Presenter Disclosures

Dr. Andrew Yan

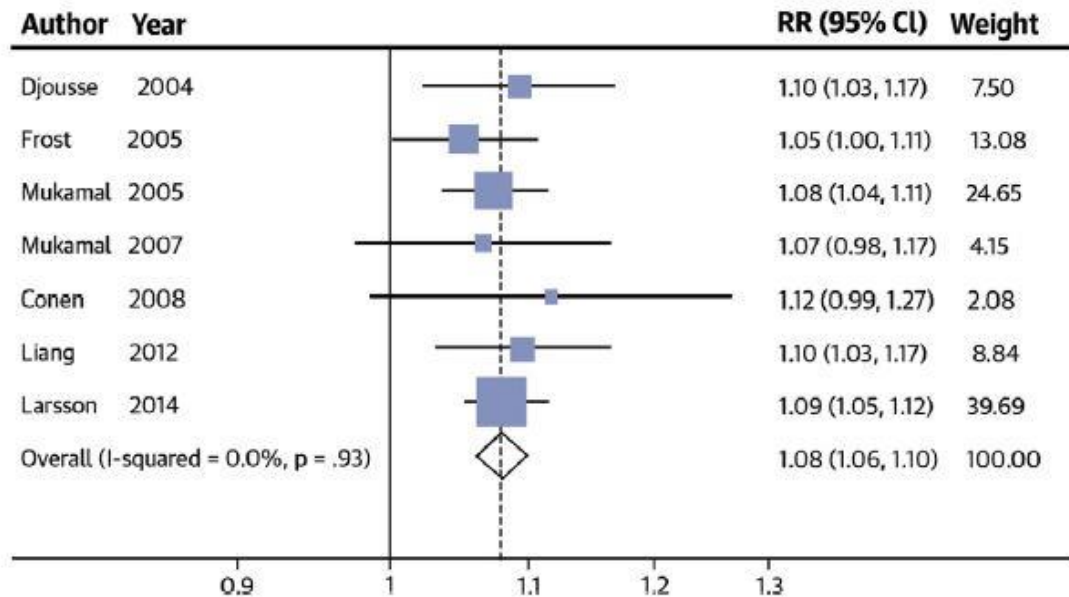## New clinical trials that impact on your practice

Relationships with financial sponsors:

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- **Patents:** N/A
- **Other:** N/A

Outline

- Alcohol Abstinence in Drinkers with Atrial Fibrillation

- Comparison of Two LDL Cholesterol Targets after Ischemic Stroke
  - Treat Stroke to Target

- Low-Dose Colchicine after Myocardial Infarction
  - COLCOT

Alcohol and Atrial Fibrillation

| Author	Year	RR (95% CI)	Weight
Djousse	2004	1.10 (1.03, 1.17)	7.50
Frost	2005	1.05 (1.00, 1.11)	13.08
Mukamal	2005	1.08 (1.04, 1.11)	24.65
Mukamal	2007	1.07 (0.98, 1.17)	4.15
Conen	2008	1.12 (0.99, 1.27)	2.08
Liang	2012	1.10 (1.03, 1.17)	8.84
Larsson	2014	1.09 (1.05, 1.12)	39.69
Overall (I-squared = 0.0%, p = .93)		1.08 (1.06, 1.10)	100.00

Meta-analysis of 7 prospective studies

206 073 subjects

12 554 cases of AF

RR per 1 drink/day increment = 1.08

Larsson SC et al. *J Am Coll Cardiol* 2014

Alcohol consumption and atrial fibrillation
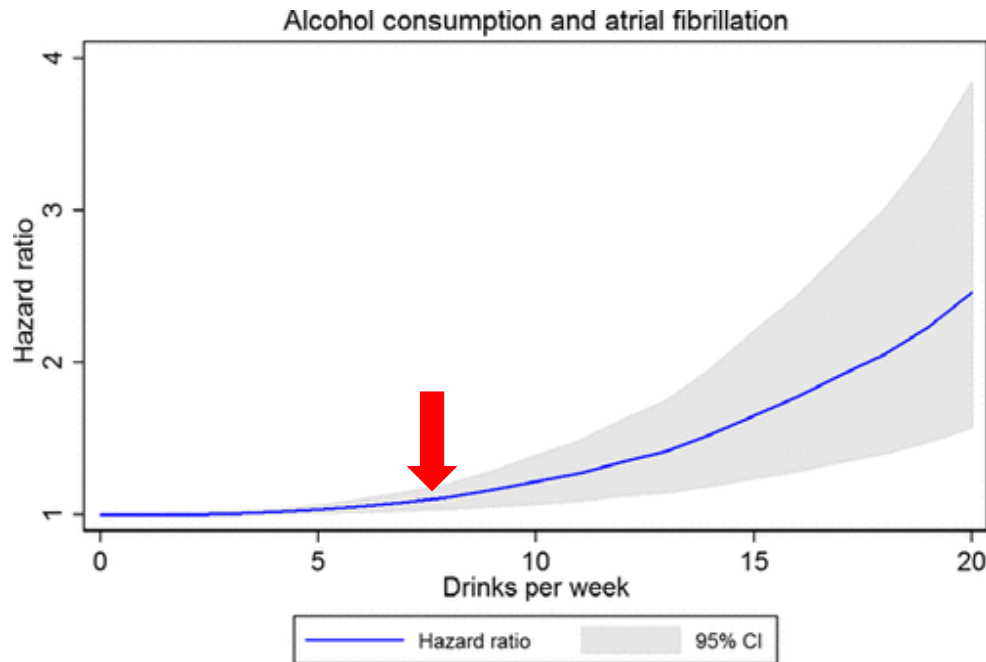
Population-based cohort study

47 002 subjects

1697 cases of AF

Gemes K et al. *J Am Heart Assoc* 2017

Adjusted for sex, height, marital status, SES, smoking, physical activity, BMI and diabetes

ORIGINAL ARTICLE

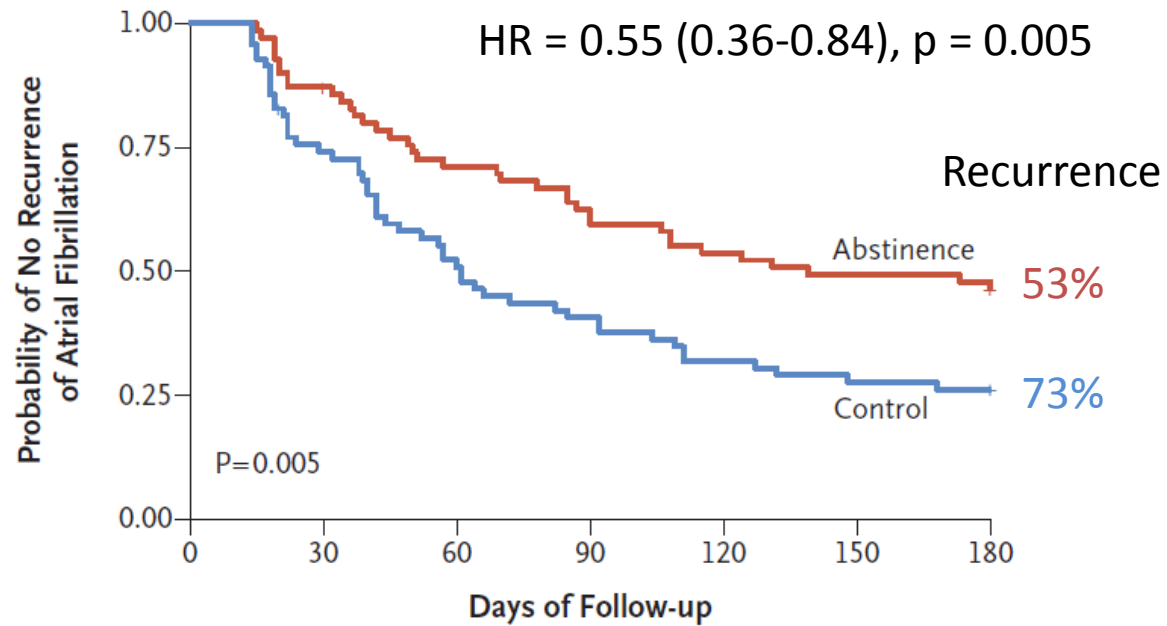# Alcohol Abstinence in Drinkers with Atrial Fibrillation

Aleksandr Voskoboinik, M.B., B.S., Ph.D., Jonathan M. Kalman, M.B., B.S., Ph.D.,
Anurika De Silva, Ph.D., Thomas Nicholls, M.B., B.S., Benedict Costello, M.B., B.S.,
Shane Nanayakkara, M.B., B.S., Sandeep Prabhu, M.B., B.S., Ph.D.,
Dion Stub, M.B., B.S., Ph.D., Sonia Azzopardi, R.N., Donna Vizi, R.N.,
Geoffrey Wong, M.B., B.S., Chrishan Nalliah, M.B., B.S.,
Hariharan Sugumar, M.B., B.S., Michael Wong, M.B., B.S., Ph.D.,
Emily Kotschet, M.B., B.S., David Kaye, M.B., B.S., Ph.D.,
Andrew J. Taylor, M.B., B.S., Ph.D., and Peter M. Kistler, M.B., B.S., Ph.D.

- Prospective, multicentre, open-label, randomized, controlled trial

- age 18-85 years; symptomatic paroxysmal atrial fibrillation or symptomatic persistent atrial fibrillation with a rhythm control strategy; regular alcohol consumption (≥10 standard drinks alcohol / week)

- Key exclusion: alcohol abuse/dependence, LVEF<35%

Voskoboinik A et al. *N Engl J Med* 2020

- Randomized 1:1 to abstinence or control group
- 140 patients (median age 62; 85% men; BMI 29)
- Paroxysmal AF 63%; 11% had CAD; 41% had hypertension; 66% on anti-arrhythmic
- Mean alcohol intake ~17 drinks/week; binge drinking 26%
- Follow-up: 6 months (originally planned for 12)
- Primary outcome: recurrence of atrial fibrillation (after a 2-week "blanking period") and total atrial fibrillation burden (proportion of time in atrial fibrillation)
- ECG, mobile app, implanted device, Holter---reviewed by 2 independent cardiologists

Voskoboinik A et al. *N Engl J Med* 2020

Abstinence group:
Mean 17 drinks/week to 2/week
(61% complete abstinence)

Control group:
Mean 16 drinks/week to 13/week

HR = 0.55 (0.36-0.84), p = 0.005

Probability of No Recurrence of Atrial Fibrillation

1.00
0.75
0.50
0.25
0.00

Recurrence

Abstinence
53%

Control
73%

P=0.005

0   30   60   90   120   150   180
Days of Follow-up

No. at Risk

Abstinence	70	61	49	43	37	34	33
Control	70	51	36	28	22	19	18

Atrial Fibrillation Burden (%)

Control
Abstinence

>5

0–5

0

0   5   10   15   20   25   30   35   40   45   50
Percent of Participants

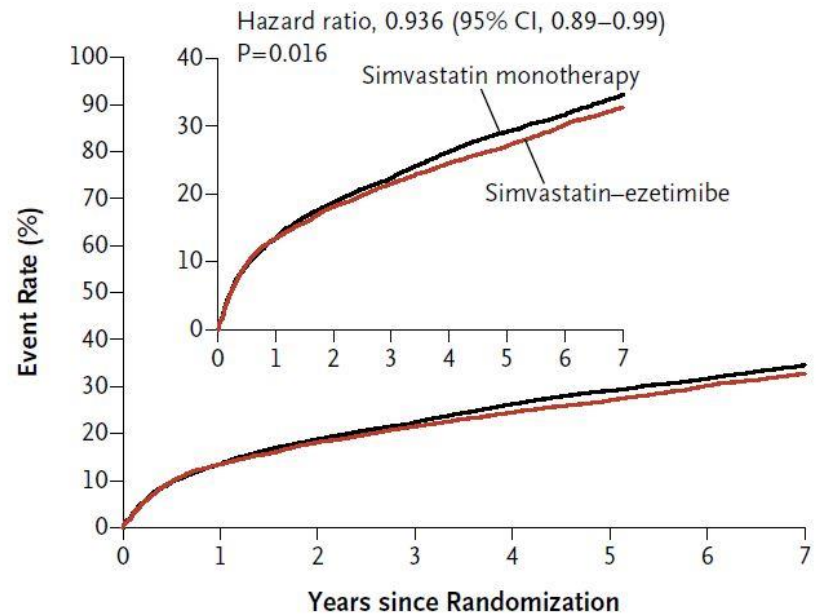Voskoboinik A et al. *N Engl J Med* 2020
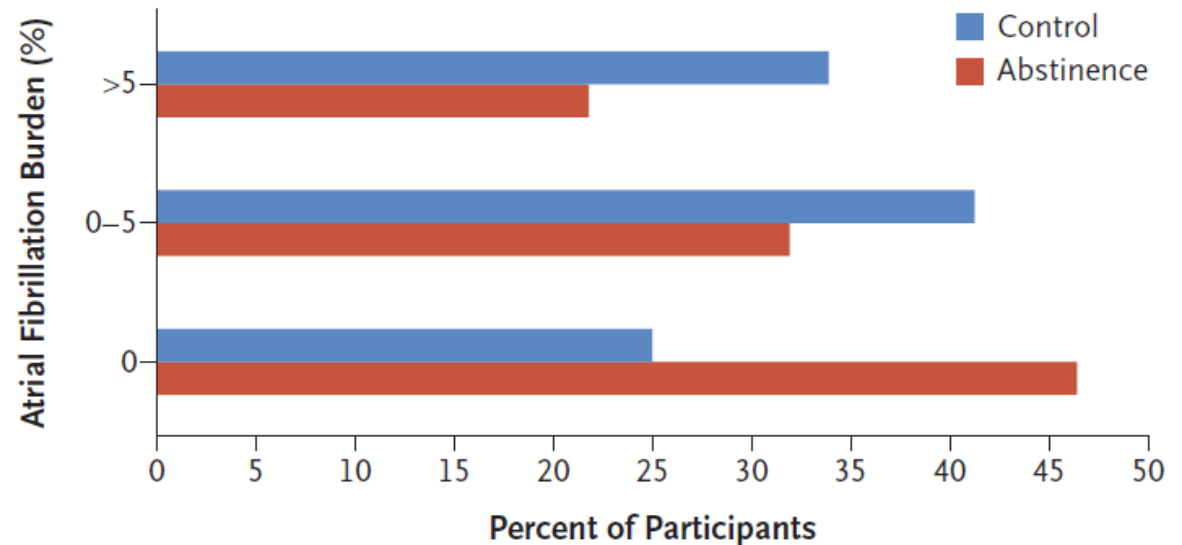
Interpretation

- "Abstinence from alcohol reduced arrhythmia recurrences in regular drinkers with atrial fibrillation"
- Generalizability:
  - Highly selected patients
  - Accuracy of alcohol consumption?
- Outcomes:
  - Reduced AF burden
  - "Hard" outcomes?
  - Quality of life? (due to missing data)
  - Long-term?
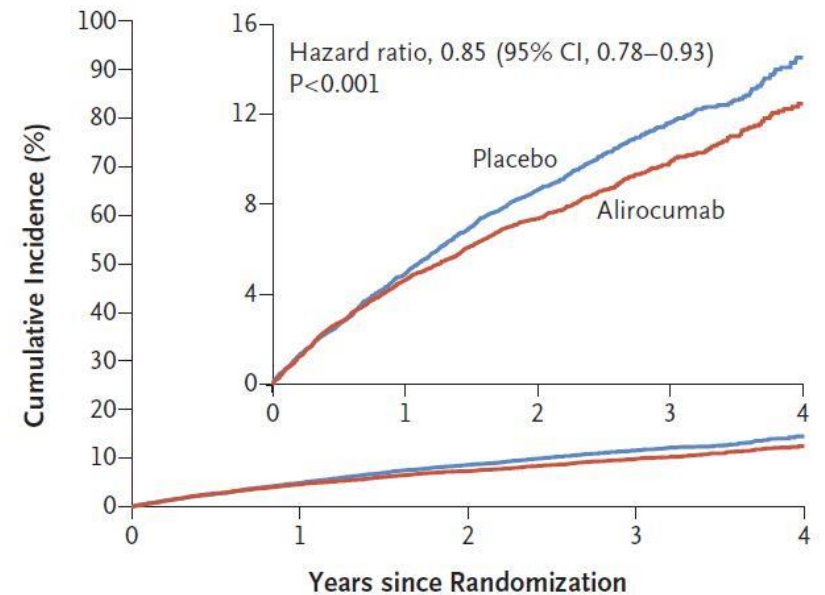- Other benefits (reduction in weight and BP)

Voskoboinik A et al. *N Engl J Med* 2020

Lower is Better!

IMPROVE IT
Median LDL-C 1.4 vs 1.8 mmol/L

ODYSSEY OUTCOMES
12 mo mean LDL-C 1.2 vs 2.5 mmol/L

Cannon CP et al. *N Engl J Med* 2015

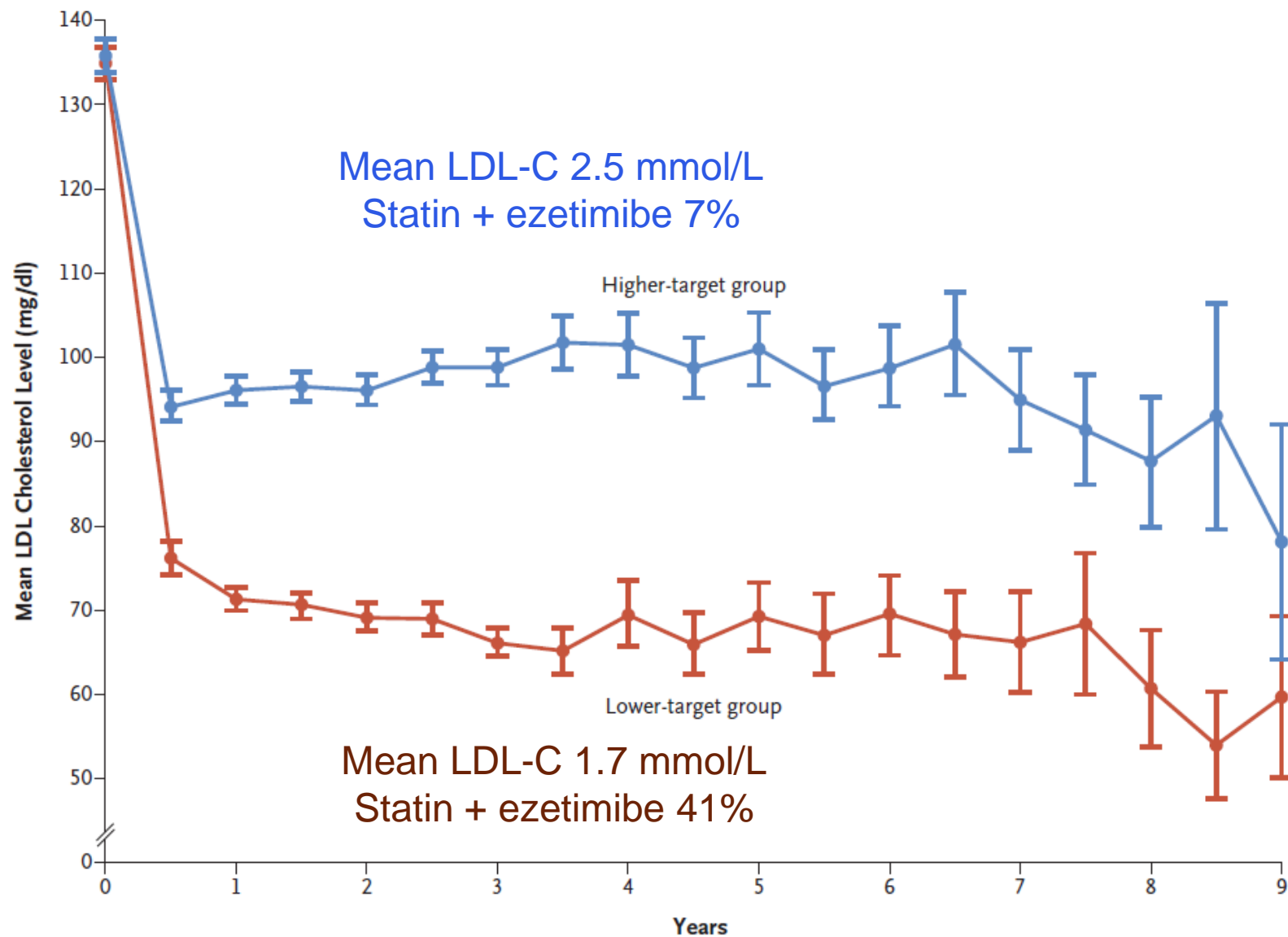Schwartz GG et al. *N Engl J Med* 2018

A Comparison of Two LDL Cholesterol Targets after Ischemic Stroke

P. Amarenco, J.S. Kim, J. Labreuche, H. Charles, J. Abtan, Y. Béjot, L. Cabrejo, J.-K. Cha, G. Ducrocq, M. Giroud, C. Guidoux, C. Hobeanu, Y.-J. Kim, B. Lapergue, P.C. Lavallée, B.-C. Lee, K.-B. Lee, D. Leys, M.-H. Mahagne, E. Meseguer, N. Nighoghossian, F. Pico, Y. Samson, I. Sibon, P.G. Steg, S.-M. Sung, P.-J. Touboul, E. Touzé, O. Varenne, É. Vicaut, N. Yelles, and E. Bruckert, for the Treat Stroke to Target Investigators*

- Prospective, multi-centre, open-label, blinded outcome randomized controlled trial
- Adult patients with ischemic stroke ≤3 months or TIA ≤15 days, with evidence of atherosclerotic cerebrovascular or coronary artery disease

Amarenco P et al. *N Engl J Med* 2020

- Randomized to a <u>lower</u> target LDL-C < 1.8 mmol/L
     or a <u>higher</u> target LDL-C range 2.3-2.8 mmol/L
- Investigators are allowed to prescribe any type or dose of statin ± ezetimibe

- 2860 patients (mean age 66; 67% men)
- 86% ischemic stroke
- Baseline mean LDL-C 3.5 mmol/L

- Median follow-up 3.5 years
- Primary outcome: composite of ischemic stroke, myocardial infarction, urgent coronary or carotid revascularization, or cardiovascular death

Amarenco P et al. *N Engl J Med* 2020

LDL Cholesterol Level, According to Target Group

Mean LDL-C 2.5 mmol/L
Statin + ezetimibe 7%

Higher-target group

Lower-target group

Mean LDL-C 1.7 mmol/L
Statin + ezetimibe 41%

Mean LDL Cholesterol Level (mg/dl)

Years

No. at Risk																		
Higher target	1420	1115	989	787	792	681	598	292	242	185	164	133	114	80	83	67	31	22	5
Lower target	1414	1102	965	879	774	653	570	277	227	180	169	141	126	81	73	46	26	21	6
Absolute difference	−1.14	−18.3	−24.7	−26.1	−27.1	−29.8	−32.5	−36.6	−32.0	−32.8	−31.9	−29.5	−29.4	−34.6	−29.0	−23.2	−26.9	−39.2	−18.5

Amarenco P et al. *N Engl J Med* 2020

Absolute risk reduction = 2.4%
Number Needed to Treat = 42

Primary End Point

Cumulative Incidence (%)

Adjusted hazard ratio in the lower-target group,
0.78 (95% CI, 0.61–0.98)
P=0.04

Higher-target group

Lower-target group

Years
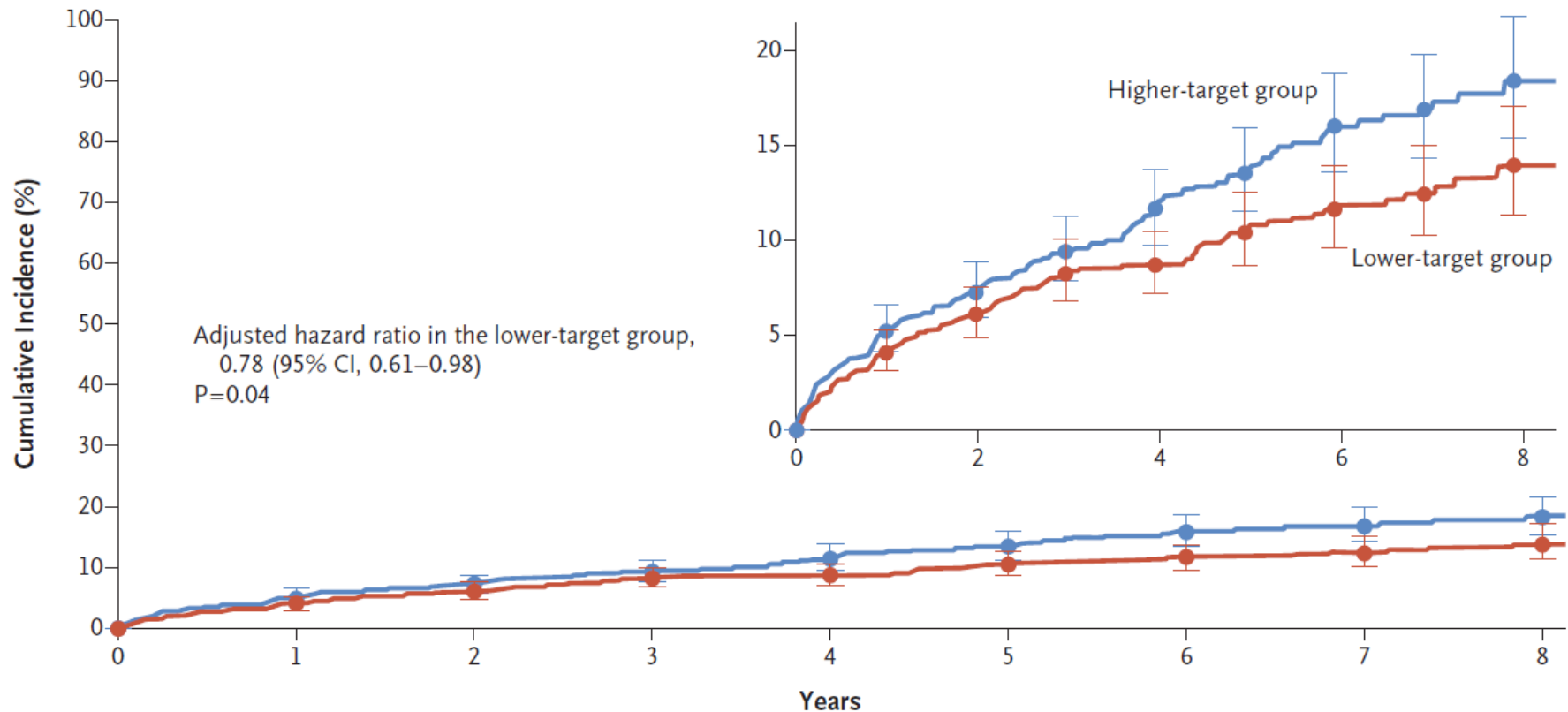
No. at Risk

|								
Higher target	1430	1146	973	730	590	487	392	253	106
Lower target	1430	1128	964	740	586	475	353	238	104

Interpretation

- "After an ischemic stroke or TIA with evidence of atherosclerosis, patients who had a target LDL-C <1.8mmol/L had a lower risk of subsequent cardiovascular events than those who had a target range of 2.3-2.8 mmol/L"

- Premature cessation of the trial

- Open-label

- Composite endpoint (stroke? CV death?)
  - Clinically important

- Benefits of further LDL-C reduction?

- Intracranial hemorrhage numerically higher in the lower LDL-C target arm

Amarenco P et al. *N Engl J Med* 2020

Atherosclerosis and Inflammation

CENTRAL ILLUSTRATION: Evolution of Concepts of the Pathogenesis of Atherosclerosis
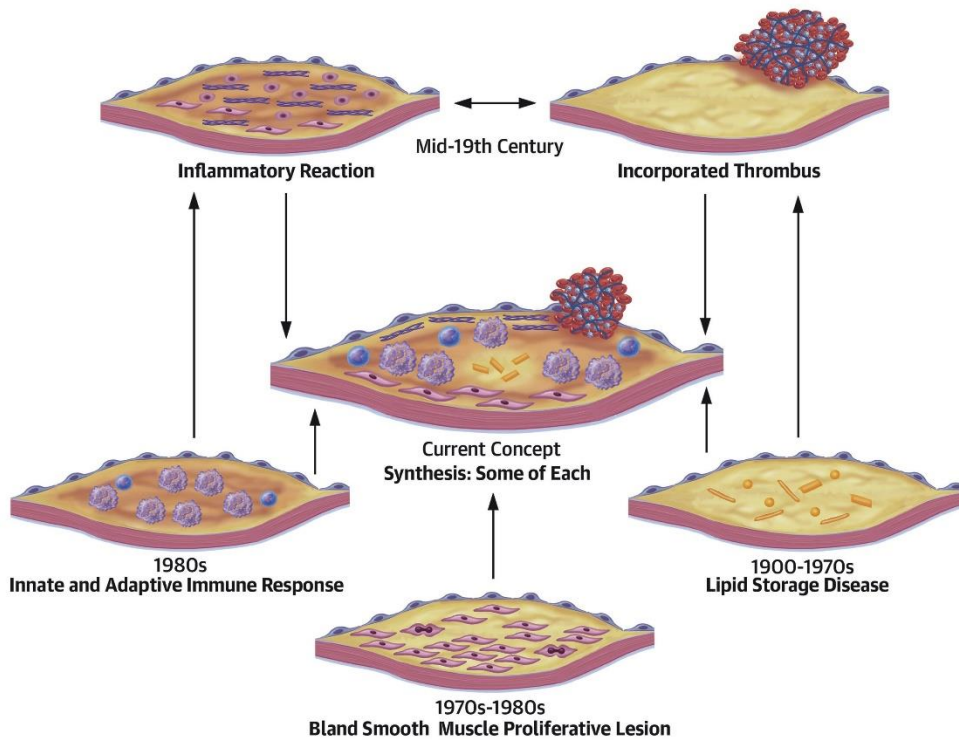
Libby, P. et al. J Am Coll Cardiol. 2019;74(12):1594–607.
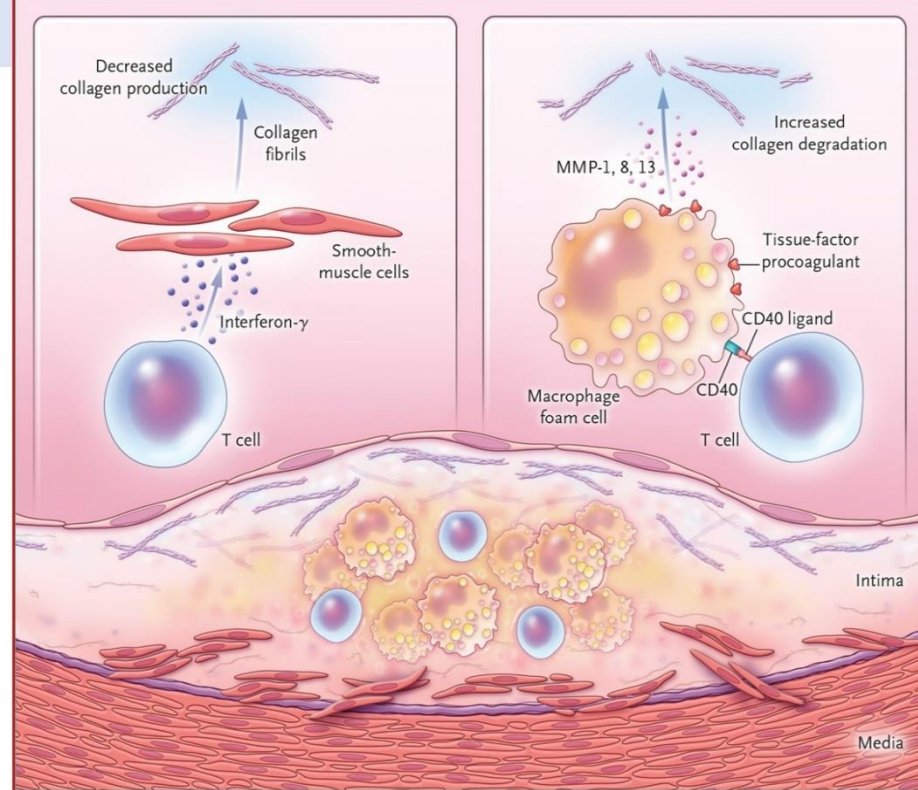
Libby P. *N Engl J Med* 2013

## Efficacy and Safety of Low-Dose Colchicine after Myocardial Infarction

Jean-Claude Tardif, M.D., Simon Kouz, M.D., David D. Waters, M.D., Olivier F. Bertrand, M.D., Ph.D.,
Rafael Diaz, M.D., Aldo P. Maggioni, M.D., Fausto J. Pinto, M.D., Ph.D., Reda Ibrahim, M.D., Habib Gamra, M.D.,
Ghassan S. Kiwan, M.D., Colin Berry, M.D., Ph.D., José López-Sendón, M.D., Petr Ostadal, M.D., Ph.D.,
Wolfgang Koenig, M.D., Denis Angoulvant, M.D., Jean C. Grégoire, M.D., Marc-André Lavoie, M.D.,
Marie-Pierre Dubé, Ph.D., David Rhainds, Ph.D., Mylène Provencher, Ph.D., Lucie Blondeau, M.Sc.,
Andreas Orfanos, M.B., B.Ch., Philippe L. L'Allier, M.D., Marie-Claude Guertin, Ph.D.,
and François Roubille, M.D., Ph.D.

- Prospective, multi-centre, randomized, double-blind placebo-controlled trial
- Adult patients with myocardial infarction (MI) within 30 days who had completed any planned revascularization, treated according to national guidelines

Tardif J-C et al. *N Engl J Med* 2020

- Exclusion criteria: severe heart failure, LVEF<35%, stroke within past 3 mo, type 2 MI, planned CABG, severe renal disease
- 4747 patients (mean age 61; 19% women)
- >97% ASA, antiplatelet, and statin; 93% had PCI
- colchicine 0.5 mg daily or placebo

- Median follow-up 23 months
- Primary endpoint: composite of cardiovascular death, resuscitated cardiac arrest, MI, stroke, or urgent hospitalization for angina requiring revascularization

Tardif J-C et al. *N Engl J Med* 2020

Absolute risk reduction = 1.6%
Number Needed to Treat = 63
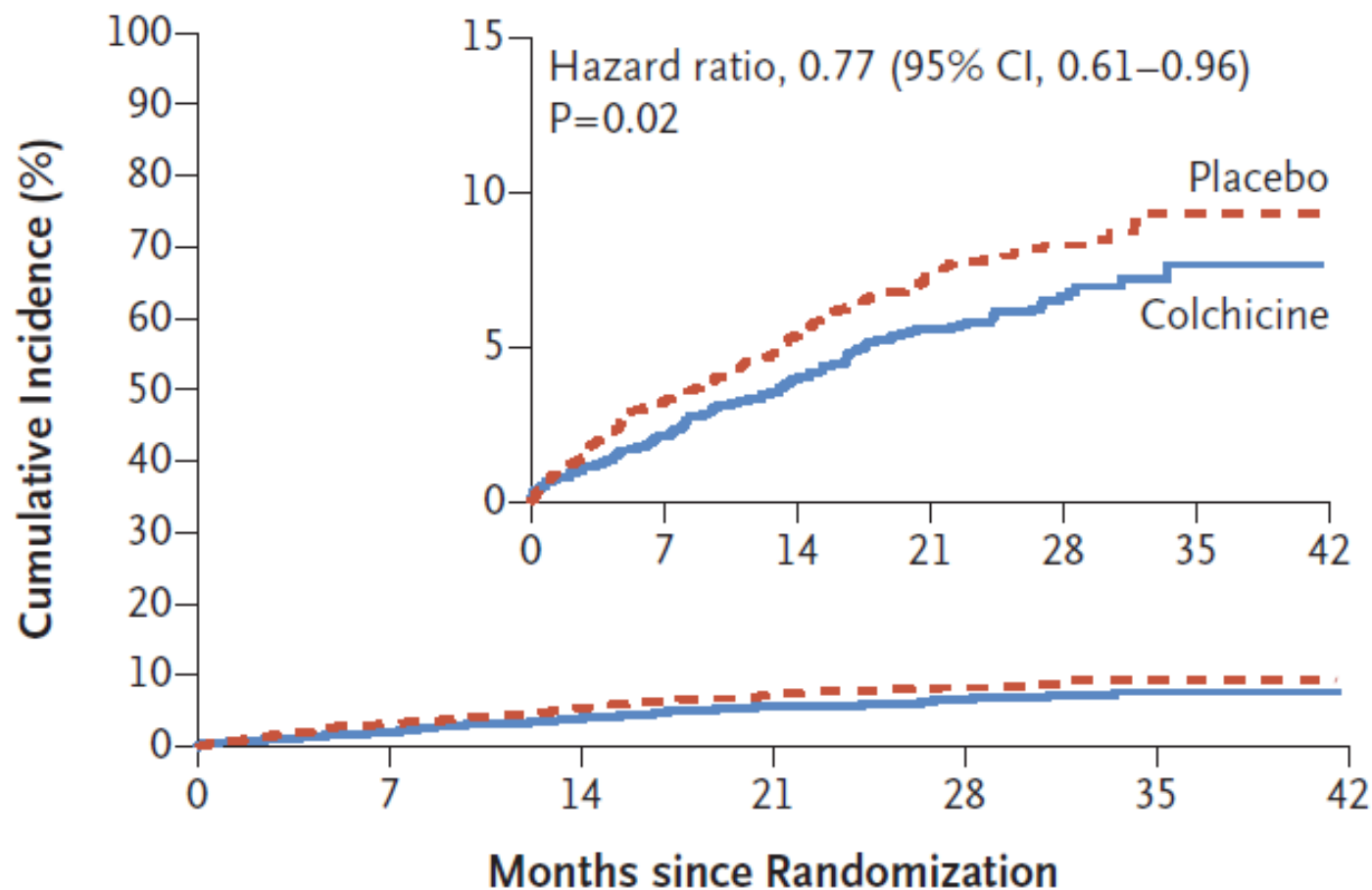
No. at Risk

Placebo	2379	2261	1854	1224	622	144	0
Colchicine	2366	2284	1868	1230	628	153	0

Tardif J-C et al. *N Engl J Med* 2020

Table 2. Major Clinical End Points (Intention-to-Treat Population).*

End Point	Colchicine (N=2366)	Placebo (N=2379)	Hazard Ratio (95% CI)	P Value
	number (percent)			
Primary composite end point	131 (5.5)	170 (7.1)	0.77 (0.61–0.96)	0.02†
Components of primary end point				
Death from cardiovascular causes	20 (0.8)	24 (1.0)	0.84 (0.46–1.52)	
Resuscitated cardiac arrest	5 (0.2)	6 (0.3)	0.83 (0.25–2.73)	
Myocardial infarction	89 (3.8)	98 (4.1)	0.91 (0.68–1.21)	
Stroke	5 (0.2)	19 (0.8)	0.26 (0.10–0.70)	
Urgent hospitalization for angina leading to revascularization	25 (1.1)	50 (2.1)	0.50 (0.31–0.81)	
Secondary composite end point‡	111 (4.7)	130 (5.5)	0.85 (0.66–1.10)	
Death	43 (1.8)	44 (1.8)	0.98 (0.64–1.49)	
Deep venous thrombosis or pulmonary embolus	10 (0.4)	7 (0.3)	1.43 (0.54–3.75)	
Atrial fibrillation	36 (1.5)	40 (1.7)	0.93 (0.59–1.46)	

Tardif J-C et al. *N Engl J Med* 2020

Interpretation

- "Among patients with a recent myocardial infarction, colchicine at a dose of 0.5 mg daily led to a significantly lower risk of ischemic cardiovascular events than placebo."
- Overall adverse events similar
  - Nausea (but not diarrhea) more common
  - Pneumonia more frequent
- Relatively inexpensive
- Longer term effects unknown
- Confirmatory data

Tardif J-C et al. *N Engl J Med* 2020

Take Home Messages (1)

- Among drinkers (≥10 drinks/week) with AF, abstinence or decreased alcohol consumption reduces AF recurrence and burden
  - Consistent with the general recommendation

- A lower LDL-C target (<1.8 mmol/L) is beneficial in patients with recent ischemic stroke or TIA
  - Similar to other high risk atherosclerotic disease
  - No clear threshold effect

Take Home Messages (2)

- Colchicine (0.5 mg/d) reduces the risk of ischemic cardiovascular events in patients with recent MI and is generally well tolerated over ~2 years.
    - Incremental benefits beyond revascularization and contemporary secondary prevention therapies
    - Ongoing trials

Thank you!