Fresh BEATS in CARDIOLOGY

WITH PEER

FMF Nov 6, 2025

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PEER PATIENTS EXPERIENCE EVIDENCE RESEARCH

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- Consulting Fees: N/A
- Grants/Research Support: N/A
- Patents: N/A
- Other: Salary – University of Manitoba

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- Consulting Fees: N/A
- Grants/Research Support: N/A
- Patents: N/A
- Other: Salary- CFPC

Objective:

- Describe and apply recent practice-changing or reaffirming papers related to cardiology topics relevant to primary care

WHEN TO DOSE?

A.M. *vs* HS

JAMA | Original Investigation
2025;333;(23):2061-2072

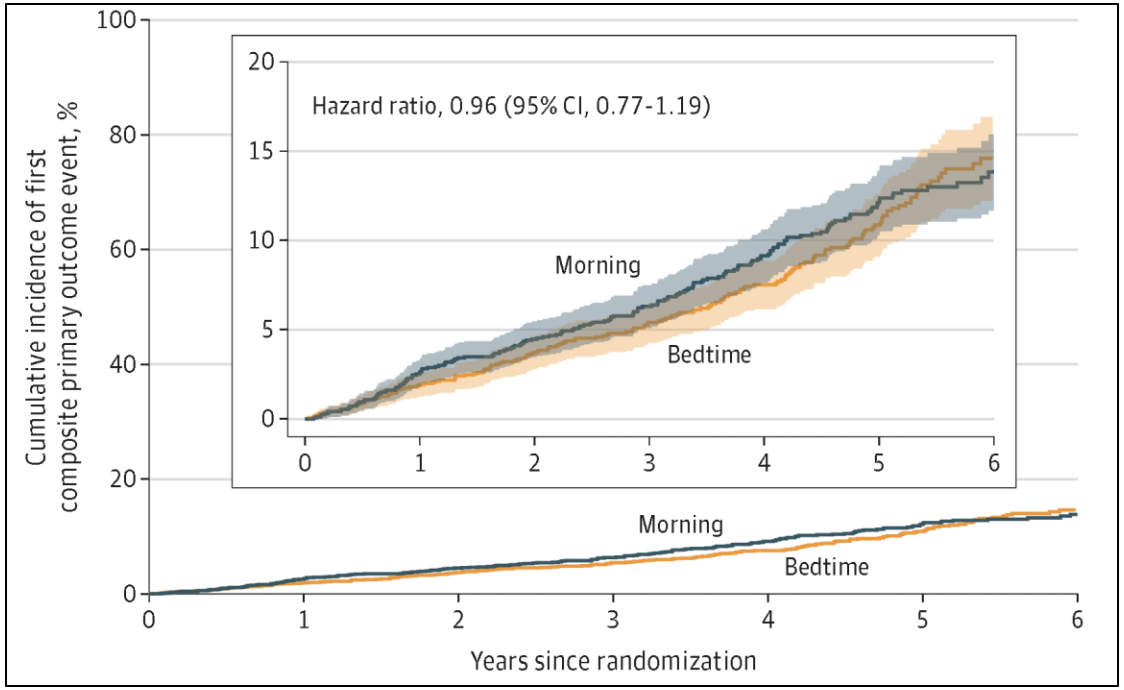
Antihypertensive Medication Timing and Cardiovascular Events and Death
The BedMed Randomized Clinical Trial

WHO: n=3357 (56% female; age 67 years; 54% monotherapy)
- from 436 🇨🇦 (71% AB) primary care clinicians

WHAT: pragmatic: took own meds, randomized to a.m. or HS X 4.6 yrs (ACEi or ARB 66%, CCB 29%, thiazide 27%)

RESULTS: Primary outcome (death, adm for ACS, stroke, HF)…

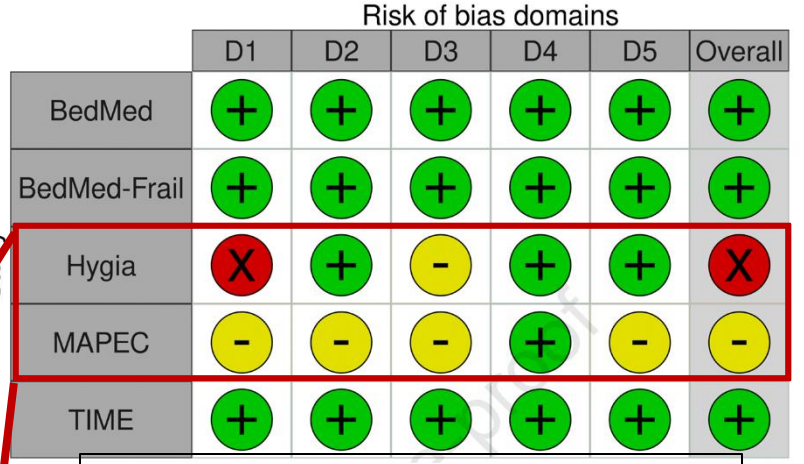
2.3 (HS) vs. **2.4 (am) →HR 0.96 (0.77-1.19)**



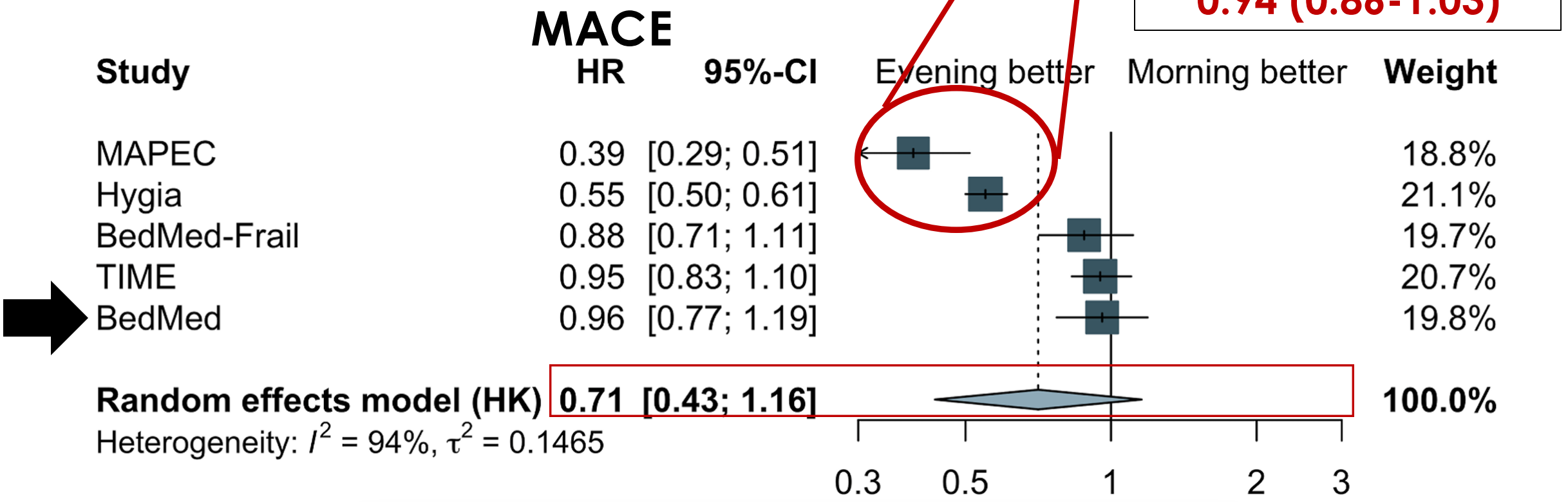
WHEN TO DOSE?

A.M. *vs* HS

TAKE HOME: let the patient choose



HR for **low RoB** trials:
0.94 (0.86-1.03)



CJC Aug 2025 https://doi.org/10.1016/j.cjca.2025.08.328

HOW LOW CAN WE GO?

even **LOWER BP** in **HIGH-RISK** people…

2 open-label RCTs comparing **SBP <120** to **SBP <140**:

- **ESPRIT**: 11,255 **at increased CV risk**, mean age 65
- **BPROAD**: 12,821 **with T2D at increased CV risk**, mean age 64

ESPRIT (3.4 yrs):

- **MACE: 9.7** vs **11.1% (ARR=1.4%, NNT=75)**
- **Death: 2.8** vs **3.6% (ARR=0.8%, NNT=131)**
- **AE:** syncope (0.4% vs 0.1%)
  hypo-Na (1.6% vs 1.1%)
  sustained eGFR decline ≥40%
  3.0 vs **1.8% (ARI=1.2%, NNH=84)**

Lancet 2024 Jul 20;404(10449):245-255

BPROAD (4.2 yrs):

- **MACE: 6.1** vs **7.7% (ARR=1.6%, NNT=65)**
- **Death: no difference**
- **AE:** hyper-K+
  2.8 vs **2.0% (ARI=0.8%, NNH=125)**

N Engl J Med 2025;392:1155-1167

HOW LOW CAN WE GO?

even **LOWER BP** in **HIGH-RISK** people…

? A few questions:

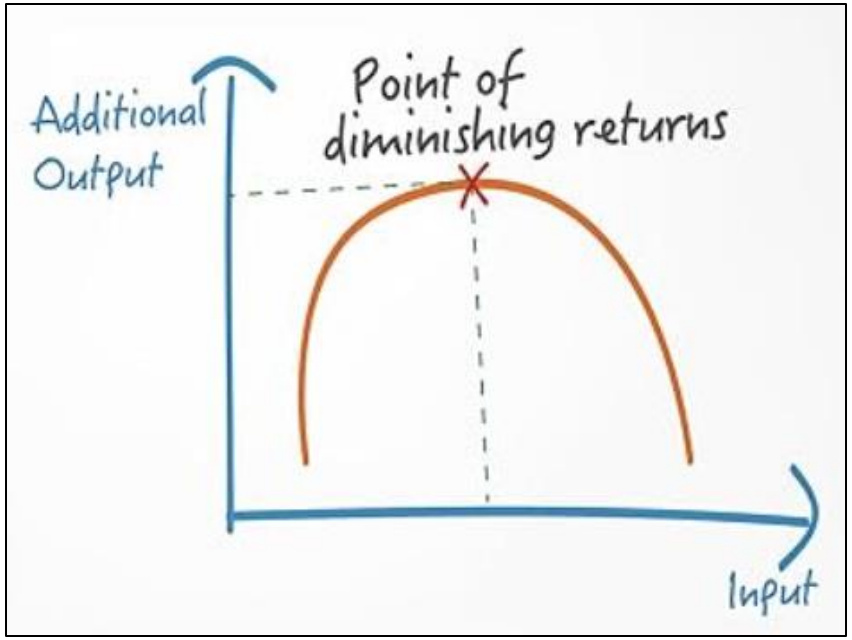
1. What is "high-risk"

   → ESPRIT/BPROAD **FRS ~25-40%**

   i.e. small ARR likely even smaller for many patients

2. What about other vascular outcomes?

   - ESPRIT: as we saw… sustained eGFR decline ≥40% → **ARI=1.2%, NNH=84**
   - BPROAD: onset/progression of CKD → **no difference**
   - Previous MA (BMJ 2016): **no reduction** in ESKD with SBP<130



Lancet 2025; 406:1009-19

Benefit–harm trade-offs of intensive blood pressure control versus standard blood pressure control on cardiovascular and renal outcomes: an individual participant data analysis of randomised controlled trials

Lancet 2025: intensive BP control vs standard BP control, at 3.2 yrs:

- **Net difference in BP -12.6mmHg**
- **5.3% vs 7.1% (ARR=1.7%) NNT 58**

Harms (hypotension, syncope, renal-related events):

- **7.2% vs 5.4% (ARI=1.8%) NNH 55**

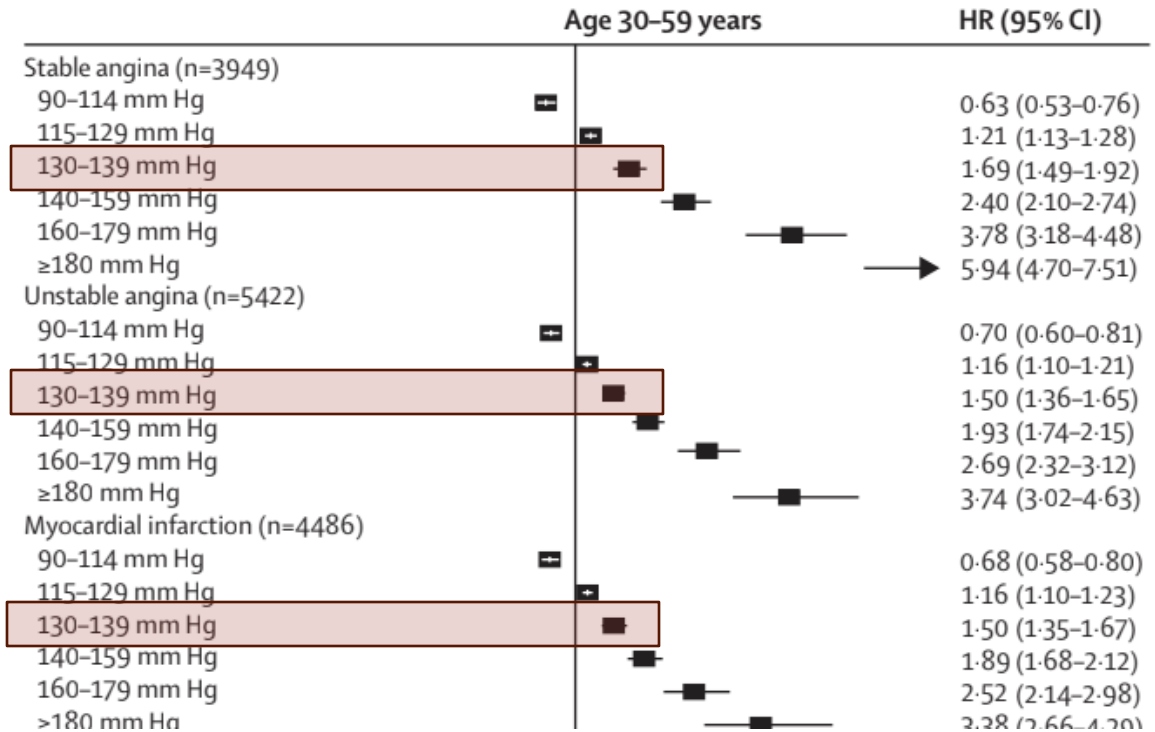
What do you say, Hypertension Canada?

HYPERTENSION CANADA 2025

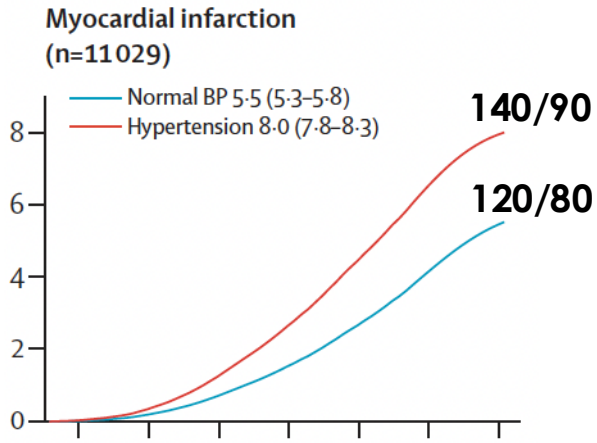
HYPERTENSION CANADA 2025

Recommendation	Strength of recommendation	Certainty of evidence
The definition of hypertension in adults is recommended as BP ≥ 130/80 mm Hg when measured with a validated device under optimal conditions.	Strong	Moderate
Treatment, including healthy lifestyle changes with or without pharmacotherapy, is recommended for adults with hypertension to achieve a target systolic BP < 130 mm Hg, provided the treatment is well tolerated.	Strong	High
For adults with hypertension requiring pharmacotherapy, low-dose combination therapy (ideally as a single-pill combination) is recommended as initial treatment, which includes drugs from 2 of the following 3 complementary classes of medications: ACEIs or ARBs, thiazide or thiazide-like diuretics, and long-acting dihydropyridine CCBs.	Strong	Moderate

DIAGNOSIS >130/80



Prospective cohort data
(2 studies, >1 million patients each)
As SBP ↑ >90, CV outcomes ↑
Above SBP 130, most outcomes SS ↑
>130/90 vs <120/80 HR 1.56



1. Lancet 2014;**383**:1899–911 2. Curr Hypertens Rep 2013;**15**:703–16

What we have here is a failure to communicate…

HTN Canada: *CMAJ 2025 May 26;197:e549-64*

Recommendation	Strength of recommendation	Certainty of evidence
Treatment, including healthy lifestyle changes with or without pharmacotherapy, is recommended for adults with hypertension to achieve a target systolic BP < 130 mm Hg, provided the treatment is well tolerated.	Strong	High

✓ **Presentation of mortality and MACE benefits:**

- **22% RRR** from MA of 7 RCTs (HTN 2024) for SBP <130
- NNT from SPRINT

??
- NNT mortality = **90**… but in cited MA above = **213**
- SPRINT was SBP <120, not <130

→ at ~3.5 yrs

?

✓ ???

Presentation of harms (from HTN MA):

- hypotension NNH **508** **3.5 yr NNH=130**
- acute kidney injury/failure NNH **1657** **3.5 yr NNH=212**

TREATMENT

- Start with 2 agents:
  - **They will need >1 eventually?** (US data)[1]: Canadian survey data, 46-48% patients on 2+ antiHTN drugs[2]
  - **Additive effects**: **One** agent ↓ SBP ~**8**mmHg, **two** decreases SBP ~**15**mmHg[3]
  - **Minimizes adverse effects?** Most are dose-related[4]; no difference in withdrawals due to AEs, but dizziness 5.4% vs 3.2%, NNH 46[5]

- Combination medication vs multiple single agents:
  -  ACEi-HCTZ combos similar cost as ACEi single entity, cost-savings (2009) Alberta ≈ $1-2 million, Canada≈ $27-45 million[6]
  - Adherence better in some studies[7]

OTHER CONSIDERATIONS… Side effects? Drug-drug interactions? Pill burden? Deprescribing? Patient preference?

1.Circulation 2012;126:2105-14. 2. Statistics Canada, 2018. 3. Lancet 2025;406:915-25. 4. BMJ 2003;326:1427. 5. J Hypertens 2019;37:1768-74. 6. Can J Clin Pharmacol 2009;16:e151-5. 7. Hypertension 2021;77:692-705.

for

Shot ~~Through~~

the Heart?

Does Influenza vaccination reduce CV events?

- Evidence: from 5 SRs (5-8 RCTs, 4,211-12,029 patients, follow-up 1.5-12 months).
- Largest, highest-quality, multi-country (mostly European) RCT compared one-time influenza vax to placebo in 2,532 pts ≤3 days after MI. At 1 year:
  - Death: 2.9% vs 4.9% placebo.
  - CVEs (death, myocardial infarction, stent thrombosis): 5.3% vs 7.2% placebo.
  - AEs: Local injection reactions: ~5% absolute increase.
- Primary Prevention: no diff in CVE (2 RCTs; 12 total events)
- CHF patients: RCT of 5129 pts: vaccination: @ 2 years, CVEs: 15% vs 18% placebo (NSS)

Bottom Line: For every 100 patients vaccinated for influenza within ~1 month after an acute coronary syndrome, there will be 2 fewer CVEs and 2 fewer deaths at one year. The impact of influenza vaccination in primary cardiovascular prevention and other cardiovascular conditions is less clear.

Shingles jab may reduce risk of heart attack, pioneering research reveals

First global systematic review finds vaccine associated with 18% lower risk of stroke or heart attack in adults

HTTPS://WWW.THEGUARDIAN.COM/SOCIETY/2025/AUG/28/SHINGLES-VACCINE-HEART-CARDIOVASCULAR-MEDICAL-RESEARCH ACCESSE

make an image of robert kennedy junior getting vaccinated

ChatGPT. 29-AUG-2025.

again but make him happier

ZOSTER VACCINATION AND CVD

- Observational study of **live** zoster vaccine and CVD
- Included all South Koreans aged >/=50 w/o CVD who received zoster vax (live vaccine only!) and unvaccinated control
  - propensity score matching, adjusted for sex, age, comorbididites, etc
- N=635961 vax vs 635961 control
- Mean age 61, 43% male. Median f/up 6 years

Eur Heart J. 2025;46:2991-3002.

	Events, *n* (%)		
	Unvaccinated	Vaccinated	HR (95% CI)
Any cardiovascular diseases outcome	102,776 (16.16)	78,463 (12.34)	**0.77 (0.76 to 0.78)**
MACE	14,549 (2.29)	10,284 (1.62)	**0.74 (0.71 to 0.77)**
Cerebrovascular disorders	23,249 (3.66)	17,040 (2.68)	**0.76 (0.74 to 0.78)**
Stroke	13,602 (2.14)	9626 (1.51)	**0.74 (0.71 to 0.77)**
Transient ischemic attack	11,022 (1.73)	8364 (1.32)	**0.79 (0.75 to 0.82)**
Dysrhythmia	40,233 (6.33)	30,740 (4.83)	**0.79 (0.77 to 0.81)**
Atrial fibrillation	5825 (0.92)	4025 (0.63)	**0.71 (0.67 to 0.76)**
Sinus tachycardia	3260 (0.51)	2405 (0.38)	**0.78 (0.73 to 0.85)**
Sinus bradycardia	1290 (0.20)	960 (0.15)	**0.77 (0.68 to 0.87)**
Ventricular arrhythmias	32,681 (5.14)	25,274 (3.97)	**0.80 (0.78 to 0.82)**
Inflammatory heart disease	125 (0.020)	96 (0.015)	0.76 (0.51 to 1.13)
Pericarditis	63 (0.010)	45 (0.007)	0.70 (0.40 to 1.23)
Myocarditis	62 (0.010)	54 (0.008)	0.88 (0.51 to 1.51)
Ischaemic heart disease	40,774 (6.41)	31,167 (4.90)	**0.78 (0.76 to 0.80)**
Acute coronary disease	12,610 (1.98)	10,118 (1.59)	**0.83 (0.80 to 0.86)**
Myocardial infarction	2999 (0.47)	1879 (0.30)	**0.65 (0.59 to 0.71)**
Angina	32,109 (5.05)	24,064 (3.78)	**0.77 (0.75 to 0.79)**
Other cardiac disorders	10,084 (1.59)	7177 (1.13)	**0.73 (0.70 to 0.77)**
Heart failure	9995 (1.57)	7122 (1.12)	**0.74 (0.70 to 0.77)**
Cardiac arrest	88 (0.014)	52 (0.008)	**0.56 (0.33 to 0.95)**
Cardiogenic shock	10 (0.0016)	13 (0.0020)	1.42 (0.44 to 4.52)
Thrombotic disorders	6633 (1.04)	4960 (0.78)	**0.78 (0.74 to 0.83)**
Arterial embolism and thrombosis	1441 (0.23)	1058 (0.17)	**0.76 (0.67 to 0.86)**
Pulmonary embolism	758 (0.12)	576 (0.09)	**0.83 (0.71 to 0.98)**
Deep vein thrombosis	4641 (0.73)	3452 (0.54)	**0.78 (0.73 to 0.83)**

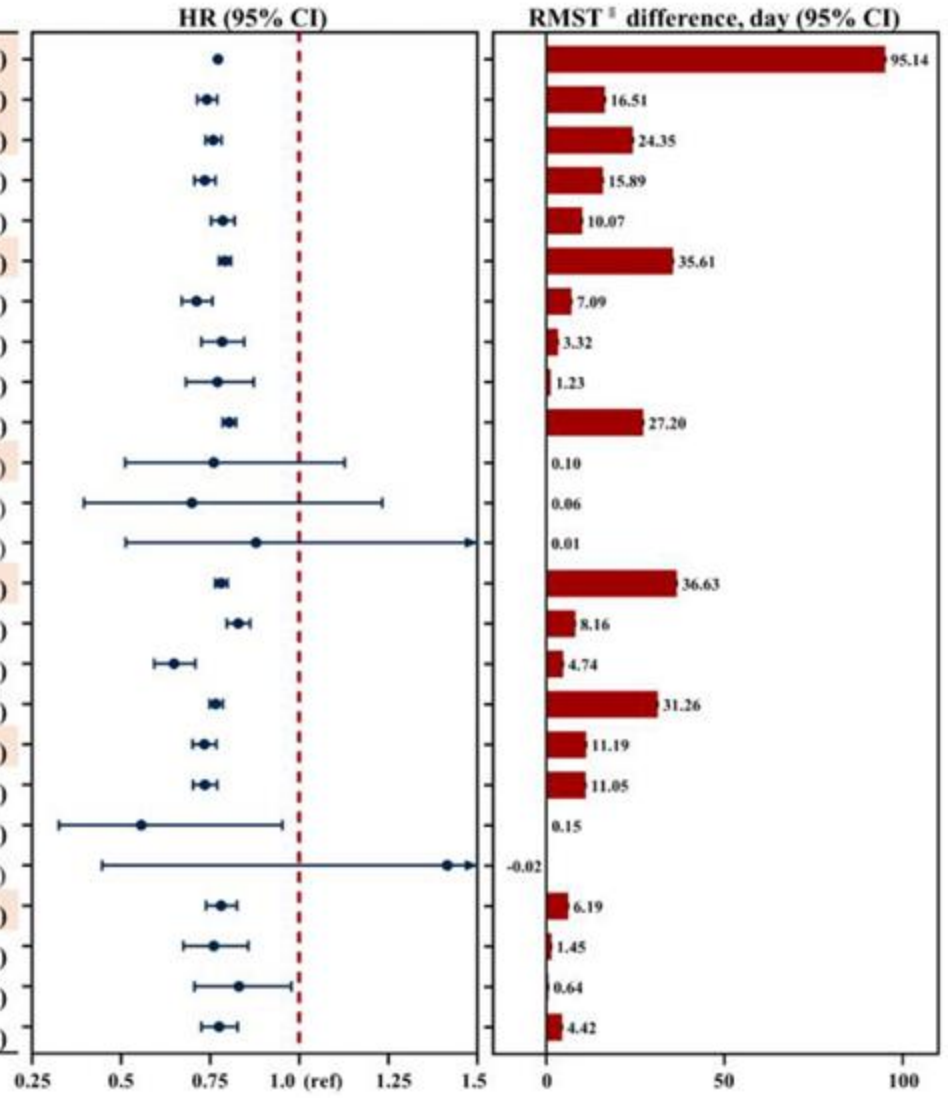


Figure 2 Hazard ratio (95% confidence interval) and restricted mean survival time for incident risk of overall cardiovascular events after zoster vaccination in the overlap-weighted cohort. ‖Estimated restricted mean survival time up to 10 years

	Exposure group		Comparison			
	n	No. of event	n	No. of event	HR (95% CI)	P value
Any HZ vaccine versus no HZ vaccine (model 1 matched population)						
MACE	45 958	3474	45 958	4060	0.76 (0.72 to 0.79)	<0.001
Coronary artery disease	45 958	1902	45 958	2331	0.73 (0.69 to 0.78)	<0.001
Stroke	45 958	1863	45 958	2116	0.79 (0.74 to 0.84)	<0.001
All-cause mortality	45 958	2793	45 958	4794	0.54 (0.52 to 0.57)	<0.001
Shingrix versus no HZ vaccine (model 2 matched population)						
MACE	14 142	858	14 142	1294	0.84 (0.76 to 0.91)	<0.001
Coronary artery disease	14 142	468	14 142	770	0.78 (0.69 to 0.88)	<0.001
Stroke	14 142	445	14 142	650	0.87 (0.77 to 0.99)	0.035
All-cause mortality	14 142	569	14 142	1561	0.53 (0.48 to 0.58)	<0.001
Zostavax versus no HZ vaccine (model 3 matched population)						
MACE	11 285	1674	11 285	1030	0.81 (0.75 to 0.88)	<0.001
Coronary artery disease	11 285	910	11 285	616	0.72 (0.65 to 0.80)	<0.001
Stroke	11 285	952	11 285	530	0.90 (0.81 to 1.01)	0.065
All-cause mortality	11 285	1496	11 285	1203	0.58 (0.53 to 0.62)	<0.001
Shingrix versus Zostavax (model 4 matched population)						
MACE	10 505	615	10 505	1574	1.09 (0.98 to 1.21)	0.104
Coronary artery disease	10 505	335	10 505	859	1.16 (1.01 to 1.34)	0.036
Stroke	10 505	310	10 505	900	0.96 (0.83 to 1.11)	0.582
All-cause mortality	10 505	378	10 505	1400	0.99 (0.87 to 1.12)	0.824

BMJ Open. 2025;15:e090428.

ZOSTER (SHINGLES VACCINE)

- ACC: 2 doses of recombinant zoster vaccine 2-6 months apart for those adults aged >/= 50 y
  - "to protect against increased risk of stroke and heart attack when infected. People with heart disease are at an increased risk of shingles infection."

https://www.acc.org/About-ACC/Press-Releases/2025/08/26/13/46/American-College-of-Cardiology-Issues-Vaccine-Guidance-for-Adults-with-Heart-Disease accessed 21-OCT-2025. Heidenreich et al. JACC online ahead of print.

ZOSTER VACCINE AND CVD

- My bottom line: Causation not established. Need RCTs.

Routine Beta-Blockers in Secondary Prevention — Approaching Retirement?

Tomas Jernberg, M.D., Ph.D.

NEJM Aug 30, 2024DOI: 10.1056/NEJMe2409646

BB POST-ACUTE MI RCTs

Acute MI: **2-4 days ago**
Mean age **61-65 years**, **77-81% male**
BB: **metoprolol or bisoprolol**

REDUCE-AMI n=5020 LVEF ≥50% (100%≥50%)	**ARR (%) @3.5 yrs**
Death or new MI	no diff
Death	no diff
MI	no diff
HF adm	no diff
AFib adm	no diff

NO

REBOOT n=8438 LVEF >40% (88%≥50%)	**ARR (%) @3.7 yrs**
Death, MI, HF adm	no diff
Death	no diff
MI	no diff
HF adm	no diff
VFib	no diff

NO

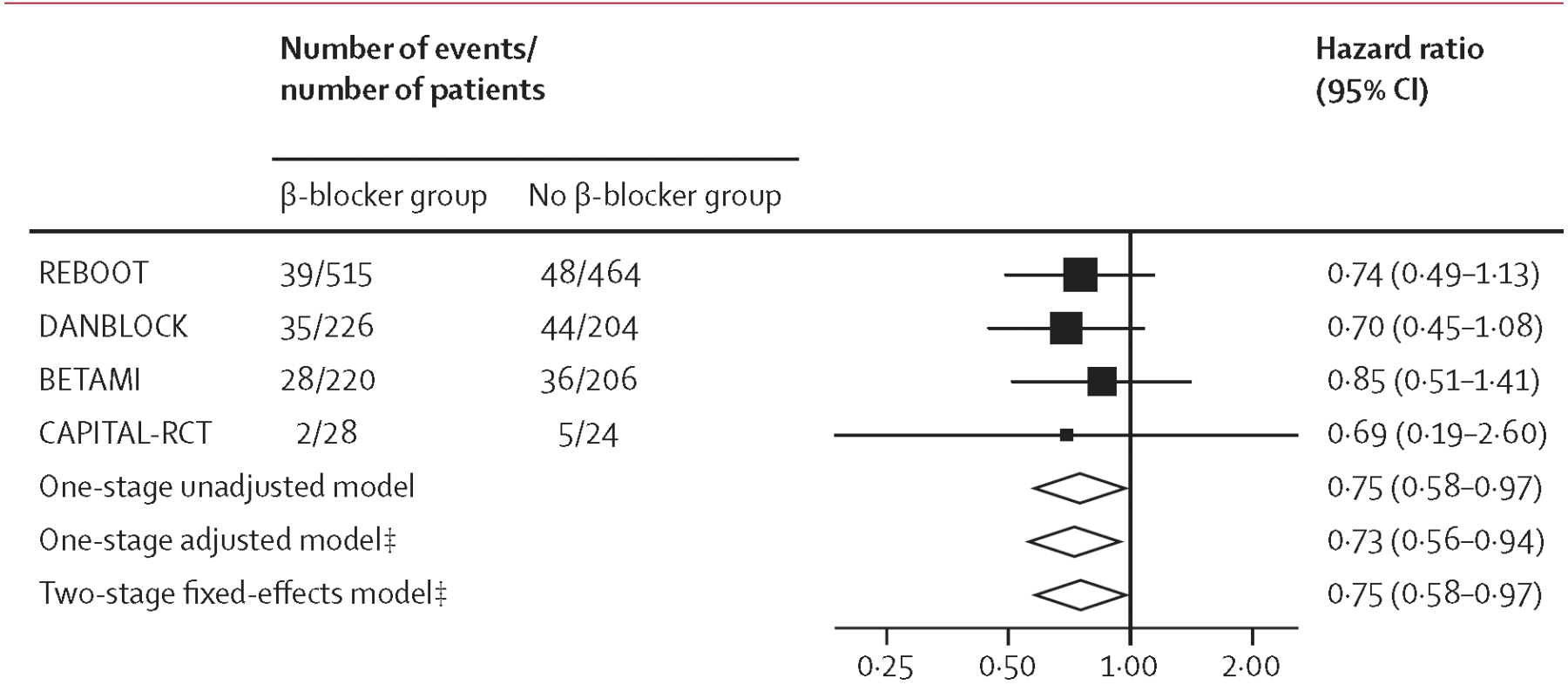
BETAMI-DANBLOCK n=5574 LVEF ≥40% (77%≥50%)	**ARR (%) @3.5 yrs**
Death, MI, stroke, HF, revasc, VA	**2.1**
Death	no diff
MI	**1.6**
HF adm	no diff
VArrhythmia	no diff

YES

β blockers after myocardial infarction with mildly reduced ejection fraction: an individual patient data meta-analysis of randomised controlled trials

=40-49%

Lancet Aug 30, 2025



ARR = 2.3%

*Composite of all-cause death, new myocardial infarction, or heart failure.

MAKING SENSE OF THIS

- **Future MA** (being done): null findings in the 13500 would likely override the small positive in the 5500 and drive the overall to a null

  → i.e. BB probably unnecessary for most patients post-MI, if they do something (e.g. in mildly reduced EF) it's likely small

- **Future guidelines**: BB post-MI won't likely be a quality measure of good care and if their use remains a recommendation/suggestion, it will be a weak/conditional one

"The meta-lesson of these strong trials is that our established therapies require expiration dates. As practice changes, we should be open to challenging established beliefs. Few better examples exist in medicine than the post-MI beta-blocker story." ***- John Mandrola (Medscape Aug 31, 2025)***

BB post-MI RCTs (2024-2026)

But what about my patient who's **already on a BB?**

Acronym†	ClinicalTrials.gov No.	No. of Patients	Trial Location	Patients' Condition
✓ REDUCE-AMI[8]	NCT03278509	5000	Sweden, Estonia, and New Zealand	Acute MI with LVEF >50% and receipt of angiography
✓ DANBLOCK	NCT03778554	2760	Denmark	≤2 wk after MI and LVEF >40%
✓ BETAMI	NCT03646357	2900	Norway	Type 1 MI treated with PCI or lysis
✓ REBOOT	NCT03596385	8468	Spain and Italy	MI without heart failure and with LVEF >40%
SMART DECISION **Mar 2026**	NCT04769362	2540	South Korea	Receiving beta-blockers for ≥1 yr after MI
✓ AβYSS	NCT03498066	3700	France	STEMI or NSTEMI treated with beta-blocker, without heart failure or LVEF <40%
ABBREVIATE **Dec 2026**	NCT05081999	8500	Canada	Stable ischemic heart disease, without left ventricular dysfunction or heart failure

N Engl J Med 2024;390:1434-1436

ORIGINAL ARTICLE

Beta-Blocker Interruption or Continuation after Myocardial Infarction

ABYSS

WHO: n=3698

- age 63, 83% male
- Time since MI **2.9 yrs**, LVEF **≥40%**
- meds: ASA/statin 95%, ACEi/ARB 74%

WHAT:

- stop BB (tapered if high dose) vs. continue BB (72% bisoprolol) **X 3 yrs**

PRIMARY outcome:

- death, non-fatal MI or stroke, **(hard)** or other CV hospital admission **(softer)**

RESULTS:

21.1% (BB) vs **23.8%** (no BB)

ARI = 2.8% (95%CI <0.1-**5.5**)

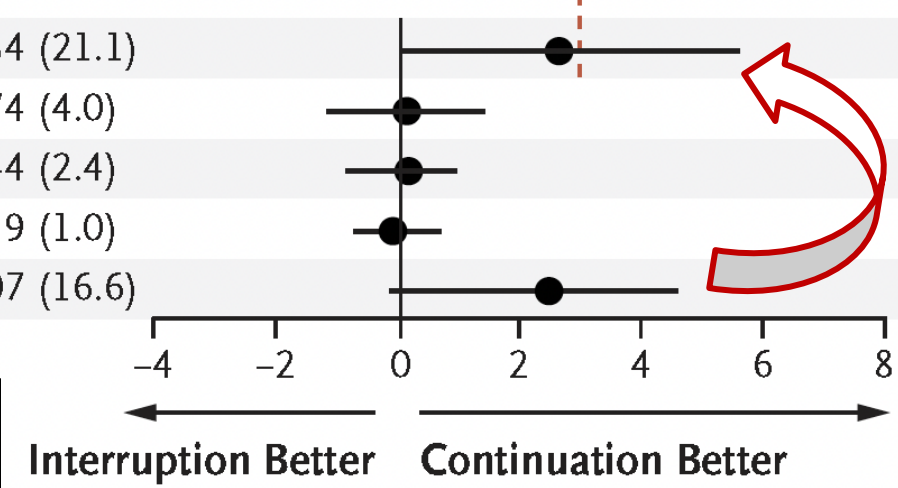
i.e. NOT non-inferior

NEJM 2024, Aug 30. DOI: 10.1056/NEJMoa2404204

WHAT'S IN YOUR COMPOSITE GIFT BASKET?

(i.e. what's driving our outcome?)

End Point	Beta-Blocker Interruption (N=1846)	Beta-Blocker Continuation (N=1852)	Risk Difference (95% CI) (percentage points)
	no. of patients with event (%)		
Primary end point	432 (23.8)	384 (21.1)	2.8 (<0.1 to 5.5)
Death	76 (4.1)	74 (4.0)	0.1 (–1.2 to 1.4)
Myocardial infarction	46 (2.5)	44 (2.4)	0.1 (–0.9 to 1.1)
Stroke	18 (1.0)	19 (1.0)	–0.1 (–0.7 to 0.6)
Hospitalization for cardiovascular reason	349 (18.9)	307 (16.6)	2.3 (–0.1 to 4.8)



Which outcome is softest?
Which outcome is most affected by non-blinding?

	stop	keep
Hospitalization for cardiovascular reason — no. (%)	349 (18.9)	307 (16.6)
Coronary-related reason	263 (14.2)	221 (11.9)
Angina or ischemia	67 (3.6)	55 (3.0)
Angiography	146 (7.9)	117 (6.3)
Percutaneous coronary intervention	90 (4.9)	84 (4.5)
Coronary-artery bypass grafting	4 (0.2)	4 (0.2)
Heart failure	34 (1.8)	23 (1.2)
Tachycardia		
Supraventricular	28 (1.5)	28 (1.5)
Ventricular	6 (0.3)	7 (0.4)
Syncope or dizziness	28 (1.5)	25 (1.3)
Invasive procedure aside from pacemaker implantation	31 (1.7)	24 (1.3)
Pacemaker or equivalent implantation	11 (0.6)	11 (0.6)
Conduction disorder	2 (0.1)	2 (0.1)
High blood pressure	5 (0.3)	3 (0.2)
Peripheral artery disease or limb ischemia	34 (1.8)	23 (1.2)
Aortic dissection or aneurysm	4 (0.2)	8 (0.4)
Valvular reason	4 (0.2)	4 (0.2)
Bleeding event	18 (1.0)	15 (0.8)
Other cardiovascular event	18 (1.0)	11 (0.6)

WHAT'S CONSTITUTES A **HOSPITALIZATION** THESE DAYS?

"you've been taken off of your BB… I'm concerned you're having angina → angiography please"

More stable CAD trials to come. In the meantime…

- *If patient already on BB chronically…*
  - **stopping won't cause death, MI, or stroke**

    BUT MAY increase CV hospitalization risk (NNH 44)?

And now it's time for…

IMPORTANT QUESTIONS *from medscape.com*

Is a Year of Dual Antiplatelet Therapy Magical Thinking?

Should Aspirin Be the Second-Line Antiplatelet in CAD?

Why Are Scientists Getting Mice Drunk?

a**DAPT**ing our understanding

DAPT knowledge over time…

2001

CURE trial: ASA+clopidogrel vs ASA alone → **DAPT good**

2006

DAL Academic Detailing Service: ASA+clopidogrel deep dive → **DAPT good with most benefit in first 3 months**

2015

Longer for DAPT DES?

BMJ MA:

3-6m vs 12 m → less bleeds + no diff in MI or death

2021

MASTER DAPT: in high bleeding risk, **1-month not worse than 3 for net adverse clinical events**

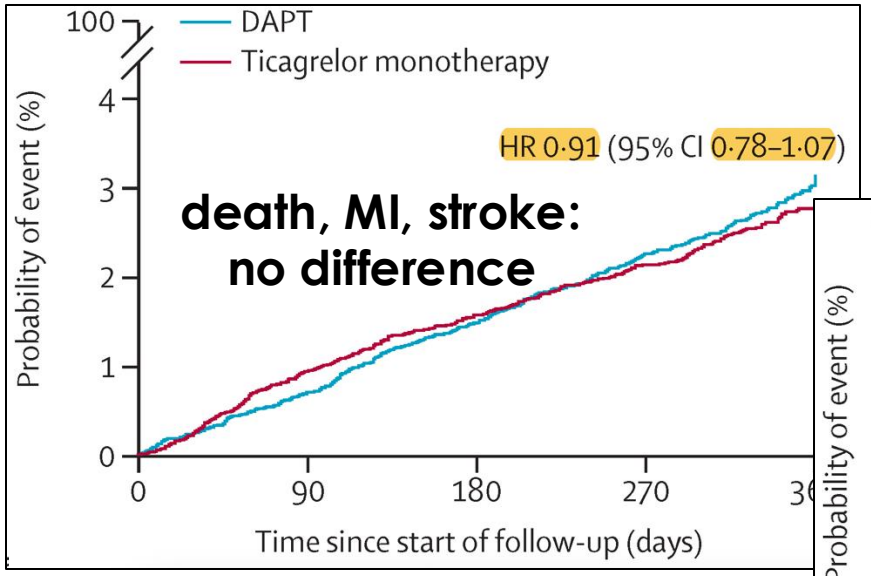
aDAPTing with TICAGRELOR

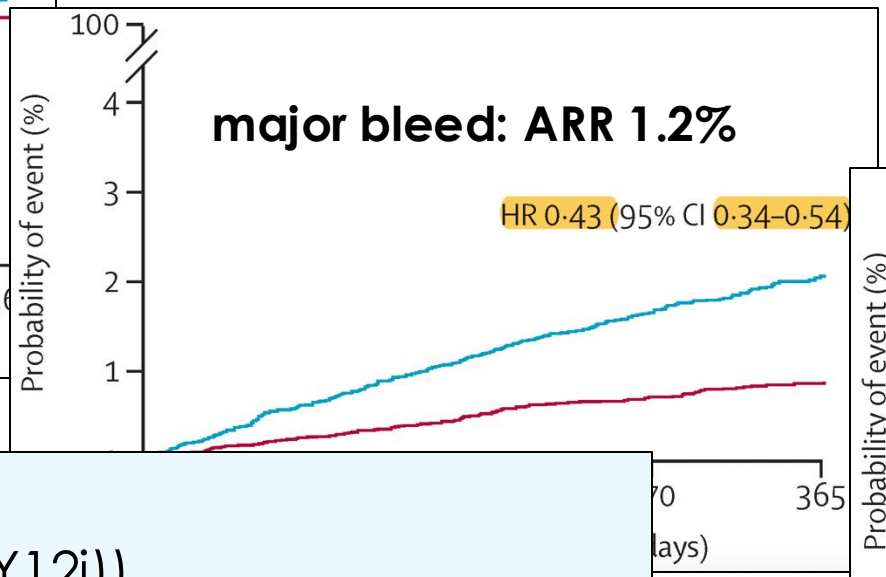
De-escalation to ticagrelor monotherapy versus 12 months of dual antiplatelet therapy in patients with and without acute coronary syndromes: a systematic review and individual patient-level meta-analysis of randomised trials

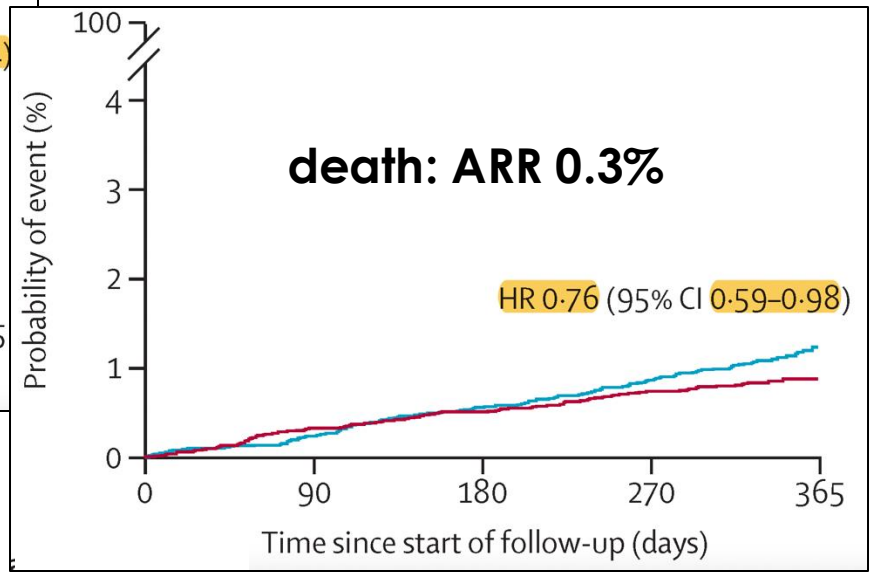
Lancet 2024 Sep 7;404(10456):937-948

6 RCTs (2019-2024), **n=24,407**
- PCI with DES (74% ACS)

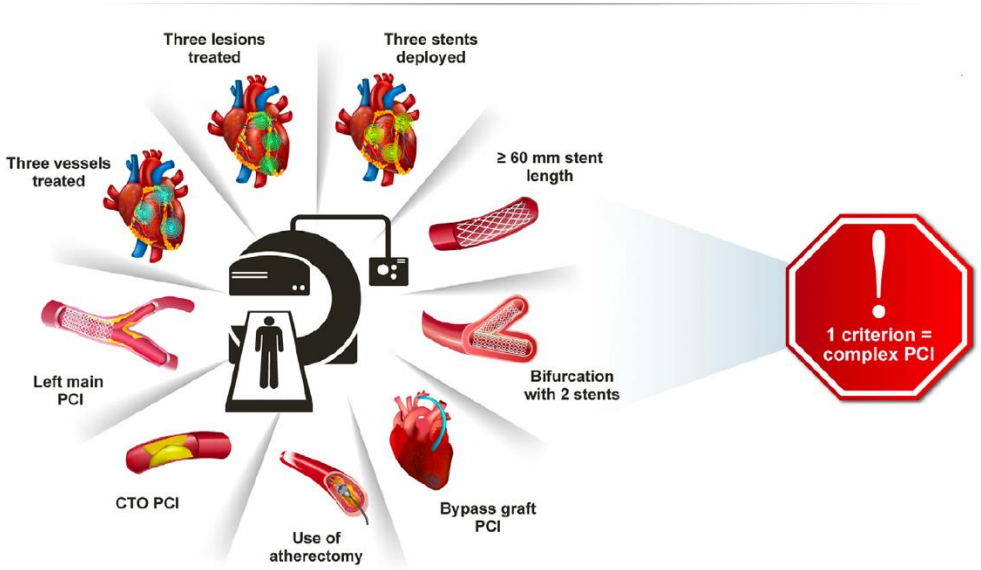
INTERVENTION:
- **LONG DAPT = 12 months** vs.
- ✓ **SHORT DAPT = ~3 months** (median; range 2-14 wks)







Similar findings in:
Am J Cardiol 2024 MA (any P2Y12i))
Ann Intern Med 2025 MA (ticagrelor)
JAMA Open 2024 MA (older adults, any P2Y12i or ASA)



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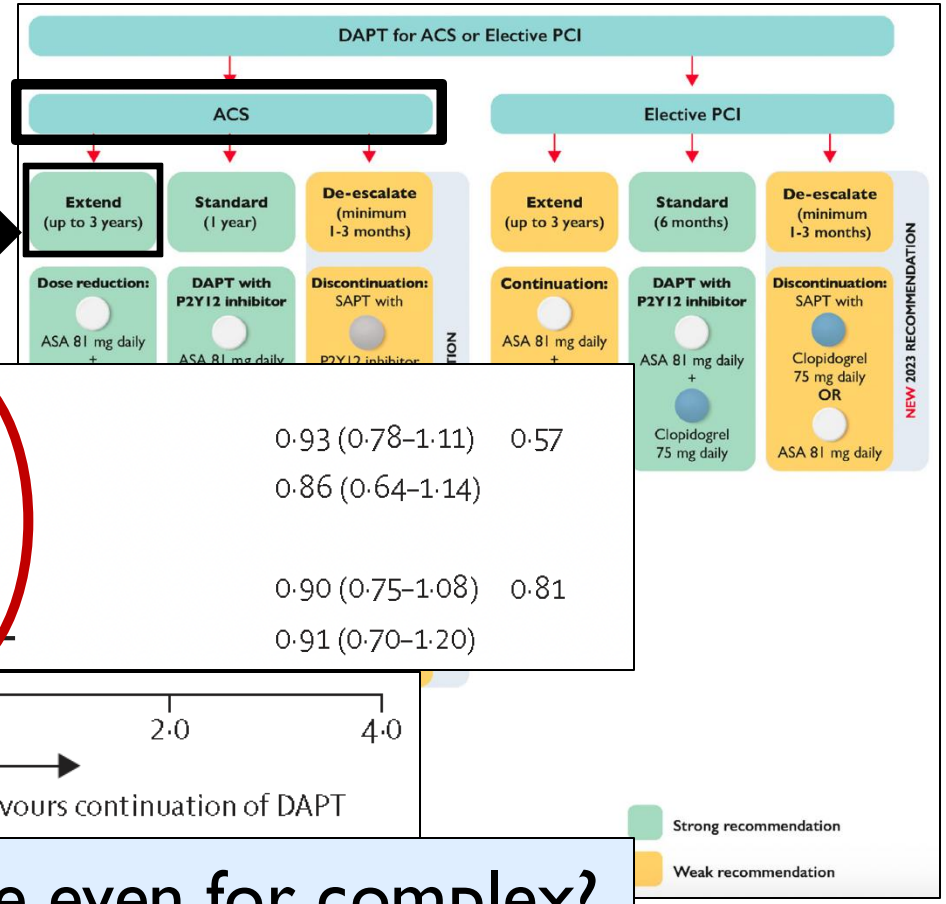
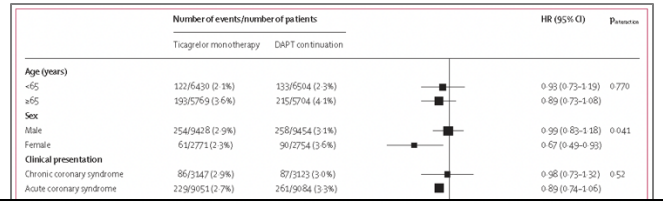
"longer duration of DAPT may be considered"

GUIDELINES AREN'T CLEAR

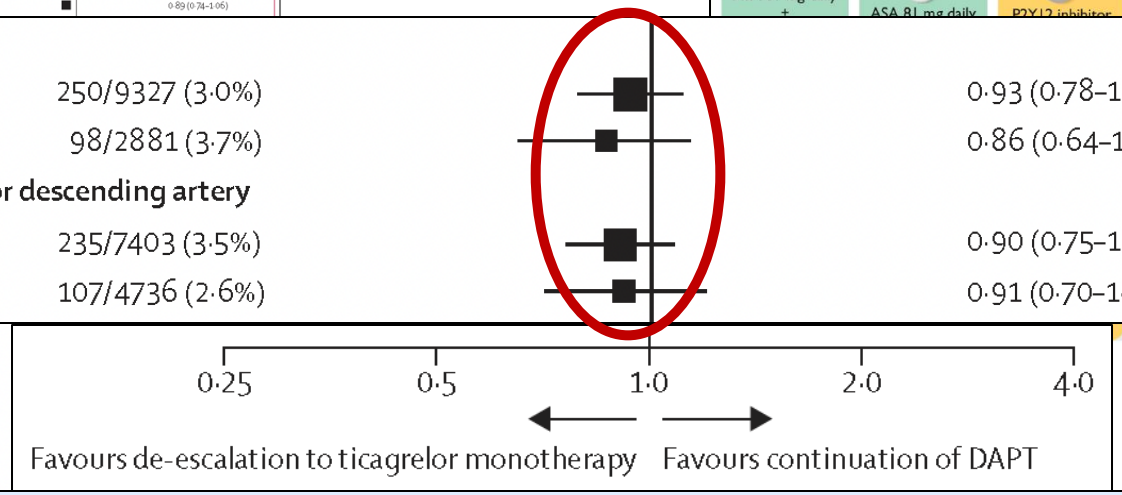


Lancet 2024;404(10456):937-948

De-escalation to ticagrelor monotherapy versus 12 months of dual antiplatelet therapy in patients with and without acute coronary syndromes: a systematic review and individual patient-level meta-analysis of randomised trials



Complex percutaneous coronary intervention				
No	230/9260 (2·7%)	250/9327 (3·0%)	0·93 (0·78–1·11)	0·57
Yes	85/2939 (3·2%)	98/2881 (3·7%)	0·86 (0·64–1·14)	
Percutaneous coronary intervention of left main or left anterior descending artery				
No	209/7339 (3·1%)	235/7403 (3·5%)	0·90 (0·75–1·08)	0·81
Yes	99/4790 (2·3%)	107/4736 (2·6%)	0·91 (0·70–1·20)	



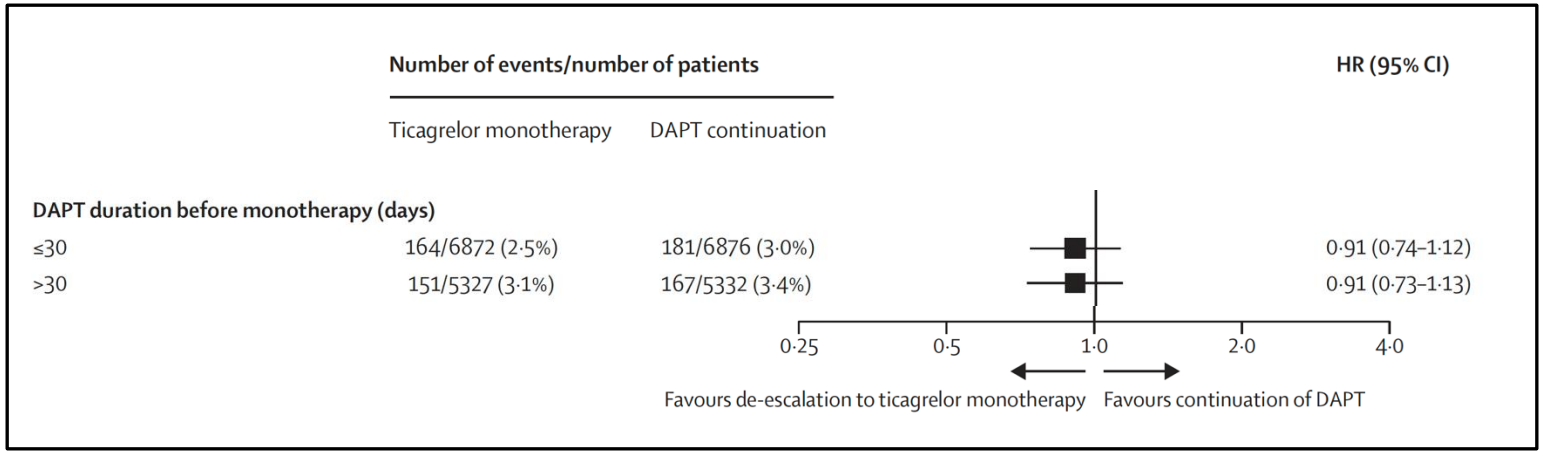
≤3 months of DAPT seems fine even for complex?

Lancet 2024;404(10456):937-948

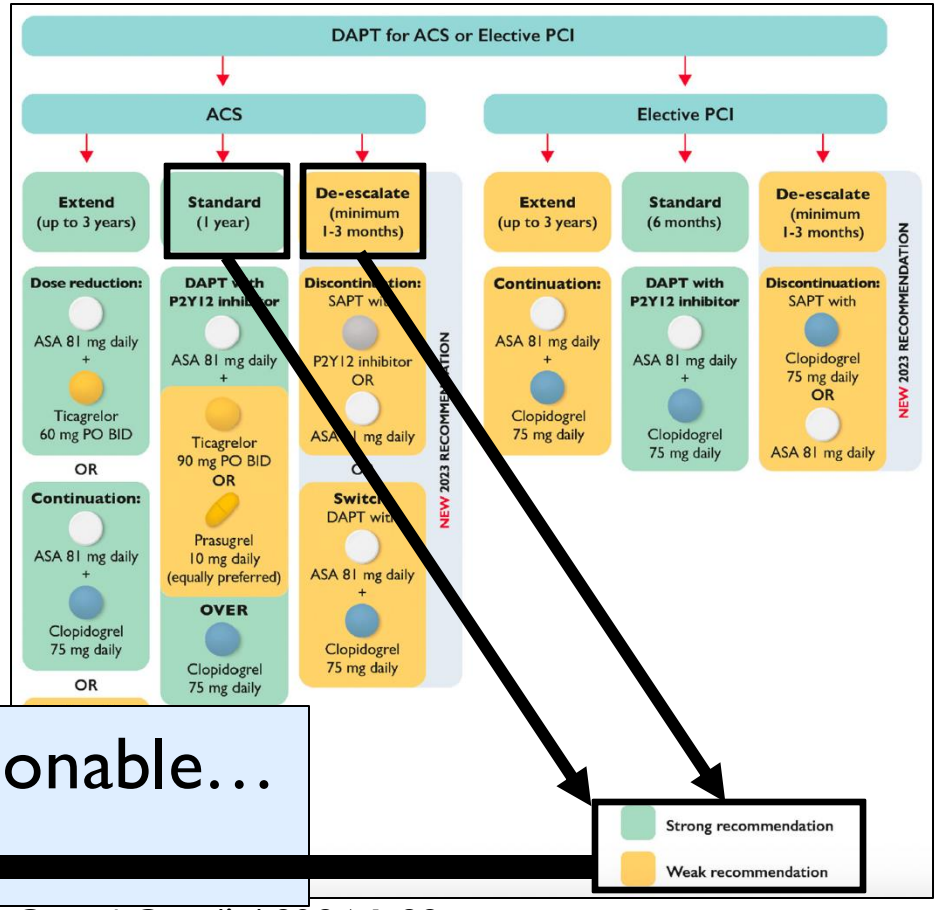
De-escalation to ticagrelor monotherapy versus 12 months of dual antiplatelet therapy in patients with and without acute coronary syndromes: a systematic review and individual patient-level meta-analysis of randomised trials

BUT…

in subgroup analysis



GUIDELINES AREN'T CLEAR



Shorter (1-3 months) is looking more reasonable…
and "weak" is getting stronger

Can J Cardiol 2024:1-22

THIS JUST IN…

too long

1-month vs 12-month DAPT…

TARGET-FIRST (NEJM Aug 31, 2025):

- **WHO:** n=1942 acute MI + PCI
  - DAPT X 1 m w/o ischemia or bleeding
- **INTERVENTION:** Stop ASA (keep P2Y12i) vs. continue DAPT X another 11 m
- **RESULTS:**
  - MACE: **no difference** (1.6 vs 1.6%)
  - Major bleed: **no difference** (0.7 vs 0.7%)
  - Clinically important bleed: **3% ARR**

too short

4 days vs 12-month DAPT…

NEOMINDSET (NEJM Aug 31, 2025):

- **WHO:** n=3410 acute MI + PCI
  - within 4 d of hospitalization
- **INTERVENTION:** Stop ASA (keep P2Y12i) vs. continue DAPT X 12 m
- **RESULTS:**
  - MACE: **ARI 1.5%** (not non-inferior)
  - Maj bleed: **3% ARR**

1-3
MONTHS
SEEMS JUST
RIGHT

DOWN with ASA?

*→ what's the best **single** antiplatelet?*

2 IPD meta-analyses… long term DAPT → **monotherapy with P2Y12i *vs* ASA**

- *BMJ* 2025;389:e082561 (Giacoppo):
  - 5 RCTs, n=16,117
  - **P2Y12i (= ticagrelor or clopidogrel) vs ASA**
- *Lancet* 2025, Aug 31 (Valgimigli):
  - 7 RCTs, n=28,982
  - **P2Y12i (=clopidogrel) vs ASA**

@ ~5 yrs…

- MACE: **NNT 46**
- Major bleed: **no difference**

clopidogrel or ticagrelor?
→ subgroup analysis:
no difference

BOTTOM LINE…

- When stepping down → P2Y12i better
- Which P2Y12i? → either (clopidogrel $55/90d less)
- Should we switch patients currently on ASA**???**

SPEAKING OF

ING

What about switching warfarin to DOAC in frail adults?

https://imgur.com/gallery/funny-newspaper-headline-fails-ldlmhK3. 23-OCT-2025

DOACs ARE GREAT AND ALL…

BUT DO WE UPSET THE APPLE CART?

FRAIL-AF Randomized Controlled Trial

WHO: n=1323

- age ≥75 yrs (mean 83)
- AFib (on warfarin) + frailty
- eGFR 63, BMI 27
- mean CHADVS2-vasc = 4

WHAT:

- switch from warfarin → DOAC vs. stay on warfarin (INR 2-3) **X 1 yr**

PRIMARY outcome:

- major bleed or clinically relevant non-major bleed complication

BOTTOM-LINE: Switching to a DOAC in frail older adults on warfarin results in more bleeding (non-major, NNH 17) and no change in thromboembolic events.

RESULTS:

15.3% (DOAC) vs 9.4% (warfarin)
ARI: 5.9% (NNH 17)

Major bleeding:
3.6% (DOAC) vs **2.4%** (warfarin) (NS)

No difference in thromboembolic events (2.4% vs 2.0%) or death (6.7% vs 7%)

Circulation 2024;149:279–289

then along came…

COMBINE-AF (JACC 2025;86(6):426-39)

- Post-hoc analysis of the 4 big DOAC vs warfarin RCTs (n=58,634)

→ n=5913 frail, ≥75, and VKA-experienced

BOTTOM-LINE: Switching to DOAC in frail older adults on warfarin is reasonable if you/patient prefer

TABLE 2 Efficacy Outcomes in COMBINE-AF of DOAC vs Warfarin

	Frail, Elderly, VKA Experienced Patients (N = 5,903)				
	Warfarin (n = 2,908)		SD-DOAC (n = 3,005)		
	n	%/y	n	%/y	HR (95% CI)
Stroke or SEE	137	2.39	119	1.99	0.83 (0.65-1.07)
Stroke	125	2.17	109	1.82	0.84 (0.65-1.08)
Ischemic	86	1.49	93	1.55	1.04 (0.78-1.40)
Hemorrhagic	34	0.58	13	0.21	0.37 (0.19-0.70)
Disabling or fatal	75	1.29	65	1.08	0.83 (0.59-1.16)
SEE	13	0.22	13	0.21	0.96 (0.45-2.08)
All-cause death	387	6.61	383	6.30	0.95 (0.83-1.10)
CV death	228	3.90	214	3.52	0.91 (0.75-1.09)
Hospitalization	1,202	27.23	1,229	26.96	0.99 (0.92-1.07)

TABLE 3 Safety and Net Clinical Outcomes in COMBINE-AF of DOAC vs Warfarin Group

	Frail, Elderly, VKA Experienced Patients (n = 5,903)				
	Warfarin (n = 2,908)		SD-DOAC (n = 3,005)		
	n	%/y	n	%/y	HR (95% CI)
Major bleeding	269	5.58	282	5.89	1.06 (0.90-1.25)
Fatal bleeding	27	0.54	12	0.24	0.46 (0.23-0.90)
Intracranial bleeding	66	1.33	19	0.38	0.29 (0.17-0.48)
Major or CRNM bleeding	649	14.67	634	14.42	1.00 (0.90-1.12)
GI bleeding	91	1.85	164	3.37	1.83 (1.42-2.36)
CRNM bleeding	432	9.52	407	8.97	0.97 (0.85-1.11)
Primary NCO[a]	658	11.92	682	12.05	1.01 (0.91-1.13)
Secondary NCO[b]	481	8.39	457	7.64	0.91 (0.80-1.03)

GLP-1s & HFpEF

SEMAGLUTIDE… HAVE YOU HEARD OF IT?

CURRENT RCTs:	n	duration (y)	outcome
SUSTAIN-6 (DM2+CVD or CKD) 1mg	3297	2	↓ MACE
SELECT (Obesity/Overwt+CVD, no DM) 2.4mg	17604	3.3	↓ MACE
FLOW (CKD+DM2) 1mg	3533	3.4	↓ MACE, death, eGFR drop ≥50%
STEP-HFpEF (obesity+HFpEF) 2.4mg **STEP-HFpEF DM** (obesity+HFpEF+DM) 2.4mg	1145	1	Improved HF symptoms, QoL, exercise function

All 4 RCTs… - Involved patients with or history of **HFpEF**
- Analyzed **HF-related outcomes** within the HFpEF population of each trial either prespecified (SELECT, STEP-HFpEF, and STEP-HFpEF DM) or post-hoc (FLOW)

SEMAGLUTIDE… FOR HARD HF OUTCOMES?

Lancet 2024;404: 949–61

Semaglutide versus placebo in patients with heart failure and mildly reduced or preserved ejection fraction: a pooled analysis of the SELECT, FLOW, STEP-HFpEF, and STEP-HFpEF DM randomised trials

- **WHO**: n=3743, 85% NYHA class I/II, 25% DM2, 76% CVD, mean BMI 34

	Concomitant medications		
	β blockers	1542 (80·6%)	1495 (81·7%)
*	SGLT2 inhibitor	133 (6·9%)	125 (6·8%)
	Diuretics	1136 (59·4%)	1137 (62·2%)
	Loop diuretics	672 (35·1%)	681 (37·2%)
*	Mineralocorticoid receptor agonists	421 (22·0%)	415 (22·7%)
	Thiazides	211 (11·0%)	218 (11·9%)
	ACE inhibitors, ARB, or ARNIs	1587 (82·9%)	1521 (83·2%)

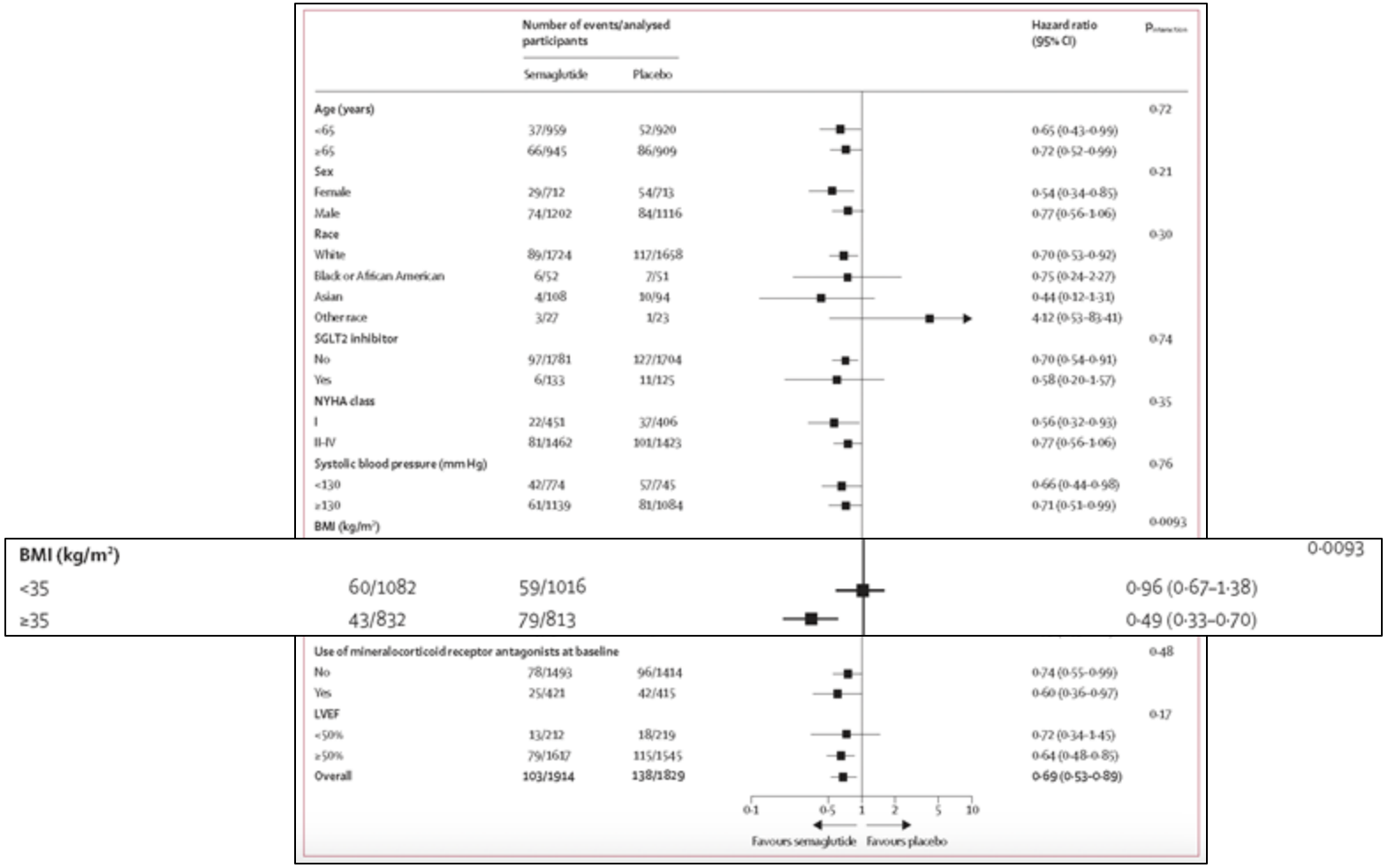
- **PRIMARY OUTCOME:** CV death or worsening HF (hosp or urgent visit)
  - **ARR = 0.9%/yr**
  - Individual components:

Worsening HF → **ARR 0.7%/yr**

CV death → **no different**

- AEs leading to d/c → **ARI 5.3%/yr**

SEMAGLUTIDE… FOR HARD HF OUTCOMES?



	Semaglutide	Placebo	Hazard ratio (95% CI)	$P_{interaction}$
Age (years)				0·72
<65	37/959	52/920	0·65 (0·43–0·99)	
≥65	66/945	86/909	0·72 (0·52–0·99)	
Sex				0·21
Female	29/712	54/713	0·54 (0·34–0·85)	
Male	74/1202	84/1116	0·77 (0·56–1·06)	
Race				0·30
White	89/1724	117/1658	0·70 (0·53–0·92)	
Black or African American	6/52	7/51	0·75 (0·24–2·27)	
Asian	4/168	10/94	0·44 (0·12–1·31)	
Other race	3/27	1/23	4·12 (0·53–83·41)	
SGLT2 inhibitor				0·74
No	97/1781	127/1704	0·70 (0·54–0·91)	
Yes	6/133	11/125	0·58 (0·20–1·57)	
NYHA class				0·35
I	22/451	37/406	0·56 (0·32–0·93)	
II–IV	81/1462	101/1423	0·77 (0·56–1·06)	
Systolic blood pressure (mm Hg)				0·76
<130	42/774	57/745	0·66 (0·44–0·98)	
≥130	61/1139	81/1084	0·71 (0·51–0·99)	
BMI (kg/m²)				0·0093
BMI (kg/m²)				0·0093
<35	60/1082	59/1016	0·96 (0·67–1·38)	
≥35	43/832	79/813	0·49 (0·33–0·70)	
Use of mineralocorticoid receptor antagonists at baseline				0·48
No	78/1493	96/1414	0·74 (0·55–0·99)	
Yes	25/421	42/415	0·60 (0·36–0·97)	
LVEF				0·17
<50%	13/212	18/219	0·72 (0·34–1·45)	
≥50%	79/1617	115/1545	0·64 (0·48–0·85)	
Overall	103/1914	138/1829	0·69 (0·53–0·89)	

BOTTOM LINE: In those with **HFpEF, semaglutide…**

- reduces HF-related urgent visits & hospitalizations (NNT 143/yr) (primarily in obese patients, most not on MRA or SGLT2i)
- has no effect on CV death
- improves QoL (NNT 6/yr for clinically meaningful change)
- Increases withdrawal due to AEs (NNH 18/yr)

Lancet 2024;404: 949–61.

SEMAGLUTIDE OBESITY & HFpEF

- Pooled analysis of STEP-HFpEF and STEP-HFpEF DM RCTs
- Mean age: 70, 50% female, BMI 37, 104kg, KCCQ-CCS=60, 6-minute walk: 295m, 71% class II
- N=1145. Median follow-up 400 days
- KCCQ-CCS improved 15 vs 7.5 (placebo). SS
  - Proportion improved: 43% vs 28% (placebo), SS
- 6-minute walk improved: 16.7m vs worsened 0.3m (placebo), SS
  - Proportion improved: 47% vs 33%
- Hospitalization or urgent visit for HF: 1% vs 5% (SS); note this is 1 event vs 30 in placebo…

Lancet. 2024;403:1635-48.

TIRZEPATIDE: OBESITY & HFpEF

- 731 patients with HFpEF and obesity given tirzepatide 15mg weekly or placebo x 52 weeks
- Baseline weight 103kg, BMI 38, NYHA class II, Baseline KCCQ-CSS 53, 6-minute walk distance ~300m, 48% had T2DM
- Median follow-up: 104 weeks
- Death from CVD or worsening HF (composite): 9.9% versus 15.3% placebo, SS
  - Only 13 total deaths from CVD
  - HF hospitalization: 3.3% vs 7.1% (placebo), SS
  - All-cause hospitalizations not reported
- KCCQ-CSS change at 52 weeks: 19.5 vs 12.7 (placebo), SS
- 6-minute walk at 52 weeks: 26 versus 10 (placebo), SS
- Stopping for AE: 6.3% vs 1.4% (placebo)

NEJM. 2025;392:427-37.

SUMMARY

- Let patients choose what time they take BP meds
- Hypertension Canada Guidelines: Lowering treatment thresholds?? and targets decreases overall CV risk but increases adverse events a similar amount…how low is dependent on CV risk, risk of harm, and preference
  - Initial treatment with multiple drugs: maybe.
- Flu vaccine for secondary CVD prevention: Yes! Shingles vaccine for CVD prevention: Not yet.
- BB likely unnecessary for most patients post-MI; may provide small benefit in mildly reduced EF; if already on BB chronically for CAD, uncertain if stopping is bad… more to come
- 1-3 months of DAPT makes sense for most patients post-MI… step down to ticagrelor or clopidogrel vs ASA
- Switching to DOAC in frail older adults on warfarin is reasonable if you/patient prefer
- GLP-1s and obesity with HFpEF: ~43% will have improved QoL vs 28% placebo at ~1 year, and ~47% will be able to walk (22m) further in a 6-minute walk test vs 33% placebo. Tirzepatide may reduce HF hospitalizations.

QUESTIONS?

University of Manitoba