Real World Outcomes for Clopidogrel Versus Ticagrelor Treated Patients with Acute Coronary Syndrome: A Systematic Literature Review and Meta-Analysis

Dirk Sibbing[1], Dara Paek[2], Michael del Aguila[2], Shalini Girotra[3], Thomas Cuisset[4]

[1] Department of Cardiology, LMU München, Munich, Germany and DZHK (German Centre for Cardiovascular Research), Partner site Munich Heart Alliance, Munich, Germany | [2] Doctor Evidence, Santa Monica, CA, United States | [3] Sanofi, Global Medical Department, Singapore, Republic of Singapore | [4] Departement de Cardiologie, CHU Timone, Marseille, France

INTRODUCTION

- The ischaemic benefit of ticagrelor over clopidogrel seen in randomised trials has not been fully reproduced in real world cohorts. Published trial results showed better clinical benefit with ticagrelor than clopidogrel in the treatment of ACS,[1,2] however, the real-world data shows varying results that suggest ticagrelor may not be superior to clopidogrel.[3,4]
- This may reflect a trend in clinical practice for physicians to prescribe ticagrelor in patients with a safer risk profile,[5] while clopidogrel is commonly used in patients with more comorbidities and older age.[6,7]
- The effectiveness of ticagrelor compared to clopidogrel on clinical outcomes may be influenced by prescribing biases for patients with ischaemic and bleeding risk factors.

PURPOSE

- To conduct a systematic literature review and meta-analysis to compare cardiovascular and bleeding outcomes for clopidogrel versus ticagrelor in real-world populations with ACS.
- To provide insights in patient care for ACS patients with high levels of comorbidities.

METHODS

SYSTEMATIC LITERATURE REVIEW

A standardized review protocol was used to define the eligibility criteria:

Population	Adult patients with ACS, including STEMI, NSTEMI, UA
Intervention	Clopidogrel
Comparator	Ticagrelor
Outcomes	• Major adverse cardiovascular event (MACE), defined as mortality, MI, or stroke • Cardiovascular death • Myocardial infarction (MI) • Stroke • Stent thrombosis • Overall bleeding & major bleeding events
Study design	Observational comparative studies
Additional criteria	• PubMed and Embase (via OVID) searched on January 2018 • Conference abstracts via Embase from January 2015 onwards • Updated search conducted on February 21, 2019

ACS: acute coronary syndrome; STEMI: ST-elevation myocardial infarction; NSTEMI: non-ST-elevation myocardial infarction; UA: unstable angina.

META-ANALYSIS

- Pairwise meta-analysis performed for proportion of patients (n%) experiencing outcomes using unadjusted random effects model to estimate odds ratios (OR) with 95% confidence intervals (CI).
- Heterogeneity assessed using the I^2 statistic.
- Descriptive analysis to compare patient characteristics at baseline.

RESULTS

Search

- A total of 29 studies were selected for descriptive analysis; of these, 24 studies were selected for meta-analysis for efficacy and safety outcomes (**Figure 1**).
- Among 214,068 patients included in the evidence base, 152,317 (71%) patients received clopidogrel and 61,751 (29%) patients received ticagrelor.

FIGURE 1. PRISMA FLOW DIAGRAM OF STUDY SELECTION

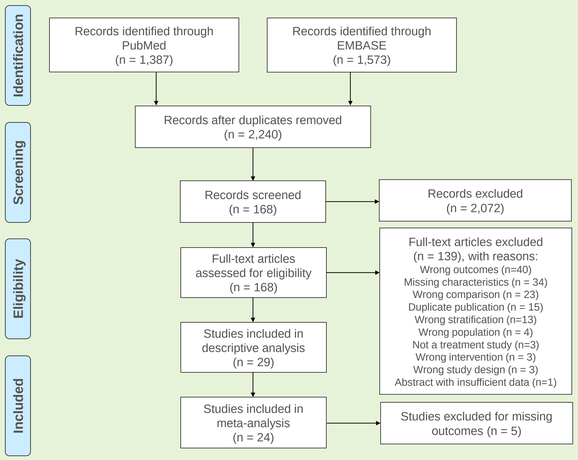


FIGURE 2. CARDIOVASCULAR OUTCOMES AND BLEEDING EVENTS

Outcome	No. of studies	C vs. T (n%)	OR [95% CI]
Cardiovascular outcomes			
MACE	5	13.6 vs. 10.1	1.41 [0.93, 2.14]
Cardiovascular death	7	2.8 vs. 2.1	1.38 [0.77, 2.46]
Myocardial infarction	16	2.7 vs. 2.1	1.27 [1.09, 1.48]
Stroke	17	1.2 vs. 0.93	1.35 [0.96, 1.90]
Stent thrombosis	12	0.8 vs. 0.6	1.33 [0.92, 1.93]
Bleeding events			
Overall bleeding	21	2.0 vs. 2.2	0.90 [0.69, 1.18]
Major bleeding	18	2.5 vs. 2.2	1.13 [0.89, 1.42]

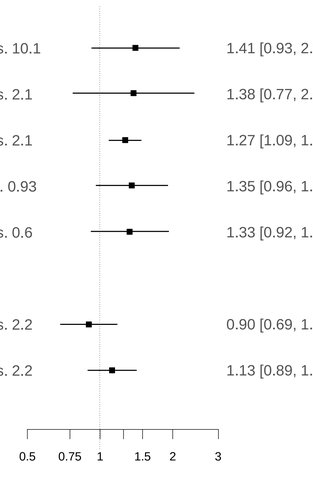
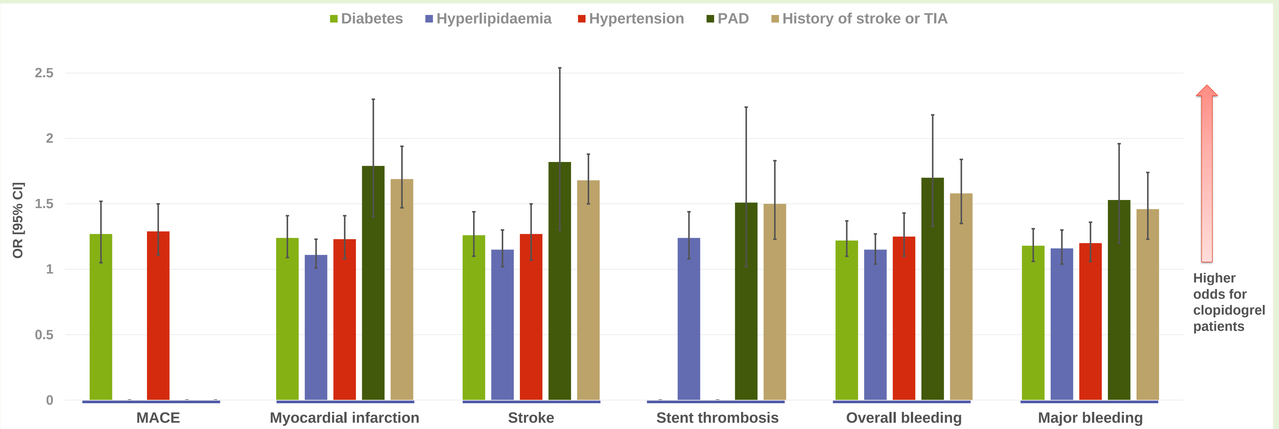


FIGURE 3. COMORBIDITIES SIGNIFICANTLY HIGHER IN CLOPIDOGREL VERSUS TICAGRELOR–TREATED PATIENTS (GROUPED BY ANALYSIS)



Analysis (Outcomes)

- Slightly higher risk of MI was observed for clopidogrel vs. ticagrelor (**Figure 2**).
- No statistical difference found for risk of MACE, despite clopidogrel patients having significantly more diabetes and hypertension.
- Similarly, the risks of cardiovascular death, stroke, and stent thrombosis were not statistically differentiable.
- No significant differences in overall bleeding events (major or minor, as defined by study) or major bleeding.
- Significant heterogeneity (I^2 >60%) was observed amongst studies for MACE, cardiovascular death, stroke, overall bleeding, and major bleeding.

Analysis (Characteristics)

- At baseline, clopidogrel-treated patients were significantly more likely to have comorbidities among studies analysed for MACE, MI, stroke, stent thrombosis, overall and major bleeding (**Figure 3**).
- More clopidogrel patients had a history of stroke/TIA in studies analysed for cardiovascular death, but the difference was not statistically significant (7.3% vs. 5.3%; OR 1.42 [0.99-2.05]).

CONCLUSION

- Results of the analysis showed there was no statistical difference between clopidogrel and ticagrelor for secondary prevention of MACE, cardiovascular death, stroke, and stent thrombosis. There was a higher risk of MI in patients prescribed clopidogrel for ACS.
- There was no statistical difference shown in risk of overall bleeding events and major bleeding between clopidogrel and ticagrelor.
- Comparison of baseline characteristics suggests clopidogrel-treated patients had more comorbidities than ticagrelor-treated patients, which may introduce a bias with negative impact on their outcomes.
- Despite this circumstance, with the exception of MI, this analysis showed no statistical difference in ischaemic benefit between clopidogrel and ticagrelor therapy following ACS in the real-world setting.
- The analysis was conducted using published observational data and heterogeneity across studies are inherent limitations in this review.
- Further research in larger registries and individual patient data is needed to inform prescribing guided by patient ischaemic-bleeding risk profiles.

DECLARATION OF INTEREST

This study was funded by Sanofi. Dirk Sibbing reports research grants from Roche Diagnostics and Daiichi Sankyo as well as speaker fees or fees for advisory board activities from Bayer AG, Sanofi, Pfizer, Haemonetics and Astra Zeneca, outside of this work. Dara Paek and Michael del Aguila declare employment by Doctor Evidence which was contracted to conduct this SLR and meta-analysis. Shalini Girotra declares employment by Sanofi. Thomas Cuisset reports consulting fees from AstraZeneca and Sanofi, outside of this work, in addition to lectures fees from AstraZeneca, Boston Scientific, Bayer, Medtronic, Sanofi, and Terumo.

REFERENCES

1. Lindholm D, Varenhorst C, Cannon CP, et al. Ticagrelor vs. clopidogrel in patients with non-ST-elevation acute coronary syndrome with or without revascularization: results from the PLATO trial. European heart journal. 2014;35(31):2083-2093.
2. Wang D, Yang X-H, Zhang J-D, Li R-B, Jia M, Cui X-R. Compared efficacy of clopidogrel and ticagrelor in treating acute coronary syndrome: a meta-analysis. BMC cardiovascular disorders. 2018;18(1):217.
3. Wang H-Y, Li Y, Xu X-M, Li J, Han Y-L. Impact of Baseline Bleeding Risk on Efficacy and Safety of Ticagrelor versus Clopidogrel in Chinese Patients with Acute Coronary Syndrome Undergoing Percutaneous Coronary Intervention. Chinese medical journal. 2018;131(17):2017-2024.
4. Kumar V, Kumar V, Kumari K, et al. Clinical safety profile of ticagrelor compared to clopidogrel in 1208 patients: Real world evidence. The Egyptian heart journal : (EHJ) : official bulletin of the Egyptian Society of Cardiology. 2018;70(4):375-378.
5. Harding SA, Holley A, Wilkins B, Fairley S, Simmonds M, Larsen PD. Contemporary antiplatelet therapy in acute coronary syndromes: are there differences in outcomes and discontinuation between clopidogrel and ticagrelor? Intern Med J. 2017;47(11):1298-1305.
6. Alexopoulos D, Xanthopoulou I, Deftereos S, et al. Contemporary antiplatelet treatment in acute coronary syndrome patients undergoing percutaneous coronary intervention: 1-year outcomes from the GReek AntiPlatElet (GRAPE) Registry. J Thromb Haemost. 2016;14(6):1146-1154.
7. Sheikh Rezaei S, Gerstlinger A, Heinze G, Reichardt B, Wolzt M. Clopidogrel, prasugrel, or ticagrelor use and clinical outcome in patients with acute coronary syndrome: A nationwide long-term registry analysis from 2009 to 2014. Int J Cardiol. 2017;235:61-66.