CLEAR SYNERGY (OASIS 9)

CoLchicine and spironolactonE in patients with myocARdial infarction/SYNERGY Stent Registry – Organization to Assess Strategies of Ischemic Syndromes 9

Sanjit Jolly, on behalf of CLEAR investigators

Population Health Research Institute
HEALTH THROUGH KNOWLEDGE

Hamilton Health Sciences

McMaster University HEALTH SCIENCES

Disclosures

- Grant support from Boston Scientific
- Grant support from Canadian Institutes of Health Research (CIHR)

NATURE INSIGHT IN THIS ISSUE: THE EARLY UNIVERSE

27 April 2006 | www.nature.com/nature | $10

THE INTERNATIONAL WEEKLY JOURNAL OF SCIENCE

nature

RECORD RAINFALL FIGURES
Human fingerprints on the hydrological cycle

VIRTUAL ARCHAEOLOGY
Good science or good game?

BIRDSONG GRAMMAR
It's almost human

AIMING FOR THE HEART

C-reactive protein as a target for cardioprotective drugs

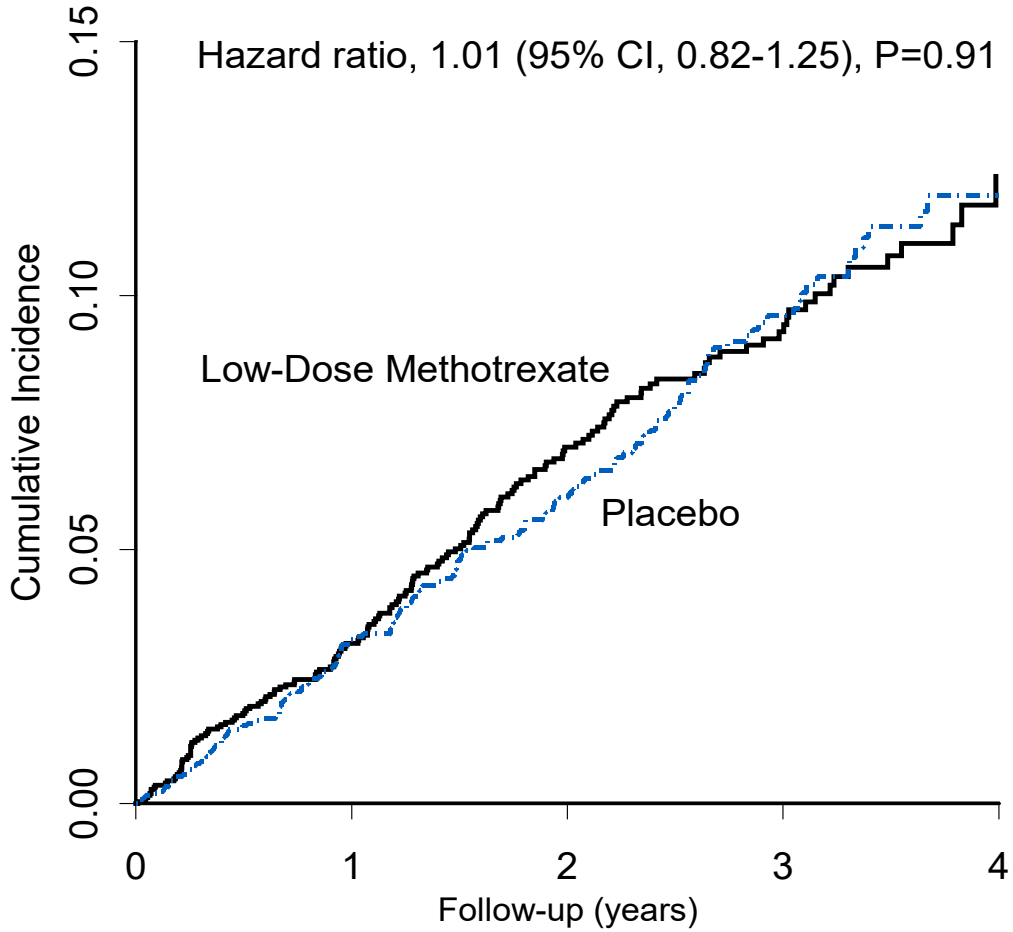
TECHNOLOGY FEATURE
Gene expression

$10.00US $12.99CAN
17>
0 71486 03070 6


TRY
FAIL
SUCCESS

Cardiovascular Inflammation Reduction Trial (CIRT)

Methotrexate did not reduce MACE



MACE
N (Incidence Rate Per 100 person years)

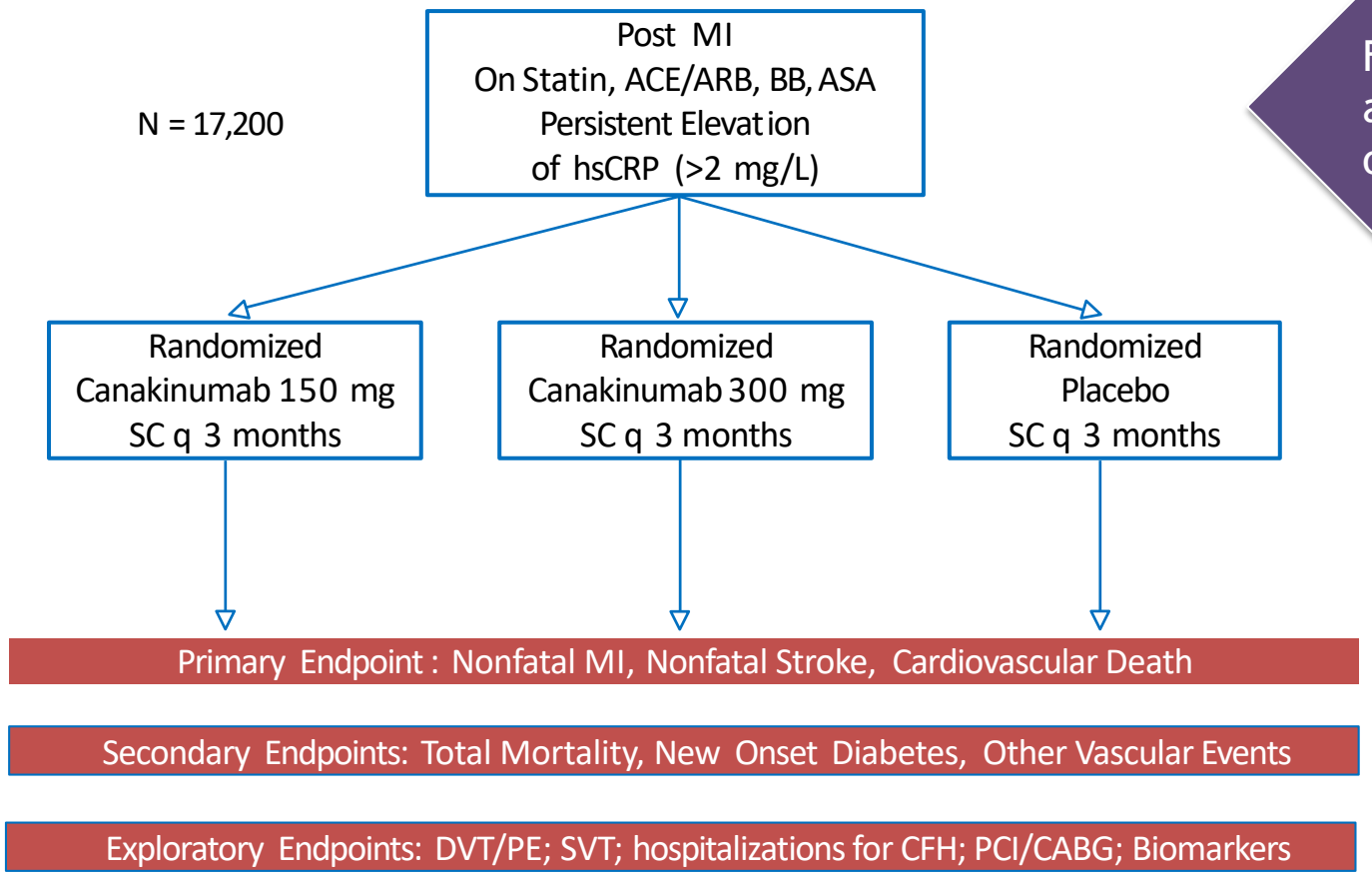
170 (3.46) LD-MTX
167 (3.43) Placebo

No. at risk:

Low-Dose Methotrexate	2391	1771	1193	621	157
Placebo	2395	1745	1194	612	148

Success

Canakinumab Anti-inflammatory Thrombosis Outcomes Study (CANTOS)



First trial that showed that an IL-1 inhibitor improved outcomes post-MI

Trial Rationale -Canakinumab

Anti-inflammatory Thrombosis Outcomes Study (CANTOS)

Primary Clinical Outcome Effects on MACE a

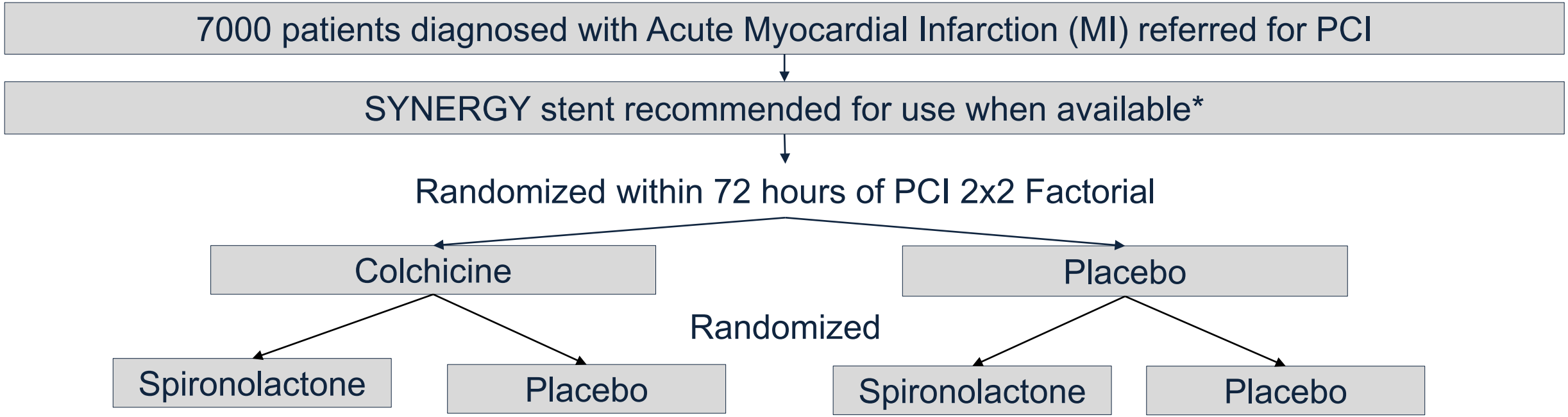
		Canakinumab SC q 3 months			
	Placebo (N=3347)	50 mg (N=2170)	150 mg (N=2284)	300 mg (N=2263)	P-trend
Primary Endpoint CV death, MI or stroke (per 100 person years) HR 95%CI P	4.5 1.0 (referent) (referent)	4.1 0.93 0.80-1.07 0.30	3.9 0.85 0.74-0.98 0.021*	3.9 0.86 0.75-0.99 0.031	0.020
Secondary Endpoint Primary + Unstable angina requiring revasc (per 100 person years) HR 95%CI P	5.1 1.00 (referent) (referent)	4.6 0.90 0.78-1.03 0.11	4.3 0.83 0.73-0.95 0.005*	4.3 0.83 0.72-0.94 0.004	0.003

*Statistically significant, adjusted for multiplicity, in accordance with the pre-specified closed-testing procedures

Ridker, ESC, 2017

- The higher doses reduced CV death, MI, or stroke by over 15% during follow-up
- When unstable angina requiring revasc was added, there was nearly a 20% reduction

CLEAR SYNERGY OASIS 9 Trial

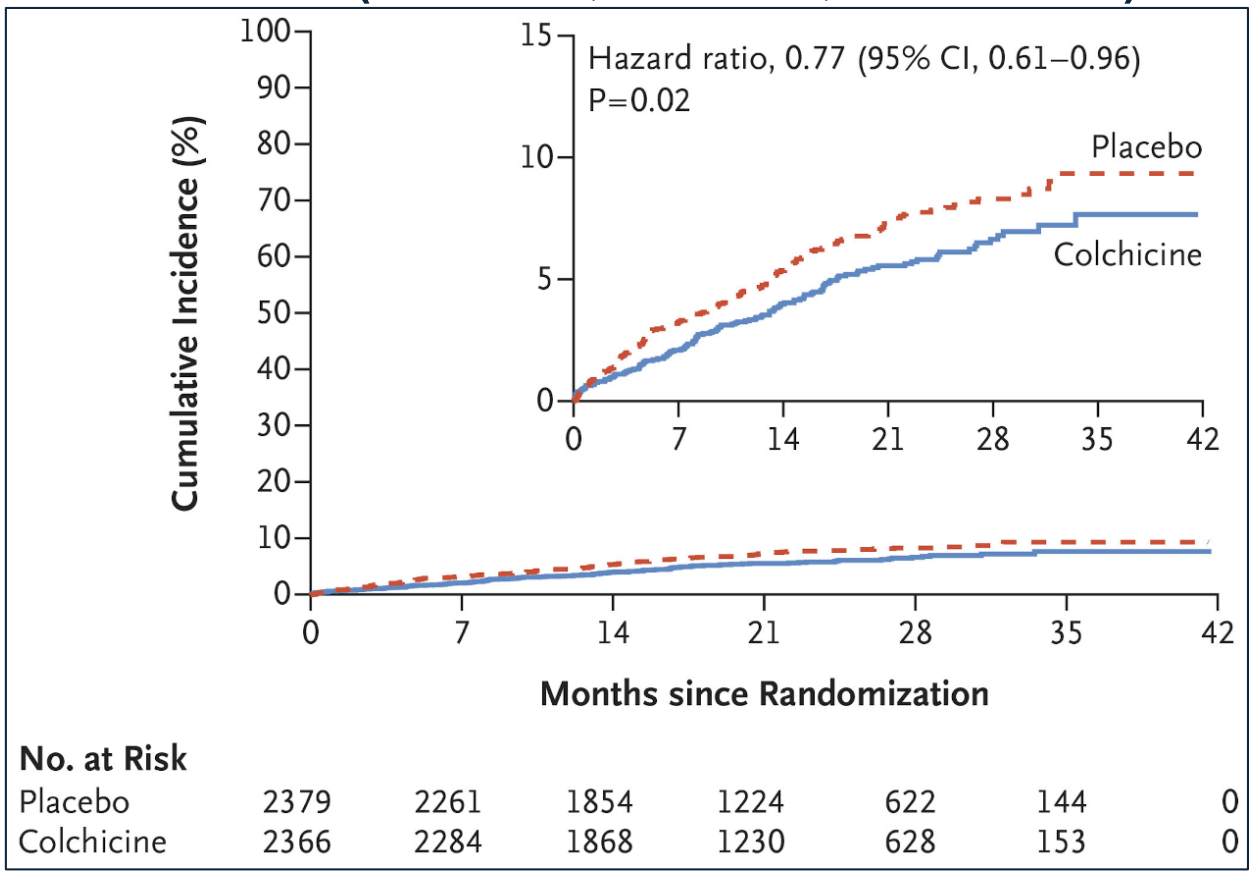


Primary Outcome

Colchicine vs. placebo: Composite of CV death, MI, stroke or IDR

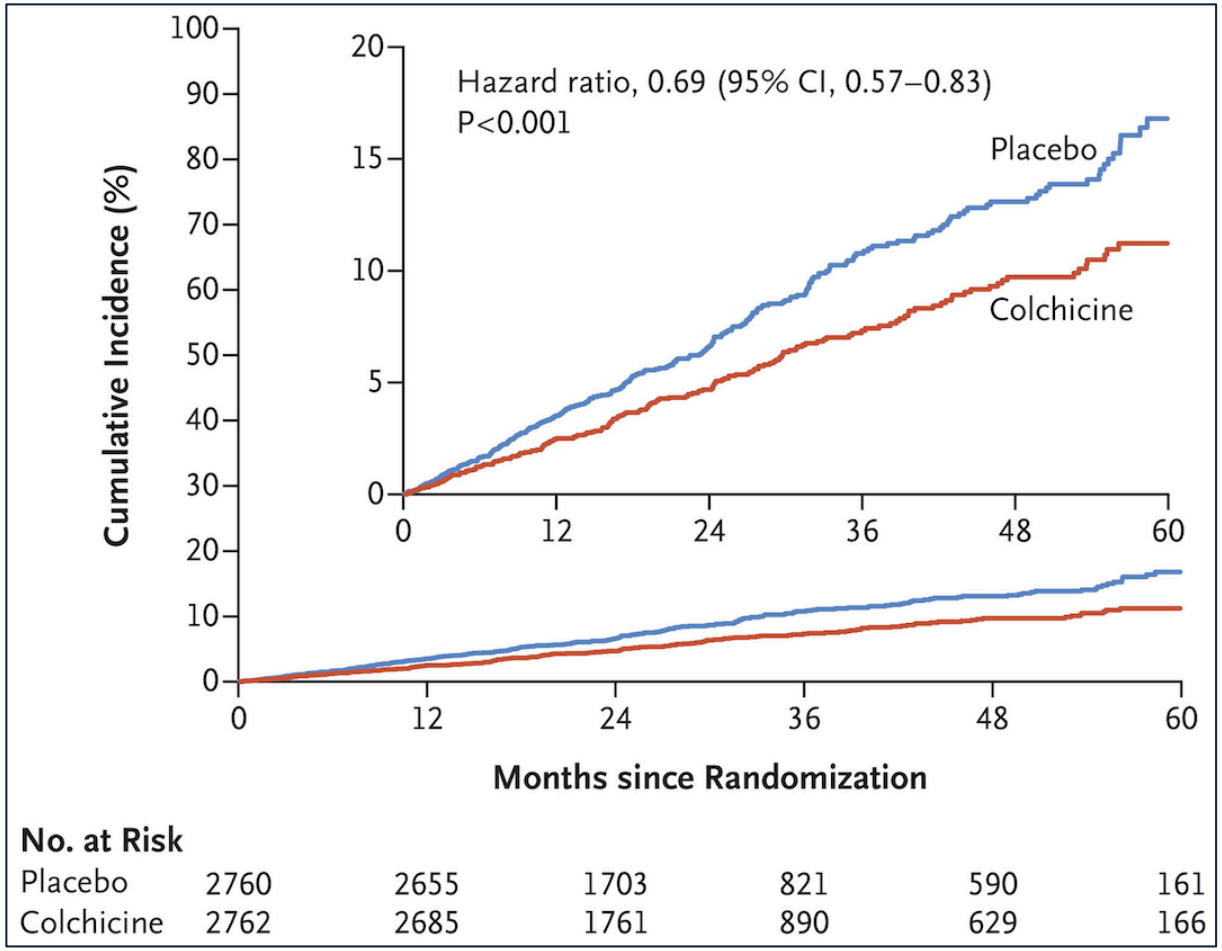
Background: Acute and Chronic CAD

COLCOT (N = 4745, MACE +, 301 events)



No. at Risk							
Placebo	2379	2261	1854	1224	622	144	0
Colchicine	2366	2284	1868	1230	628	153	0

LODOCO2 (N = 5522, MACE +, 451 events)



No. at Risk						
Placebo	2760	2655	1703	821	590	161
Colchicine	2762	2685	1761	890	629	166

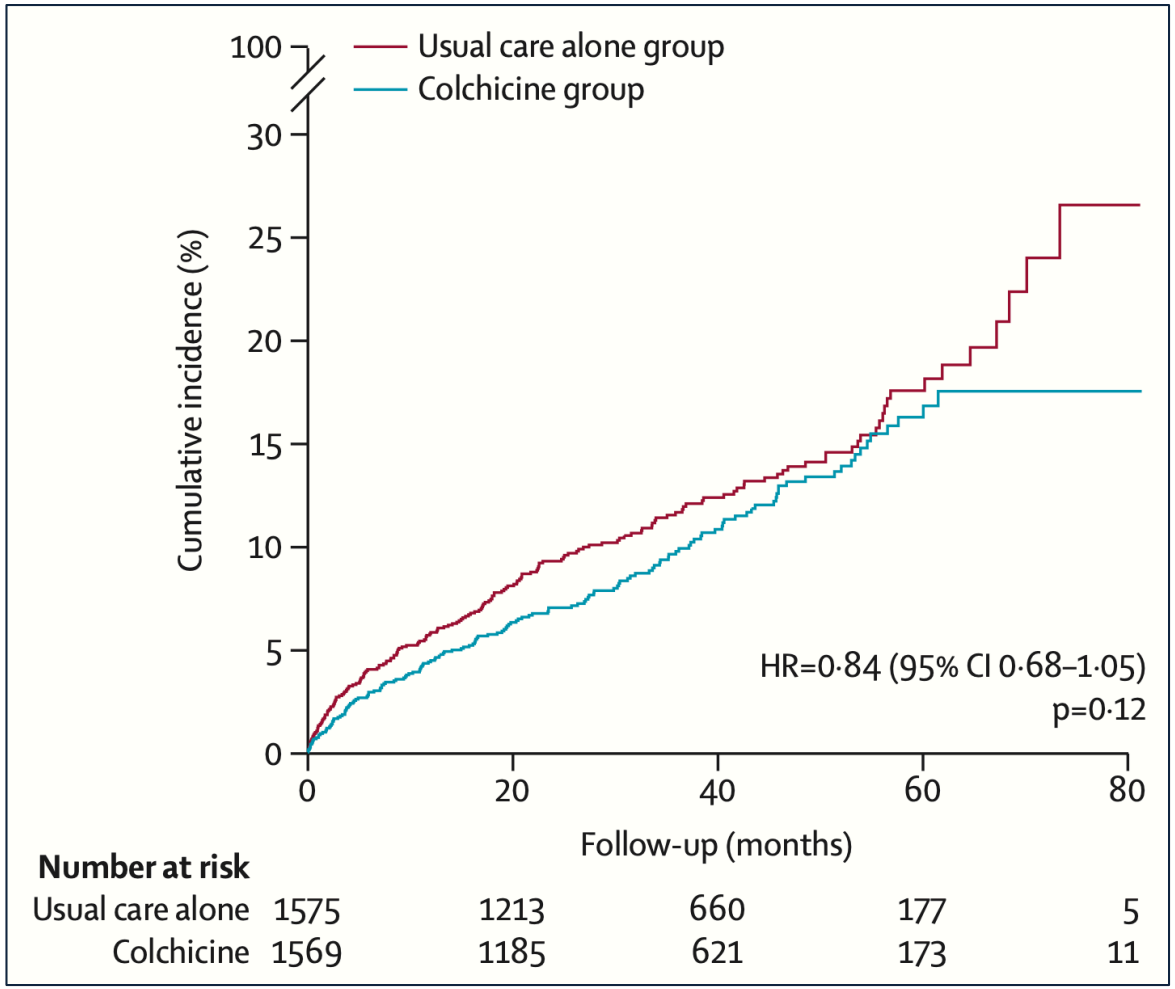
Population Health Research Institute
HEALTH THROUGH KNOWLEDGE

www.phri.ca

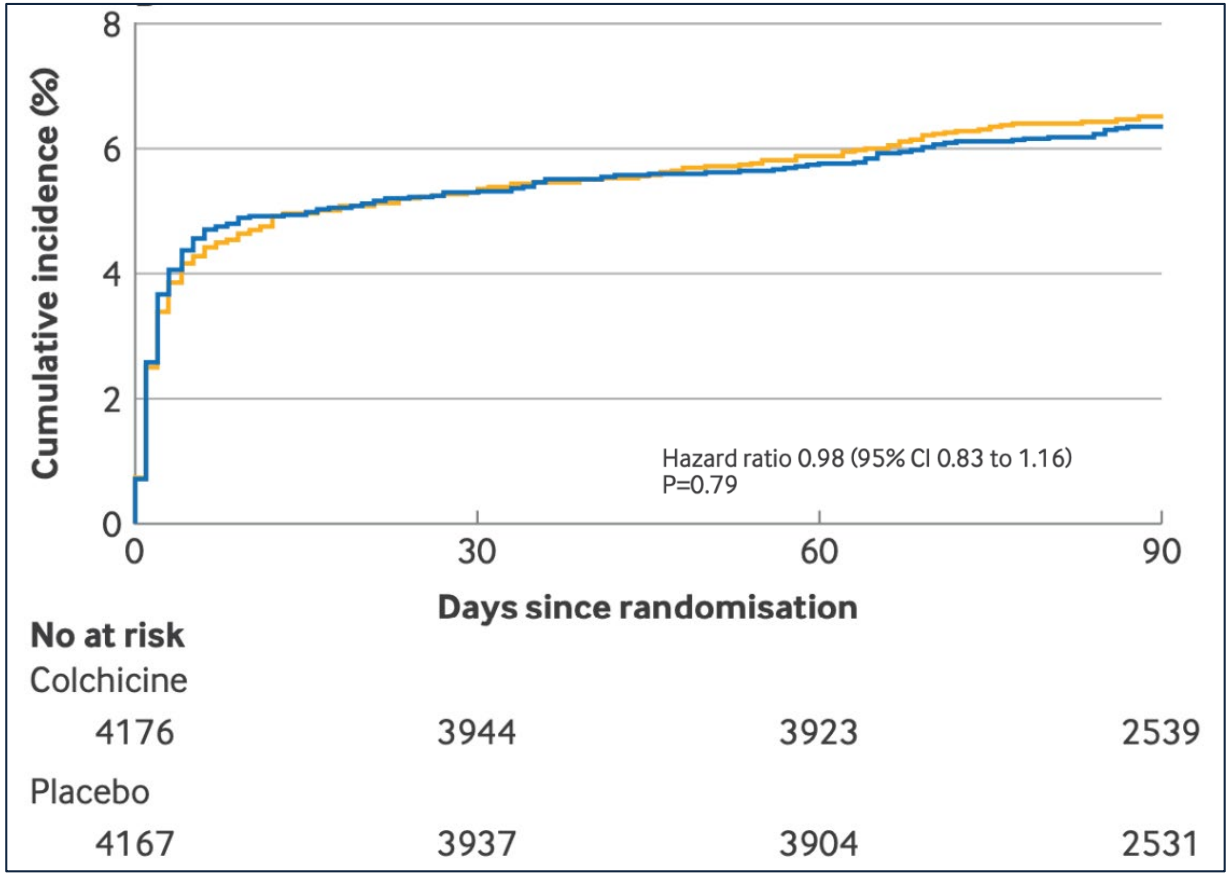
Tardif JC et al. NEJM 2019.
Nidorf M et al. NEJM 2020.

Background: Cerebrovascular Disease

CONVINCE (N = 3154, MACE+, 338 events)



CHANCE3 (N = 8343, all stroke, 534 events)



CV death, stroke or MI: HR 0.96 (95%CI 0.82 – 1.13)

Population Health Research Institute
HEALTH THROUGH KNOWLEDGE

www.phri.ca

Kelly P et al. Lancet 2024.
Li J et al. BMJ 2024.

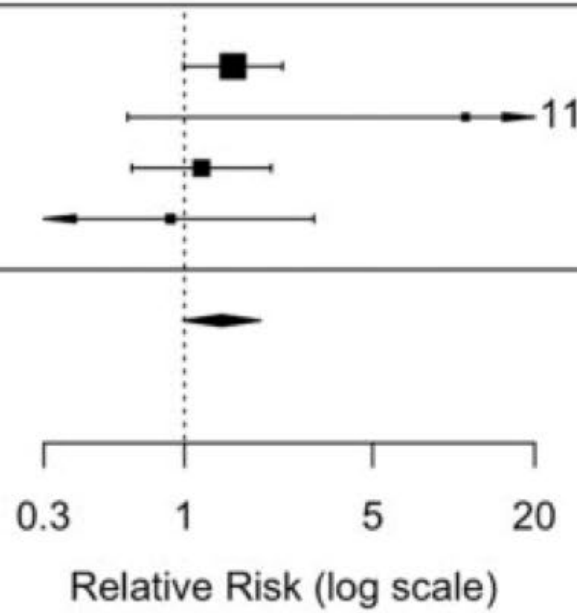
Does Colchicine Increase Non-CV Death?

Meta-analysis

Non-cardiovascular death

Acronym or author	Colchicine Events/total (%)	Comparator Events/total (%)	Weight (GIV)	Relative Risk (95% CI)
LoDoCo2, 2020	53/2762 (1.9%)	35/2760 (1.3%)	60.6 %	1.51 (0.99 to 2.31)
COPS, 2020	5/396 (1.3%)	0/399 (0.0%)	1.3 %	11.08 (0.61 to 199.77)
COLCOT, 2019	23/2366 (1.0%)	20/2379 (0.8%)	30.8 %	1.16 (0.64 to 2.10)
LoDoCo, 2013	5/282 (1.8%)	5/250 (2.0%)	7.3 %	0.89 (0.26 to 3.03)
Totals:	86/5806	60/5788	100 %	1.38 (0.99 to 1.92)

I^2 = 0.4%. Random effects model for overall effect, p = 0.060



Fiolet ATL et al. EHJ 2021

CLEAR SYNERGY

Rationale

- CLEAR started before the results of COLCOT
- Larger confirmatory trial with more power
- Replications of prior results are important for Class 1 indications in guidelines

Primary Objective

In patients with STEMI or large NSTEMI:

Does routine low-dose colchicine, compared to placebo, reduce the composite of CV death, myocardial infarction, stroke, or ischemia driven revascularization?

Baseline Characteristics

	Colchicine N=3528	Placebo N=3534
Mean Age	60.6	60.7
Female	20.5%	20.2%
STEMI	95.3%	94.8%
NSTEMI	4.7%	5.2%
Diabetes	18.7%	18.3%
Prior MI	8.8%	9.2%

Medications at Discharge

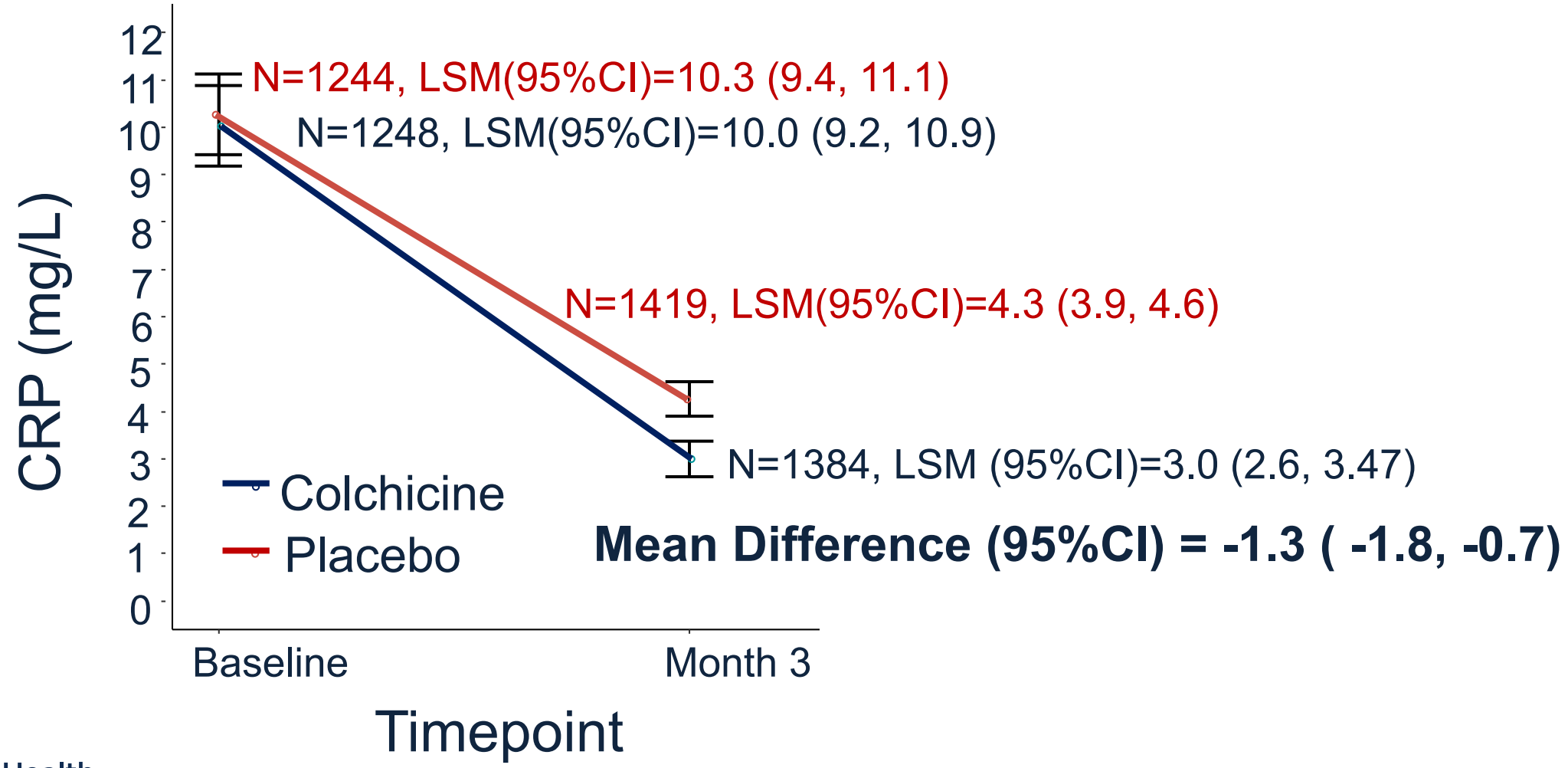
	Colchicine N=3528	Placebo N=3534
Aspirin	97.2%	96.3%
Clopidogrel	41.9%	42.4%
Ticagrelor	45.7%	44.5%
Prasugrel	10.8%	11.7%
ACE or ARB	77.9%	78.3%
Statin	96.6%	96.7%
SLGT2 inhibitor	3.1%	2.9%

CLEAR SYNERGY

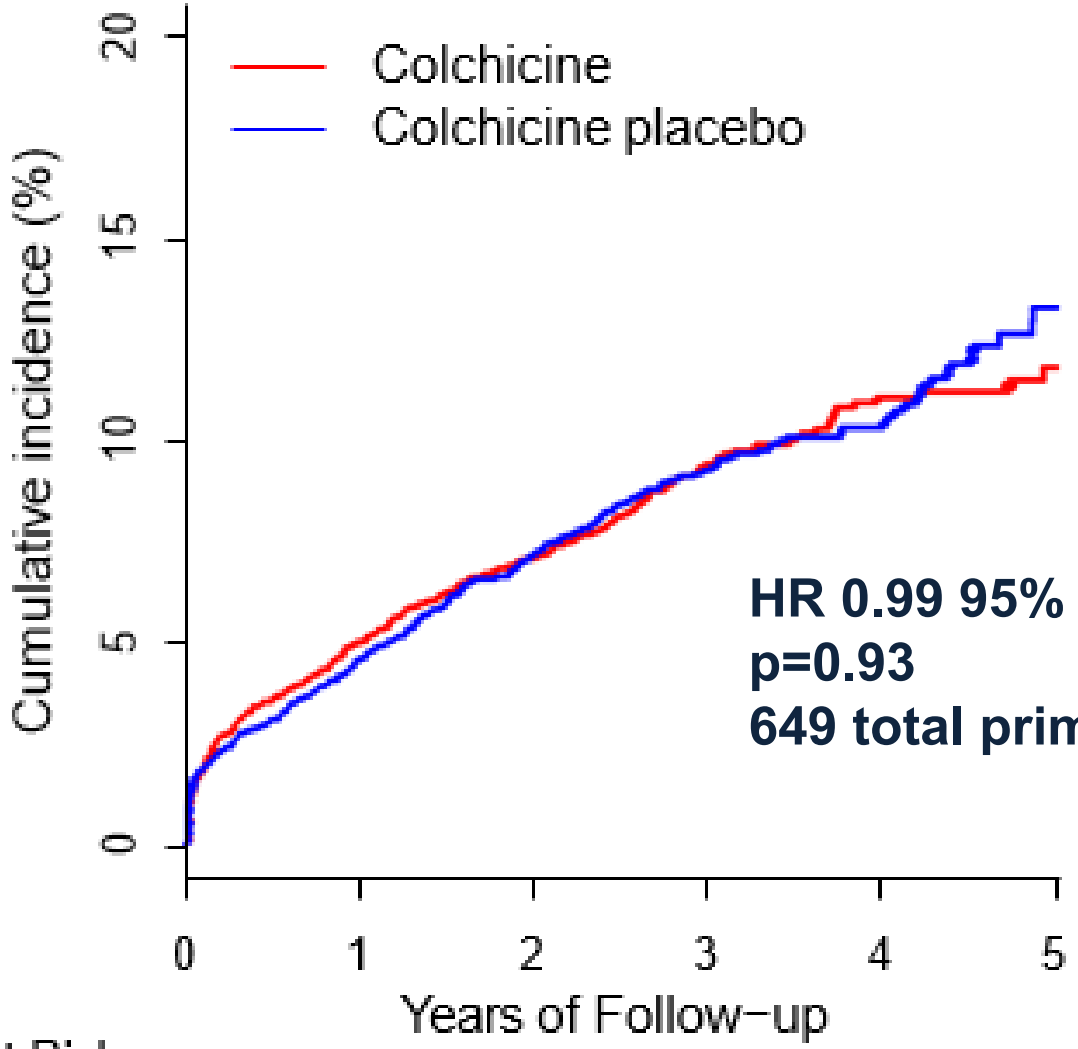
Initial PCI Procedure

	Colchicine N=3528	Placebo N=3534
Bare metal stent	0.3%	0.2%
Drug-eluting stent	96.3%	95.8%
Angioplasty only	3.0%	3.4%
Number of stents (median)	1.0	1.0
Stent length (mm) mean	23.8	23.8
Stent diameter (mm) mean	3.2	3.1
Multivessel coronary disease	49.2%	49.3%

CRP was Reduced with Colchicine



Primary Outcome of CV Death, MI, Stroke or Ischemia Driven Revascularization



HR 0.99 95% CI 0.85-1.16
p=0.93
649 total primary outcome events

Population Health Research Institute
HEALTH THROUGH KNOWLEDGE

www.phri.ca

CLEAR SYNERGY

Results – Intention to Treat

	Colchicine (N=3528) (%)	Placebo (N=3534) (%)	HR	95% CI	p
CV death, MI, stroke or ischemia driven revascularization	9.1%	9.3%	0.99	0.85-1.16	0.93
CV death	3.3%	3.2%	1.03	0.80-1.34	
MI	2.9%	3.1%	0.88	0.66-1.17	
Stroke	1.4%	1.2%	1.15	0.72-1.84	
Ischemia driven revascularization	4.6%	4.7%	1.01	0.81-1.17	
CV death, MI or stroke	6.8%	7.1%	0.98	0.82-1.17	
All cause death	4.6%	5.1%	0.90	0.73-1.12	
Non-CV death	1.3%	1.9%	0.68	0.46-0.99	

CLEAR SYNERGY

Results – On Treatment

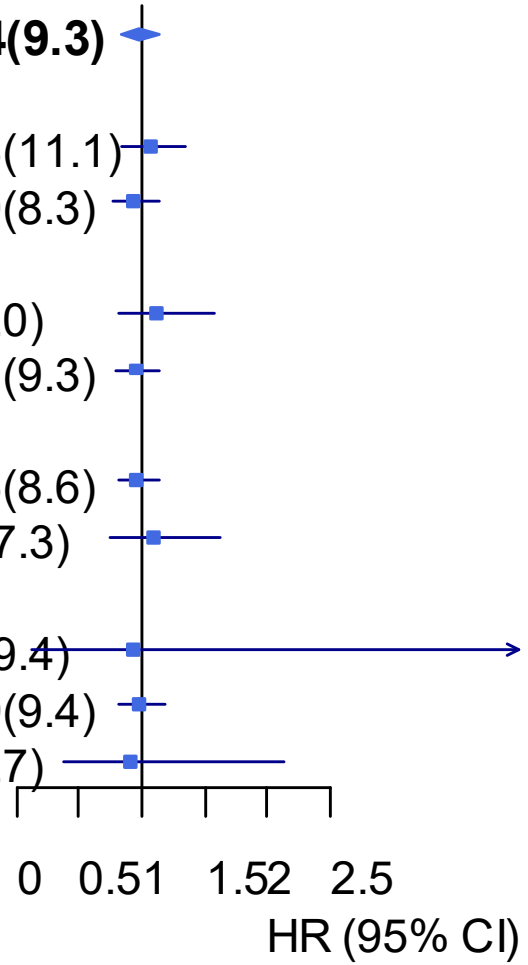
	Colchicine (N=3488) (%)	Placebo (N=3492) (%)	HR	95% CI	p
CV death, MI, stroke or ischemia driven revascularization	7.5%	7.5%	0.99	0.85-1.16	0.93
CV death	2.7%	2.5%	1.04	0.80-1.35	
MI	2.3%	2.4%	0.89	0.67-1.18	
Stroke	1.1%	1.0%	1.09	0.68-1.75	
Ischemia driven revascularization	3.9%	3.8%	1.03	0.82-1.29	
CV death, MI or stroke	5.5%	5.7%	0.97	0.81-1.16	
All cause death	3.4%	3.8%	0.90	0.70-1.15	
Non-CV death	0.7%	1.3%	0.71	0.49-1.04	

Adverse Events

	Colchicine (N=3528) (%)	Placebo (N=3534) (%)	p
Serious Adverse Events	6.7%	7.4%	0.22
Adverse Events	31.9%	31.7%	0.86
Serious Infection	2.5%	2.9%	0.85
Diarrhea	10.2%	6.6%	<0.001

Forest plot of Primary Outcome in pre-specified subgroups (I)

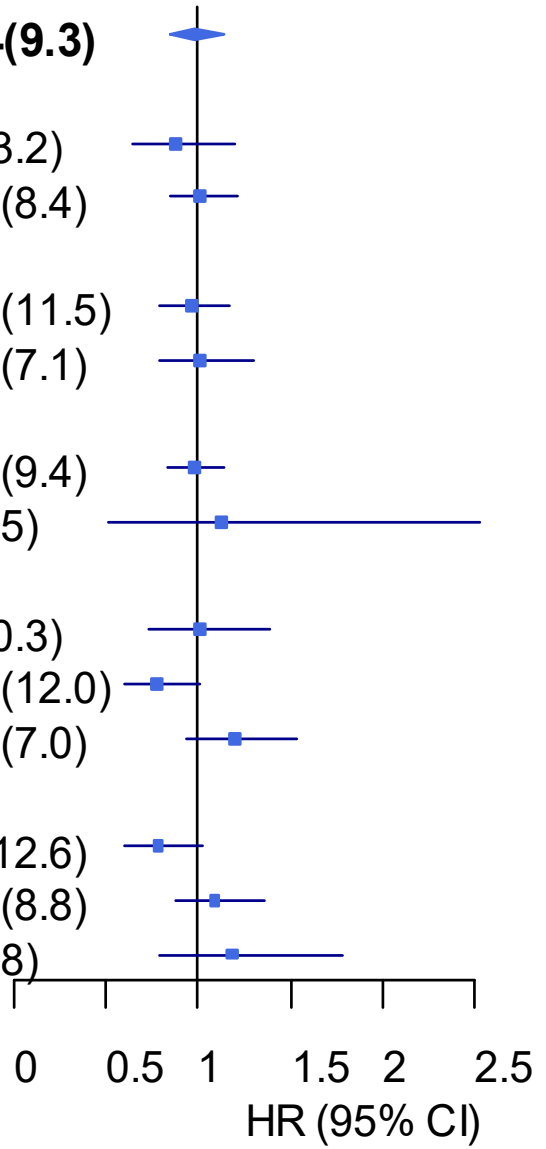
	Colchicine Count/Total (%)	Placebo Count/Total (%)	Hazard Ratio (95% CI)	P value f Interacti
Outcomes				
CVD/MI/Stroke/Revas	**322/3528(9.1)**	**327/3534(9.3)**	**0.98 (0.84-1.15)**	
Age				**0.418**
Age>= 65	140/1185(11.8)	135/1214(11.1)	1.06 (0.84-1.34)	
Age<65	182/2343(7.8)	192/2320(8.3)	0.93 (0.76-1.14)	
Gender				**0.384**
Female	72/725(9.9)	64/713(9.0)	1.12 (0.80-1.57)	
Male	250/2803(8.9)	263/2821(9.3)	0.95 (0.80-1.13)	
GFR level				**0.5**
GFR>=60	266/3237(8.2)	279/3256(8.6)	0.96 (0.81-1.13)	
GFR<60	56/291(19.2)	48/278(17.3)	1.10 (0.75-1.62)	
Region				**0.951**
North America	96/1010(9.5)	95/1012(9.4)	0.93 (0.1*1-7.66)	
Europe	216/2356(9.2)	221/2359(9.4)	0.97 (0.81-1.17)	
Other region	10/162(6.2)	11/163(6.7)	0.90 (0.38-2.13)	



*HR at 1 year using a time-dependent Cox Model to account for the PH assumption violation.

Forest plot of Primary Outcome in pre-specified subgroups (II)

	Colchicine Count/Total (%)	Placebo Count/Total (%)	Hazard Ratio (95% CI)	P value for Interaction
Outcomes				
CVD/MI/Stroke/Revas	**322/3528(9.1)**	**327/3534(9.3)**	**0.98 (0.84-1.15)**	
Diabetes				**0.432**
Yes	79/658(12.0)	85/645(13.2)	0.88 (0.65-1.20)	
No	243/2870(8.5)	242/2889(8.4)	1.01 (0.85-1.21)	
Single/Multi-vessel status				**0.745**
Multi	192/1735(11.1)	200/1742(11.5)	0.97 (0.79-1.18)	
Single	130/1793(7.3)	127/1792(7.1)	1.02 (0.80-1.30)	
MI Type				**0.741**
STEMI	310/3363(9.2)	315/3350(9.4)	0.98 (0.84-1.15)	
NSTEMI	12/165(7.3)	12/184(6.5)	1.13 (0.51-2.52)	
Dosing				**0.054**
Once daily (<70Kg)	74/721(10.3)	72/697(10.3)	1.01 (0.73-1.40)	
Twice daily (>=70kg)	110/1161(9.5)	136/1137(12.0)	0.78 (0.61-1.00)	
Once daily (>=70kg)	138/1646(8.4)	119/1700(7.0)	1.20 (0.94-1.54)	
Covid Phase				**0.098**
Pre-covid	100/998(10.0)	125/991(12.6)	0.78 (0.60-1.02)	
During covid	170/1773(9.6)	159/1799(8.8)	1.09 (0.88-1.35)	
Post- covid	52/757(6.9)	43/744(5.8)	1.19 (0.79-1.78)	



Population Health Research Institute
HEALTH THROUGH KNOWLEDGE

www.phri.ca

Conclusions

- Acute and long term colchicine did not reduce composite of CV death, MI, stroke or ischemia driven revascularization
- Colchicine was associated with an increase in diarrhea
- CLEAR is the largest trial of colchicine in acute MI with substantially more events than prior trials

Implications

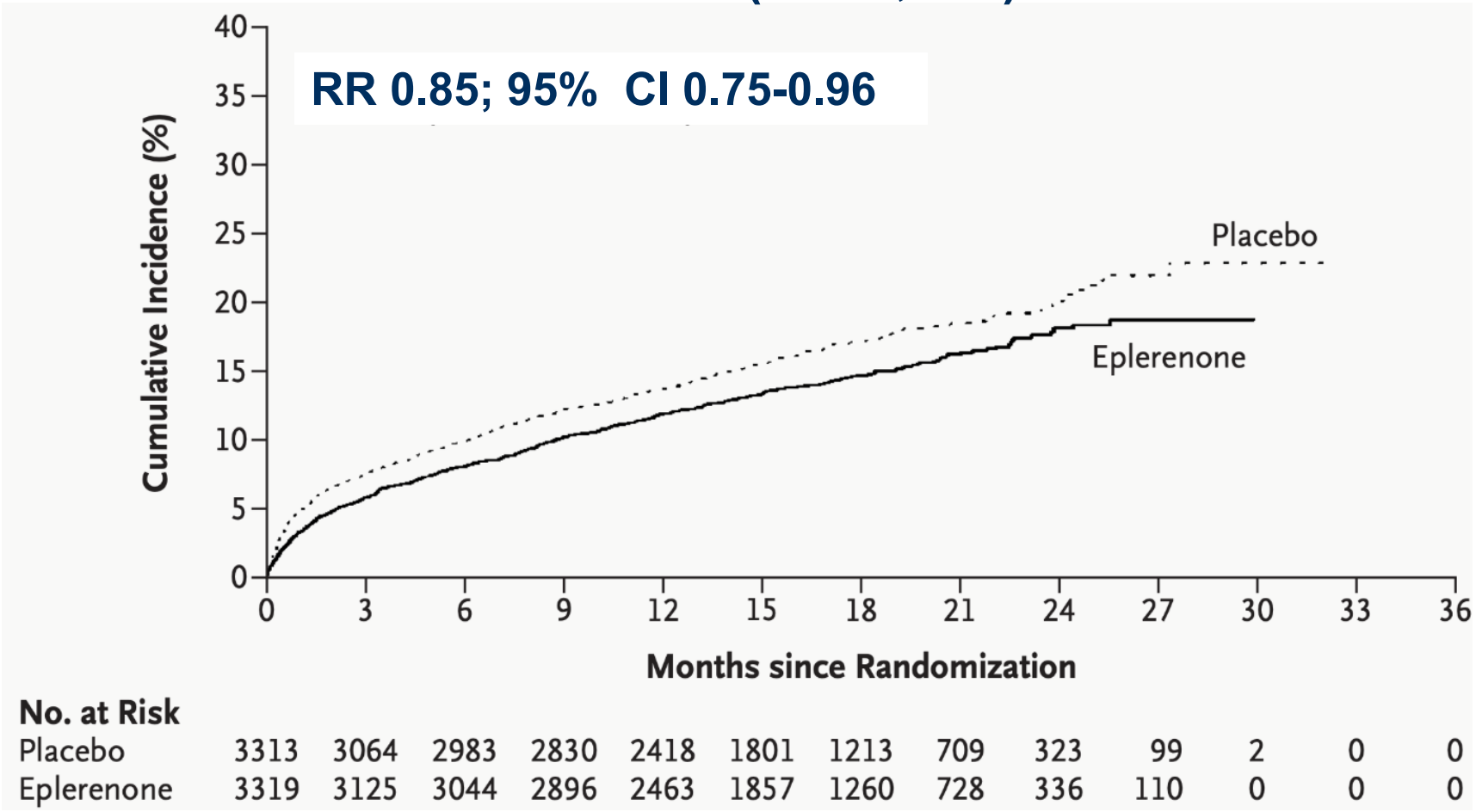
- The role of colchicine post myocardial infarction long term is uncertain

Discussion

Spironolactone Factorial

In Patients With MI and CHF, Eplerenone Beneficial

EPHESUS (N = 6,632)



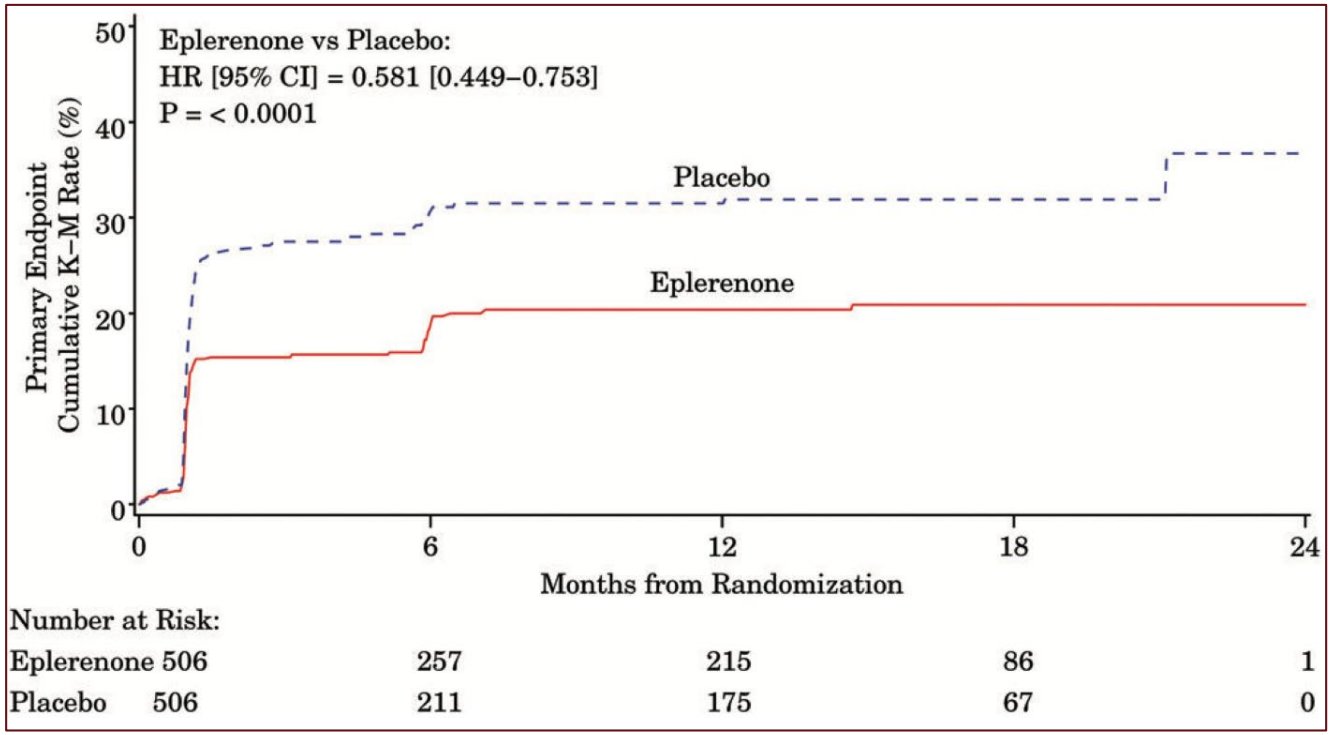
No. at Risk													
Placebo	3313	3064	2983	2830	2418	1801	1213	709	323	99	2	0	0
Eplerenone	3319	3125	3044	2896	2463	1857	1260	728	336	110	0	0	0

All-cause mortality
(1,032 events)

Pitt B et al. NEJM 2019.

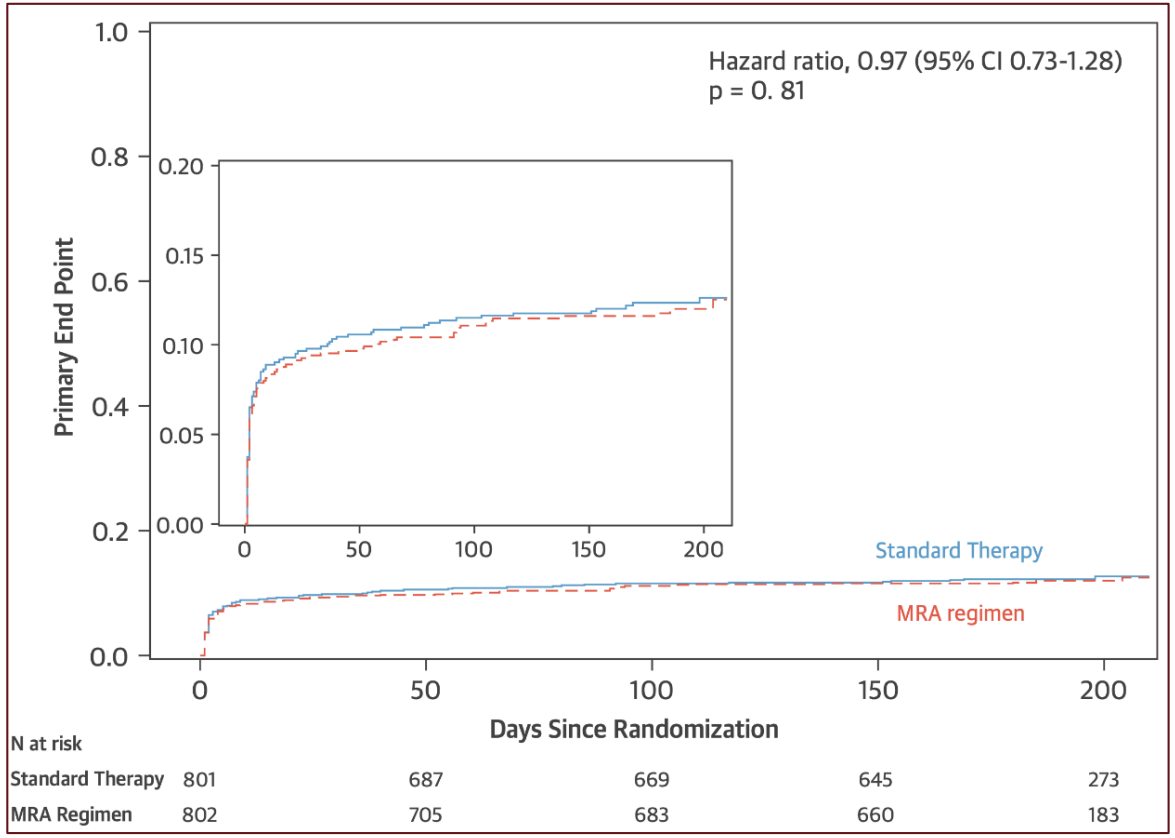
Unclear if Routine MRA Beneficial Post-MI

REMINDER (N = 1,012)



CV death, HF, VT/VF, EF < 40% or elevated BNP (241 events)

ALBATROSS (N = 1,603)



Death, cardiac arrest, VT/VF, ICD implantation, HF (193 events)

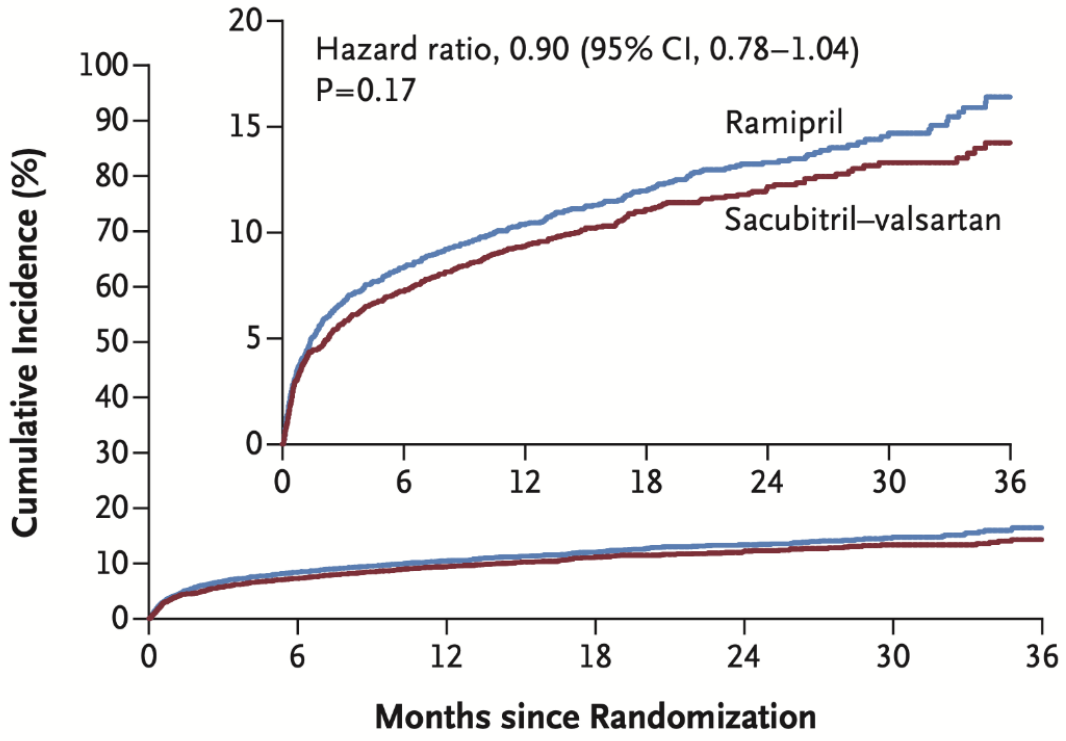
Population Health Research Institute
HEALTH THROUGH KNOWLEDGE

Montalescot G et al. EHJ 2014.
Beygui F et al. JACC 2016.

Hamilton Health Sciences
McMaster University HEALTH SCIENCES

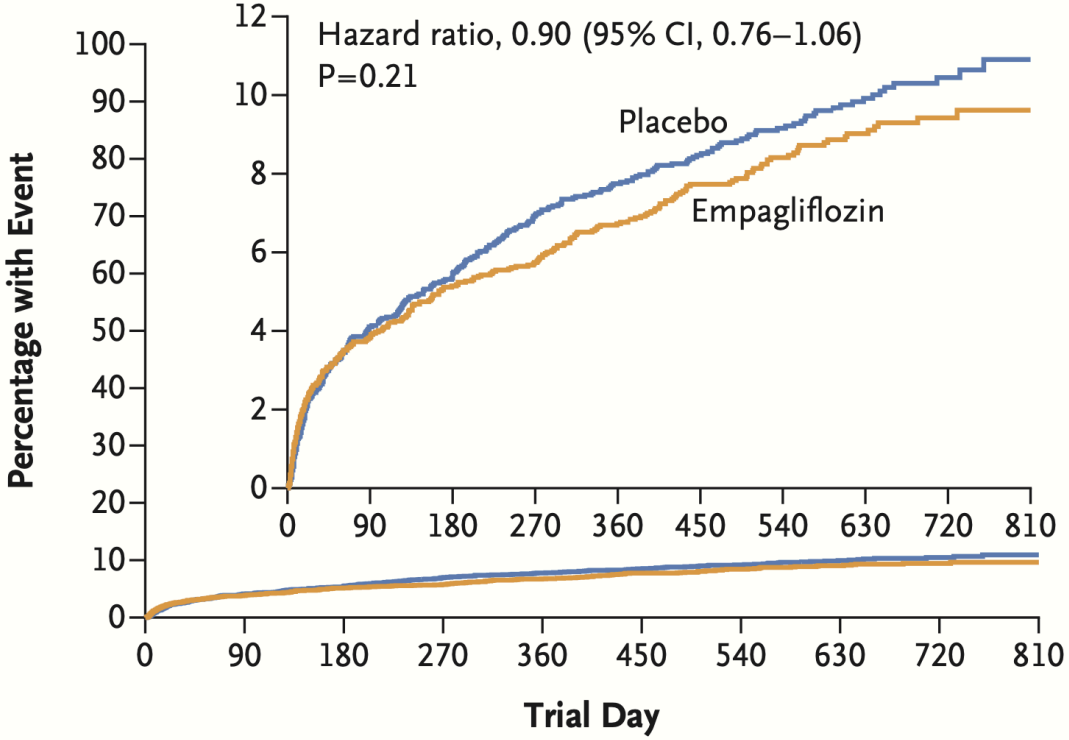
Background

PARADISE-MI (N = 5661, CV death or HF)



No. at Risk							
Ramipril	2831	2577	2318	1725	1091	570	278
Sacubitril–valsartan	2830	2614	2342	1732	1101	568	280

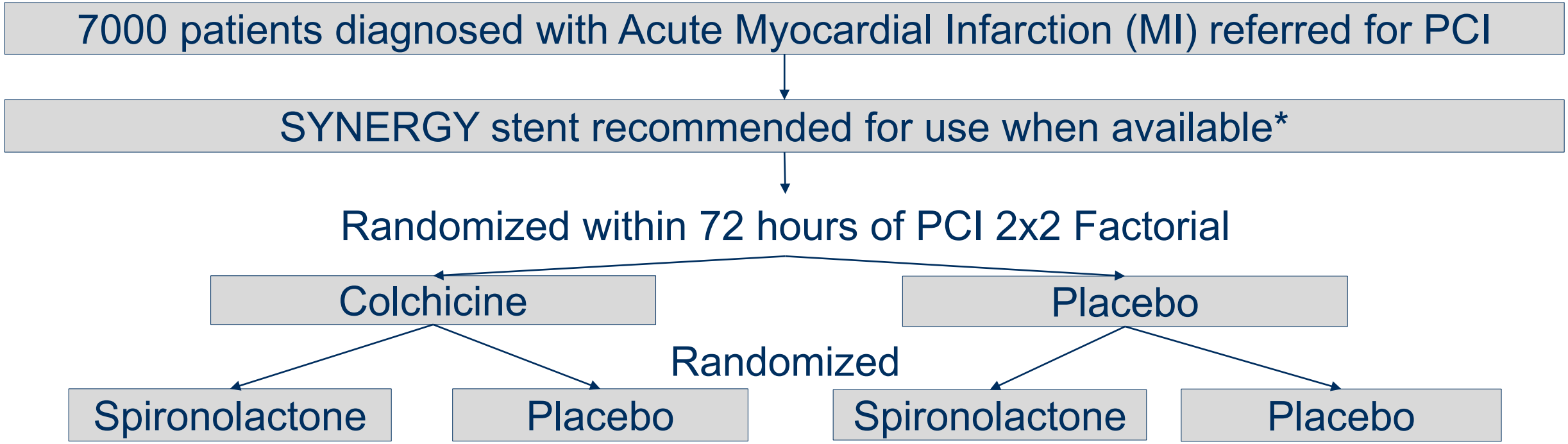
EMPACT-MI (N = 6522, death or HF)



No. at Risk										
Placebo	3262	3092	3044	2832	2486	2071	1556	1040	551	137
Empagliflozin	3260	3111	3060	2881	2532	2107	1566	1048	531	134

Pfeffer M.A. et al. NEJM 2021.
Butler J et al. NEJM 2024.

CLEAR SYNERGY OASIS 9 Trial



Primary Outcomes

***Spironolactone vs. placebo*: 1)** Co-primary 1. Composite of CV death or HF (total events)

2) Co-primary 2. Composite of CV death, HF, stroke or MI

Primary Objective

In patients with STEMI or large NSTEMI:

Does a routine spironolactoneompared to placebo long term reduce i) CV death or new or worsening heart failure and ii) CV death, MI, stroke or new worsening heart failure

Study Power and Follow Up

Study power: 84% power for a 31.5% RRR for a 6% control event rate, co-primary 1 and 80% power for a 26%RRR for co-primary 2

Analysis: Intention-to-treat Cox proportional hazards model, stratified by STEMI vs. NSTEMI and spironolactone vs. placebo,

Sensitivity: On treatment analysis

Follow up: 99.4% in both groups

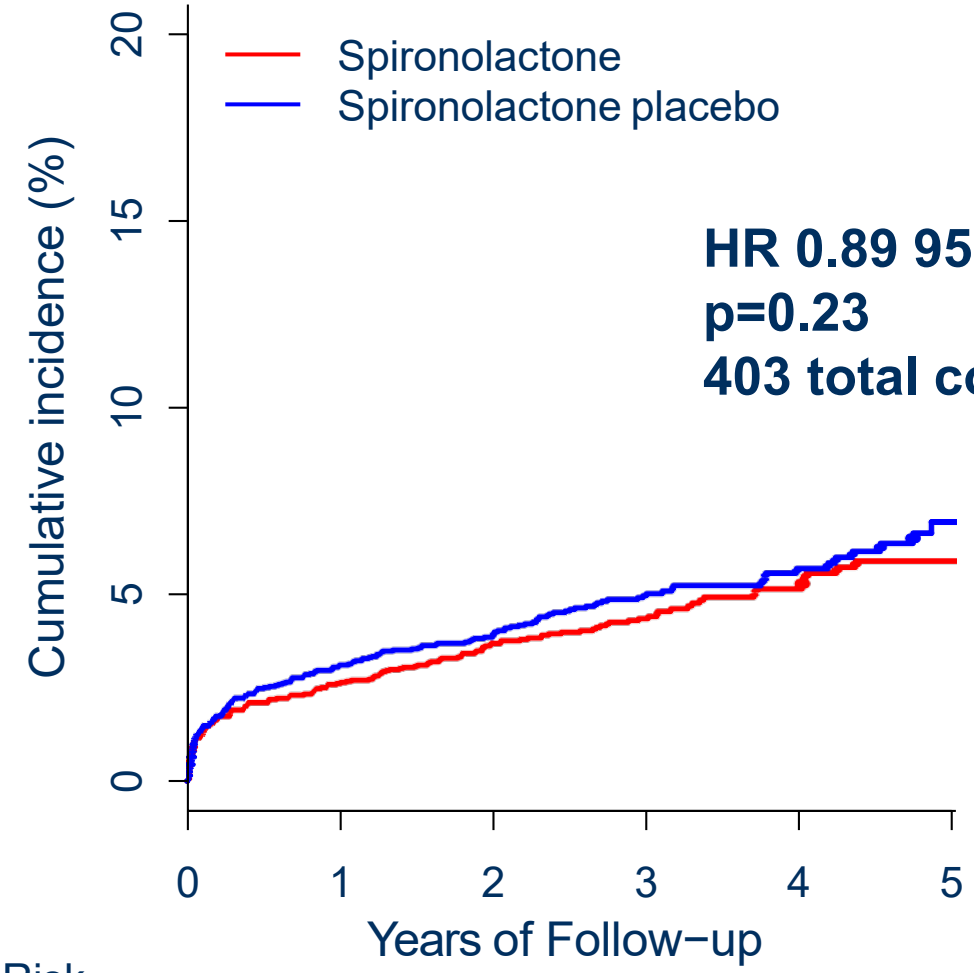
Baseline Characteristics

	Spironolactone N=3537	Placebo N=3525
Mean Age (years)	60.9	60.4
Female	21.5%	19.2%
STEMI	95.3%	94.9%
Killip ≥ 2 at presentation	0.7%	0.7%
Anterior STEMI	39.0%	39.3%
Previous heart failure	0.7%	1.0%

Medications at Discharge

	Spironolactone N=3537	Placebo N=3525
Aspirin	96.6%	96.9%
Clopidogrel	42.4%	41.9%
Ticagrelor	45.1%	45.0%
Prasugrel	11.1%	11.4%
ACE or ARB	77.6%	78.7%
Statin	96.4%	96.9%
SLGT2 inhibitor	3.2%	2.8%

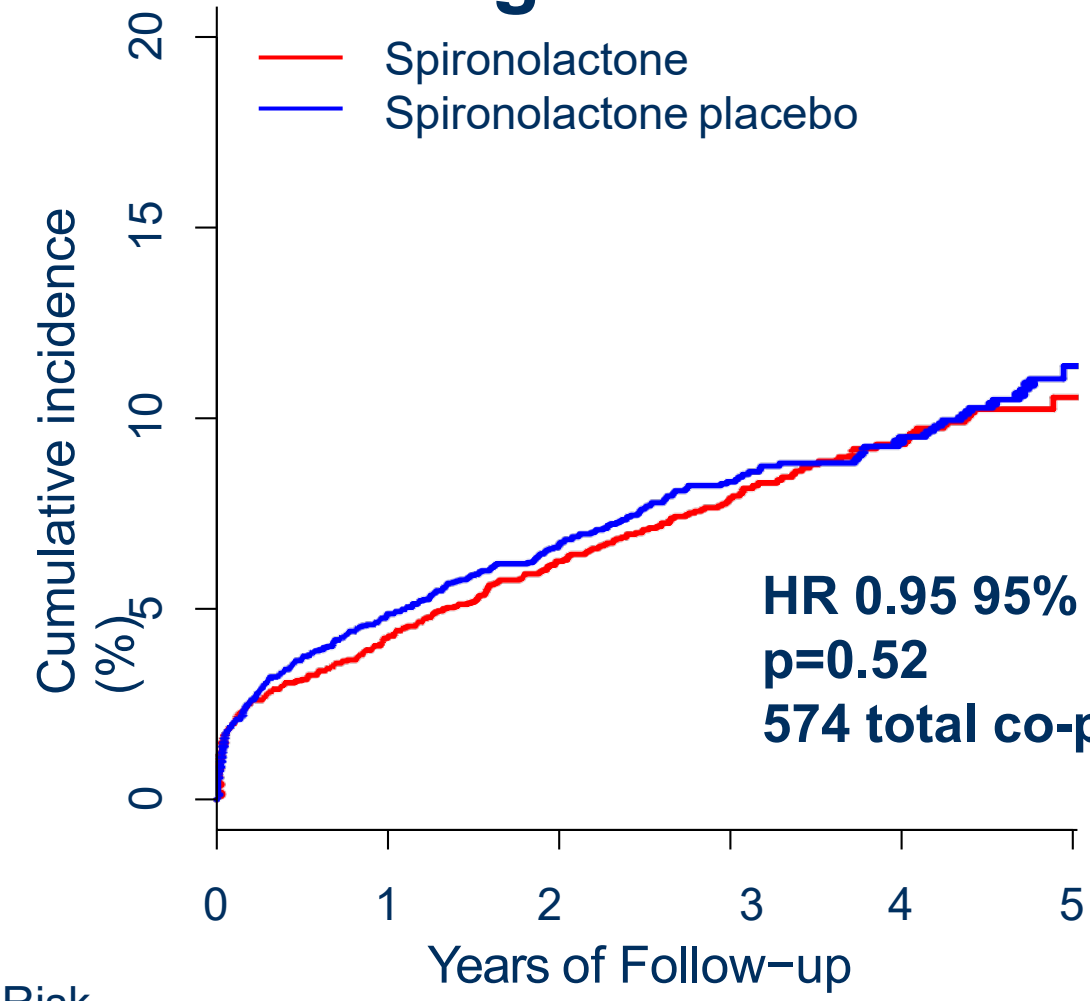
Co-Primary 1 Outcome of CV Death or New or Worsening Heart Failure



HR 0.89 95% CI 0.73-1.08
p=0.23
403 total co-primary outcome events

No. at Risk						
Spironolactone	3537	3422	2788	1778	704	183
Placebo	3525	3392	2785	1754	735	194

Co-Primary 2 Outcome of CV Death, MI, Stroke or New or Worsening Heart Failure



HR 0.95 95% CI 0.80-1.12
p=0.52
574 total co-primary outcome events

No. at Risk						
Spironolactone	3537	3365	2712	1721	681	173
Placebo	3525	3331	2707	1695	707	184

Results - Intention to Treat

	Spironolactone (N=3537) (%)	Placebo (N=3525) (%)	HR	95% CI	p
Co – primary 1: CV death or new or worsening heart failure	1.7%	2.1%	0.89	0.73-1.08	0.23
Co – primary 2: CV death, MI, stroke or new or worsening heart failure	7.9%	8.3%	0.95	0.80-1.12	0.52
CV death	3.2%	3.3%	0.98	0.76-1.27	
Recurrent MI	3.0%	3.0%	0.99	0.75-1.29	
Stroke	1.4%	1.2%	1.21	0.81-1.83	
New or worsening heart failure	1.6%	2.4%	0.69	0.49-0.96	
Significant arrythmia	0.6%	0.5%	1.18	0.62-2.24	

Results - On Treatment

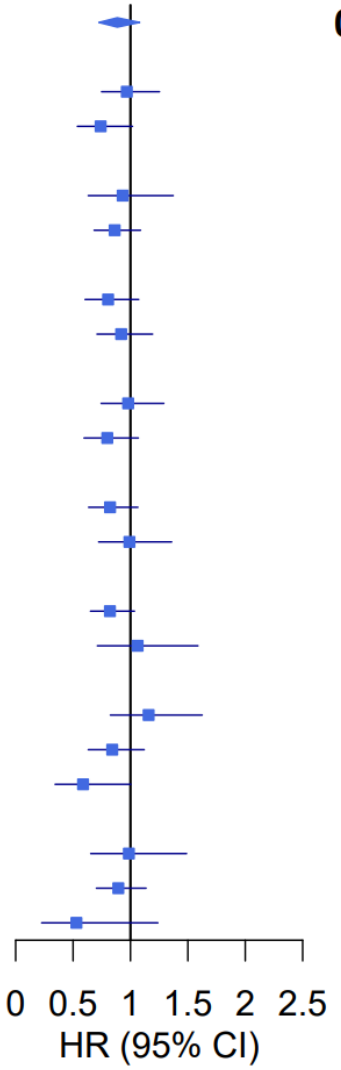
	Spironolactone (N=3497) (%)	Placebo (N=3483) (%)	HR	95% CI	p
Co – primary 1: CV death or new or worsening heart failure	1.5%	2.0%	0.79	0.63-1.00	0.047
Co – primary 2: CV death, MI, stroke or new or worsening heart failure	5.8%	7.2%	0.83	0.69-1.00	0.046
CV death	2.3%	2.9%	0.84	0.62-1.12	
Recurrent MI	2.0%	2.6%	0.80	0.58-1.09	
Stroke	1.0%	1.0%	1.06	0.66-1.68	
New or worsening heart failure	1.3%	2.0%	0.67	0.46-0.98	
Significant arrythmia	0.5%	0.5%	1.15	0.57-2.29	

Adverse Events

	Spironolactone (N=3537) (%)	Placebo (N=3525) (%)	p
Serious Adverse Events	7.2%	6.8%	0.54
HyperK+ leading to study drug discontinuation	1.1%	0.05%	0.01
Gynecomastia	2.3%	0.5%	<0.001

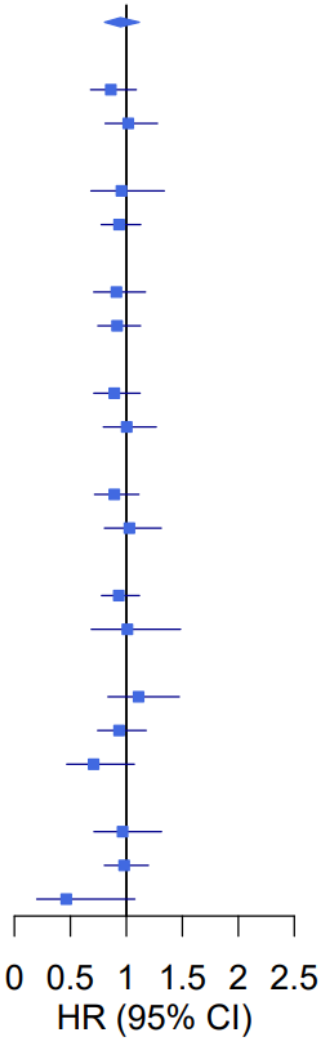
Forest Plot of Co-Primary 1 in Pre-Specified Subgroups

	Spironolactone Count(Rate)	Placebo Count(Rate)	Hazard Ratio (95% CI)	P value for Interaction
Co−Primary 1:(total event)				
CVD/New or Worsening HF	**183 (1.72)**	**220 (2.07)**	**0.89 (0.73−1.08)**	
Age				**0.246**
Age>= 65	114 (1.07)	127 (1.19)	0.97 (0.75−1.25)	
Age<65	69 (0.65)	93 (0.88)	0.74 (0.54−1.02)	
Gender				**0.934**
Female	49 (0.46)	56 (0.53)	0.93 (0.63−1.37)	
Male	134 (1.26)	164 (1.54)	0.86 (0.68−1.09)	
MI type				**0.45**
Anterior STEMI	83 (0.78)	114 (1.07)	0.80 (0.60−1.07)	
Other	111 (1.04)	123 (1.16)	0.92 (0.71−1.19)	
Baseline serum Potassium level				**0.329**
Potassium>=4 mmol/L	101 (0.95)	110 (1.04)	0.98 (0.74−1.29)	
Potassium<4 mmol/L	82 (0.77)	110 (1.04)	0.80 (0.60−1.07)	
History of Hypertension				**0.329**
Yes	106 (1.00)	142 (1.34)	0.82 (0.63−1.07)	
No	77 (0.72)	78 (0.73)	0.99 (0.72−1.36)	
GFR level				**0.157**
GFR>=60	132 (1.24)	170 (1.60)	0.82 (0.65−1.03)	
GFR<60	51 (0.48)	50 (0.47)	1.06 (0.71−1.59)	
Covid Phase				**0.022**
pre−covid	73 (0.69)	72 (0.68)	1.16 (0.83−1.62)	
During covid	87 (0.82)	108 (1.02)	0.84 (0.63−1.12)	
post− covid	23 (0.22)	40 (0.38)	0.59 (0.34−1.00)	
Region				**0.18**
North America	49 (0.46)	49 (0.46)	0.99 (0.65−1.49)	
Europe	126 (1.19)	154 (1.45)	0.89 (0.70−1.14)	
Other region	8 (0.08)	17 (0.16)	0.53 (0.23−1.24)	



Forest Plot of Co-Primary 2 in Pre-Specified Subgroups

	Spironolactone Count/Total (%)	Placebo Count/Total (%)	Hazard Ratio (95% CI)	P value for Interaction
Co−Primary 2:(First event)				
CVD/MI/Stroke/New or Worsening HF	**280/3537(7.9)**	**294/3525(8.3)**	**0.95 (0.80−1.12)**	
Age				**0.326**
Age>= 65	133/1233(10.8)	146/1166(12.5)	0.86 (0.68−1.09)	
Age<65	147/2304(6.4)	148/2359(6.3)	1.02 (0.81−1.28)	
Gender				**0.888**
Female	71/760(9.3)	65/678(9.6)	0.96 (0.68−1.34)	
Male	209/2777(7.5)	229/2847(8.0)	0.94 (0.78−1.13)	
MI type				**0.701**
Anterior STEMI	116/1315(8.8)	128/1315(9.7)	0.91 (0.71−1.17)	
Other	174/2366(7.4)	185/2323(8.0)	0.92 (0.75−1.13)	
Baseline serum Potassium level				**0.483**
Potassium>=4 mmol/L	138/1777(7.8)	154/1789(8.6)	0.89 (0.71−1.12)	
Potassium<4 mmol/L	142/1760(8.1)	140/1736(8.1)	1.00 (0.79−1.27)	
History of Hypertension				**0.411**
Yes	149/1600(9.3)	168/1633(10.3)	0.89 (0.72−1.11)	
No	131/1937(6.8)	126/1891(6.7)	1.03 (0.80−1.31)	
GFR level				**0.734**
GFR>=60	227/3250(7.0)	243/3243(7.5)	0.93 (0.78−1.12)	
GFR<60	53/287(18.5)	51/282(18.1)	1.01 (0.69−1.48)	
Covid Phase				**0.211**
pre−covid	100/991(10.1)	91/998(9.1)	1.11 (0.83−1.47)	
During covid	142/1798(7.9)	149/1774(8.4)	0.94 (0.74−1.18)	
post− covid	38/748(5.1)	54/753(7.2)	0.71 (0.47−1.07)	
Region				**0.238**
North America	80/1009(7.9)	82/1013(8.1)	0.97 (0.71−1.31)	
Europe	192/2366(8.1)	195/2349(8.3)	0.98 (0.80−1.20)	
Other region	8/162(4.9)	17/163(10.4)	0.46 (0.20−1.08)	



Conclusion

- Routine spironolactone post MI did not reduce either co-primary outcome
- There was a reduction in heart failure
- On treatment analysis suggests potential benefit
- Outcomes have improved remarkably over the last 20 years

Conclusions

- Routine spironolactone post MI did not reduce either co-primary outcome
- There was a reduction in heart failure
- On treatment analysis suggests potential benefit
- Outcomes have improved remarkably over the last 20 years