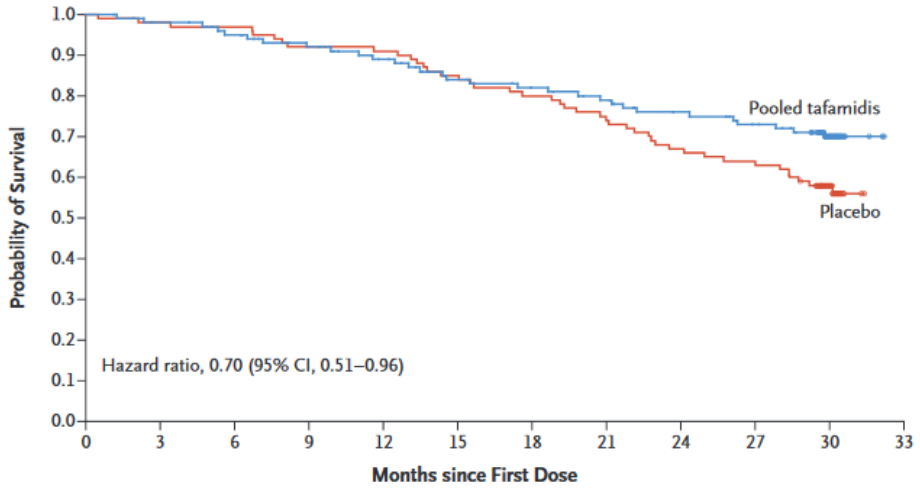
- 2 doses of Tafamidis : 20 mgs and 80 mgs.
- 30 months F/U.
- Primary endpoint : all cause death then cardiovascular hospitalizations.
- 6 minutes walking distance & KCCQ.

ATTR-ACT

A Primary Analysis, with Finkelstein–Schoenfeld Method

	No. of Patients	P Value from Finkelstein–Schoenfeld Method	Win Ratio (95% CI)	Patients Alive at Mo 30	Average Cardiovascular-Related Hospitalizations during 30 Mo among Those Alive at Mo 30
				no. (%)	*per patient per yr*
Pooled Tafamidis	264	<0.001	1.70 (1.26–2.29)	186 (70.5)	0.30
Placebo	177			101 (57.1)	0.46

B Analysis of All-Cause Mortality



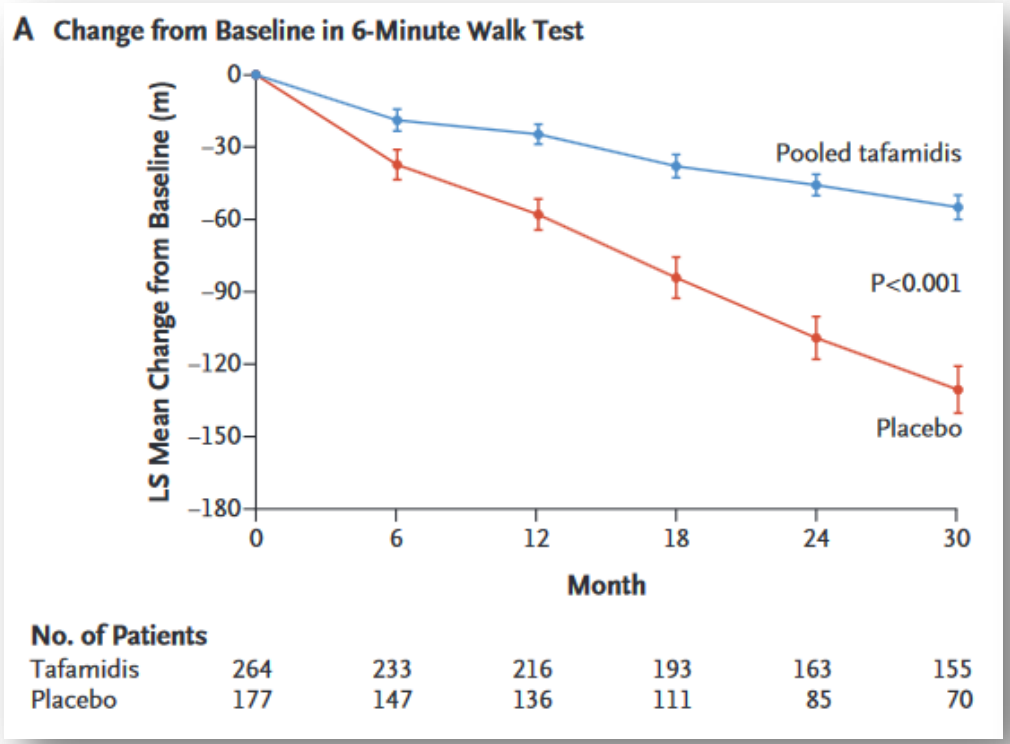
No. at Risk (cumulative no. of events)

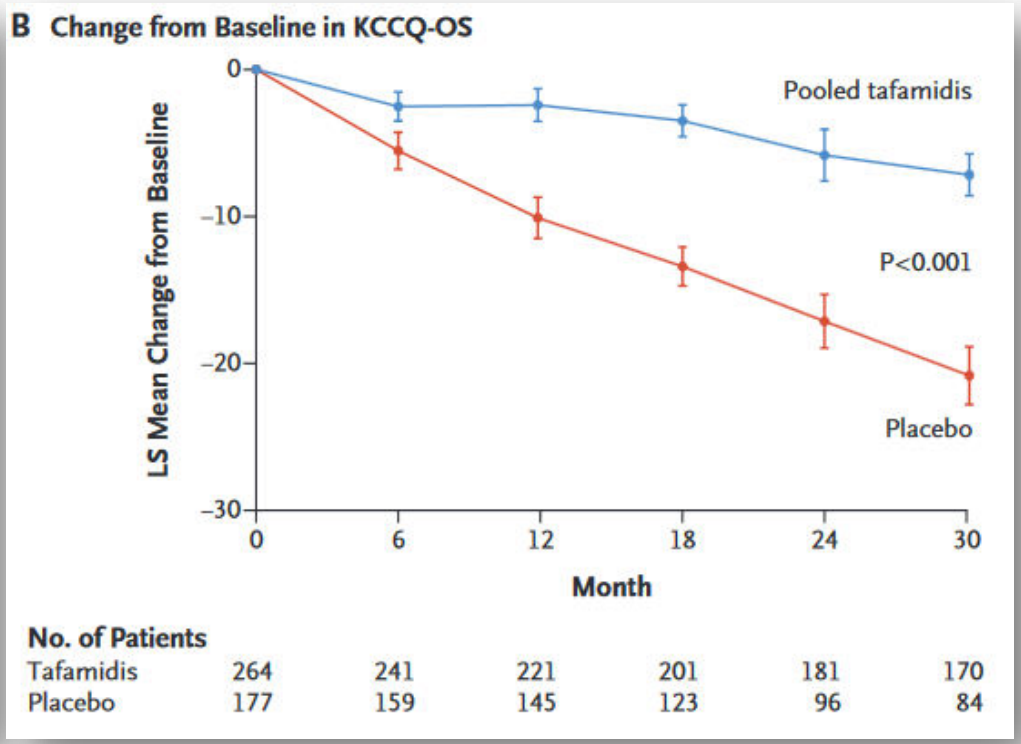
Pooled tafamidis	264 (0)	259 (5)	252 (12)	244 (20)	235 (29)	222 (42)	216 (48)	209 (55)	200 (64)	193 (71)	99 (78)	0 (78)
Placebo	177 (0)	173 (4)	171 (6)	163 (14)	161 (16)	150 (27)	141 (36)	131 (46)	118 (59)	113 (64)	51 (75)	0 (76)

C Frequency of Cardiovascular-Related Hospitalizations

	No. of Patients	No. of Patients with Cardiovascular- Related Hospitalizations	Cardiovascular- Related Hospitalizations	Pooled Tafamidis vs. Placebo Treatment Difference
		total no. (%)	*no. per yr*	*relative risk ratio (95% CI)*
Pooled Tafamidis	264	138 (52.3)	0.48	0.68 (0.56–0.81)
Placebo	177	107 (60.5)	0.70	

Maurer MS, et al, New Engl J Med, 2018 Aug 27. doi: 10.1056/NEJMoa1805689





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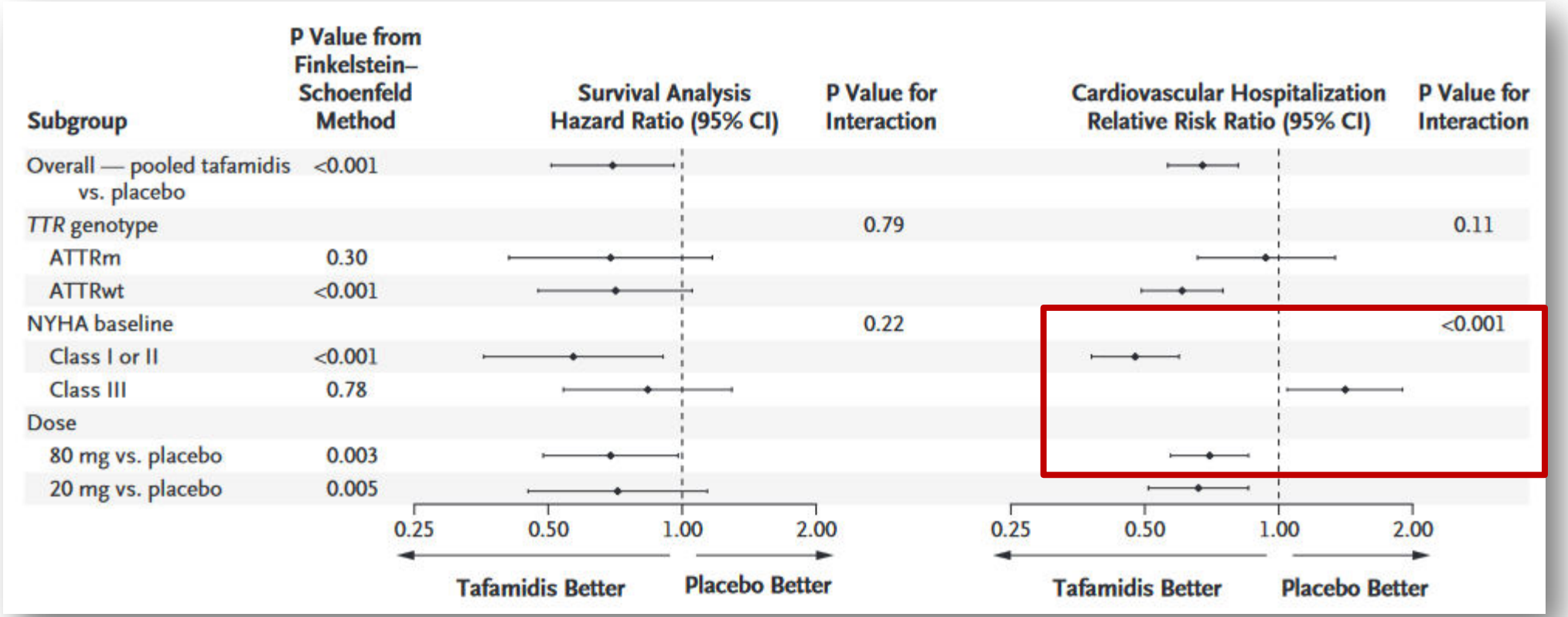

Maurer MS, et al, New Engl J Med, 2018 Aug 27. doi: 10.1056/NEJMoa1805689

HEART FAILURE & CARDIOMYOPATHIES

- **Technology: Remote monitoring has favorable effects (TIM HF2)**
- **Insulin associated with poor outcomes in HF: causality or risk marker?**
- **Risk factors control in type 2 DM not associated with prevention of HF**
- **Rivaroxaban low dose does not improve outcomes in HFrEF in sinus rhythm**
- **Tafamidis slows down progression of TTR amyloidosis**

MERCI