Top trials of 2022: STRONG-HF

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No relevant disclosures.

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Articles

Safety, tolerability and efficacy of up-titration of guideline-directed medical therapies for acute heart failure (STRONG-HF): a multinational, open-label, randomised, trial

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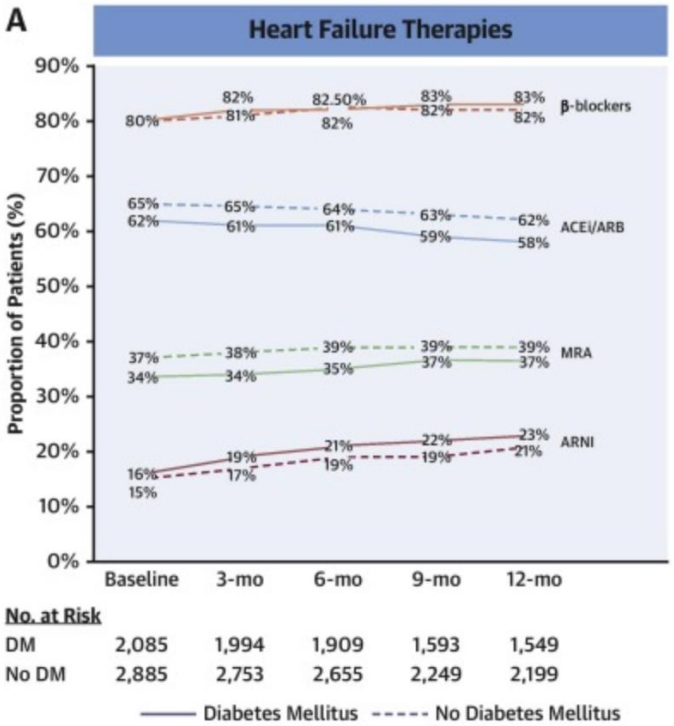
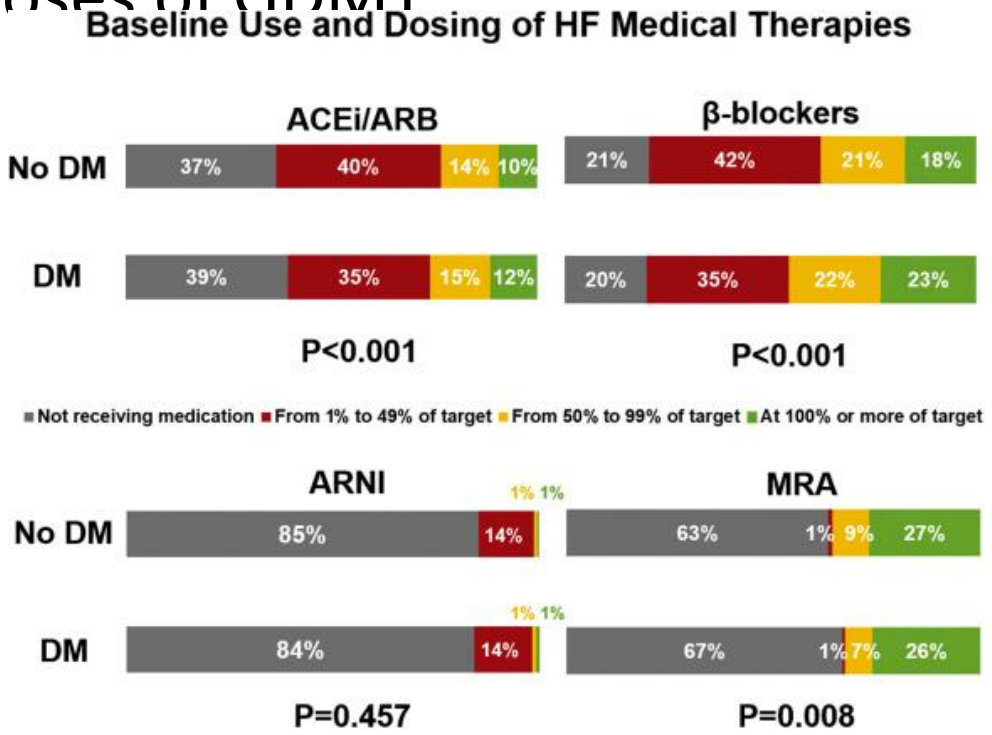
Background - HF treatment implementation

- Several effective therapies for HF, but there is little explicit guidance regarding initiation and titration of medications
- Few patients with HFrEF at target doses of GDMT





Vaduganathan M, Fonarow GC, Greene SJ, et al. Contemporary Treatment Patterns and Clinical Outcomes of Comorbid Diabetes Mellitus and HFrEF: The CHAMP-HF Registry. *JACC Heart Fail.* 2020;8(6):469-480. doi:10.1016/j.jchf.2019.12.015

Aim

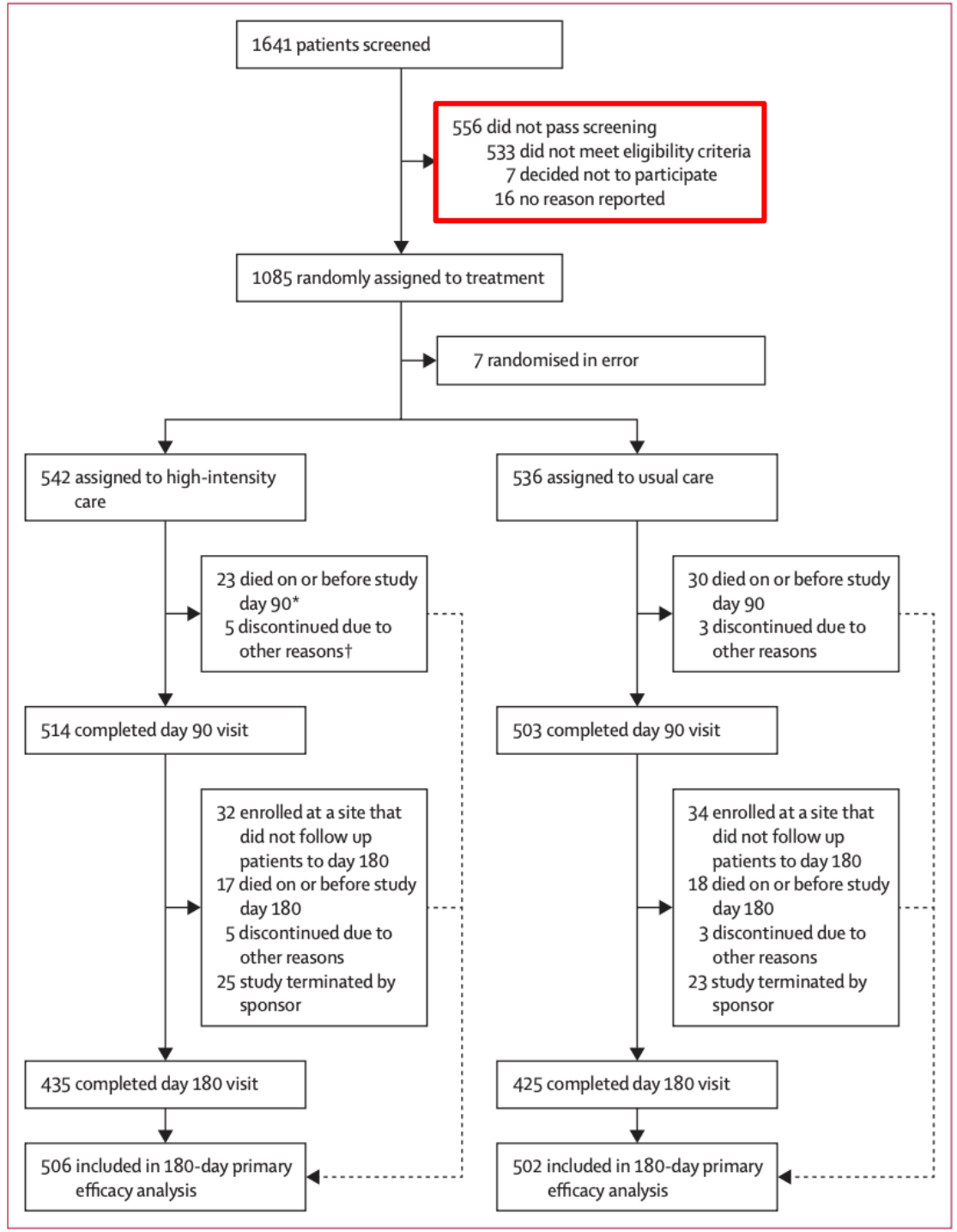
- To assess the safety and efficacy of rapid up-titration of GDMT for HFrEF during an admission for acute decompensated heart failure and in the following 2-3 weeks, as opposed to usual care

Study design

- Multi-national, multi-center, open label, randomized, parallel-group
- 87 hospitals, 15 countries, planned 1800 study participants
- Inclusion criteria
  - age 18-85
  - admitted within 72h for acute heart failure
  - hemodynamically stable
  - NT-proBNP >2500 pg/mL at screening, fell by at least 10% since admission
- Exclusion criteria
  - prior intolerance of high dose BB, ACE/ARB, MRA
  - MI, unstable angina, cardiac surgery within past 3 months
  - heart transplant or VAD
  - eGFR 30 or less
  - reversible cause of HF

Intervention

- High-intensity strategy
  - prior to discharge, start 50% target dose BB, MRA, ACE/ARB/ARNI
  - week 1 - safety check (vitals, labs, exam, history)
  - week 2 - if BP, labs, exam acceptable, increase to 100% target dose
  - week 3, week 6 - safety check (vitals, labs, exam, history)
- Usual care
  - under direction of local cardiologist
  - on average 1 visit in the 3 months post-hospitalization


1641 patients screened
556 did not pass screening
533 did not meet eligibility criteria
7 decided not to participate
16 no reason reported
1085 randomly assigned to treatment
7 randomised in error
542 assigned to high-intensity care
536 assigned to usual care
23 died on or before study day 90*
5 discontinued due to other reasons†
30 died on or before study day 90
3 discontinued due to other reasons
514 completed day 90 visit
503 completed day 90 visit
32 enrolled at a site that did not follow up patients to day 180
17 died on or before study day 180
5 discontinued due to other reasons
25 study terminated by sponsor
34 enrolled at a site that did not follow up patients to day 180
18 died on or before study day 180
3 discontinued due to other reasons
23 study terminated by sponsor
435 completed day 180 visit
425 completed day 180 visit
506 included in 180-day primary efficacy analysis
502 included in 180-day primary efficacy analysis

Study Population

	High-intensity care group (n=542)	Usual care group (n=536)	Total (N=1078)
Demographics			
Age, years	62·9 (13·5)	63·0 (13·7)	63·0 (13·6)
Sex			
Female	216 (40%)	200 (37%)	416 (39%)
Male	326 (60%)	336 (63%)	662 (61%)
Self-reported race			
Black	115 (21%)	115 (21%)	230 (21%)
White or Caucasian	418 (77%)	414 (77%)	832 (77%)
Native American	1 (<1%)	0	1 (<1%)
Other*	7 (1%)	5 (1%)	12 (1%)
Pacific Islander	1 (<1%)	0	1 (<1%)
Missing	0	2 (<1%)	2 (<1%)
Systolic blood pressure at baseline, mm Hg			
Mean	123·4 (13·30)	122·2 (12·56)	122·8 (12·95)
≤Median (120 mm Hg)	267/542 (49%)	276/534 (52%)	543/1076 (50%)
>Median	275/542 (51%)	258/534 (48%)	533/1076 (49%)
NT-proBNP at screening, ng/L†	7310·4 (4991·26)	6908·3 (4326·78)	7110·7 (4675·17)
NT-proBNP at baseline, ng/L†	4120·8 (3676·59)	3929·2 (3213·36)	4025·6 (3453·98)
History of atrial fibrillation or atrial flutter or present at screening	229 (42%)	254 (47%)	483 (45%)
Geographical region			
Africa	122 (23%)	118 (22%)	240 (22%)
Eastern and western Europe	47 (9%)	47 (9%)	94 (9%)
Russia	351 (65%)	352 (66%)	703 (65%)
South America	22 (4%)	19 (4%)	41 (4%)
Stroke or transient ischaemic attack	56 (10%)	43 (8%)	99 (9%)
Severe liver disease	3 (1%)	3 (1%)	6 (1%)
Psychiatric or neurological disorder	8 (1%)	12 (2%)	20 (2%)
Malignancies	18 (3%)	11 (2%)	29 (3%)
Diabetes	152 (28%)	161 (30%)	313 (29%)
Diabetes control method			
Insulin	50 (9%)	32 (6%)	82 (8%)
Diet only	102 (19%)	100 (19%)	202 (19%)
Oral antidiabetic agents	110 (20%)	124 (23%)	234 (22%)
Pulmonary embolism	13 (2%)	6 (1%)	19 (2%)
Acute coronary syndrome	166 (31%)	145 (27%)	311 (29%)
Coronary artery bypass surgery	27 (5%)	32 (6%)	59 (5%)
Percutaneous transluminal coronary intervention	80 (15%)	72 (13%)	152 (14%)
Angina Canadian Cardiovascular Society class 2 or higher	74 (14%)	51 (10%)	125 (12%)
Moderate or severe chronic obstructive pulmonary disease or asthma	14 (3%)	13 (2%)	27 (3%)
Sustained ventricular arrhythmia (with syncopal episodes in past 3 months)	0	1 (<1%)	1 (<1%)
Cardiac resynchronisation therapy	3 (1%)	3 (1%)	6 (1%)
Automatic internal cardiac defibrillator	3 (1%)	6 (1%)	9 (1%)
History of heart failure	465 (86%)	451 (84%)	916 (85%)

	High-intensity care group (n=542)	Usual care group (n=536)	Total (N=1078)
(Continued from previous page)			
NYHA class 1 month before hospital admission			
I	29/508 (6%)	34/492 (7%)	63/1000 (6%)
II	147/508 (29%)	160/492 (33%)	307/1000 (31%)
III	216/508 (43%)	199/492 (40%)	415/1000 (42%)
IV	116/508 (23%)	99/492 (20%)	215/1000 (22%)
Primary cause of heart failure			
Ischaemic	260/541 (48%)	254/534 (48%)	514/1075 (48%)
Non-ischaemic	281/541 (52%)	280/534 (52%)	561/1075 (52%)
LVEF category at baseline			
≤40%	365 (67%)	366 (68%)	731 (68%)
>40%	177 (33%)	170 (32%)	347 (32%)
<50%	452/540 (84%)	460/535 (86%)	912/1075 (85%)
≥50%	88/540 (16%)	75/535 (14%)	163/1075 (15%)
LVEF at baseline, %‡	36·7 (12·57)	35·9 (12·47)	36·3 (12·52)
Hospitalised for heart failure in the past year	140 (26%)	133 (25%)	273 (25%)
Number of heart failure hospitalisations in the past year	0·3 (0·68)	0·4 (1·42)	0·3 (1·11)
History of atrial fibrillation or atrial flutter	238 (44%)	258 (48%)	496 (46%)
Type of atrial fibrillation or atrial flutter			
Paroxysmal	57/234 (24%)	60/256 (23%)	117/490 (24%)
Permanent	137/234 (59%)	156/256 (61%)	293/490 (60%)
Persistent	40/234 (17%)	40/256 (16%)	80/490 (16%)
Oral heart failure medications taken before randomisation			
ACE inhibitors	208/540 (38%)	211/534 (39%)	419/1074 (39%)
ARBs	104/540 (19%)	76/534 (14%)	180/1074 (17%)
ARN inhibitors	42/540 (8%)	48/534 (9%)	90/1074 (8%)
β blockers	184/540 (34%)	200/534 (37%)	384/1074 (36%)
Mineralocorticoid receptor antagonists	509/540 (94%)	510/534 (96%)	1019/1074 (95%)
Loop diuretic	520/540 (96%)	509/534 (95%)	1029/1074 (96%)

Outcome

- Primary Outcome
  - hospitalization for heart failure or all-cause death at 180 days
- Secondary Outcomes
  - Change in quality of life from baseline to day 90 (EQ-5D visual analog scale)
  - Change in all-cause death at 180 days
  - Change in hospitalization for heart failure or all-cause death at 90 days
  - Safety - incidence of treatment-related adverse events up to 90 days
- Trial stopped early by DSMB after interim analysis at 1069 patients
  - felt withholding intensive treatment would be unethical

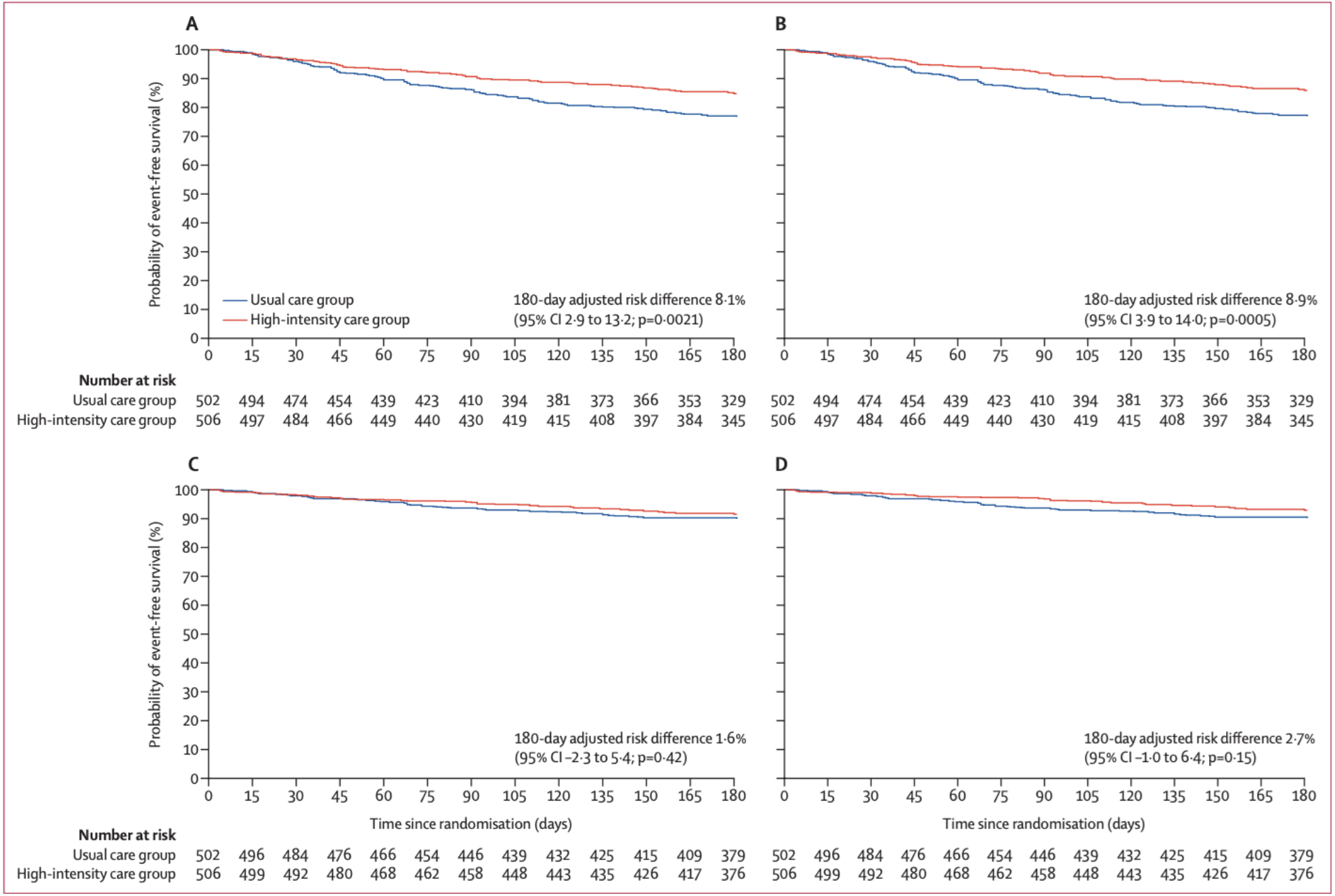
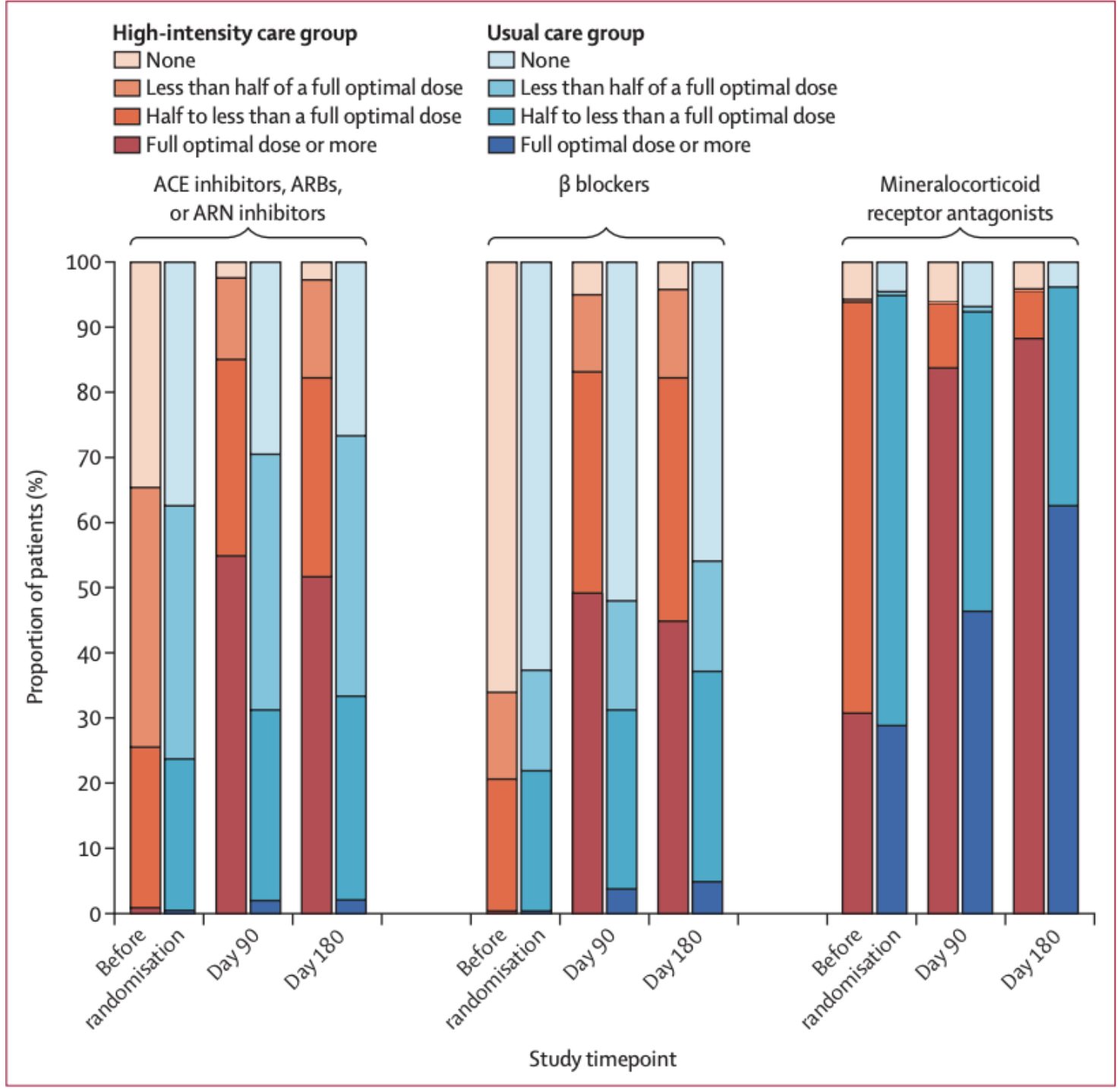


***Figure 3*: Adjusted Kaplan-Meier estimates of cumulative event-free survival with down-weighting of cohort 1 for all-cause death or heart failure readmission (A), all-cause death or heart failure excluding deaths due to COVID-19 (B), all-cause mortality (C), and all-cause mortality excluding deaths due to COVID-19 (D), from randomisation up to day 180**

Adjusted 180-day risk differences are given. Analyses excluding COVID-19-related deaths were prespecified sensitivity analyses.


High-intensity care group
None
Less than half of a full optimal dose
Half to less than a full optimal dose
Full optimal dose or more
Usual care group
None
Less than half of a full optimal dose
Half to less than a full optimal dose
Full optimal dose or more
ACE inhibitors, ARBs, or ARN inhibitors
β blockers
Mineralocorticoid receptor antagonists
Proportion of patients (%)
100
90
80
70
60
50
40
30
20
10
0
Before randomisation
Day 90
Day 180
Before randomisation
Day 90
Day 180
Before randomisation
Day 90
Day 180
Study timepoint

Secondary endpoints

- Improved NYHA class by 1.36
- Lower SBP (-5.4 mmHg difference between groups)
- Increased adverse events in intensive treatment group
  - hypotension - 5% vs. <1%
  - hyperkalemia - 3% vs. <1%
  - no difference in serious adverse events

Conclusion

“The STRONG-HF study shows that most patients admitted for acute heart failure and not treated with optimal doses of oral heart failure therapies can be rapidly and safely up-titrated to recommended doses of drugs within a few weeks after discharge, with frequent visits comprising clinical and laboratory assessments, including NT-proBNP, to ensure the safety of such up-titration and indicate the need for additional visits.”

Discussion

- Rapid initiation safe of GDMT safe and effective, with improvement in quality of life
- Generalizability may be limited
  - relatively few comorbidities, with ~30% patients screened not randomized
- More hypotension and hyperkalemia in intensive treatment group
  - did not result in net harm
- Systems of care for GDMT optimization are important

Thank you!

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Acetazolamide in Acute Decompensated Heart Failure with Volume Overload

W. Mullens, J. Dauw, P. Martens, F.H. Verbrugge, P. Nijst, E. Meekers, K. Tartaglia, F. Chenot, S. Moubayed, R. Dierckx, P. Blouard, P. Troisfontaines, D. Derthoo, W. Smolders, L. Bruckers, W. Droogne, J.M. Ter Maaten, K. Damman, J. Lassus, A. Mebazaa, G. Filippatos, F. Ruschitzka, and M. Dupont, for the ADVOR Study Group*

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No disclosures

OHIO CHAPTER

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Background- HF

5.7 million people in the US have HF with 26 million worldwide

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MARCH 3, 2011 VOL. 364 NO. 9

Diuretic Strategies in Patients with Acute Decompensated Heart Failure

G. Michael Felker, M.D., M.H.S., Kerry L. Lee, Ph.D., David A. Bull, M.D., Margaret M. Redfield, M.D., Lynne W. Stevenson, M.D., Steven R. Goldsmith, M.D., Martin M. LeWinter, M.D., Anita Deswal, M.D., M.P.H., Jean L. Rouleau, M.D., Elizabeth O. Ofili, M.D., M.P.H., Kevin J. Anstrom, Ph.D., Adrian F. Hernandez, M.D., Steven E. McNulty, M.S., Eric J. Velazquez, M.D., Abdallah G. Kfoury, M.D., Horng H. Chen, M.B., B.Ch., Michael M. Givertz, M.D., Marc J. Semigran, M.D., Bradley A. Bart, M.D., Alice M. Mascette, M.D., Eugene Braunwald, M.D., and Christopher M. O'Connor, M.D., for the NHLBI Heart Failure Clinical Research Network*

End Point	Bolus Every 12 Hr (N=156)	Continuous Infusion (N=152)	P Value	Low Dose (N=151)	High Dose (N=157)	P Value
AUC for dyspnea at 72 hr	4456±1468	4699±1573	0.36	4478±1550	4668±1496	0.04
Freedom from congestion at 72 hr — no./total no. (%)	22/153 (14)	22/144 (15)	0.78	16/143 (11)	28/154 (18)	0.09
Change in weight at 72 hr — lb	−6.8±7.8	−8.1±10.3	0.20	−6.1±9.5	−8.7±8.5	0.01

Recommendations	Class[a]	Level[b]
It is recommended that patients hospitalized for HF be carefully evaluated to exclude persistent signs of congestion before discharge and to optimize oral treatment.[427,472]	I	C

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- Multicenter (27 centers in Belgium)
- Parallel group
- Double blind
- Randomized
- Placebo controlled
- Investigator initiate

- Adults
- ADHF admission
- 40 of po furosemide or equivalent
- Plasma NT BNP >1000 or BNP >250
- LVEF assessment

2,915

Main exclusion criteria
Receipt of SGLT-2 I
SBP <90 mmHg
GFR <20 ml/per min
Treatment with IV Lasix 80 mg

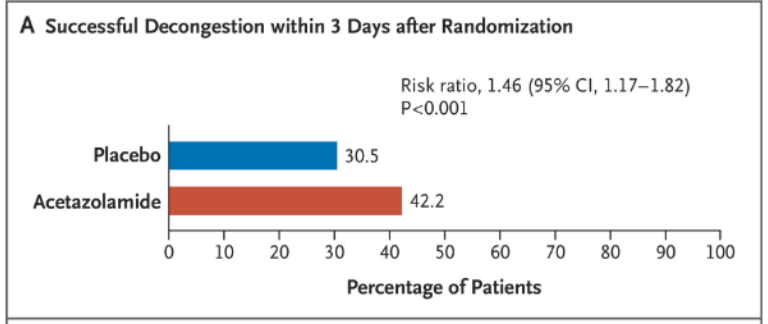
259
IV acetazolamide (500 mg OD) + IV loop diuretic

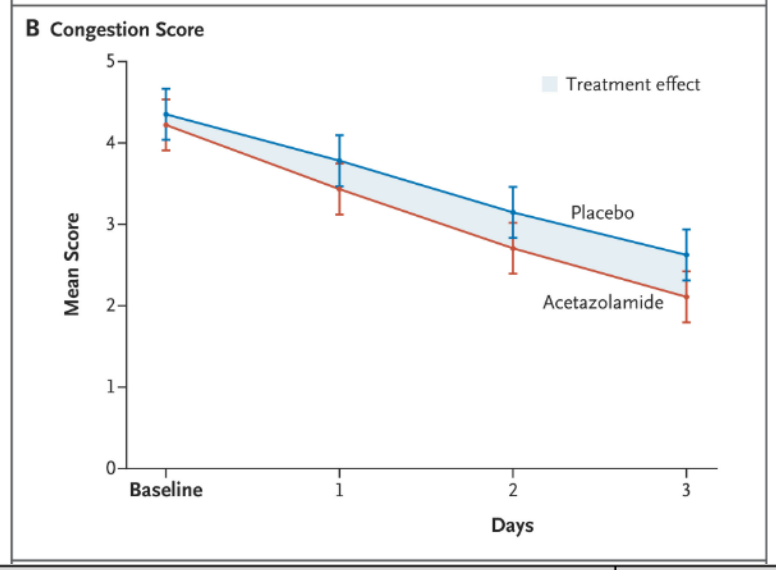
260
Placebo + IV loop diuretic

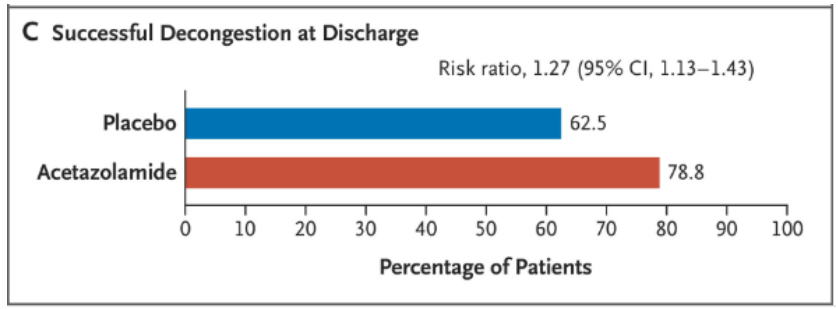
Table 1. **Characteristics of the Patients at Baseline.***

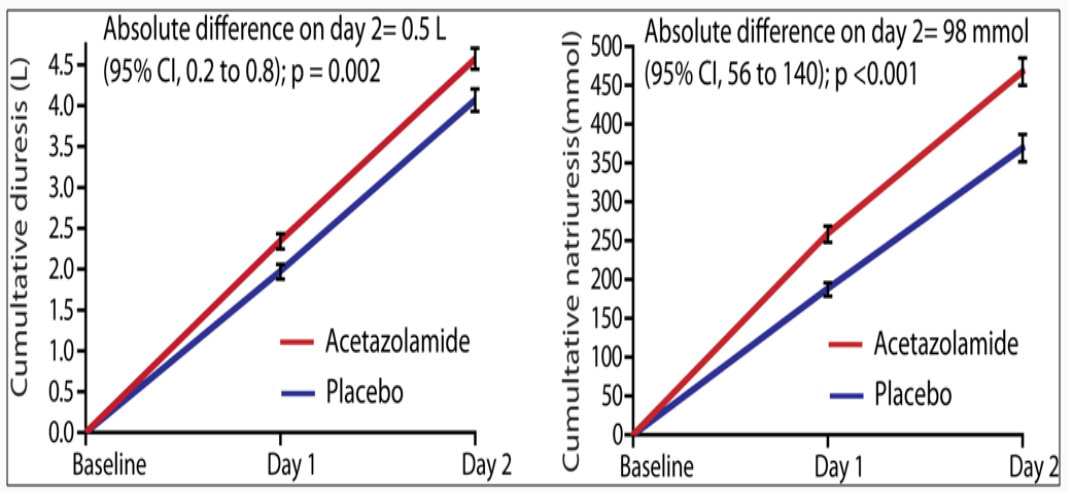
Characteristic	Placebo (N=260)	Acetazolamide (N=259)	Total (N=519)
Age — yr	78.5±8.8	77.9 ±9.0	78.2±8.9
Male sex — no. (%)	155 (59.6)	170 (65.6)	325 (62.6)
White race — no. (%)†	256 (98.5)	258 (99.6)	514 (99.0)
Heart rate — beats/min	77±18	79±19	78±18
Blood pressure — mm Hg			
Systolic	127±22	126±20	127±21
Diastolic	73±13	72±13	72±13
Weight — kg	84.4±19.7	85.3±23.0	84.8±21.4
Median congestion score at baseline (IQR)‡	4 (3–6)	4 (3–5)	4 (3–6)
Components of congestion score — no. (%)			
Edema§	241 (92.7)	237 (91.5)	478 (92.1)
Pleural effusion	143 (55.0)	130 (50.2)	273 (52.6)
Ascites	25 (9.6)	21 (8.1)	46 (8.9)
Median home maintenance dose of furosemide equivalent (IQR) — mg	60 (40–100)	80 (40–120)	60 (40–100)
Left ventricular ejection fraction			
Mean — %	43±15	43±15	43±15
≤40% — no. (%)	111 (42.7)	113 (43.6)	224 (43.2)
Median NT-proBNP (IQR) — pg/ml	6483 (3262–11,839)	5600 (3034–10,100)	6173 (3068–10,896)
NYHA functional class — no. (%)			
II	35 (13.5)	31 (12.0)	66 (12.7)
III	148 (56.9)	148 (57.1)	296 (57.0)

Primary Endpoint









Secondary Endpoint

Outcomes	Placebo	Acetazolamide	Risk Ratio, Geometric Mean or Hazard Ratio [95%CI]	p-value
Secondary endpoint				
Length of stay (days)	9.9 (9.1-10.8)	8.8 (8.0-9.5)	GM 0.89 (0.81 to 0.98)	0.016
All-cause mortality and hospitalization for heart failure at 3months	72 (27.8%)	76 (29.7%)	HR 1.07 (0.78 to 1.48)	ns
All-cause mortality at 3 months	31 (12.0%)	39 (15.2%)	HR 1.28 (0.78 to 2.05)	ns
Hospitalization for heart failure at 3 months	45 (17.4%)	47 (18.4%)	HR 1.07 (0.71 to 1.59)	ns

Safety and Adverse Events

Variable	Placebo (N=259)	Acetazolamide (N=256)	Treatment Effect (95% CI)	P Value
Adverse events				
During treatment phase — no. (%)				
Combined renal safety end point	2 (0.8)	7 (2.7)	—	0.10
Doubling of serum creatinine level from baseline	0	2 (0.8)	—	0.24
≥50% sustained decrease in estimated GFR	1 (0.4)	4 (1.6)	—	0.21
Renal-replacement therapy during index hospitalization	1 (0.4)	4 (1.6)	—	0.21
Severe metabolic acidosis¶	0	0	—	—
Hypokalemia‖	10 (3.9)	14 (5.5)	—	0.39
Hypotension**	9 (3.5)	17 (6.6)	—	0.11
During 3 mo of follow-up — no. (%)				
Serious adverse event	124 (47.9)	123 (48.0)	—	1.00
Adverse event related to placebo or acetazolamide	3 (1.2)	8 (3.1)	—	0.14
Cardiovascular adverse event	122 (47.1)	113 (44.1)	—	0.53

Conclusions

- Largest diuretic study
- Combination therapy resulted in higher incidence of decongestion by 3 days, increased natriuresis and diuresis when compared to loop monotherapy, shorter hospital stay and more likely to be discharged without residual signs of volume overload
- Median GFR 39

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 OCTOBER 13, 2022 VOL. 387 NO. 15

Percutaneous Revascularization for Ischemic Left Ventricular Dysfunction

Divaka Perera, M.D., Tim Clayton, M.Sc., Peter D. O'Kane, M.D., John P. Greenwood, Ph.D., Roshan Weerackody, Ph.D., Matthew Ryan, Ph.D., Holly P. Morgan, M.B., B.Ch., Matthew Dodd, M.Sc., Richard Evans, B.A., Ruth Canter, M.Sc., Sophie Arnold, M.Sc., Lana J. Dixon, Ph.D., Richard J. Edwards, Ph.D., Kalpa De Silva, Ph.D., James C. Spratt, M.D., Dwayne Conway, M.D., James Cotton, M.D., Margaret McEntegart, Ph.D., Amedeo Chiribiri, Ph.D., Pedro Saramago, Ph.D., Anthony Gershlick, M.D., Ajay M. Shah, M.D., Andrew L. Clark, M.D., and Mark C. Petrie, M.D., for the REVIVED-BCIS2 Investigators*

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I have no disclosures

Background

- Most common cause of HF worldwide is CAD
- Recovery of EF after CABG > concept of myocardial hibernation
- Reversal of hibernation by PCI not studied previously
- Most prior PCI studies excluded severe systolic dysfunction

Hypothesis

- In patients with severe systolic dysfunction and CAD
  1. PCI + OMT vs OMT > improved event-free survival
  2. PCI would improve systolic function

Study Design

- Prospective
- Multicenter (40 centers in UK)
- Randomized
- Open label

- Adults
- EF < 35%
- Extensive CAD
- Viability >4 segments, PCI-able

Excluded
- Acute MI <4 weeks pre-randomization
- ADHF <72 hrs pre-randomization
- Ventricular arrhythmias <72 hrs pre-randomization

PCI + OMT
(n= 347)

OMT only
(n= 353)

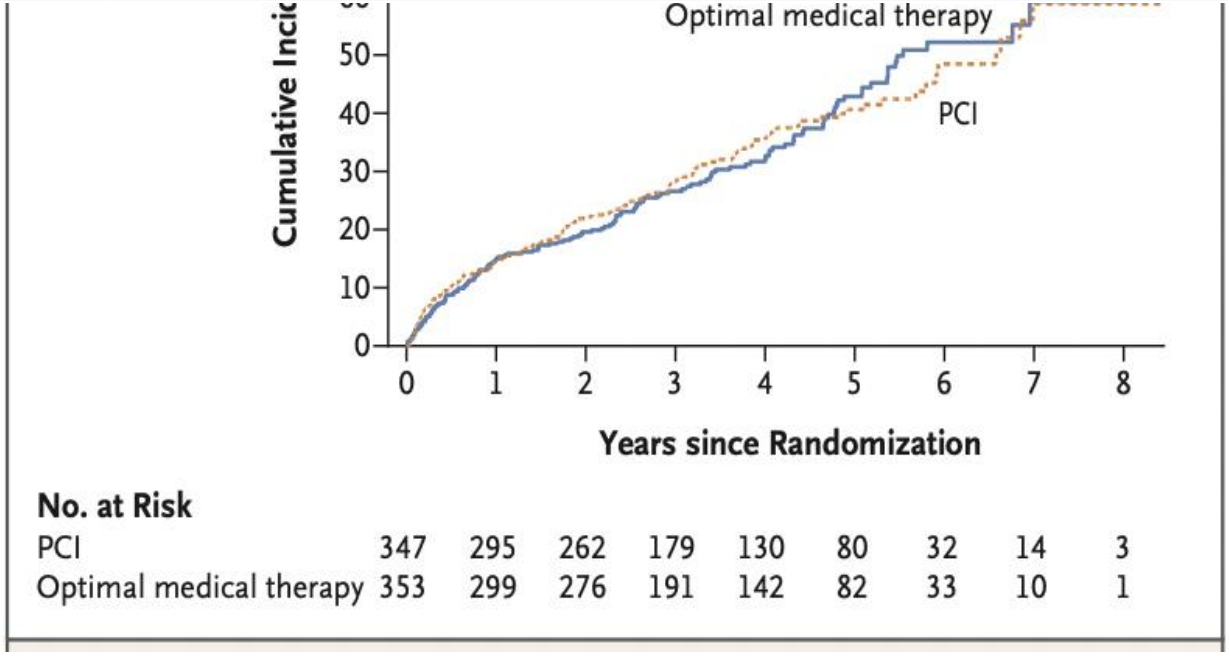
Results

Demographics and Clinical Characteristics of the Patients at Baseline

Characteristic	PCI (n=347)	Optimal Medical Therapy (n=353)
Age – yr	70 ∓ 9	68.8 ∓ 9.1
Male sex – no. (%)	302 (87)	312 (88)
Race – no. (%)		
White	306 (88)	328 (93)
Asian	32 (9)	17 (5)
Black	3 (1)	3 (1)
Mixed, other	6 (2)	5 (1)
BMI	28.4 ∓ 5.5	28.7 ∓ 5.4
NYHA class – no./total no. (%)		
I or II	265/345 (77)	248/350 (71)
III or IV	80/345 (23)	102/350 (29)
CCS angina – no./total no. (%)		
No angina	248/346 (66)	236/351 (67)
I or II	111/346 (32)	107/351 (30)
III	7/346 (2)	8/351 (2)
LVEF - %	27 ∓ 6.6	27 ∓ 6.9
CAD characteristics		
Median BCIS score (IQR)	10 (8-12)	10 (8-12)
LM CAD – no./total no. (%)	50/346 (14)	45/352 (13)
3 vessel CAD – no./total no. (%)	133/346 (38)	148/352 (42)
2 vessel CAD – no. (%)	178 (51)	166 (47)
Median NT-proBNP – [g/ml (IQR)	1376 (697-3426)	1461 (712-3365)

Results – Primary Outcome

Outcome	PCI (n= 347)	Optimal Medical Therapy (n= 353)	Treatment Effect (95% CI)
Primary Outcome			
Death from any cause or hospitalization for HF – no. (%)	129 (37.2)	134 (38)	0.99 (0.78-1.27)



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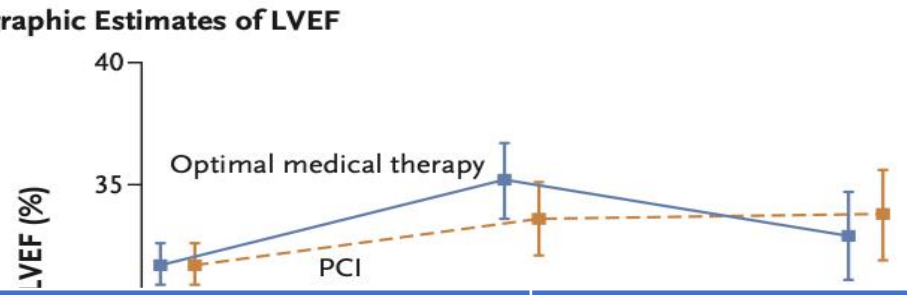
Results ·



Outcome	PCI (n= 347)	Optimal Medical Therapy (n= 353)	Treatment Effect (95% CI)
Secondary Outcome			
Components of the 1ary outcome			
Death from any cause	110 (31.7)	115 (32.6)	0.98 (0.75-1.27)
HF hospitalization	51 (14.7)	54 (15.3)	0.97 (0.66-1.43)
Death from CV causes – no. (%)	76 (21.9)	88 (24.9)	0.88 (0.65-1.2)
Acute MI – no. (%)	37 (10.7)	38 (10.8)	1.01 (0.64-1.6)
Periprocedural – no. (%)	14 (37.8)	0	
Spontaneous – no. (%)	18 (48.7)	33 (86.8)	
Sudden death – no. (%)	5 (13.5)	5 (13.2)	
Unplanned revascularization – no. (%)	10 (2.9)	37 (10.5)	0.27 (0.13-0.53)
PCI – no. (%)	9 (90)	29 (78.4)	
CABG – no. (%)	1 (10)	8 (21.6)	
Major bleeding – no. (%)			
At 1 yr	10/319 (3.1)	2/316 (0.6)	4.95 (1.09-22.43)
At 2 yr	10/292 (3.4)	7/290 (2.4)	1.42 (0.55-3.68)

Discussion and limitations

- Multivessel PCI did not improve all-cause mortality or LV systolic function
- No signal of harm
- Highlights importance of GDMT
- Multiple limitations exist
  - Slightly underpowered
  - Shorter follow-up period than STICH trial
  - Discordance between EF and extent of CAD
  - Lack of objective angiographic data

Updates from ACC 23

- Discussed LV systolic function recovery by viability
  - All viable myocardium: OR 1.22 (95% CI 1.08-1.37)
  - Dysfunctional, but viable myocardium: OR 1.01 (95% CI 0.93-1.11)
  - Scar burden: OR 0.69 (95% CI 0.56-0.84)

  > Baseline scar burden may predict likelihood of LV recovery

- Effect of Alirocumab Added to High-Intensity Statin Therapy on Coronary Atherosclerosis in Patients With Acute Myocardial Infarction.

April 3, 2022

The PACMAN-AMI Randomized Clinical Trial

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NO DISCLOSURES

Background:

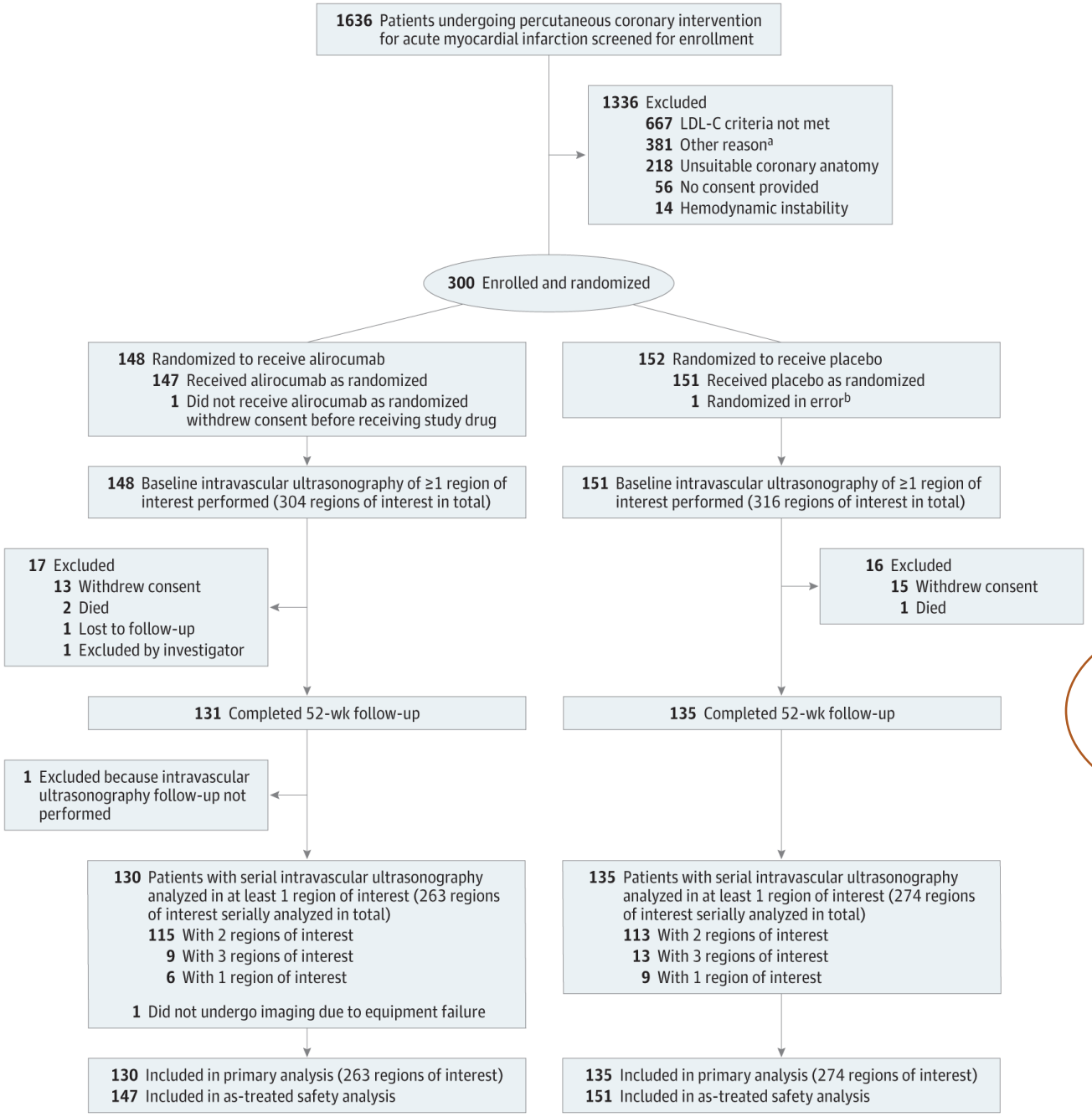
- Coronary plaques with large atheroma burden, lipid rich pool and thin fibrous caps are frequently responsible for acute myocardial infarction (AMI). Intracoronary imaging enables visualization of these high-risk plaque characteristics.

- Among patients with acute myocardial infarction, does the addition of the PCSK-9 inhibitor alirocumab to high-intensity statin therapy affect coronary plaque characteristics in non–infarct-related arteries?

Aim:

- To determine the effect of early administration of the PCSK9 inhibitor alirocumab on coronary atherosclerosis, assessed by serial, 2-vessel, multimodality intracoronary imaging (IVUS, NIRS, and OCT) of the non-infract related arteries in patients presenting with Acute MI.

IVUS, intravascular ultrasound; NIRS, near infrared spectroscopy; OCT, optical coherence tomography



Double blinded, Placebo controlled RCT

300 Patients

EXCLUSION CRITERIA:

- left main or 3-vessel coronary artery disease (CAD)
- History of coronary artery bypass surgery
- severe kidney dysfunction, liver disease, or known statin intolerance.

INCLUSION CRITERIA:

- NSTEMI/STEMI patients with successful PCI of culprit vessel and have 2 non-infarct vessels (stenosis 20-50%) assessed with intracoronary imaging.
- LDL-C ≥ 125 mg/dl (off statin), or ≥ 70 mg/dl (on statin).

Initiated <24 hrs after PCI

Alirocumab 150mg SubQ Biweekly + Rosuvastatin 20mg (N = 148)

Placebo + Rosuvastatin 20mg (N = 152)

Baseline:
IVUS, NIRS, OCT of non-infract vessels.
Baseline LDL-C levels

Follow-up:
Week-52: IVUS, NIRS and OCT of Non-infract vessels
Blood sampling at 4 week and week 52.

Primary outcomes:

Change in mean IVUS-derived percent atheroma volume from baseline to week 52:

Alirocumab: -2.13% vs. Placebo: -0.92%, difference: -1.21%, P<0.001

Table 1. Baseline Characteristics of Patients in a Study of Alirocumab vs Placebo Added to High-Intensity Statin on Coronary Atherosclerosis in Patients With Acute Myocardial Infarction

Characteristics[a]	No. (%)	
	Alirocumab (n = 148)	Placebo (n = 152)[d]
Demographic characteristics		
Age, mean (SD), y	58.4 (10.0)	58.6 (9.4)
Women	24 (16.2)	32 (21.1)
Men	124 (83.8)	119 (78.3)
BMI, mean (SD)	27.3 (4.1)	28.2 (4.5)
Medical history[b]		
Current smoking	77 (52.0)	65 (42.8)
Arterial hypertension	60 (40.5)	70 (46.1)
Diabetes	12 (8.1)	19 (12.5)
Insulin-dependent diabetes	4 (2.7)	4 (2.6)
Previous myocardial infarction	2 (1.4)	5 (3.3)
Previous PCI	2 (1.4)	5 (3.3)
Peripheral arterial disease	2 (1.4)	4 (2.6)
Family history of CAD	44 (29.7)	54 (35.5)
Statin use	17 (11.5)	20 (13.2)
High-intensity statin[c]	11 (7.4)	9 (5.9)
Ezetimibe use	0	1 (0.7)
Other cardiac medications		
ARB	20 (13.5)	21 (13.8)
Antiplatelet therapy	14 (9.5)	17 (11.2)
β-Blocker	12 (8.1)	17 (11.2)
ACE inhibitor	12 (8.1)	12 (7.9)
Type of acute myocardial infarction		
NSTEMI	70 (47.3)	72 (47.4)
STEMI	78 (52.7)	80 (52.6)

Abbreviations: ACE, angiotensin converting enzyme; ARB, angiotensin receptor blocker; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CAD, coronary artery disease; NSTEMI, non-ST-elevation myocardial infarction; PCI, percutaneous coronary intervention.

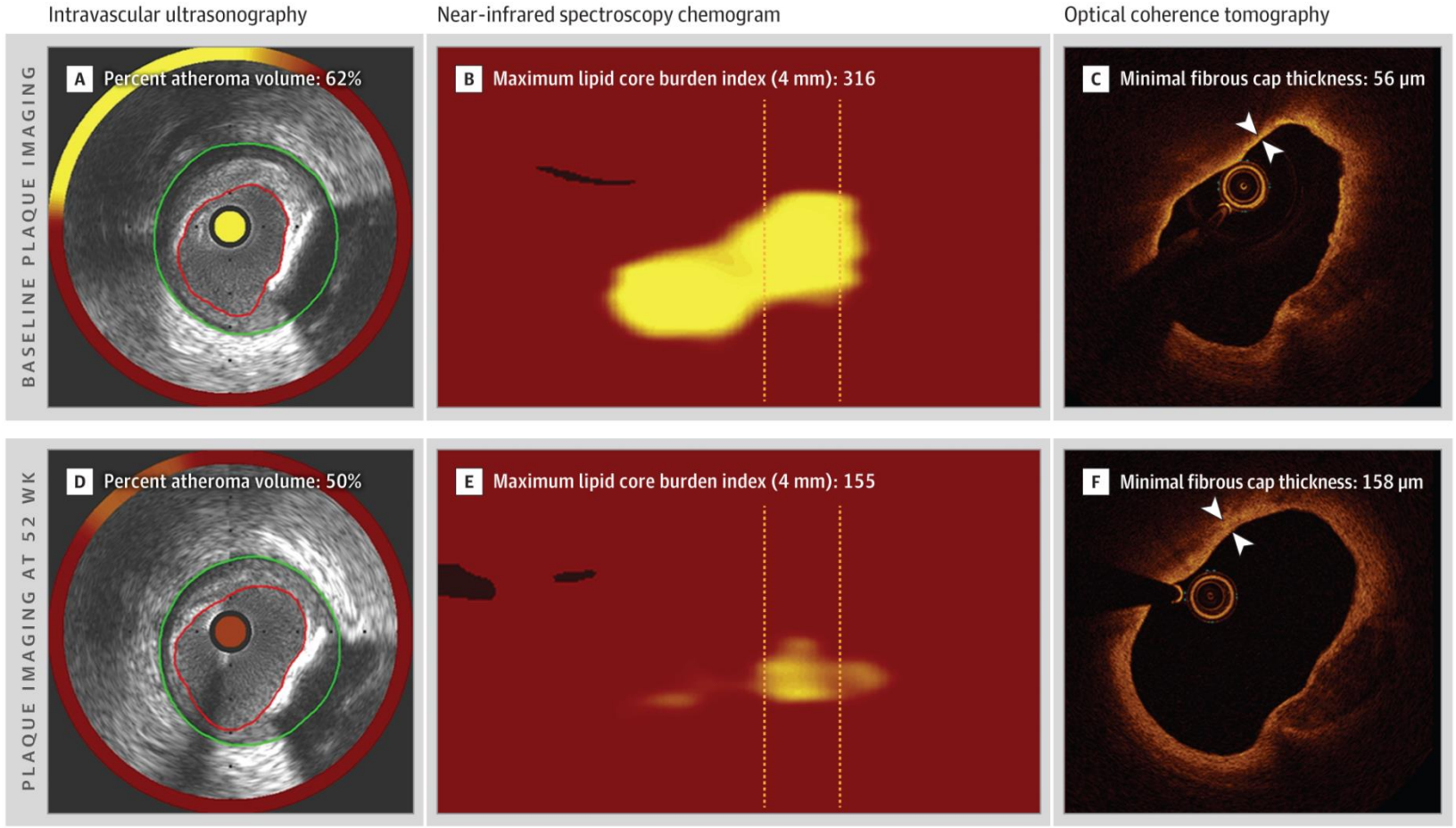
[a] Age and body mass index were normally distributed.

[b] Determined through medical record review.

[c] Atorvastatin ≥40 mg or rosuvastatin ≥20 mg.

[d] In the placebo group, due to exclusion immediately following randomization, 1 patient had missing values in all variables except "Age" and "Type of acute myocardial

Primary Endpoint: Change in **percent atheroma volume** (PAV) by greyscale **IVUS.**
Powered Secondary Endpoint: Change in **maximal lipid-core burden index** ($maxLCBI_{4mm}$) by **NIRS and** Change in **minimal fibrous cap thickness** (FCT_{min}) by **OCT.**



$$\frac{\Sigma(EEM_{CSA} - LumenCSA)}{\Sigma EEM_{CSA}} \times 100$$

$maxLCBI_{4mm}$ = a measure of lipid probability at the 4 mm with maximal lipid load of a vessel imaged by NIRS

FCT_{min} = minimal fibrous cap thickness anywhere in lipid rich plaques imaged by OCT

Table 3. Primary and Secondary Imaging Outcomes Assessed by Intravascular Ultrasonography, Near-Infrared Spectroscopy, and Optical Coherence Tomography[a]

Outcome	Baseline, mean (SD)		Week 52, mean (SD)		Change from baseline to week 52, mean (95% CI)		Difference in change (95% CI)	*P* value[b]
	Alirocumab	Placebo	Alirocumab	Placebo	Alirocumab	Placebo		
Primary								
No. of vessels imaged with intravascular ultrasonography (No. of patients)	263 (130)	274 (135)	263 (130)	274 (135)				
Percent atheroma volume, %	40.91 (8.61)	43.01 (9.84)	38.78 (8.20)	42.09 (9.94)	−2.13 (−2.53 to −1.73)	−0.92 (−1.28 to −0.56)	−1.21 (−1.78 to −0.65)	<.001
Secondary								
Normalized total atheroma volume, mm^3[c]	261.37 (121.42)	250.41 (112.69)	235.25 (107.89)	235.44 (107.72)	−26.12 (−30.07 to −22.17)	−14.97 (−18.14 to −11.80)	−11.55 (−17.44 to −5.66)	<.001
Patients with percent atheroma volume regression, No. (%)[d]			110 (84.6)	89 (65.9)			18.7% (7.8 to 29.6); odds ratio, 2.8 (95% CI, 1.6 to 5.2)	
No. of vessels imaged with near-infrared spectroscopy (No. of patients)	252 (129)	260 (134)	252 (129)	260 (134)				
Maximum lipid core burden index at 4 mm[e]	260.60 (184.49)	276.23 (195.65)	181.17 (171.93)	238.63 (194.51)	−79.42 (−100.39 to −58.46)	−37.60 (−57.40 to −17.80)	−41.24 (−70.71 to −11.77)	.006
Total lipid core burden index	73.16 (76.39)	82.11 (84.19)	43.86 (57.03)	69.73 (82.35)	−29.30 (−37.52 to −21.08)	−12.38 (−20.66 to −4.10)	−17.29 (−28.98 to −5.60)	.004
No. of vessels imaged with optical coherence tomography (No. of patients)	245 (122)	270 (133)	245 (122)	270 (133)				
Minimal fibrous cap thickness, μm[e]	106.97 (70.19) [173 vessels (105 patients)][f]	110.53 (84.98) [197 vessels (116 patients)][f]	169.64 (97.78) [173 vessels (105 patients)][f]	143.72 (84.03) [197 vessels (116 patients)][f]	62.67 (48.84 to 76.50)	33.19 (22.22 to 44.16)	29.65 (11.75 to 47.55)	.001
Mean fibrous cap thickness, μm	328.74 (97.25) [173 vessels (105 patients)][f]	328.91 (112.58) [197 vessels (116 patients)][f]	419.69 (108.79) [173 vessels (105 patients)][f]	391.27 (100.29) [197 vessels (116 patients)][f]	90.95 (72.96 to 108.94) [173 vessels (105 patients)]	62.36 (46.23 to 78.50) [197 vessels (116 patients)]	28.22 (3.21 to 53.23)	.03
Mean angular extension of macrophages, °	58.54 (20.81) [232 vessels (121 patients)][g]	57.57 (22.51) [251 vessels (131 patients)][g]	32.57 (21.01) [232 vessels (121 patients)][g]	41.62 (22.25) [251 vessels (131 patients)][g]	−25.98 (−29.35 to −22.61) [232 vessels (121 patients)]	−15.95 (−19.02 to −12.87) [251 vessels (131 patients)]	−10.08 (−14.72 to −5.43)	<.001

[a] Analyses were conducted on vessel-level values at 2 time points (baseline and week 52) using repeated-measures mixed-effect models accounting for the multiple vessels per patient. For continuous variables, values are vessel-level mean (SD), or vessel-level mean change (95% CI). Difference in change are marginal differences computed from mixed-effect models. For the categorical variable "Patients with PAV regression," values are count (%) and the corresponding odds ratio with associated 95% CIs.

[b] *P* value for between-group comparison.

[c] Normalized total atheroma volume was calculated as mean atheroma area multiplied by the median length of the regions of interest.

[d] Patients with PAV regression are those with negative change in PAV from baseline averaged across vessels.

[e] Powered secondary end point.

[f] No. of imaged vessels (No. of patients) with fibroatheromas.

[g] No. of imaged vessels (No. of patients) with macrophages.

Prespecified Adverse Events and Safety Findings:

	Alirocumab (n=147*)	Placebo (n=151*)
Any adverse event	104 (71%)	110 (73%)
Serious adverse event	47 (32%)	50 (33%)
Adverse events resulting in study drug discontinuation	2 (1.4%)	0 (0.0%)
Adverse events of special interest		
Local injection site reaction	9 (6.1%)	5 (3.3%)
General allergic reaction	5 (3.4%)	0 (0.0%)
Neurocognitive event	3 (2.0%)	0 (0.0%)
ALT increase > 3x ULN	1 (0.7%)	0 (0.0%)

* Includes patients who received at least one dose of the study drug

Conclusions:

- Compared with placebo, administration of alirocumab 150 mg biweekly within 24 hours after PCI on top of high-intensity statin therapy resulted in greater decrease in percent atheroma volume, larger reduction in lipid burden and higher increase in minimal fibrous cap thickness of non-culprit vessel at 52 weeks. These findings indicate incremental coronary plaque regression, greater reduction in plaque burden and plaque stabilization.

- All patients were also on high-dose rosuvastatin. LDL-C levels were reduced by nearly 85% with alirocumab plus rosuvastatin compared with 51% with rosuvastatin alone. Clinical events were low. These results favor early initiation of very intensive LDL-C lowering in the setting of acute MI.

- This provides further data regarding the utility of PCSK9 inhibitors for secondary prevention in high-risk patients (such as those with AMI) as combination therapy with high-dose statin therapy.

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