In-Hospital Survival After Out of Hospital Cardiac Arrest

We read with keen interest the description of etiology and determinants of in-hospital survival after an out of hospital cardiac arrest (OHCA).[1] Among the noncardiac causes, pulmonary embolism (PE) is reported to be the most common. It is particularly challenging to diagnose pulmonary (PE) as a cause of OHCA, but it often presents as a nonshockable rhythm, which was predictive for nonsurvival. The emergence of mobile-application based ultrasound systems where the ubiquitous smartphones can be transformed into an ultrasound by plugging in a transducer or through a Bluetooth will facilitate the diagnosis of PE in OHCA.[2] These patients should receive thrombolytic therapy if rapid imaging with a device confirms the suspicion of PE. We have demonstrated that cardiopulmonary resuscitation after a dose of lytic with the bolus agent tenecteplase, should range from 60 to 90 minutes[3] preferably with a manual compression device. Prolonged CPR gives time for the lytic agent to act. The outcomes may improve in those with noncardiac causes and nonshockable rhythms, especially if PE is the cause of OHCA.

Boban Thomas, MD[a]*
Imad Hassan, MD[b]
Carla Nobre, MD, MSc[c]
[a] University Hospital Kerry, Tralee, Republic of Ireland
[b] Our Lady's Hospital, Navan, Republic of Ireland
[c] Centro Hospitalar Barreiro Montijo, Barreiro, Portugal
1 September 2020

1. Khan AJ, Liao CJ, Kabir C, Hallak O, Samee M, Potts S, Klein L. Etiology and determinants of in-hospital survival in patients resuscitated after out-of-hospital cardiac arrest in an urban medical center. *Am J Cardiol* 2020;130:78–84.
2. Chamsi-Pasha MA, Sengupta P, Zoghbi WA. Handheld echocardiography. Current state and future perspectives. *Circulation* 2017;136:2178–2188.
3. Nobre C, Thomas B, Santos L, Tavares J. Prolonged chest compressions during cardiopulmonary resuscitation for in-hospital cardiac arrest due to acute pulmonary embolism. *Texas Heat Inst J* 2015;42:136–138.

Declaration of interests: The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

https://doi.org/10.1016/j.amjcard.2020.09.004

Meta-Analysis of the Efficacy and Safety of Genotype-Guided Strategy for Selection of $P2Y_{12}$ Inhibitors in Coronary Artery Disease

Despite the development of newer and more potent antiplatelet medications, clopidogrel remained the most prescribed $P2Y_{12}$ inhibitor after percutaneous coronary intervention (PCI) in the United States.[1,2] Clopidogrel is a pro-drug, which requires activation through cytochrome P450 pathway (*CYP2C19*) to be effective. Due to genetic variation in the *CYP2C19* gene, up to 30% of the US population are poor metabolizers of clopidogrel, and are at higher risk of thrombotic complications after PCI.[1–3] Ticagrelor and prasugrel metabolism are not affected by these genetic polymorphisms. Given their increased potency, they carry a higher risk of bleeding complications.[4] In a previous meta-analysis, we reported reduced rates of major adverse cardiovascular events (MACE) in acute coronary syndrome (ACS) patients who underwent treatment with genotype-guided strategy (GGS) utilizing *CYP2C19* testing versus conventional strategy (CS).[5] The recently published Tailored Antiplatelet Initiation to Lessen Outcomes Due to Decreased Response after Percutaneous Coronary Intervention (TAILOR-PCI) trial did not show any benefit of *CYP2C19*-guided treatment.[6] The trial was possibly underpowered since the study had lower than expected event rates, and was powered to detect a large effect size of a 50% reduction in the primary endpoint with GGS. Therefore, we sought to analyze further evidence using pooled data form multiple published randomized controlled trials (RCTs).

Ethical approval: This study is exempted from ethical/IRB approval, as it is conducted utilizing publically available database.

We conducted a comprehensive search of electronic databases for all RCTs that evaluated the safety and efficacy of GGS for selection of oral $P2Y_{12}$ inhibitors in patients who underwent PCI or those with ACS. Studies with a minimum follow-up of 6 months were included. Two authors extracted and analyzed the data using Review Manager Version 5.3 (The Nordic Cochrane Center, The Cochrane Collaboration, 2014). Risk ratios (RR) and corresponding 95% confidence intervals were calculated and combined using random effects model meta-analysis. The primary outcome of our study was the rate of MACE defined as a composite of cardiovascular (CV) mortality, myocardial infarction (MI), and stroke. Secondary outcomes were individual components of MACE, stent thrombosis, and major bleeding (based on the Bleeding Academic Research Consortium 3-5 [BARC].

A total of 6,329 patients (3,143 in the GGS group and 3,186 in the CS group) were analyzed from 6 RCTs with a mean follow-up of 11.6 months (mean age 63.2 ± 4.1 years, 26% women, 61.6% with hypertension, 26% with diabetes mellitus, 40.7% with dyslipidemia, 41.5% with tobacco use [former/current], and 86.5% with ACS).[5–7] Analysis showed significant reduction in MACE (4.8% vs 6.9%; RR 0.69, 95% CI: 0.51 to 0.93, p = 0.01, $I^2 = 43\%$), MI (1.9% vs 3.29%; RR 0.59, 95% CI: 0.42 to 0.84, p = 0.004, $I^2 = 14\%$), and stent thrombosis (0.31% vs 0.91%; RR 0.36, 95% CI: 0.18 to 0.76, p = 0.007, $I^2 = 0\%$) with GGS compared with CS. No significant difference was found with respect to CV mortality, stroke, and major bleeding (Figure 1) A sensitivity analysis that restricted the study population to only ACS subjects showed similar results.

In this meta-analysis, we found a significant benefit of *CYP2C19* genotype-guided initiation of oral $P2Y_{12}$ inhibitors in patients who underwent PCI or those with ACS compared with conventional treatment without genotype testing. Our analysis showed lower risk of MACE, MI, and stent thrombosis. Although not statistically significant, there were trends toward lower risk of CV mortality and stroke with a GGS.

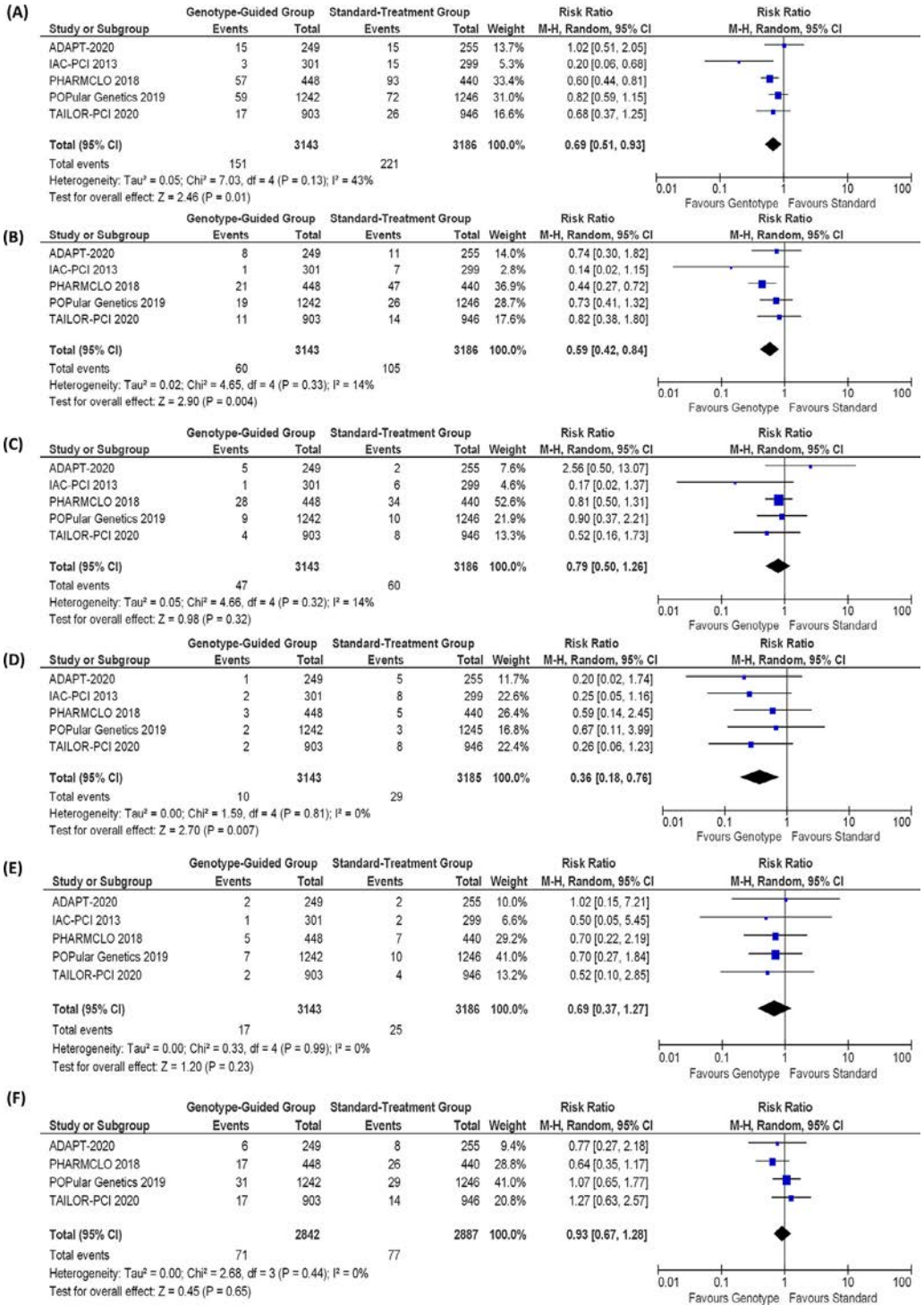

Figure 1. Forest plot showing outcomes in the genotype-guided strategy group compared to conventional strategy group; (*A*) major adverse cardiovascular events, (*B*) myocardial infarction, (*C*) cardiovascular mortality, (*D*) stent thrombosis, (*E*) stroke, (*F*) major bleeding.

Contemporary drug-eluting stents are associated with low thrombotic event rates. Hence, recent RCTs had lower than anticipated event rates,[6,8] which may partly explain the overall neutral findings in these individual trials. In our pooled analysis of multiple RCTs, significant reduction in the rates of MACE, MI, and stent thrombosis was noted with the GGS. Patients with ACS are at higher risk of thrombotic events. Therefore, in our study, we did a subgroup analysis of patients with ACS after excluding the Assessment of Prospective *CYP2C19* Genotype Guided Dosing of Anti-Platelet Therapy in Percutaneous Coronary Intervention (ADAPT) trial.[9] This trial included heterogeneous population (50% stable coronary artery disease and 50% ACS). Our findings showed similar reductions in MACE, MI, and stent thrombosis with GGS. The lower odds of MACE with GGS are possibly driven by higher use of clopidogrel in the CS group of the PHARMCLO (Pharmacogenomic Approach to Selecting Antiplatelet Therapy in Acute Coronary Syndrome) and TAILOR-PCI trials.[6,10] It is quite plausible that some of these patients were poor metabolizers of clopidogrel, and hence at higher thrombotic risk. In fact, 36% of randomized subjects in the CS group of TAILOR-PCI trial had *CYP2C19* loss of function variants. The higher use of clopidogrel in these trials may also explain the similar risk of major bleeding noted in our meta-analysis. In the study by Claassens et al included in our analysis, significantly less bleeding was noted with GGS compared to CS, likely driven by higher use of Ticagrelor (90.5%) in the CS group.[8]

In conclusion, this meta-analysis demonstrates that in patients who underwent PCI and those with ACS, a genotype-guided initiation of oral $P2Y_{12}$ inhibitors is associated with lower rates of MACE, MI, and stent thrombosis. Implementation of point-of-care genotype testing, and P2Y12 inhibitor selection algorithms into practice is needed. In addition, further research is needed to evaluate the cost-effectiveness of such treatment strategies.

Disclosures

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Salik Nazir, MD[a]
Keerat Rai Ahuja, MD[b]
Ahmed Elzanaty, MD[c]
Neha J. Patel, MD[c]
Muhammad Mahmood, MD[c]
Khalid Changal, MD[a]
Michael Macciocca, MD[b]
Rajesh Gupta, MD[a]*

[a] Division of Cardiology, University of Toledo Medical Center, Toledo, Ohio
[b] Division of Cardiology, Reading Hospital-Tower Health System, West Reading, Pennsylvania
[c] Department of Medicine, University of Toledo Medical Center, Toledo, Ohio

2 September 2020
10 September 2020

1. Sherwood MW, Wiviott SD, Peng SA, Roe MT, Delemos J, Peterson ED, Wang TY. Early clopidogrel versus prasugrel use among contemporary STEMI and NSTEMI patients in the US: insights from the National Cardiovascular Data Registry. *J Am Heart Assoc* 2014;3:e000849.
2. Fan W, Plent S, Prats J, Deliargyris EN. Trends in P2Y12 inhibitor use in patients referred for invasive evaluation of coronary artery disease in contemporary US practice. *Am J Cardiol* 2016;117:1439–1443.
3. Mega JL, Simon T, Collet J-P, Anderson JL, Antman EM, Bliden K, Cannon CP, Danchin N, Giusti B, Gurbel P, Horne BD, Hulot J-S, Kastrati A, Montalescot G, Neumann F-J, Shen L, Sibbing D, Steg PG, Trenk D, Wiviott SD, Sabatine MS. Reduced-function CYP2C19 genotype and risk of adverse clinical outcomes among patients treated with clopidogrel predominantly for PCI: a meta-analysis. *JAMA* 2010;304:1821–1830.
4. Levine GN, Bates ER, Bittl JA, Brindis RG, Fihn SD, Fleisher LA, Granger CB, Lange RA, Mack MJ, Mauri L, Mehran R, Mukherjee D, Newby LK, O'Gara PT, Sabatine MS, Smith PK, Smith SC. 2016 ACC/AHA guideline focused update on duration of dual antiplatelet therapy in patients with coronary artery disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines: an update of the 2011 ACCF/AHA/SCAI Guideline for Percutaneous Coronary Intervention, 2011 ACCF/AHA Guideline for Coronary Artery Bypass Graft Surgery, 2012 ACC/AHA/ACP/AATS/PCNA/SCAI/STS Guideline for the Diagnosis and Management of Patients with Stable Ischemic Heart Disease, 2013 ACCF/AHA Guideline for the Management of ST-Elevation Myocardial Infarction, 2014 AHA/ACC Guideline for the Management of Patients with Non-ST-Elevation Acute Coronary Syndromes, and 2014 ACC/AHA Guideline on perioperative cardiovascular evaluation and management of patients undergoing noncardiac surgery. *Circulation* 2016;134:e123–e155.
5. Nazir S, Ahuja KR, Virk HUH, Elzanaty A, Waheed TA, Changal KH, Wohlfarth K, Lakhter V, Grande RD, Eltahawy EA. A meta-analysis of efficacy and safety of genotype-guided versus standard of care treatment strategies in selecting antiplatelet therapy in patients with acute coronary syndrome. *Catheter Cardiovasc Interv* 2020. https://doi.org/10.1002/ccd.28860.
6. Pereira NL, Farkouh ME, So D, Lennon R, Geller N, Mathew V, Bell M, Bae J-H, Jeong MH, Chavez I, Gordon P, Abbott JD, Cagin C, Baudhuin L, Fu Y-P, Goodman SG, Hasan A, Iturriaga E, Lerman A, Sidhu M, Tanguay J-F, Wang L, Weinshilboum R, Welsh R, Rosenberg Y, Bailey K, Rihal C. Effect of genotype-guided oral P2Y12 inhibitor selection vs conventional clopidogrel therapy on ischemic outcomes after percutaneous coronary intervention: the TAILOR-PCI randomized clinical trial. *JAMA* 2020;324:761–771.
7. Xie X, Ma Y-T, Yang Y-N, Li X-M, Zheng Y-Y, Ma X, Fu Z-Y, Bayinsilema Ba, Li Y, Yu Z-X, Chen Y, Chen B-D, Liu F, Huang Y, Liu C, Baituola G. Personalized antiplatelet therapy according to CYP2C19 genotype after percutaneous coronary intervention: a randomized control trial. *Int J Cardiol* 2013;168:3736–3740.
8. Claassens DMF, Vos GJA, Bergmeijer TO, Hermanides RS, Hof AWJ van't, Harst P van der, Barbato E, Morisco C, Tjon Joe Gin RM, Asselbergs FW, Mosterd A, Herrman J-PR, Dewilde WJM, Janssen PWA, Kelder JC, Postma MJ, Boer A de, Boersma C, Deneer VHM, Ten Berg JM. A genotype-guided strategy for oral P2Y12 inhibitors in primary PCI. *N Engl J Med* 2019;381:1621–1631.
9. Tuteja S, Glick H, Matthai W, Nachamkin I, Nathan A, Monono K, Carcuffe C, Maslowski K, Chang G, Kobayashi T, Anwaruddin S, Hirshfeld J, Wilensky RL, Herrmann HC, Kolansky DM, Rader DJ, Giri J. Prospective CYP2C19 genotyping to guide antiplatelet therapy following percutaneous coronary intervention: a pragmatic randomized clinical trial. *Circ Genom Precis Med* 2020. https://doi.org/10.1161/CIRCGEN.119.002640.
10. Notarangelo FM, Maglietta G, Bevilacqua P, Cereda M, Merlini PA, Villani GQ, Moruzzi P, Patrizi G, Malagoli Tagliazucchi G, Crocamo A, Guidorossi A, Pigazzani F, Nicosia E, Paoli G, Bianchessi M, Comelli MA, Caminiti C, Ardissino D. Pharmacogenomic approach to selecting antiplatelet therapy in patients with acute coronary syndromes: the PHARMCLO trial. *J Am Coll Cardiol* 2018;71:1869–1877.

https://doi.org/10.1016/j.amjcard.2020.09.023

Beta Blockade in Patients After Acute Myocardial Infarction

We read with great interest the article published (on-line July 28, 2020) by Podlesnikar et al,[1] on the long-term effect of early intravenous metoprolol in ST-segment elevation myocardial infarction patients. Previously,