Institut de recherche
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Dual antiplatelet therapy (DAPT) in 2023 - The McGill Experience

James (Jay) Brophy MD PhD

Professor
Departments of Medicine and of Epidemiology, Biostatistics, and Occupational Health
McGill University

Conflicts of Interest

- None

Learning Objectives

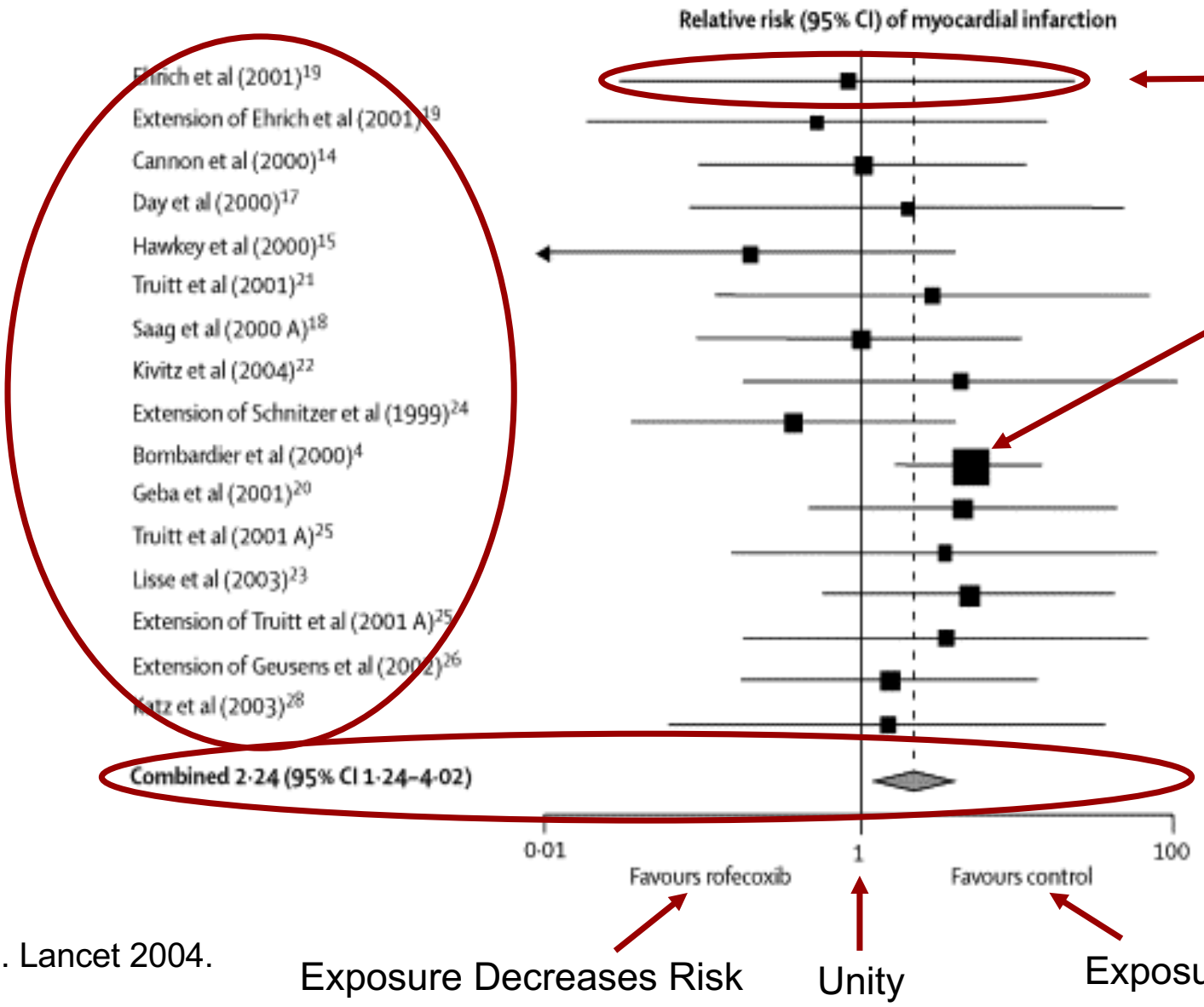
1. Understand the strengths and weaknesses of different research designs
2. Understand the current evidence base comparing different DAPT regimes
3. Appreciate the new research evidence, generated locally, into the comparative effectiveness of the different DAPT regimes

Acknowledgement

This work largely comes from Stephen Kutcher's PhD thesis

Background

Forest Plot



Included Studies

Study-Specific RR (95% CI)

Box Size = Weight

Pooled Estimate

Exposure Decreases Risk

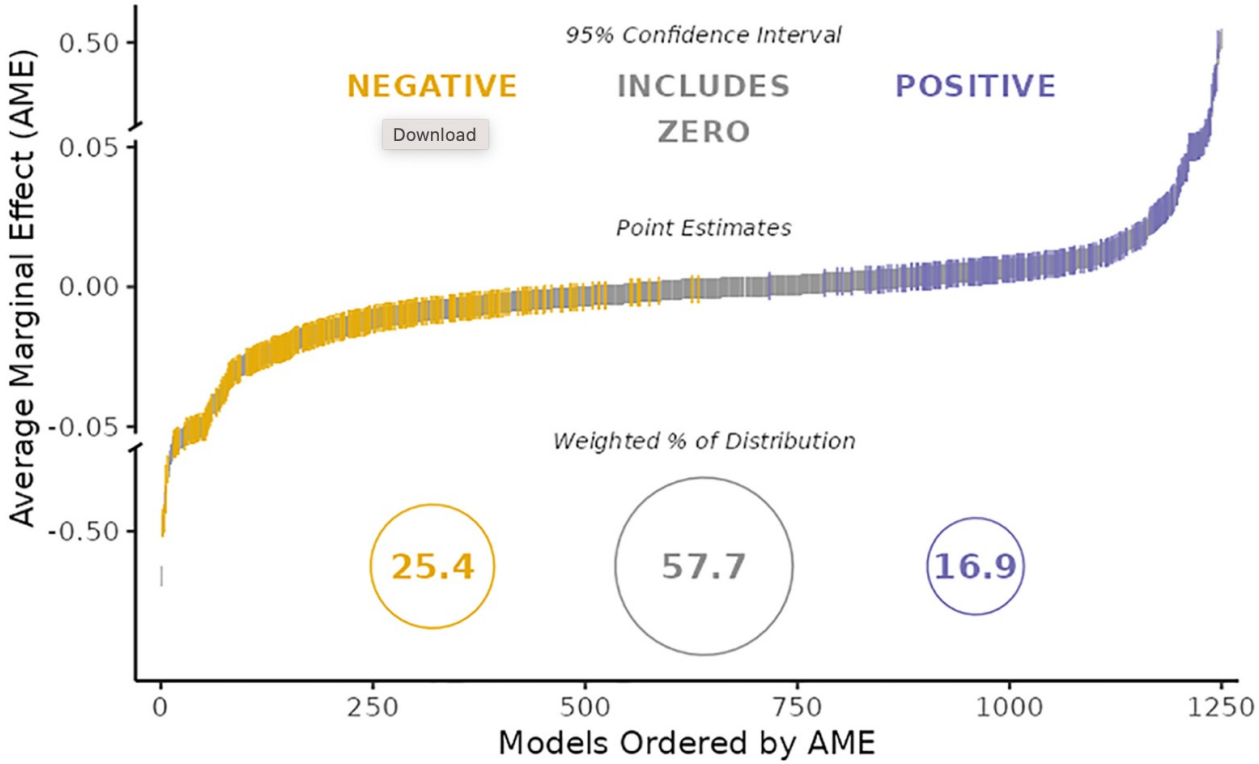
Unity

Exposure Increases Risk

Juni et al. Lancet 2004.

It’s not only about the data

- Statistical inferences require a mathematical model
- A mathematical model aims to explain the data generating mechanism -> better understanding & decision making



Broad variation in the findings from 73 teams testing the same hypothesis with the same data. The distribution of estimated AMEs across all converged models (n = 1,253) includes results that are negative (yellow; in the direction

doi:https://doi.org/10.1073/pnas.2203150119

Statistical Analyses

- Fixed-effects Models: Assume no between-study heterogeneity (i.e., all variability present is within-study variability that is due to chance alone).
  - E.g., Peto, Mantel Haenszel

- Random-effects Models: Assume the presence of both within- and between-study heterogeneity (e.g., due to differences in population, study design, etc.)
  - E.g., DerSimonian and Laird

- I^2 Statistic: Estimates the proportion of the total heterogeneity (or variance) that is due to between-study heterogeneity.
  - Can be used as basis for choice of model.

The (PICO) research question

Is a DAPT regime of ticagrelor / aspirin superior to clopidogrel / aspirin in reducing cardiovascular (CV) events in patients undergoing percutaneous coronary interventions (PCI) following an acute coronary syndrome (ACS)?

- Population – ACS pts post PCI
- Intervention - ticagrelor / aspirin
- Comparator - clopidogrel / aspirin
- Outcome - death or CV hospitalizations

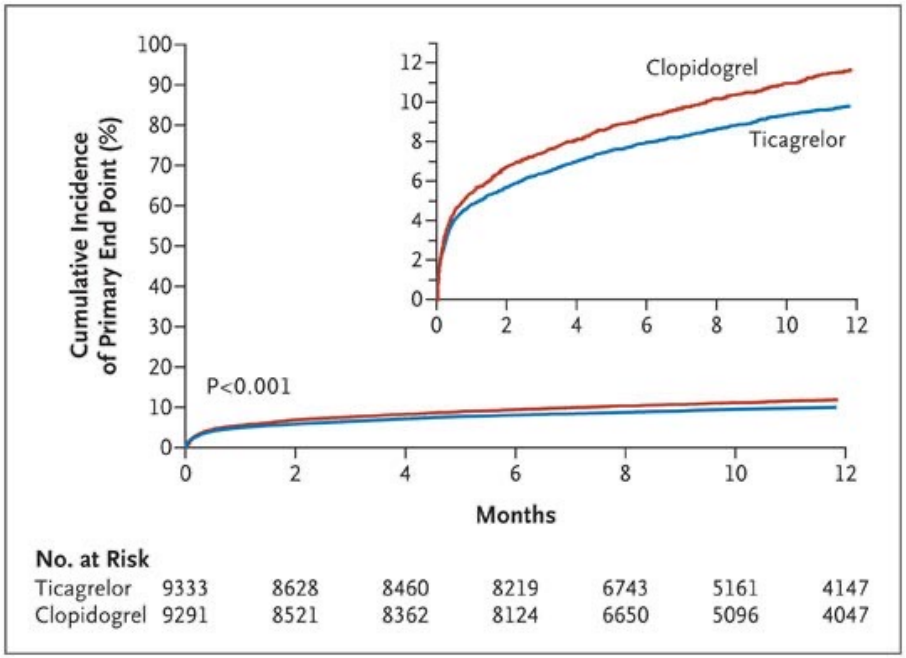
Hasn't the question already been answered?

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 SEPTEMBER 10, 2009 VOL. 361 NO. 11

Ticagrelor versus Clopidogrel in Patients with Acute Coronary Syndromes

PLATO



RESULTS

At 12 months, the primary end point — a composite of death from vascular causes, myocardial infarction, or stroke — had occurred in 9.8% of patients receiving ticagrelor as compared with 11.7% of those receiving clopidogrel (hazard ratio, 0.84; 95% confidence interval [CI], 0.77 to 0.92; P<0.001). Predefined hierarchical testing of secondary end points showed significant differences in the rates of other composite end points, as well as myocardial infarction alone (5.8% in the ticagrelor group vs. 6.9% in the clopidogrel group, P=0.005) and death from vascular causes (4.0% vs. 5.1%, P=0.001) but not stroke alone (1.5% vs. 1.3%, P=0.22). The rate of

Yes, for certain people

CCS Guidelines 2012 & 2018

Canadian Journal of Cardiology 29 (2013) 1334–1345

Society Guidelines

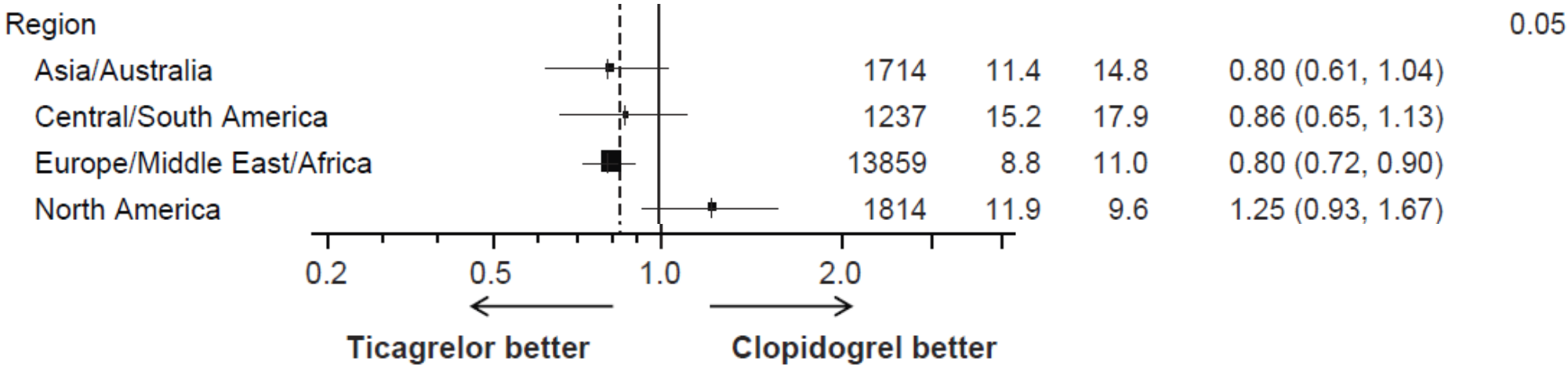
Focused 2012 Update of the Canadian Cardiovascular Society Guidelines for the Use of Antiplatelet Therapy

Jean-François Tanguay, MD, CSPQ, FRCPC, FACC, FAHA, FESC,[a] Alan D. Bell, MD, CCFP,[b] Margaret L. Ackman, BSc(Pharm), PharmD, ACPR, FCSHP,[c] Robert D.C. Bauer, MD, FRCPC, FACC,[d] Raymond Cartier, MD, FRCPC,[e] Wee-Shian Chan, MD, FRCPC,[f] James Douketis, MD, FRCPC,[g] André Roussin, MD, FRCPC,[h] Gregory Schnell, BSP, MD, FRCPC,[i]

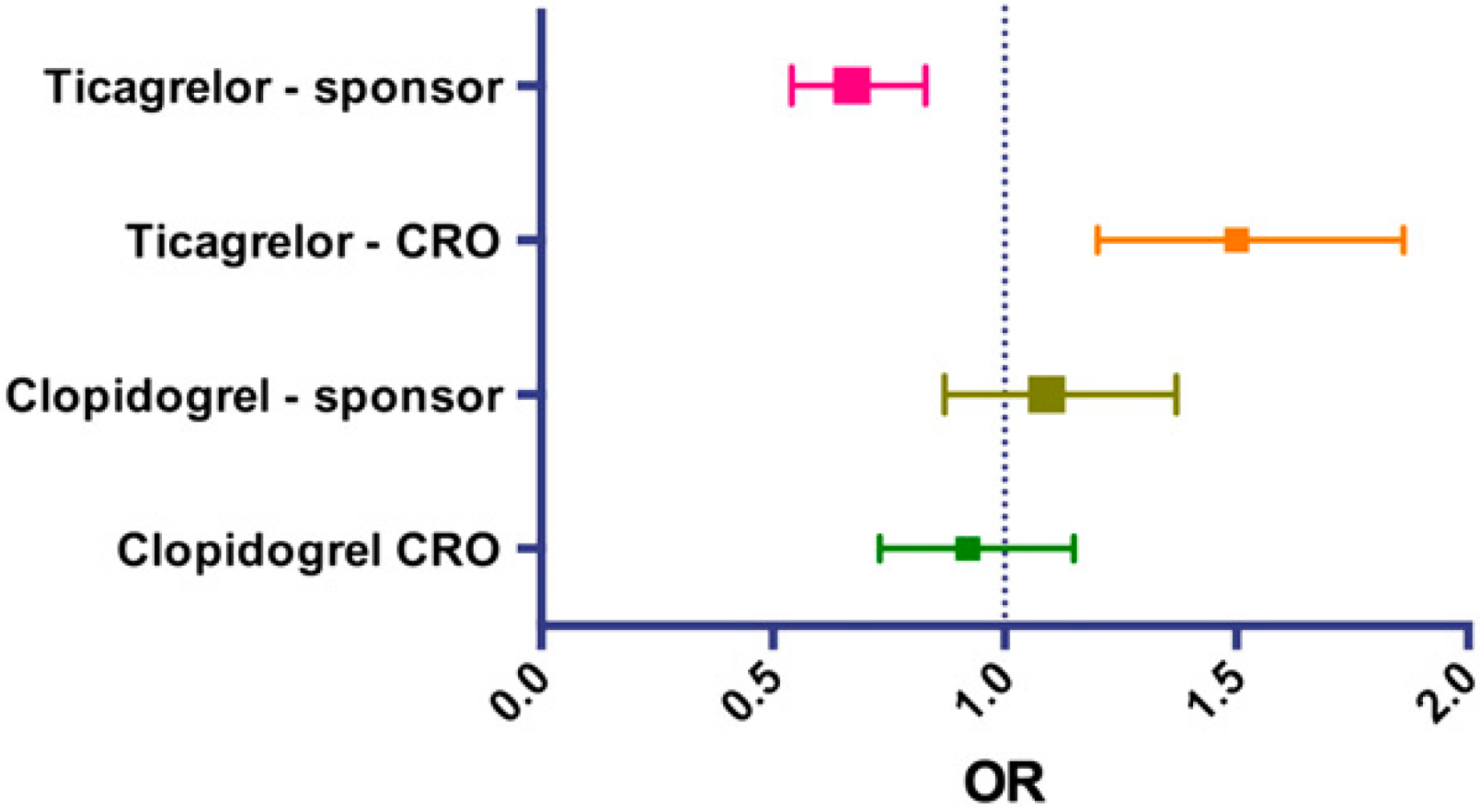
2. We recommend ticagrelor 90 mg twice daily over clopidogrel 75 mg daily for 12 months in addition to ASA 81 mg daily in patients with moderate to high risk NSTEACS (Strong Recommendation, High-Quality Evidence)

But not for everyone

- FDA refused 1st review , accepted 2nd in 2011 dissenting opinions (6-4)
  - "Lack of Robustness of PLATO Superiority with Failure in the US Makes a Confirmatory Study Mandatory."
  - "Besides failure in the US, superiority was only evident in the adjudicated results."



Another question about PLATO

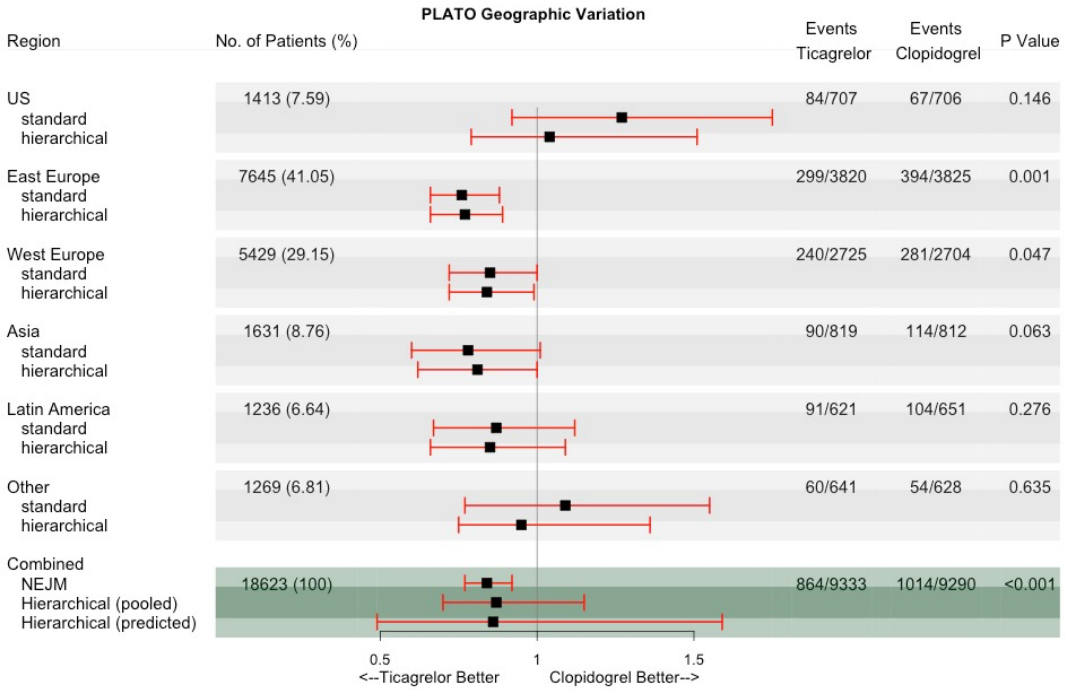


International Journal of Cardiology 168 (2013) 4076–4080

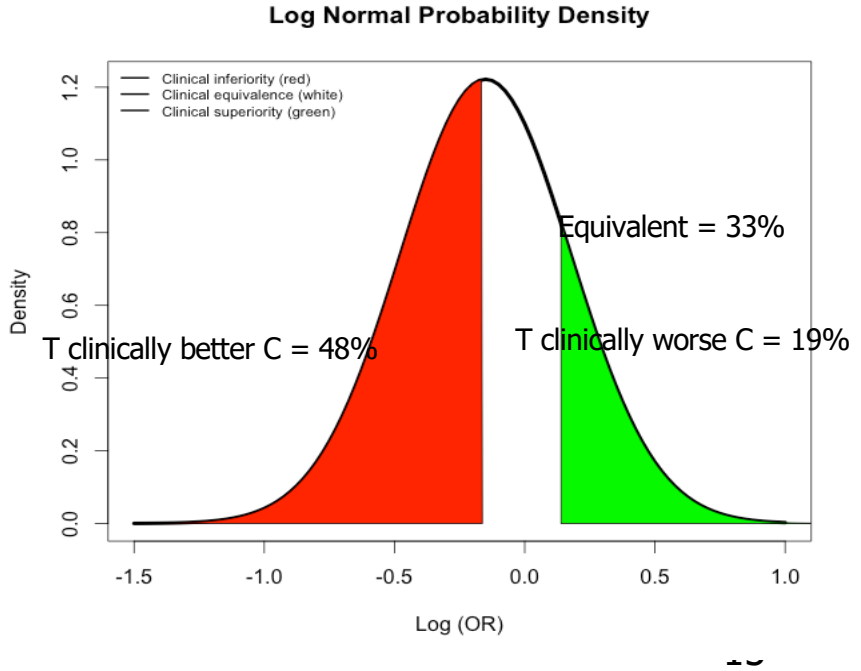
Accounting for this uncertainty

- Standard analysis treats all patients as identical and make inferences on “average patient”
- Same data but different statistical analyses -> different conclusions

Hierarchical



Bayesian

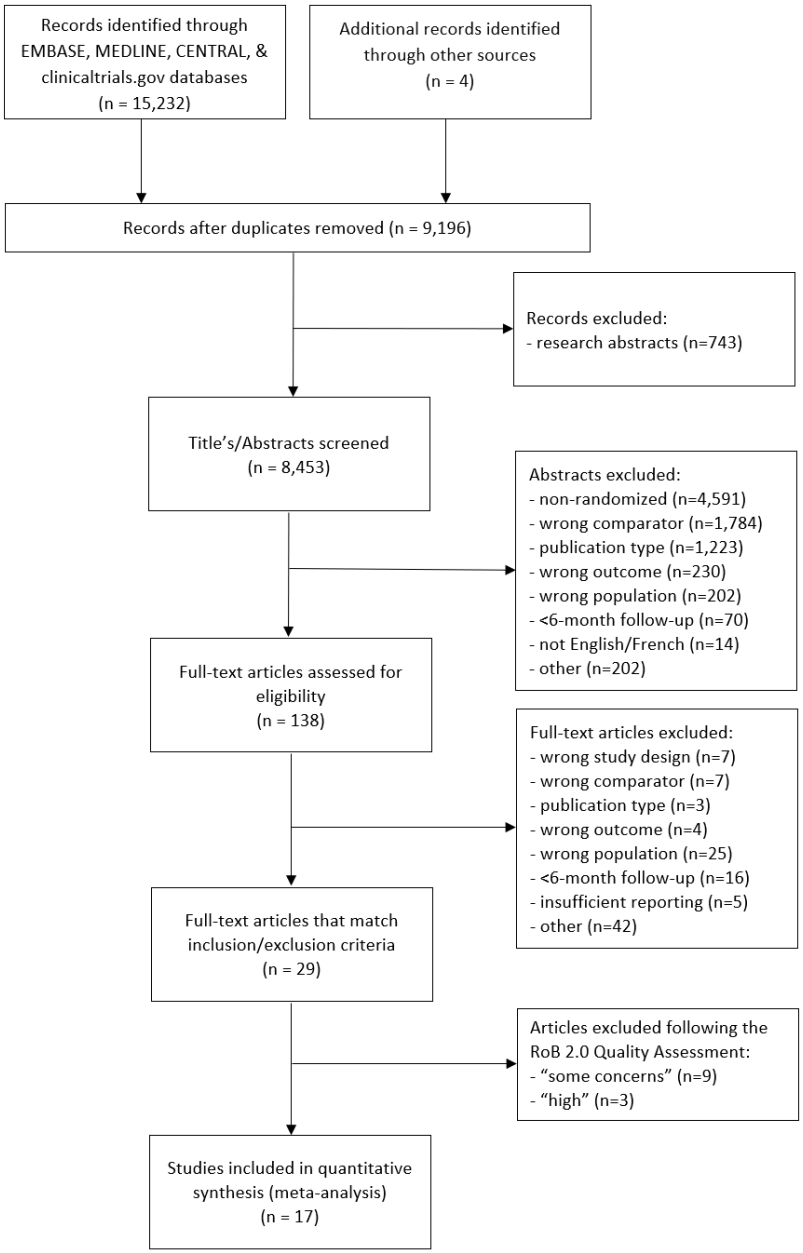


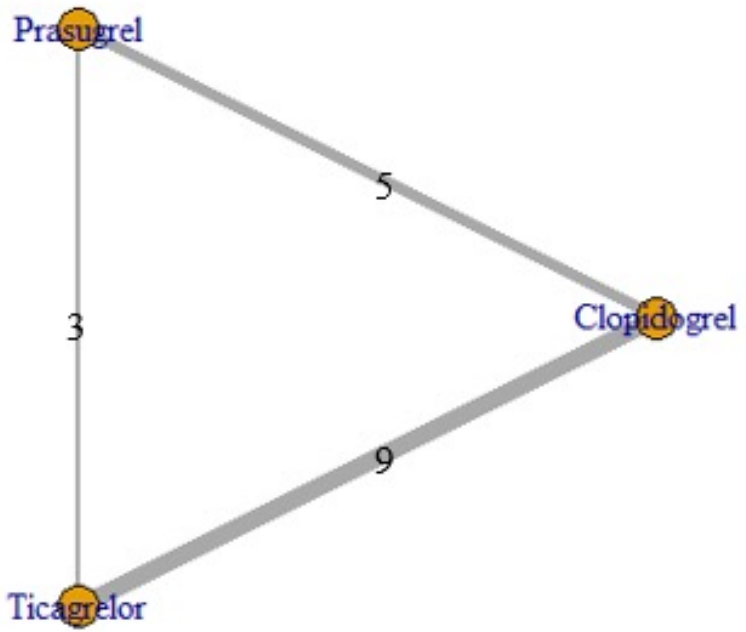
Reasons for Conducting a Systematic Review

- Summarize state of literature
  - Qualitatively via systematic review
  - Quantitatively via meta-analysis
- Address a question where multiple studies have been performed
- Explicitly examine heterogeneity of literature
- Clinical practice and public health decision making both require good evidence

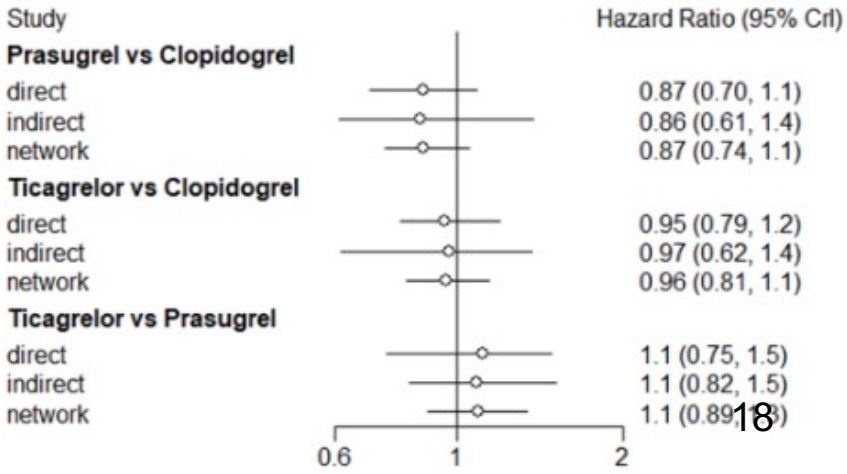
DAPT following an ACS: A systematic review and Bayesian network meta-analysis

Bayesian network meta-analysis

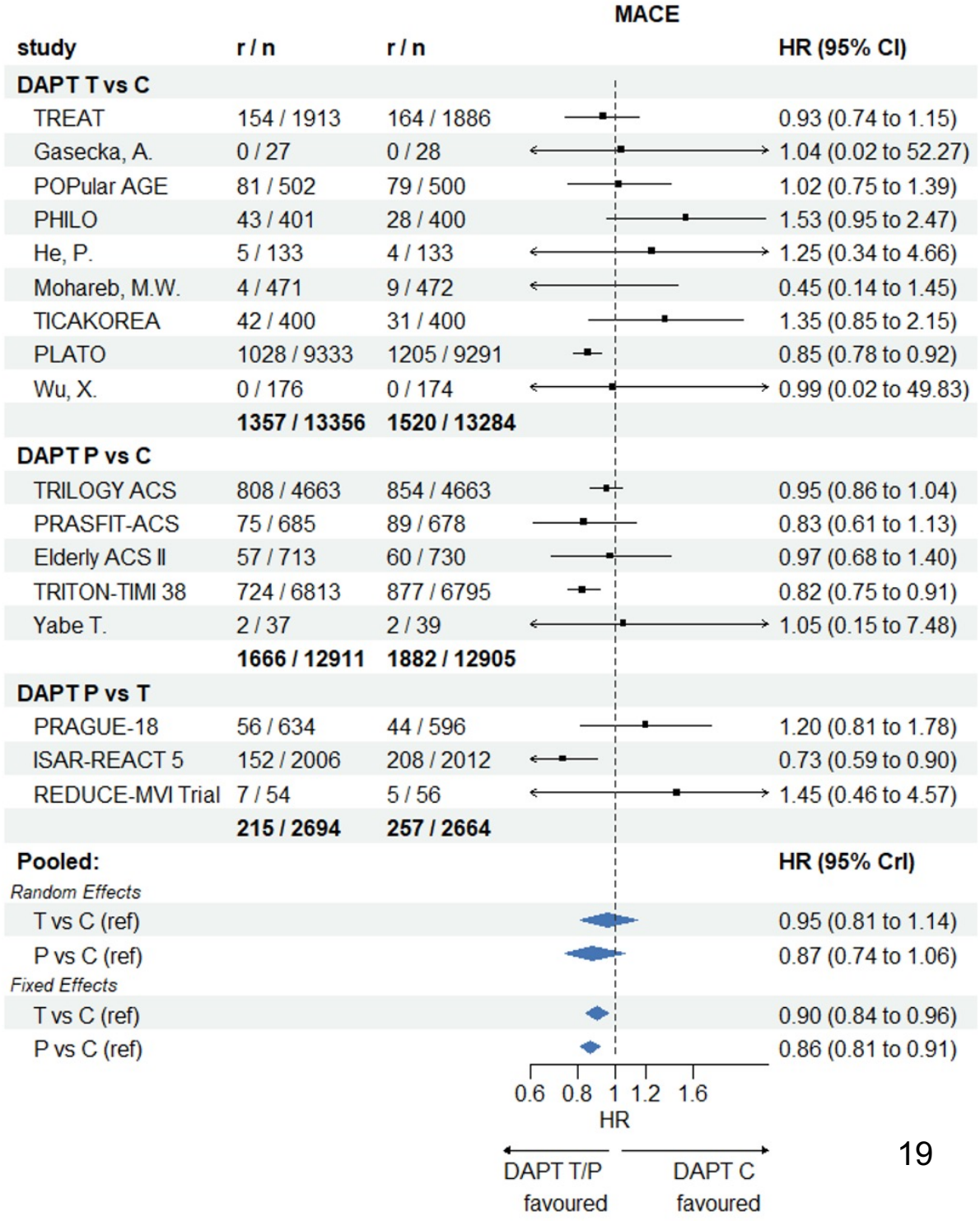




MACE



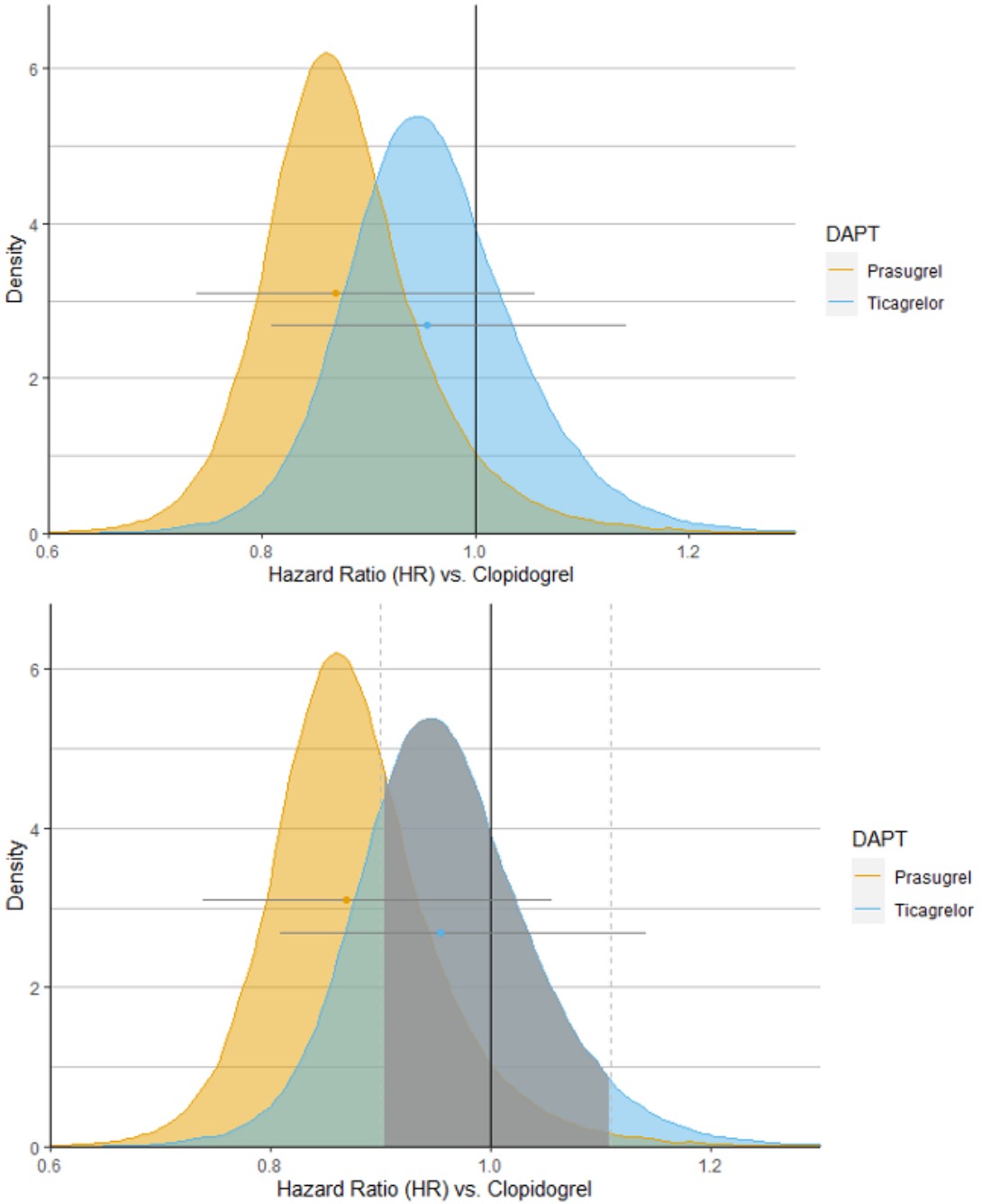
Bayesian network meta-analysis MACE



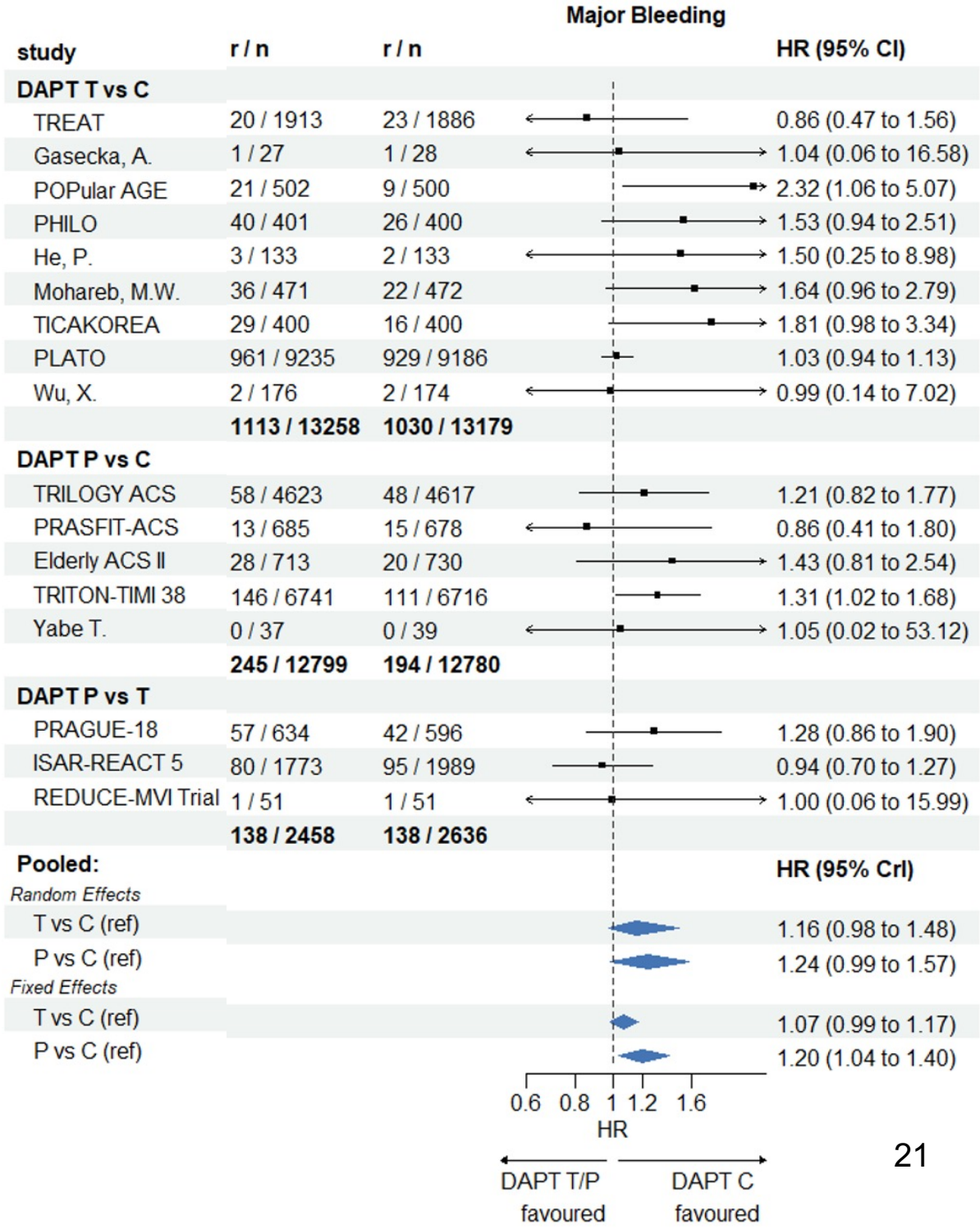
Bayesian network meta-analysis MACE

Compared to C, P & T reduced MACE by a median of 13% (HR_{PC}, 0.87; 95% CrI: 0.74, 1.06) and 5% (HR_{TC}, 0.95; 95% CrI: 0.81, 1.14),

P had a 67.5% chance of producing a clinically meaningful – greater than 10% (HR<0.9) – decrease in MACE risk while T only had a 22.4% chance of exceeding the clinically important threshold.



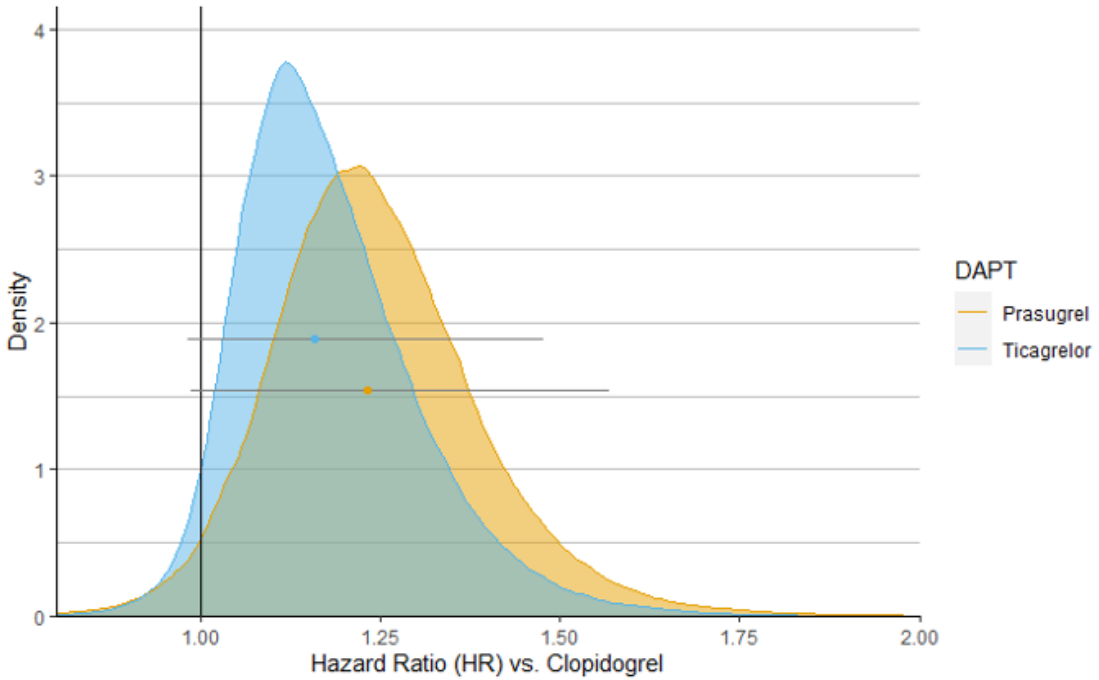
Bayesian network meta-analysis Bleeding

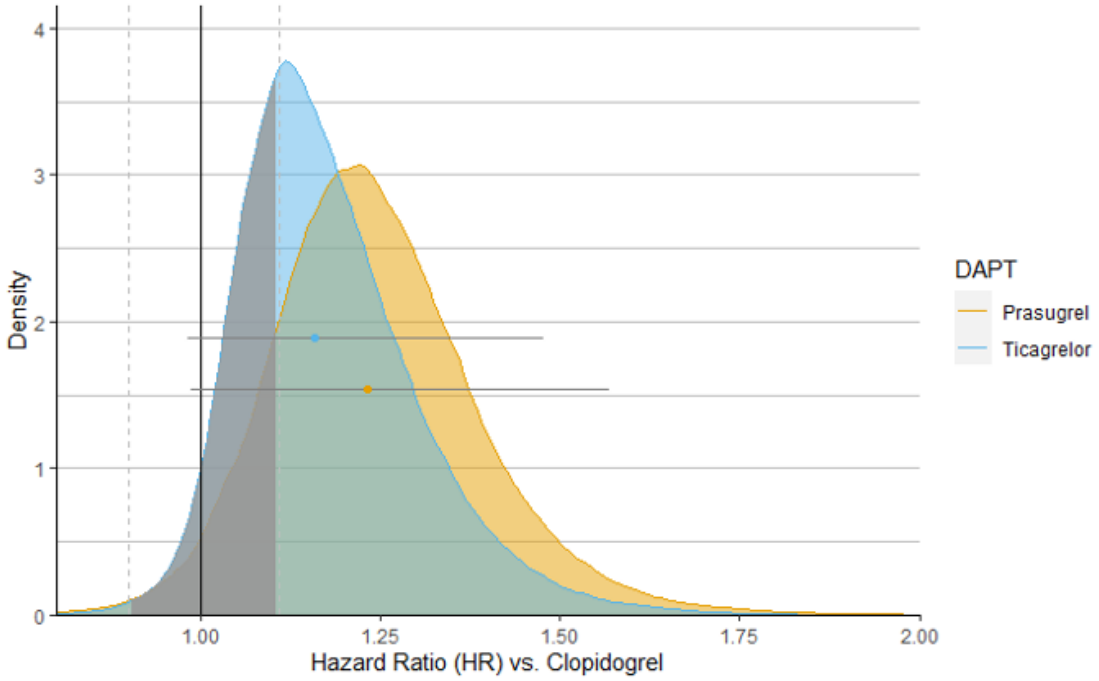


Bayesian network meta-analysis Bleeding

P (HR_{PC}, 1.23; 95% CrI: 1.04, 1.40) and T (HR_{TC}, 1.07; 95% CrI: 0.99, 1.17) increased bleeding relative to C.

Probability of a clinically meaningful increase (HR>1.11) in major bleeding of 83.7% for P and 67.7% for T, when compared to C.





Conclusions of BNMA

- When compared to clopidogrel, prasugrel and ticagrelor were associated with moderate (68%) and very modest probabilities (23%) in clinically meaningful MACE reductions, respectively.
- Prasugrel and ticagrelor had high (84%) and moderate (68%) probabilities of clinically meaningful increases in bleeding.
- Despite guideline recommendations, the net clinical benefit for these drugs compared to clopidogrel appears modest but residual uncertainty remains
- Also uncertain is the generalizability of these results to our local environment

When Can Meta-Analyses Mislead?

- When a meta-analysis is done outside of a systematic review
- When poor quality studies are included or when quality issues are ignored
- When inadequate attention is given to heterogeneity
  - Indiscriminate data aggregation can lead to inaccurate conclusions
- In the presence of reporting biases

Egger M et al. Clin Med 2001.

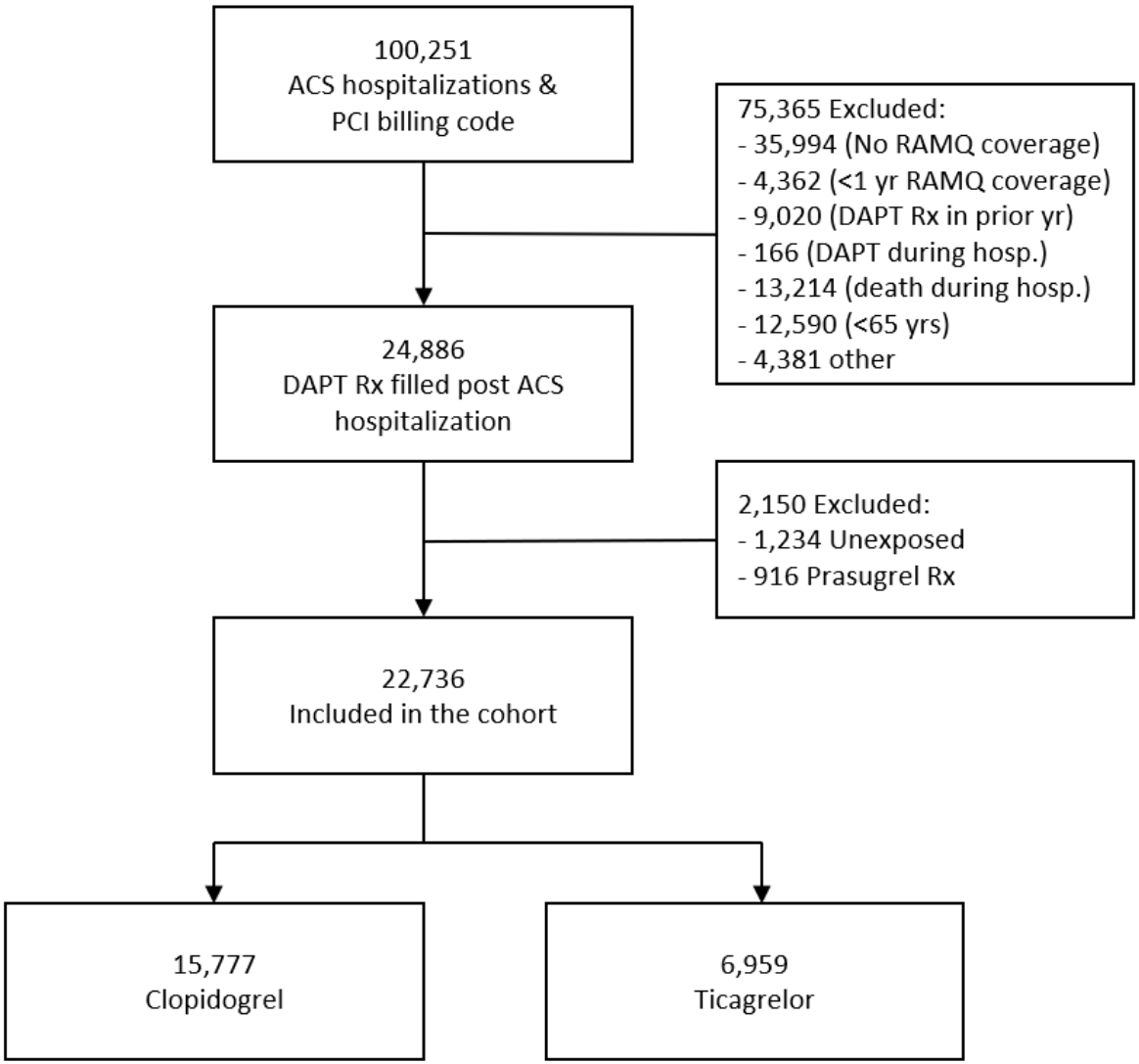
Reporting Biases

Type of reporting bias	Definition
Publication bias	The *publication* or *non-publication* of research findings, depending on the nature and direction of the results
Time lag bias	The *rapid* or *delayed* publication of research findings, depending on the nature and direction of the results
Multiple (duplicate) publication bias	The *multiple* or *singular* publication of research findings, depending on the nature and direction of the results
Citation bias	The *citation* or *non-citation* of research findings, depending on the nature and direction of the results
Language bias	The publication of research findings *in a particular language*, depending on the nature and direction of the results
Outcome reporting bias	The *selective reporting* of some outcomes but not others, depending on the nature and direction of the results

Egger M et al. Systematic Reviews in Healthcare 2001.

Real-world comparative effectiveness of clopidogrel and ticagrelor for acute coronary syndromes in Quebec

RAMQ study

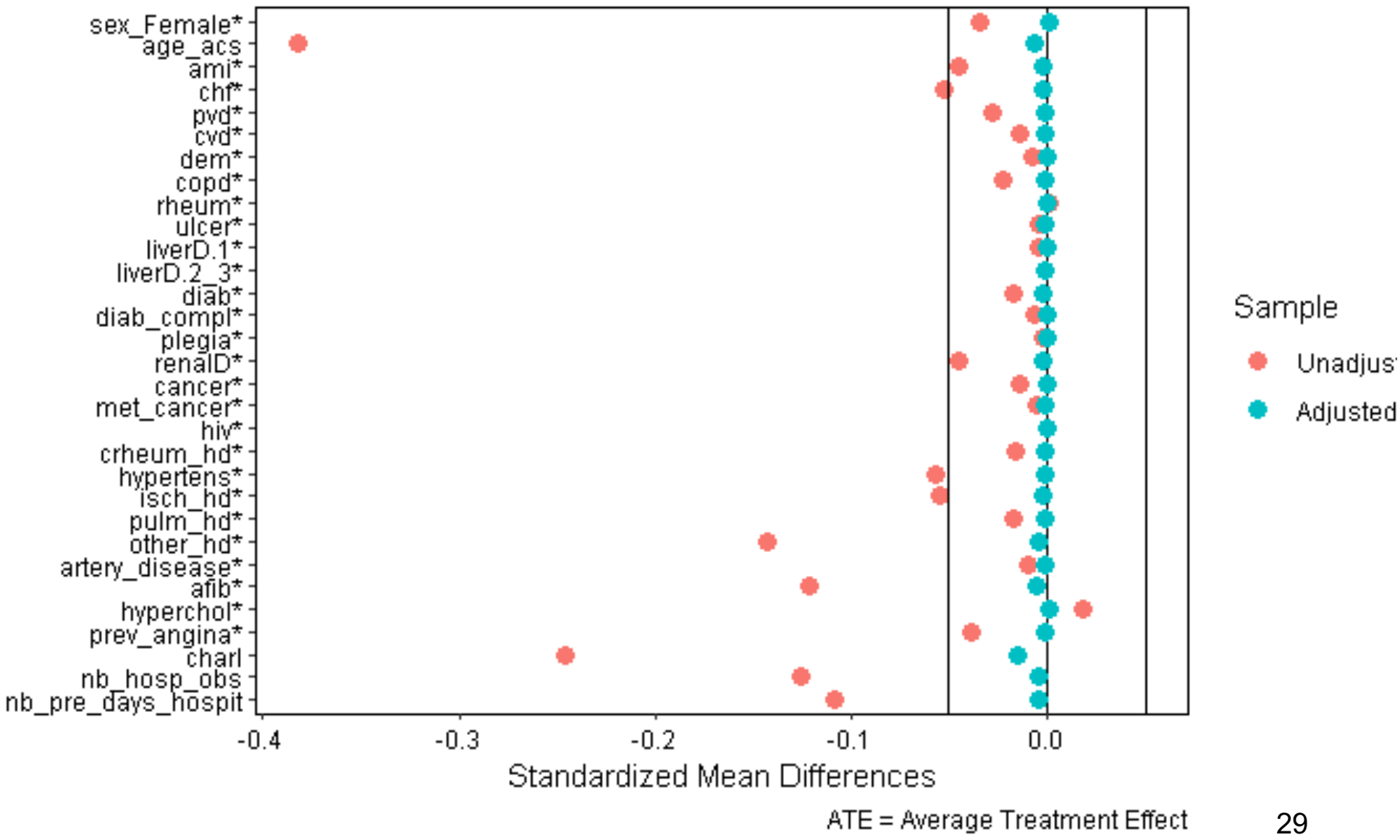

100,251
ACS hospitalizations &
PCI billing code
75,365 Excluded:
- 35,994 (No RAMQ coverage)
- 4,362 (<1 yr RAMQ coverage)
- 9,020 (DAPT Rx in prior yr)
- 166 (DAPT during hosp.)
- 13,214 (death during hosp.)
- 12,590 (<65 yrs)
- 4,381 other
24,886
DAPT Rx filled post ACS
hospitalization
2,150 Excluded:
- 1,234 Unexposed
- 916 Prasugrel Rx
22,736
Included in the cohort
15,777
Clopidogrel
6,959
Ticagrelor

Baseline data

	Clopidogrel	Ticagrelor
n	15,777	6,959
Age (mean (SD))	75.93 (7.13)	73.41 (6.06)
Sex (Female), n (%)	6294 (39.9)	2541 (36.5)
Year, n (%)		
2011	2230 (14.1)	2 (0.0)
2012	2826 (17.9)	203 (2.9)
2013	2159 (13.7)	780 (11.2)
2014	2070 (13.1)	1132 (16.3)
2015	1937 (12.3)	1270 (18.2)
2016	2039 (12.9)	1558 (22.4)
2017	2054 (13.0)	1618 (23.3)
2018	462 (2.9)	396 (5.7)
Previous MI, n (%)	1905 (12.1)	525 (7.5)
History of Angina, n (%)	1089 (6.9)	214 (3.1)
CVD, n (%)	468 (3.0)	111 (1.6)
CHF, n (%)	2082 (13.2)	552 (7.9)
Ischemic HD, n (%)	10512 (66.6)	4257 (61.2)
Pulmonary HD, n (%)	402 (2.5)	56 (0.8)
Rheumatic HD, n (%)	655 (4.2)	175 (2.5)
Other HD, n (%)	6162 (39.1)	1721 (24.7)
Atrial fibrillation, n (%)	2435 (15.4)	227 (3.3)

Clopidogrel subjects older (2.5 yrs), sicker, and treated at earlier time periods

Balancing the groups via PS



ATE = Average Treatment Effect

Results

	Ticagrelor *N=6,959*	Clopidogrel *N=15,777*	HR (95% CI) *unadjusted*	*ATE weighted + adjusted***
MACE	490 (7.0%)	1733 (11.0%)	0.66 (0.59, 0.73)	0.91 (0.81, 1.01)
All-cause mortality	137 (2.0%)	628 (4.0%)	0.51 (0.43, 0.62)	0.80 (0.66, 0.97)
MI	317 (4.6%)	937 (5.9%)	0.78 (0.69, 0.89)	0.99 (0.86, 1.13)
Stroke	36 (0.5%)	168 (1.1%)	0.50 (0.35, 0.72)	0.79 (0.53, 1.17)
Bleeding	84 (1.2%)	235 (1.5%)	0.97 (0.75, 1.24)	0.97 (0.75, 1.24)

Conclusion

After ATE weighting using propensity scores in ACS patients who underwent a PCI, ticagrelor was not significantly associated with a decrease in ischemic events nor bleeding outcomes.

Caveats: Causal inferences are limited by observational data with potential missing and residual confounding, missing data, and possible time trends

Ticagrelor **C**ompared to **C**lopidogrel in a**C**ute **C**oronary syndromes – **TC4** a pragmatic cluster randomized controlled trial

Methods

- From Oct 2018 to Mar 2021, ACS patients with PCI
- Randomized into pragmatic, open-label, time clustered, trial
- 1º endpoint composite of all-cause mortality, non-fatal MI, or ischemic stroke (MACE).
- 1º safety endpoint was hemorrhagic stroke or GI bleeding requiring hospitalization.
- Outcomes were ascertained with 12 months FU using administrative databases
- Bayesian Cox proportional hazard models were used to evaluate all outcomes, using vague, “skeptical”, “enthusiastic”, and “summary” informative priors.

Essay

Doing New Research? Don't Forget the Old

Nobody should do a trial without reviewing what is known

Mike Clarke

On May 2, 1898, George Gould used his address to the founding meeting of the Association of Medical Librarians in Philadelphia to present a vision of the future of health information. 'I look forward,' he said, 'to such an organisation of the literary records of medicine that a puzzled worker in any part of the civilised world shall in an hour be able to gain a knowledge pertaining to a subject of the experience of every other man in the world' [1]. Has his vision been realised? good quality, but some of it is not. Thus, anyone wishing to use the health literature to make well-informed decisions must both identify the relevant research from amidst this vast amount of information and then appraise it. This is an impossible task for many. Even though making access to the literature easier and cheaper will increase the ability of people to find research, it will also reveal just how much information there is out there and how daunting is the task of making sense of it.

with one or more search engines? Almost certainly, as the speed of the search increased through these four

Citation: Clarke M (2004) Doing new research? Don't forget the old. PLoS Med 1(2): e35.

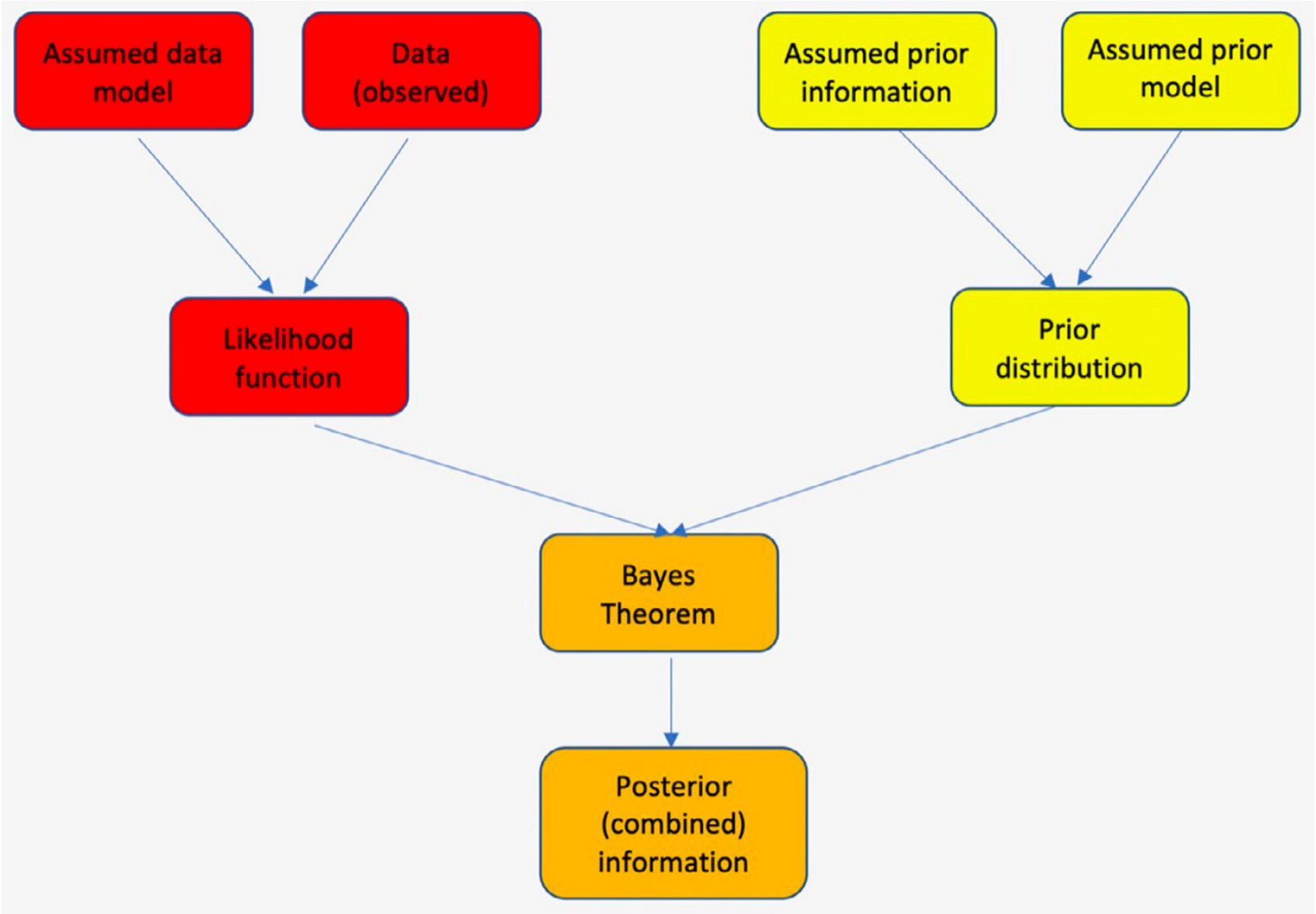
Mike Clarke is dir Cochrane Centre, mclarke@cochra

Box 1. Practical Suggestions for Researchers

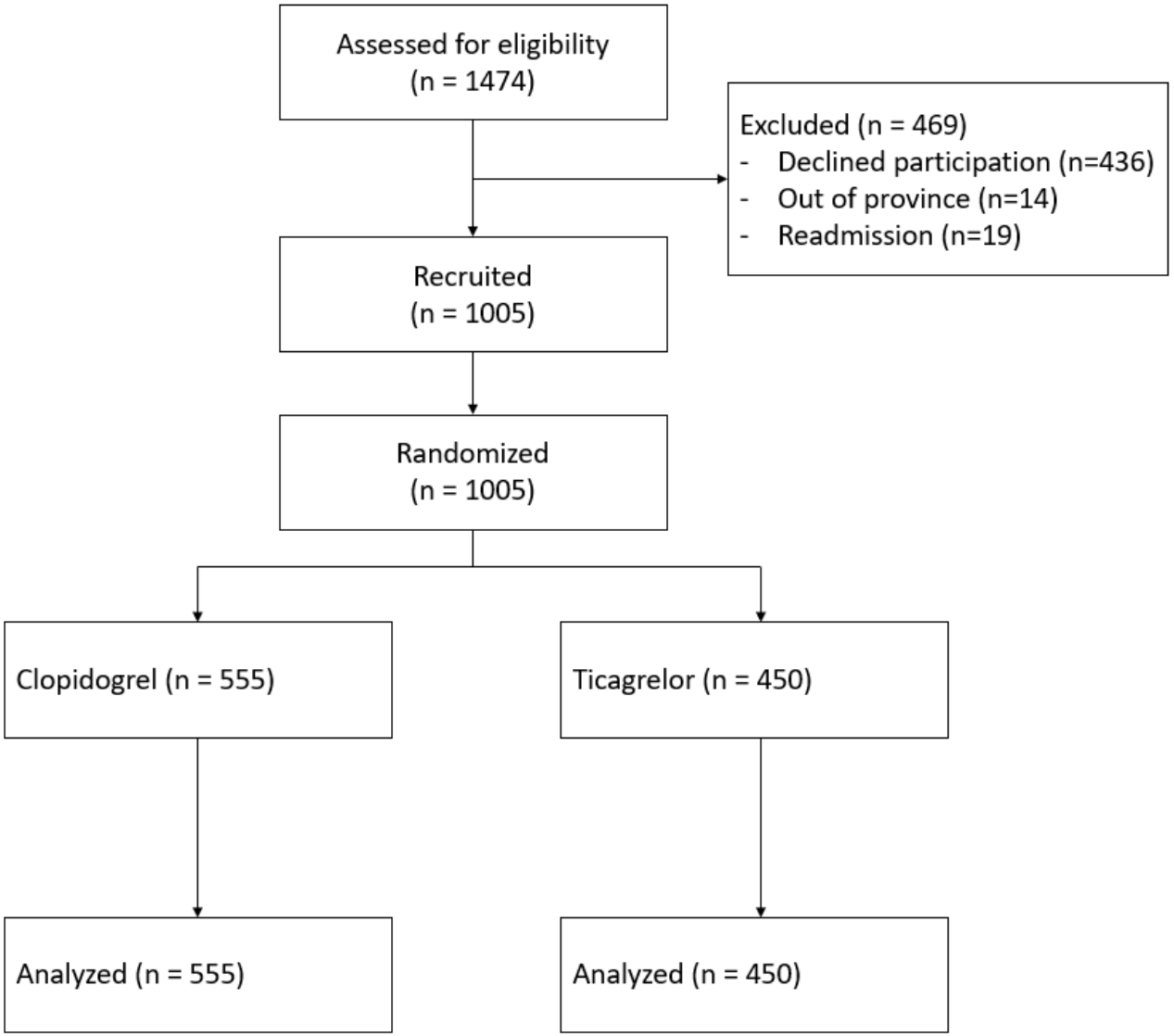
- Conduct a systematic review of your research question before embarking on a new study, or identify a relevant review done by someone else.
- Design your study to take account of the relevant successes and failures of the prior studies, and of the evidence within them.
- Discuss the findings of your study in the context of an updated systematic review of relevant research.
- Publish the systematic review within, alongside, or shortly after the report of your study.
- Provide information from your study to others doing systematic reviews of similar topics.

Clarke M. PLoS Med 2004

Bayesian paradigm



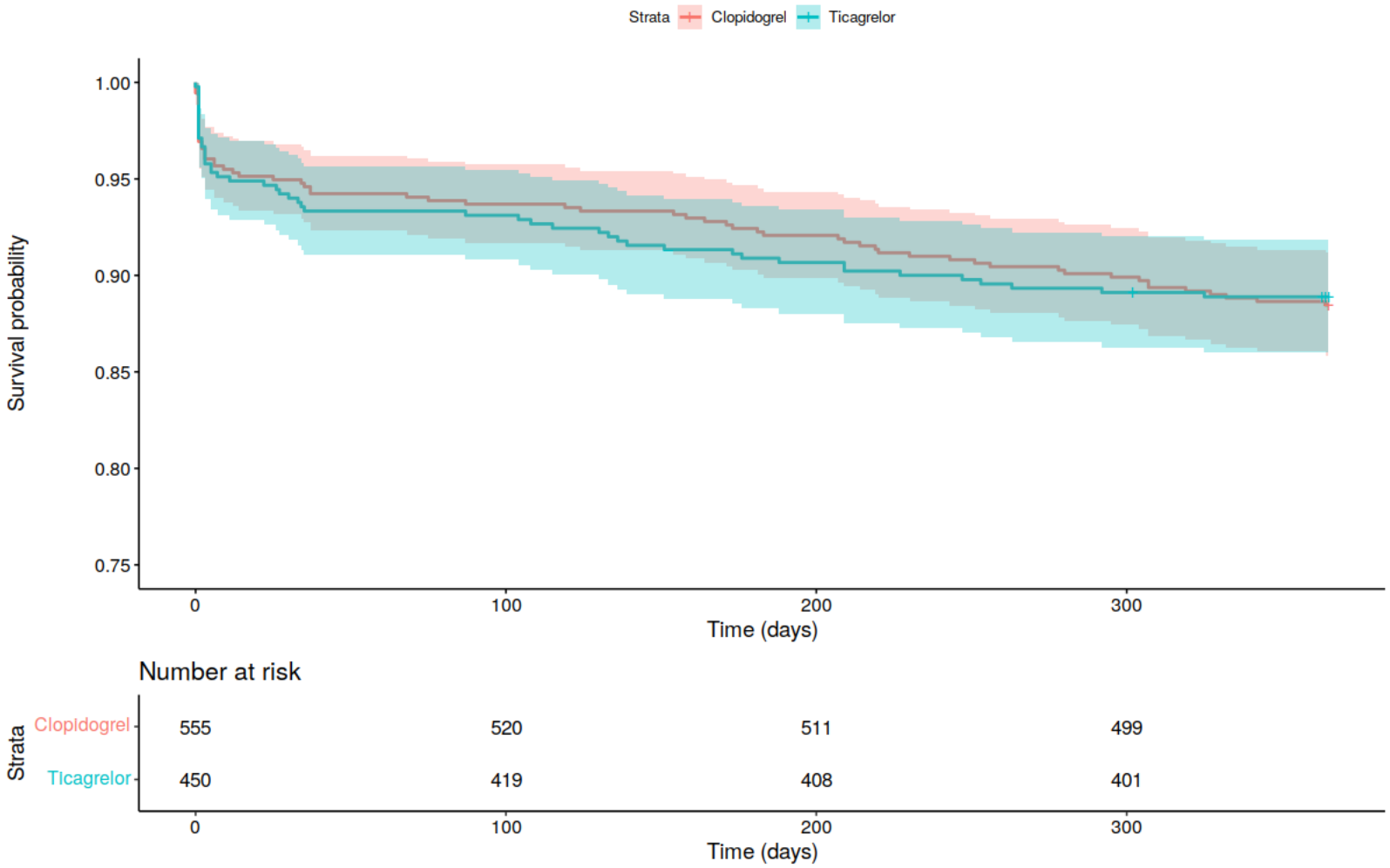
Results


Assessed for eligibility
(n = 1474)
Excluded (n = 469)
- Declined participation (n=436)
- Out of province (n=14)
- Readmission (n=19)
Recruited
(n = 1005)
Randomized
(n = 1005)
Clopidogrel (n = 555)
Ticagrelor (n = 450)
Analyzed (n = 555)
Analyzed (n = 450)

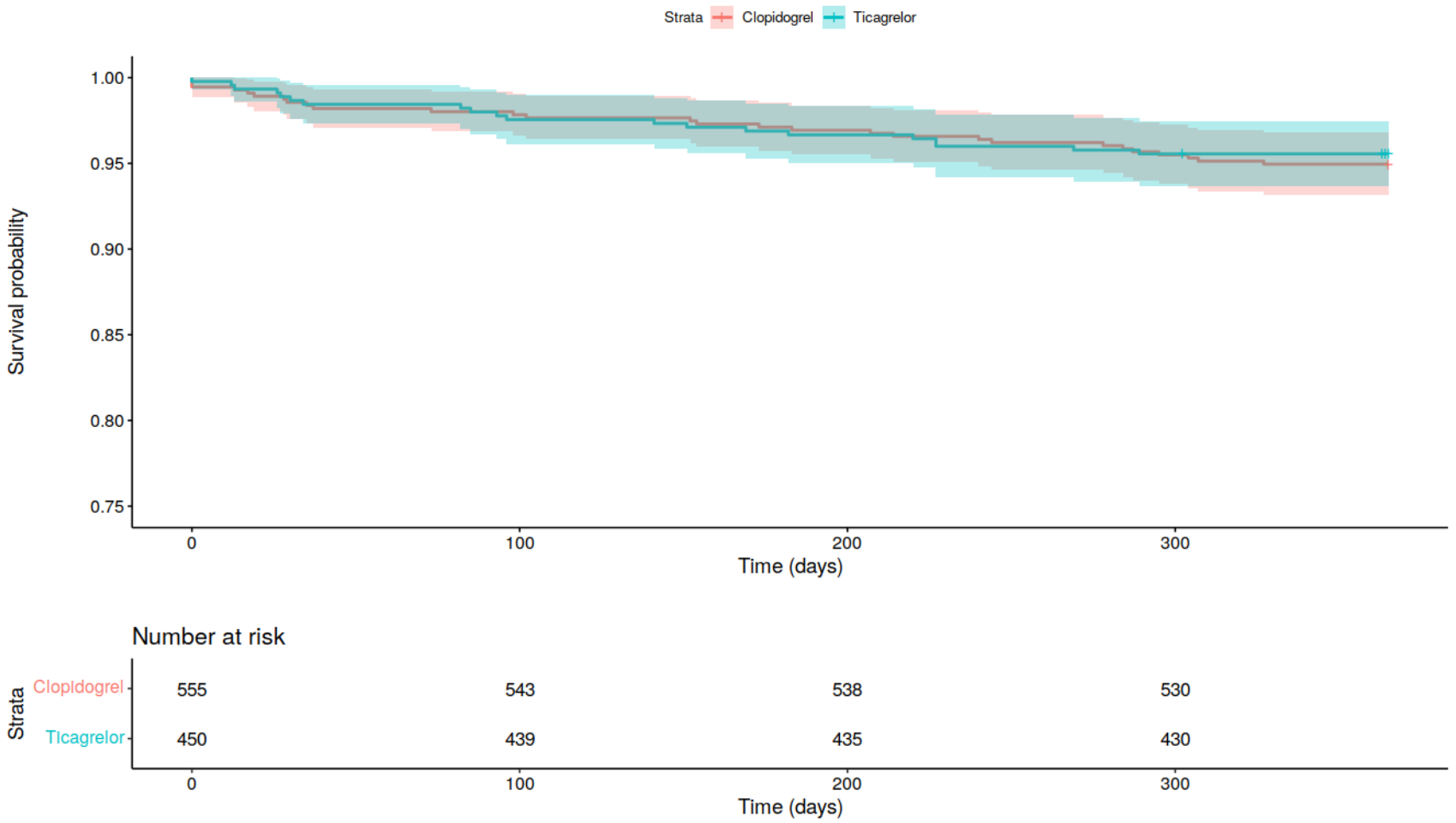
Results

	Clopidogrel	Ticagrelor
n	555	450
Age (mean (SD))	67.56 (10.92)	65.16 (11.33)
Sex (male), n (%)	420 (75.7)	338 (75.1)
Height, cm (mean (SD))	170.60 (9.47)	171.04 (9.30)
Weight, kg (mean (SD))	83.05 (21.99)	83.31 (17.78)
Smoking status, n (%)		
Current	136 (24.6)	110 (24.6)
Race, n (%)		
Caucasian	453 (81.6)	376 (83.6)
Previous DAPT, n (%)		
No	409 (74.1)	341 (76.3)
ACS diagnosis, n (%)		
STEMI	116 (20.9)	94 (20.9)
NSTEMI	210 (37.9)	207 (46.1)
Unstable Angina	89 (16.1)	69 (15.4)
Other	139(25.1)	79(17.6)
Hypertension, n (%)	387 (69.9)	300 (67.0)
SBP (mean (SD))	140.62 (22.23)	140.02 (22.62)
DBP (mean (SD))	79.72 (13.69)	80.43 (14.99)
Heart rate (mean (SD))	72.94 (15.43)	72.39 (15.11)
Dyslipidemia, n (%)	376 (68.0)	301 (67.2)
Diabetic, n (%)	185 (33.5)	139 (31.0)
Previous MI, n (%)	159 (28.6)	120 (26.9)
Previous PCI, n (%)	144 (25.9)	114 (25.4)
CHF, n (%)	32 (5.8)	15 (3.3)

Results – Kaplan Meier Curve (MACE)



Results – Kaplan Meier Curve (Bleeding)

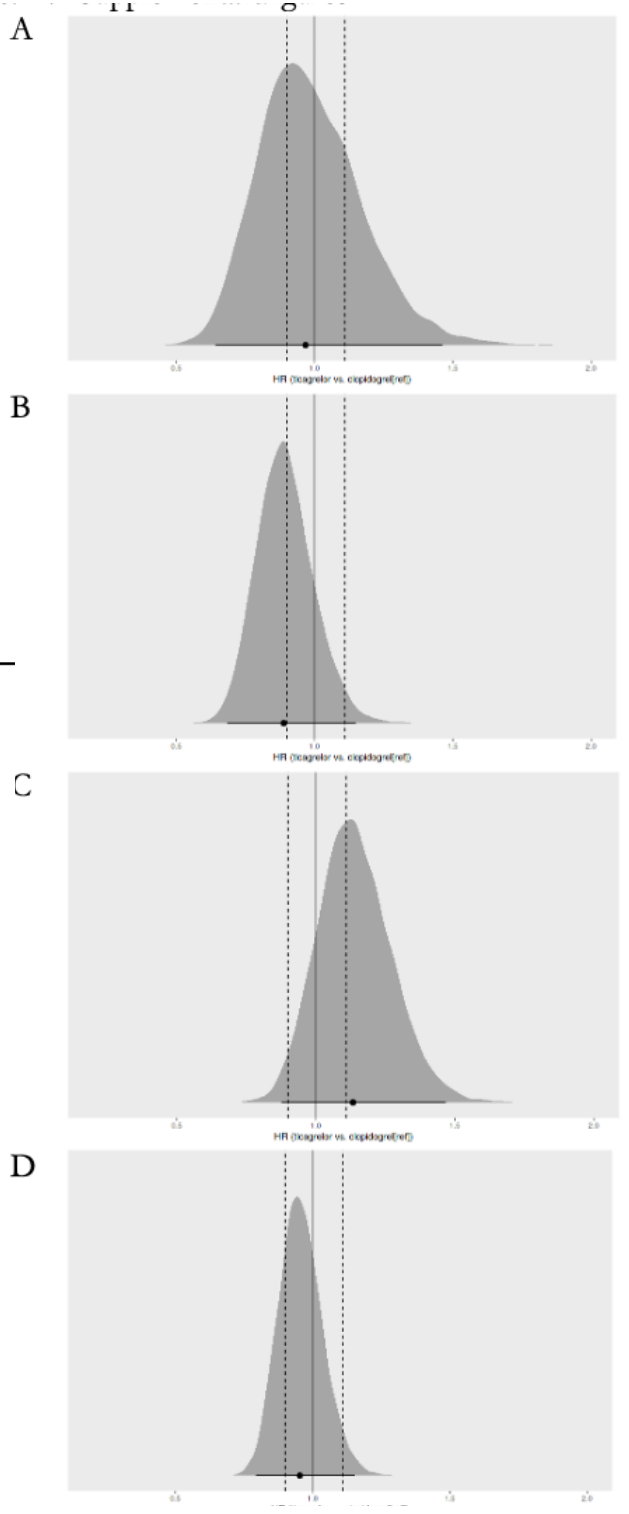


Results (MACE)

	Clopidogrel N=555	Ticagrelor N=450	Prior	HR (95% CrI) *Pooled*	Posterior distribution $Pr_{HR<0.9}$	$Pr_{HR[0.9, 1.11]}$	$Pr_{HR>1.11}$
MACE	64 (11.5%)	50 (11.1%)	Vague	0.97 (0.67, 1.40)	0.35	0.40	0.25
			skeptical	1.13 (0.90, 1.42)	0.02	0.38	0.60
			enthusiastic	0.89 (0.71, 1.11)	0.55	0.42	0.03
			summary	0.95 (0.81, 1.12)	0.24	0.72	0.04

Results (MACE)

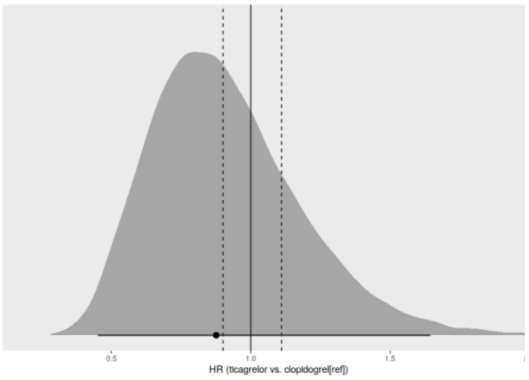
	Prior	HR (95% CrI) *Pooled*	Posterior distribution $Pr_{HR<0.9}$	$Pr_{HR[0.9, 1.11]}$	$Pr_{HR>1.11}$
A	Vague	0.97 (0.67, 1.40)	0.35	0.40	0.25
C	skeptical	1.13 (0.90, 1.42)	0.02	0.38	0.60
B	enthusiastic	0.89 (0.71, 1.11)	0.55	0.42	0.03
D	summary	0.95 (0.81, 1.12)	0.24	0.72	0.04



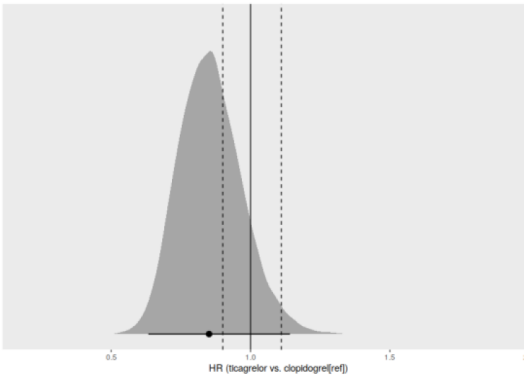
Results (Bleeding)

	Clopidogrel N=555	Ticagrelor N=450		Prior	HR (95% CrI) *Pooled*	Posterior distribution $Pr_{HR<0.9}$	$Pr_{HR[0.9, 1.11]}$	$Pr_{HR>1.11}$
Bleeding	28 (5.0%)	20 (4.4%)	E	Vague	0.88 (0.49, 1.50)	0.53	0.25	0.22
			G	skeptical	1.01 (0.76, 1.34)	0.22	0.51	0.27
			F	enthusiastic	0.85 (0.66, 1.10)	0.67	0.31	0.02
			H	summary	1.06 (0.97, 1.16)	0.00	0.77	0.23

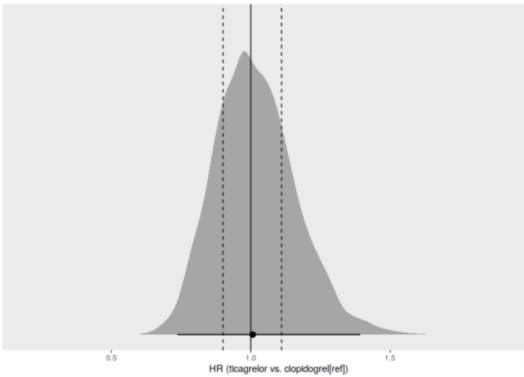
E



F



G



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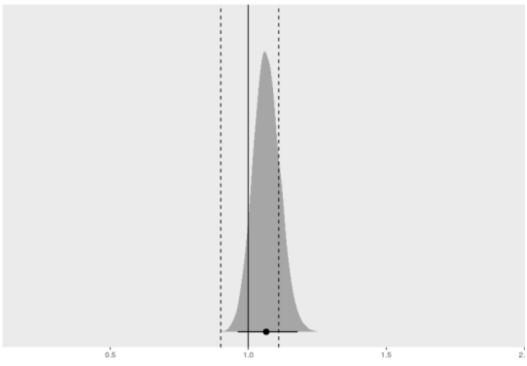

TC4 - Conclusions

- 1st RCT comparing ticagrelor to clopidogrel with NA pts since PLATO (2009), ⬆️ NA evidence base > 50%
- With vague prior MACE HR, 0.97; 95% CrI: 0.67, 1.40
- Or 35% probability of a clinically meaningful MACE benefit, 40% clinical equivalency and 25% clinically worse
- With NA PLATO prior MACE - 2% probability of a clinically meaningful benefit, 38% clinical equivalency, and 60% clinically worse
- With NMA prior (all comers, all evidence) MACE - 24% probability clinical superiority, 72% equivalency, 4% clinically worse
- WeaK evidence (≈20% probability) for clinical important (HR>1.1) risk of excessive bleeding with ticagrelor

All roads lead to Rome

All evidence suggests a low probability that ticagrelor (@$1200/y) is clinically superior to clopidogrel (@$168/y)

- Plato hierarchical reanalysis
- Bayesian network meta-analysis
- Quebec pharmacoepidemiology study
- TC4 RCT

Additional annual Quebec health care cost $25MM for a ticagrelor first policy

Ultimately, the choice is yours

Acknowledgements

This work largely comes from Stephen Kutcher's PhD thesis

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MUHC- RI doctoral training grants

CIHR project grant (#PH2-388823)

FRQS (EBM Chair) salary support

McGill

McGill Hospital Network
Consultancy Program

AstraZeneca

INVITATION TO ATTEND / HOLD THE DATE

Thursday, January 11th, 2018 Montreal, QC

On behalf of AstraZeneca Canada, we invite you to join us for a consultancy meeting – taking place in Montreal on Thursday, January 11th, 2018. This forum is for the McGill Hospital Network.

The objective of this meeting will be to identify gaps and better understand unique barriers that influence current utilization of DAPT in ACS patient management. With your help, we hope to provide AZ with recommendations on how to overcome these barriers to achieve and support CCS guideline recommended patient management.

You will be provided with an honorarium of $750.00 plus expenses.

If you are interested in joining us, please let us know by responding to this email. You will receive a confirmation note, with all the pertinent logistical and program details.

Please plan your evening from 5:30-9:00pm.

We hope you are able to join us.

With best regards,
Program co-chairs,

Chair CCS guidelines

Stéphane Rinfret, MD, SM, FSCAI
Associate Professor of Medicine, McGill University
Chief, Interventional Cardiology,
McGill University Health Centre (MUHC)
Royal Victoria Hospital
Montreal, Quebec

Shamir R. Mehta MD, FRCPC, FACC, FESC
Professor of Medicine, McMaster University
Director, Interventional Cardiology, Hamilton Health Sciences
Senior Scientist, Population Health Research Institute
Co-chair, 2017 CCS APT Guideline Committee
Hamilton, Ontario

INVITATION TO ATTEND / HOLD THE DATE

AstraZeneca

Thursday, January 11th, 2018 Montreal, QC

Letter of apology and clarification – re. email invitation for AZ Consultancy Meeting on Thursday, January 11th in Montreal. Please note this is an AstraZeneca forum (not a McGill program), and my apologizes for using the McGill logo and any confusion this may have caused. It was meant with good intentions – a note of collaboration to bring together representatives from the cardiology community within the McGill Hospital Network.

The goal of this meeting is to discuss and obtain feedback, reaction and insights from advisors on current OAP therapy approaches to ACS patient management, and align with current (and newly presented) CCS APT Guideline recommendations. For your role as advisor, you will be provided with an honorarium of $750. We are fortunate to have Dr. Stéphane Rinfret, McGill joined by Dr. Shamir Mehta, Hamilton/also co-chair of the 2017 CCS APT guideline committee as co-chairs of this consultancy meeting to support these discussions.

Again, I am sincerely sorry for this oversight.
I hope you will attend.