European Review for Medical and Pharmacological Sciences 2022; 26: 2524-2542

Cardiovascular mortality in patients with acute and chronic coronary syndrome: insights from the clinical evidence on ticagrelor

G. GARGIULO[1], F. SERINO[2], G. ESPOSITO[1]

[1]Department of Advanced Biomedical Sciences, Federico II University of Naples, Naples, Italy
[2]Division of Cardiology, AORN Cardarelli, Naples, Italy

Abstract. – OBJECTIVE: The purpose of this review is to discuss cardiovascular mortality as clinical outcome in the setting of both acute and chronic coronary syndromes (ACS and CCS) with a focus on the clinical evidence supporting the mortality benefit of ticagrelor across multiple subpopulations.

MATERIALS AND METHODS: Papers considered for this review were retrieved from a PubMed search, using different combinations of keywords (e.g., mortality AND coronary syndrome AND dual antiplatelet therapy AND ticagrelor), without limitations in terms of publication date and language.

RESULTS: Prevention of ischemic events and death is of outmost relevance in patients with ACS and CCS, given the high rate of recurrence of such events and fatalities. Owing to the evolving nature of patients with CCS, characterized by a broad spectrum of clinical presentations and previous medical history, as well as the advances in the therapeutic and invasive management of ACS, greater attention to the rate of hard clinical outcomes, improvement in the long-term prognosis, and reduction in the residual risk of recurrent events are increasingly reported among cardiologists. Dual antiplatelet therapy (DAPT) is the cornerstone of antithrombotic therapy aimed at lowering the rate of ischemic events and death in patients treated both conservatively and invasively after ACS, as well as improving prognosis in patients with CCS. Significant differences are emerging among oral $P2Y_{12}$ inhibitors with regards to mortality benefit.

CONCLUSIONS: Ticagrelor is an effective and well-tolerated option to attain a meaningful and clinically relevant reduction in cardiovascular mortality in both acute and chronic settings across a broad range of high-risk patient subpopulations with an acceptable payoff in terms of bleeding risk.

Key Words:
Mortality, Acute coronary syndrome, Chronic coronary syndrome, Ticagrelor, Dual antiplatelet therapy, Bleeding.

Introduction

Coronary artery disease (CAD) poses a significant public health burden because it contributes to significant morbidity and mortality with approximately 7.5 million deaths worldwide[1]. Death occurs in approximately 35% of patients who experience a coronary event each year and in almost one in six patients who have a myocardial infarction (MI)[2]. Therefore, one of the goals physicians caring for CAD patients are currently pursuing is to lower their risk of acute events and death as much as possible[3]. Greater knowledge of the natural history of CAD[4] as well as the evolution in current CAD management practices, including the use of functional tests of ischemia and imaging modalities, has paved the way towards the recognition that CAD is a chronic multi-faceted disease with phases of stability and instability [e.g., occurrence of an acute atherothrombotic event such as unstable angina (UA), MI with (STEMI) or without (NSTEMI) ST Segment Elevation] are closely intertwined[5]. The latest European Society of Cardiology (ESC) guidelines introduced the term "chronic coronary syndrome' to label the disease over its entire course, thus acknowledging that the clinical presentations of CAD can be categorized as either acute coronary syndrome (ACS) or chronic coronary syndrome (CCS) as commonly encountered in real-world clinical practice[5]. Viewing CAD as a dynamic process of atherosclerotic plaque accumulation and functional alterations in coronary circulation, that can be modulated by lifestyle and pharmacological and surgical procedures, supports the concept that, even during stable phases, the disease demands integrated efforts to prevent progression and reduce the incidence of acute thrombotic events and development of ventricular dysfunction[5].

Corresponding Author: Giovanni Esposito, MD, Ph.D; e-mail: espogiov@unina.it

Although adjusted mortality rates after acute MI have declined steadily over the last decade with the advances in therapeutic options, improved control of cardiovascular (CV) risk factors[6], and widespread implementation of guideline-directed medical therapy, the residual risk of recurrent ischemic events remains high even beyond one year[7] and despite adequate and complete revascularization[8-10]. Predictive factors for higher risk of recurrent events or cardiovascular death include age > 65 years, diabetes mellitus (DM), previous MI, stroke, UA, heart failure (HF), chronic kidney disease (CKD), multivessel CAD[5,11] as well as biomarkers, such as high-sensitivity troponins, C-reactive protein, and NT-proBNP[12,13]. To date, the underlying atherosclerotic condition may drive recurrent events as recently reported in a large observational study carried out in patients after MI[9]; a risk of recurrent MI not originating from a previously untreated lesion was found to be 2-fold higher than that of lesions originating from a previously treated lesion. Multivessel disease was one of the strongest predictors of future non-culprit lesion recurrent MI[9]. In a recent real-world study on patients with established atherosclerosis or at high risk for atherosclerotic complications, the proportion of patients experiencing a major adverse cardiovascular event (MACE) increased by nearly 5-fold from year 1 to year 4 of follow-up, particularly in patients with atherosclerotic disease in single or multiple vascular beds[14]. In patients well treated medically, such as those included in the international CLARIFY (ProspeCtive observational LongitudinAl RegIstry oF patients with stable coronary arterY disease) registry[15], there was a substantial residual risk for MACE with a rate of cardiovascular death, non-fatal MI, or non-fatal stroke equal to 9.5%. Similar findings emerged from the CORONOR (COROnariens stables en régionNORd-pas-de- Calais) registry with an estimated 5-year cardiovascular mortality rates varying from less than 2% to more than 50% with 40% of cardiovascular origin[3]. Overall, in routine practice it is paramount to carefully target major predictors of cardiovascular death or non-fatal MI, thus identifying patients with previous MI and angina as candidates for intensive treatment. For such high-risk patients, one of the key goals should be to reduce the residual risk and consequently subsequent events[16].

Platelet activation and aggregation underlie the symptomatic coronary thrombosis and are a key element in the pathobiology of cardiovascular ischemic events, thus providing the rationale for targeting platelet function in patients with ACS and CCS as an ischemic event prevention strategy[17,18]. Dual antiplatelet therapy (DAPT) with aspirin and an oral $P2Y_{12}$ inhibitor is the cornerstone of antithrombotic therapy after MI and/or percutaneous coronary intervention (PCI)[5], and it is recommended for long-term secondary prevention in patients with highly or at least moderately increased risk of ischemic events and without high bleeding risk (HBR)[5]. DAPT can influence the residual thrombotic risk[16], reduce ischemic recurrences in patients with ACS[19,20], in clinically stable patients undergoing PCI[21] or those who have had coronary stenting[22], as well as lower ischemic relapse in those with a history of MI[23,24]. Among oral $P2Y_{12}$ inhibitors, significant differences are emerging with regard to mortality benefit with ticagrelor showing significantly reduced cardiovascular mortality [hazard ratio, HR: 0.82; 95% confidence interval (CI), 0.72-0.92] and all-cause mortality [HR, 0.83; (95% CI, 0.75-0.92)] compared with clopidogrel as well as reduced ischemic outcomes in high-risk patients[25]. Ticagrelor has been acknowledged to have more rapid onset as well as more significant platelet inhibition function in patients with ACS[26] and is an alternative strategy in treating patients with clopidogrel intolerance or resistance[26] and a valuable option for patients with CCS and a history of MI[23].

In this narrative review, we discuss the relevance of cardiovascular mortality as clinical outcome in the settings of ACS and CCS with a focus on the broad clinical evidence supporting the mortality benefit of ticagrelor across multiple subpopulations, including those at moderate-to-high risk of an ischemic event.

Selection of Evidence

Papers considered for the present review were retrieved from a PubMed search, using different combinations of keywords (e.g., mortality AND coronary syndrome AND dual antiplatelet therapy AND ticagrelor), without limitations in terms of publication date and language. Papers were selected for inclusion according to their relevance for the topic, as judged by the authors.

Relevance of Mortality Risk and Outcome in Acute and Chronic Coronary Syndromes

Preventing ischemic events and death is of outmost relevance for patients with ACS and CCS, given the high rate of recurrence of such events and fatalities. In the ACS setting, PCI is the dominant modality for myocardial revascularization, and its short and long-term outcomes are associated with different rates of mortality[27]. Within the first 30 days, stent thrombosis accounts for MI or death in 50%-70% of cases and patients with ACS display a higher risk than those with stable CAD[27]. Over 12 months, late adverse events can increasingly occur and result from the failure of the original inserted coronary device(s) or the progression of the underlying CAD[27].

The risk of a recurrent CV event or death is the highest in the first year after an ACS event[8,28] and continues to increase for at least 5 years[29]. Even in the absence of a recurrent event within the first 12 months after MI, there is a 36% risk of MI, stroke, or death during the following 3-year period[29] with one in five individuals experiencing an event in that time period[7]. Recent epidemiological data from Italy show that the 30-day mortality rate after MI is about 9% with a stable trend in post-discharge mortality and an increased 1-year fatal readmissions (5.28% *vs.* 4.75; p=0.0019) from 2001 to 2011[30]. Therefore, it is paramount to better identify the subpopulations at risk and manage them accordingly. Among patients with ACS, subtle differences emerged in terms of mortality risk with greater all-cause mortality in STEMI *vs.* UA/NSTEMI over the first 2-3 months after the event; however, over long-term follow-up, higher mortality has been reported among patients with UA/NSTEMI *vs.* STEMI[31]. Similar findings have been observed in the IMPROVE-IT study with higher mortality rates for STEMI *vs.* UA/NSTEMI during the first month after which the mortality (both cardiovascular and non-cardiovascular) was greater for UA/STEMI *vs.* STEMI[32]. It has been suggested that the long-term higher CV and non-CV mortality among patients with UA/NSTEMI could be attributed to a higher baseline prevalence of multiple comorbidities, including multivessel CAD, HF, DM, CKD[30,31]. A recent analysis of IMPROVE-IT has shown that the relative incidence of CV and non-CV death differed based on ACS type; patients with STEMI had predominantly higher CV death for 4 years following the index event and only non-CV death after that. In contrast, patients with UA/NSTEMI remained at higher risk for CV death than non-CV death over long-term follow-up (despite advancements in pharmacotherapy and invasive management)[31].

Less is known regarding the long-term prognosis and survival outcomes in current patients with CCS for whom the risk of annual cardiac mortality is used to describe the event risk. Such limited information is mostly related to the evolving nature of patients with CCS who were previously defined largely *via* their angina symptoms but now display a broad spectrum of clinical presentations and prior medical history. Thus, previous evidence stemming from the Euro Heart survey and the REACH registry was mostly based on subpopulations of patients with CCS, who did not encompass the full spectrum of CCS and potentially received less contemporary treatment than the current CCS patients[33,34]. The international CLARIFY registry involving over 30,000 patients with CCS has recently provided useful insights on CV mortality as assessed as CV death or non-fatal MI as well as the triple composite of cardiovascular death[15]. The 5-year crude rate of CV death or non-fatal MI was 8.0%, and the CV death rate was 5.5% with 20% of CV deaths were due to MI and 10% were due to stroke. Higher rates of CV death and of non-fatal MI were reported among patients with previous MI *vs.* those without; in addition, patients with previous MI and angina symptoms had worse prognosis (5-year rate of CV death: 11.8%) compared with patients with no angina (8.2%) (p<0.001)[15]. Overall, a history of MI and angina symptoms are major determinants of adverse CV outcomes, thus placing patients with a history of MI and angina symptoms at highest risk for CV mortality. The CV mortality risk of this subgroup, which represents about 14% of patients with CCS, needs to be addressed appropriately *via* intensive monitoring and treatment.

The Role of P2Y$_{12}$ Inhibitors in DAPT: Are All Equally Effective in Preventing Cardiovascular Mortality?

DAPT is the cornerstone of antithrombotic interventions aimed at lowering the rate of hard clinical outcomes (namely, prevention of ischemic events and death) in patients treated both conservatively and invasively after ACS, as well as at improving the prognosis in patients with CCS. DAPT is recommended for patients with STEMI[35], whose in-hospital mortality rates vary between 4% and 12%, and patients with NSTE-

ACS[36] and whose cumulative incidence of CV death is approximately 2.67% at 1 year after the event[37]. The benefit of DAPT on long-term outcomes can result from both prevention of MACCE (a composite of death from any cause, stroke, MI, or repeat revascularization after 12 months) and of stent thrombosis, which in turn has an impact on cardiovascular mortality[27]. The benefit from DAPT relies on an accurate clinical assessment of the relative weight of ischemic and bleeding events on mortality as well as of the optimal (or minimal necessary) timing of duration, which in turn are heavily linked to the patient's risk profile and underlying CAD condition at baseline[17]. Clinical guidelines recommended 12-month (or longer) duration of DAPT after PCI for patients with STEMI[35] and NSTE-ACS[36] unless there is excessive risk of bleeding, but there is an increasing need to better identify subgroups that may benefit from long-term DAPT with no or acceptable bleeding risk as well as to better address those who may be candidates for prolonged DAPT such as those with DM and CKD[17,37]. Recent data from the Coronary Bifurcation Stenting Registry II[38] and RENAMI registry[39] have shed further light on the effects of prolonged DAPT duration on long-term outcomes in both patients receiving drug-eluting stents for bifurcation lesions[38] and real-life ACS patients undergoing PCI and stent implantation[39]. Compared with the group on DAPT for <12-months, prolonged DAPT duration after PCI for a coronary bifurcation lesion was associated with a reduced risk of all-cause death or MI with no difference in CV death. In contrast, in unselected patients with ACS treated with prasugrel or ticagrelor for longer than 12 months a marked reduction in fatal and non-fatal ischemic events was observed, including CV death (1.2 *vs.* 5.1 risk of death) compared with those treated for less than 12 months[39]. Nevertheless, a recent meta-analysis[40] suggested that a significant net benefit of prolonged DAPT could be documented for patients with ACS but not for those with stable CAD, thus reinforcing the notion that the duration of DAPT should be defined for each patient on an individual basis[17].

In addition to the duration of DAPT, $P2Y_{12}$ inhibitors also have different impacts on long-term outcomes, particularly mortality, as documented by contrasting results from studies on ACS[19,20,41] or on patients with CCS[22,23,42]. In patients with ACS, combining aspirin with clopidogrel or prasugrel was shown to lower MACE[20,43] but did not provide any survival benefit. In contrast, combining aspirin with ticagrelor provided a significant reduction in both the rate of all-cause death (5.9% *vs.* 4.5%; $p < 0.001$) and death from vascular causes (5.1% *vs.* 4.0%; $p = 0.001$), along with an improvement in the incidence of MACE when compared with clopidogrel[19]. In patients with CCS (e.g., with a history of MI), clopidogrel proved to be effective in reducing MACE without any effects on CV and all-cause death[44] while ticagrelor reduced the 3-year combined incidence of MI, stroke, or CV death compared with placebo in stable patients treated with aspirin with a history of MI 1-3 years previously[23]. Treatment with 60 mg of ticagrelor in a post-MI setting, when initiated according to EU-approved label, was associated with a relative risk reduction of 20% for CV death, MI, or stroke[45].

Whether subtle pharmacological differences within the $P2Y_{12}$ inhibitor family may contribute to the different mortality outcomes is currently unknown. However, it has been proposed that some features of the newer $P2Y_{12}$ antagonists prasugrel and ticagrelor, including fast onset of action, rapid offset of effect, less variable on-treatment platelet reactivity and reversibility, may lay the foundation for the greater efficacy of newer $P2Y_{12}$ *vs.* clopidogrel[17,46,47] in terms of survival after ACS[25]. Furthermore, pleiotropic effects have also been documented for ticagrelor, which, unlike clopidogrel and prasugrel, is able to inhibit the cellular uptake of adenosine by targeting its equilibrative nucleoside transporter 1 (ENT1)[48-51]. As a result, ticagrelor enhances the biological effects of endogenous adenosine by prolonging the half-life of adenosine and increasing its concentration as documented in animal models[52]. The clinical relevance of the pleiotropic effect of ticagrelor has been evaluated in patients post-ACS with contrasting results[53,54].

In the following paragraphs, we discuss in more detail the clinical evidence supporting the benefit of ticagrelor on CV mortality as documented in both acute and chronic settings across a broad spectrum of patient subgroups with high to very high risk of experiencing future CV events.

Ticagrelor Mortality Benefit in ACS: Insights from the Landmark PLATO Study

The primary goal in the management of patients with ACS is to stabilize coronary blood flow, evaluate overall CV disease burden, and initiate appropriate antithrombotic treatment to

minimize subsequent ischemic events, including MI and related mortality. Current guidelines recommend $P2Y_{12}$ in addition to aspirin for 12 months after PCI and maintained over 12 months unless there are contraindications or an excessive risk of bleeding in patients with STEMI and NSTE-ACS (indication IA)[35,36]. Ticagrelor, but not prasugrel, can be used irrespective of the planned treatment strategy (invasive or conservative) [180 mg loading dose (LD), 90 mg twice daily][36]. The evidence base for the aforementioned recommendations mostly stems from the findings of the landmark PLATO study (PLATelet inhibition and patient Outcomes)[19] as well as the TRITON-TIMI 38 (TRial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet InhibitioN with Prasugrel-Thrombolysis In Myocardial Infarction 38) trial[20].

The PLATO trial was designed to test the hypothesis that ticagrelor (180 mg LD, 90 mg twice daily) would be superior to the available standard of care (e.g., clopidogrel, 300-600 LD, 75 mg once daily) at preventing CV events and death in a very broad population (n=18,624) of patients presenting with an ACS (both STEMI and NSTE-ACS within 24 h of symptoms' onset) who were followed up for a minimum of 6 months to a maximum of 12 months[19]. The PLATO population included patients with ACS who were either initially managed medically or with PCI or with coronary artery bypass graft (CABG). The primary endpoint, a composite of death from vascular causes, MI, or stroke, was found to occur less frequently among patients treated with ticagrelor than among those receiving clopidogrel [9.8% *vs.* 11.7%; HR:0.84; $p<0.001$] on top of daily aspirin. This outcome appeared mainly driven by the reduction in both MI [5.8% *vs.* 6.9%, HR:0.84, $p<0.005$] and death from vascular causes [4.0% *vs.* 5.1%, HR:0.79, $p<0.001$], as documented as early as 30 days of therapy and sustained up to 12 months with an overall relative risk reduction (RRR) of 16%[55]. It has been estimated that such mortality benefit translates to one CV death prevented every 91 patients treated with ticagrelor[55].

Patients with ACS who are candidates for invasive management (e.g., PCI or CABG) may experience a wide range of short- and long-term outcomes, such as stent thrombosis or target lesion revascularization (TRL) which are associated with MI or death. Therefore, one of the pre-specified objectives of the PLATO trial was to compare the incidence of stent thrombosis in those treated with ticagrelor and clopidogrel. In patients who underwent stenting, ticagrelor reduced the incidence of definite (e.g., angiographically documented) stent thrombosis (1.3 *vs.* 1.9 %; HR 0.67, $p=0.0091$) and the reduction was consistent across NSTE-ACS, STEMI and regardless of stent characteristics[56]. Furthermore, in 13,408 patients in the PLATO trial for whom an invasive strategy was planned, the benefit of ticagrelor over clopidogrel on the primary endpoint [9% *vs.* 10.7%, HR: 0.84, $p=0.0025$] rate of MI [5.3% *vs.* 6.6%, HR: 0.80, $p=0.0023$], CV death [3.4 *vs.* 4.3, HR: 0.82, $p=0.0250$] and all-cause death [3.9 *vs.* 5.0, HR: 0.81, $p=0.0103$] was in line with the results for the overall population[18,57].

Patients with ACS may also be treated conservatively with 30%-60% of patients with NSTE-ACS not undergoing cardiac catheterization or even not revascularized; overall, these patients have a high prevalence of comorbidities and experiences increased morbidity and mortality compared with those undergoing invasive strategies[27]. Ticagrelor significantly lowered the incidence of the primary endpoint [12% *vs.* 14.3%, HR: 0.85, $p=0.045$] as well as CV death [5.5% *vs.* 7.2%, HR:0.76, $p=0.019$] and all-cause death [6.1% *vs.* 8.2%, HR:0.75, $p=0.010$], thus confirming that the benefits apply across diverse intervention strategies[58].

In the PLATO overall population, about 59% of patients (n=11,080) were categorized as NSTE-ACS at randomization. Patients with NSTE-ACS are characterized by a lower short-term mortality rates and higher rates of long-term mortality than those with STEMI; the overall 10-year survival rate after NSTE-ACS is approximately 50%[59,60]. Thus, the risk-benefit assessment and the clinical decision making in this subgroup appear challenging and clear evidence is required to support treatment choices. In a sub-study of the PLATO trial conducted on patients with NSTEMI, ticagrelor led to lower rates of primary endpoint [10% *vs.* 12.3%, HR: 0.83, $p=0.0013$], CV death [3.7% *vs.* 4.9%, HR:0.77, $p= 0.0070$] and all-cause death [4.3% *vs.* 5.8%, HR: 0.76, $p=0.0020$] consistent with the overall population in the PLATO trial and regardless of revascularization performed in the first 10 days[61].

After an ACS event, age is a strong predictor of adverse events, including impaired healing process and greater recurrence of ischemic events and/or complications, and a risk factor for bleeding. Thus, in the elderly population, the well-documented net clinical benefit of DAPT may be reduced, thereby warranting caution when choos-

ing a $P2Y_{12}$ inhibitor[62]. Accordingly, a pre-specified objective of the PLATO trial was to evaluate the clinical efficacy of ticagrelor in elderly (≥ 75 years of age) *vs.* younger (< 75 years of age) patients with ACS. The clinical benefit of ticagrelor over clopidogrel was not different between elderly and younger patients with ACS regarding the primary composite endpoint in line with the main PLATO cohort [17.2% *vs.* 18.3% (HR: 0.89) in the elderly; 8.6% *vs.* 10.4% (HR: 0.84) in younger patients][62]. A similar reduction has been reported in elderly patients treated with ticagrelor compared with those receiving clopidogrel with respect to CV death, MI, and all-cause mortality, with interaction p=0.56, p=0.47 and p=0.76 for the primary endpoint, CV death and all-cause mortality, respectively[62].

A recent large observational study[63] from the SWEDEHEART registry (Swedish Web-System for Enhancement and Development of Evidence-Based Care in Heart Disease Evaluated According to Recommended Therapies), questioned the benefits of ticagrelor in patients ≥80-years of age because observed that the superiority of ticagrelor over clopidogrel in terms of composite endpoint, as well as death and MI was significant in patients <80-years of age but not in older patients. It has been suggested that elderly may have a different benefit-risk ratio when treated with ticagrelor compared with clopidogrel when discharged after a MI. Although real-world data are very important, they cannot undermine the solid and consistent findings from the PLATO randomized trial given its limitations. It was an observational study, with unmeasured confounders despite adjustments, without data on eventual cross-over or interruption (only intention-to-treat data available), and without causes of death recorded. However, a different cutoff for defining age, a variable ischemic and bleeding risk in this populations, and evolution of techniques and concomitant therapies compared with the PLATO population might contribute to explain the different results. Therefore, only a future adequately powered randomized study in the elderly population can provide definitive conclusions.

Increased recurrence of CV events and bleeding complications, including intracranial bleeding, are well documented in patients with ACS with a history of stroke or transient ischemic attack (TIA), thus highlighting the relevance of balancing the antithrombotic efficacy with the bleeding risk in this high-risk and frail population. Although a very small proportion of the overall PLATO population presented with a history of stroke or TIA at randomization, in this high-risk subgroup, the benefit of ticagrelor over clopidogrel was proved with respect to the primary endpoint [19% *vs.* 20.8%, HR: 0.87 (95% CI:0.66-1.13)] along with a low risk of intracranial hemorrhage or fatal stroke with an overall 13% reduction in the rate of the primary endpoint which is comparable to the results achieved in patients without a history of stroke or TIA (e.g., 16%)[64]. Therefore, in contrast with prasugrel, this subset of patients does not represent a contraindication to the use of ticagrelor.

Patients with diabetes are more prone to recurrent ischemic events following an ACS (including 80% higher mortality risk compared with those without diabetes) and have been reported[65-67] to have higher on-treatment platelet reactivity and worse clinical outcomes when taking aspirin and clopidogrel. Therefore, whether the potent $P2Y_{12}$ inhibitor ticagrelor would be able to offer this patient population additional benefit compared with clopidogrel is a relevant issue for evaluation. In the diabetic cohort of the PLATO trial (n=4,662) ticagrelor provided consistent reduction in the occurrence of the primary composite endpoint [14.1% *vs.* 16.2%, HR:0.88 (95% CI: 0.76-1.03)] but without nominal statistical significance[68]. Moreover, cardioprotective effects of ticagrelor were observed in patients with levels of HbA_{1c} ≥ 6% or poor glycemic control on admission with a 22% reduction in all-cause death *vs.* clopidogrel [HR: 0.78 (95% CI: 0.65-0.93)]. Although no differences in major bleeding rates were reported, patients treated with ticagrelor experienced more frequent non-CABG-related bleeding than those receiving clopidogrel[68].

A higher risk of bleeding complications has been reported in patients with ACS after interventional procedures, such as CABG; therefore, in these patients, the rapid offset of $P2Y_{12}$ inhibition, in contrast to the longer offset observed with clopidogrel and/or prasugrel, can be of help. In the overall PLATO population, about 1,261 patients underwent CABG post-randomization and received the last intake of DAPT within 7 days before surgery. In these patients, total mortality was reduced from 9.7% (58 of 629) to 4.7% (29 of 629; HR: 0.49; 95% CI: 0.32 to 0.77; $p < 0.01$), in CV death from 7.9% (47 of 629) to 4.1% (25 of 629; HR: 0.52; 95% CI: 0.32 to 0.85; $p < 0.01$) without a higher risk in CABG-related bleeding[69]. Despite the shorter treatment-free interval before CABG achieved with ticagrelor therapy, no

significant differences *vs.* clopidogrel have been observed in terms of major bleeding, fatal bleeding at surgery or occurrence of reoperation. The benefit of ticagrelor over clopidogrel on mortality has also been reported in additional high-risk subpopulations who often exhibit a worse prognosis in the ACS setting including patients with CKD[70], with peripheral artery disease (PAD)[71] and STEMI[72]. Overall, the beneficial effects of ticagrelor over clopidogrel on mortality were achieved across a broad spectrum of ACS settings (Figure 1) without a significant increase in the rate of major bleeding but with an increase in the rate of non-procedure-related bleeding. To aid in clinicians' evaluation of the extent and long-term impact of such adverse events, a comprehensive analysis of bleeding complications reported in the PLATO trial has been performed by using three different scales according to the PLATO, TIMI and GUSTO (Global Use of Streptokinase and Tissue plasminogen activator to Open occluded coronary arteries)-based definitions[73]. The higher rate of non-CABG-related major bleeding in patients treated with ticagrelor was significant not before the first 30 days on treatment and was independently associated with several predictive factors, such as increasing age, reduced creatinine clearance, female sex, or previous gastrointestinal bleeding. In addition, fatal bleeding and transfusion rates were similar (0.3% *vs.* 0.3%, p=0.66 and 8.5% *vs.* 8.3%, p=0.81, respectively). In the ACS setting, ticagrelor prevents the first occurrence of the composite endpoint of MI, stroke, or CV death more effectively than clopidogrel, with the treatment effect driven by reductions in the rate of MI and CV death; in addition, the benefit of ticagrelor was seen within 30 days of treatment, maintained up to 1 year and well documented in patients with ACS managed invasively and noninvasively as well as those deemed to be at high risk of bleeding complications.

In line with this, in NSTE-ACS patients planned for conservative management earlier guidelines recommended $P2Y_{12}$ inhibition (preferably with ticagrelor) in the absence of contraindications as soon as the diagnosis is confirmed[74].

In last few years, new evidence on head-to-head comparison of ticagrelor and prasugrel has emerged. The PRAGUE-18 trial[75], compared their efficacy and safety in 1,230 patients with acute MI treated with primary or immediate PCI. Overall, there were no significant differences between the two compounds and the study did not support the hypothesis that one could be more effective or safer than the other. However, the study was open-label, underpowered, with lower than expected even rates, with a change of the primary outcome; it was terminated prematurely for futility, and thus the results remain inconclusive.

A more recent head-to-head comparison of prasugrel and ticagrelor has been performed in the ISAREACT 5 trial[41,76]. Patients with ACS (n=4,018, 41.1% with STEMI) planned for invasive management were randomly assigned to a prasugrel-based or to ticagrelor-based strategy. The former was superior in reducing the incidence of death, MI, or stroke at 1 year (6.9% *vs.* 9.3%, p = 0.006), and this result was driven

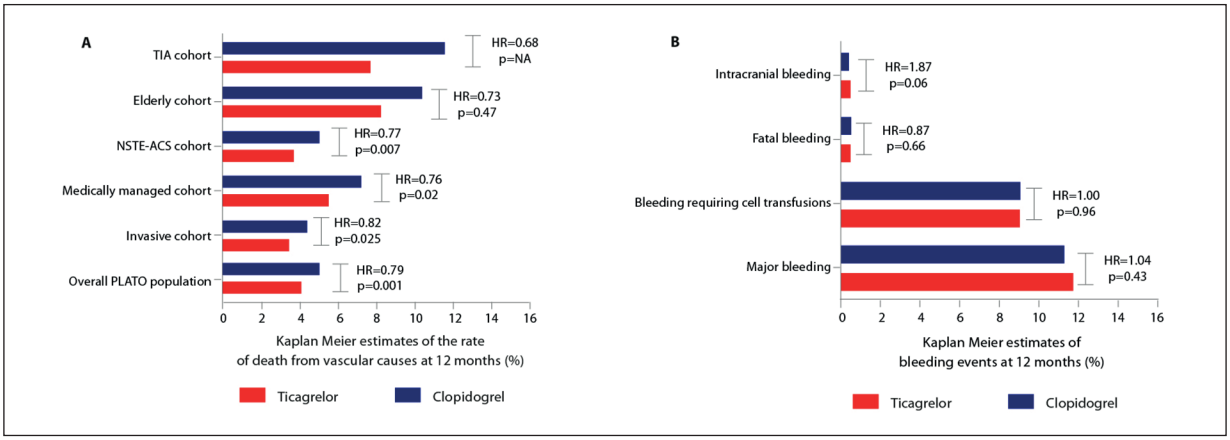

Figure 1. Cardiovascular protective benefit of ticagrelor over clopidogrel in patients with ACS. Mortality benefit (panel **A**) and bleeding risk (panel **B**). The percentages are Kaplan–Meier estimates of the rate of the end point at 12 months. Graphical elaboration of previously published data in[19,57,58,61,62,64,68,69]. HR, hazard ratio; NSTE-ACS, acute coronary syndromes without ST segment elevation; TIA, transient ischemic attack.

by a significant reduction of 1.8 percentage points in the incidence of recurrent MI, with no significant difference in major bleeding. However, some relevant limitations should be considered: a) open-label design, b) unexpected results (in the opposite direction of the primary hypothesis), c) lower than expected event rate in the prasugrel arm (6.9% *vs.* 12.9%), d) events mainly ascertained through telephone contact, with limited site-based follow-up (10%), e) not negligible lost-to-follow-up patients (19 *vs.* 18, which were higher than the 17 corresponding to the difference in all-cause death), f) high discontinuation rate (30-35%) of which 19% before discharge, g) differential exclusion from safety analysis (23 ticagrelor *vs.* 233 prasugrel) and h) some confounding effect related to different treatment strategies between randomized therapies (loading dose of ticagrelor started as soon as possible after randomization, while timing of the loading dose of prasugrel was based on clinical presentation, being as soon as possible in cases of STEMI and after coronary angiography in cases of NSTE-ACS). In NSTE-ACS patients undergoing PCI, the time from randomization to the loading dose was 6 minutes in the ticagrelor arm and 61 minutes in the prasugrel arm. Moreover, since the trial design mandated routine pretreatment with ticagrelor in all patients but no pretreatment with prasugrel in NSTE-ACS patients, the loading dose was given to more patients in the ticagrelor arm (98.7%) compared with the prasugrel arm (86.1%). The ISAR-REACT 5 trial had a relevant impact on the most recent ESC-NSTE-ACS guidelines in which a preference for prasugrel over ticagrelor was acknowledged for the first time (prasugrel should be considered in preference to ticagrelor for NSTE-ACS patients who proceed to PCI, IIa, B)[36]. However, it does not mean that all NSTE-ACS will be treated with prasugrel. The same guidelines introduced another important practice-changing recommendation: "it is not recommended to administer routine pre-treatment with a $P2Y_{12}$ receptor inhibitor in patients in whom coronary anatomy is not known and an early invasive management is planned (III, A)"[36]. Additional evidence against the utility of $P2Y_{12}$ inhibitor pre-treatment in cases of NSTE-ACS has also been provided by the recent DUBIUS trial[77]. Overall, this recommendation will determine that most patients with NSTE-ACS undergoing PCI will be $P2Y_{12}$ inhibitor naïve, thus opening the door to a wider use of cangrelor in this setting. Given that ticagrelor, but not prasugrel or clopidogrel, can be given immediately after starting cangrelor, one could argue that, when cangrelor is used, ticagrelor might be the preferred oral $P2Y_{12}$ inhibitor to limit drug-drug interactions and potential risks of a variable time-window with inadequate platelet inhibition at the end of cangrelor infusion[78-81].

Ticagrelor Mortality Benefit in Secondary Prevention: Insights from the PEGASUS Trial

The optimal duration of antithrombotic therapy for secondary prevention, and strategies for tailoring this based on patient profile, in patients at high risk of ischemic events is a matter of debate mostly owing to the conflicting results of several randomized trials[22,44,82,83] and depending on the relative contribution of ischemic and bleeding events on mortality[84]. Therefore, although some alternative approaches have been the focus of recent research (i.e., short DAPT, monotherapy, de-escalation), in clinical practice establishing whether continuation of DAPT beyond 1 year offers a substantial reduction in important cardiovascular outcomes as well as to identify patients who may derive benefit from shortened or extended DAPT courses for secondary prevention of CAD remains challenging[17,85,86]. This assessment is particularly difficult when considering that a variable but not negligible proportion of patients are at HBR[87-91]. In addition, such considerations are particularly relevant in high-risk populations, such as MI survivors who exhibit a 30% higher risk of all-cause death and cardiovascular outcomes (including cardiovascular death) than the general population at both 1-3 years and 3-5 years after MI thus remaining at heightened risk for recurrent events[92,93].

The role of DAPT with aspirin and ticagrelor (tested at two dose intensities: 60 and 90 mg) in stable patients with a history of MI between 1 and 3 years and at least one additional atherothrombotic risk factor [e.g., diabetes, evidence of multivessel disease (MVD) or PAD], as an effective option to promote secondary prevention, has been defined by the Prevention of Cardiovascular Events in Patients with Prior Heart Attack Using Ticagrelor Compared with Placebo on a Background of Aspirin-Thrombolysis in Myocardial Infarction 54 (PEGASUS-TIMI 54) trial[23,94]. The primary endpoint, a composite of cardiovascular death, MI, or stroke at 3 years, was found to occur less frequently in patients treated with

ticagrelor [Kaplan-Meier (KM) event rates at 3 years of 7.77% (60 mg) or 7.85% (90 mg)] compared with placebo (KM: 9.04%)[23]. Overall, both dose regimens provided a mortality benefit with a consistent treatment effect over the entire study period, yielding a 16% RRR and 1.27% absolute risk reduction (ARR) for ticagrelor 60 mg and a 15% RRR and 1.19% ARR for ticagrelor 90 mg[55]. Notably, the rates of TIMI major bleeding were reported to be greater with both ticagrelor dose regimens compared with placebo with no significant differences in either fatal or intracranial bleeding[23].

Although the two dose regimens displayed a similar extent of efficacy in the intention-to-treat analysis, patients receiving the lower dose intensity presented with lower rates of bleeding, dyspnea, and treatment discontinuation, thus unveiling a better tolerability profile with the 60 mg dose. Notably, the 60 mg dose is currently approved in many countries for the prevention of atherothrombotic events in patients with a history of MI and a high risk of developing an atherothrombotic event; therefore, we will mostly discuss the results of the 60 mg treatment group[23]. A subsequent analysis focusing on the effects of extended treatment with ticagrelor 60 mg in patients treated according to the approved label was performed and showed, compared with placebo, a 20% reduction in the composite primary endpoint (HR:0.80) as well as 28% and 29% reduction in coronary heart and cardiovascular death, respectively[45]. The findings were found to be translated to a net clinical benefit equal to 10 prevented CV deaths every 1,000 patients treated with ticagrelor for 3 years[45]. Furthermore, when yearly long-term effects of ticagrelor were also analyzed, a sustained benefit without late waning in efficacy was observed[95]. Such mortality benefit occurs only in high-risk patients; it has not been reported in either clinically stable patients >2 years from the MI or more than 1-year after stopping previous treatment with an ADP receptor inhibitor[55]. An earlier study[96] highlighted a three-fold gradient in the cumulative risk of cardiovascular death, MI or stroke within a large set of patients at various stages along the atherosclerotic continuum, ranging from 7% in nondiabetic patients with other risk factors for atherothrombosis to 25% in patients with poly-vascular disease and previous ischemic event. Therefore, there are additional risk factors that identify patients who should undergo a more intensive treatment and follow-up and for whom an established mortality benefit is highly desirable. The PEGASUS overall population (n=21,162) comprised 6,806 patients with diabetes who experienced 17% reduction in the primary composite endpoint, 26% reduction in cardiovascular death and 36% reduction in coronary heart disease death after treatment with ticagrelor 60 mg. Among patients at high-risk for recurrent ischemic events and mortality, i.e., at least 2-fold higher MACE risk, individuals with PAD had an ARR of 5.2% at 3 years after treatment with ticagrelor 60 mg along with a significant 31% reduction in the primary composite endpoint (p=0.045) and a 53% reduction in cardiovascular death (p=0.014) *vs.* placebo[96]. This observation is relevant if one considers that PAD is often accompanied by further markers of atherothrombotic risk including renal dysfunction, diabetes, and smoking.

It has been suggested that the association between the duration of DAPT (short- *vs.* prolonged) and clinical outcomes would be influenced by patients' underlying disease and, in presence of angiographic MVD, shorter duration of DAPT was associated with increased risk of MACE, thus hypothesizing that prolonged therapy could be favored in this subset of patients[97]. Almost 60% (59.4%) of PEGASUS overall population had a history of MVD and displayed a greater risk of coronary events compared with those without MVD. In this high-risk patient subgroup, treatment with ticagrelor provided a 19% reduction in the composite primary endpoint [HR.0.81 (95% CI: 0.7-0.95), $p_{interaction}$=0.55] and a 36% reduction in the event rate for coronary death compared with placebo [HR: 0.64, (95% CI: 0.45-0.89) $p_{interaction}$=0.045][98]. Therefore, these data provide the first evidence that ticagrelor can be offered to patients with MVD for long-term therapy. Overall, the PEGASUS trial provided a clear evidence of a favorable benefit-risk balance for long-term ticagrelor 60 mg in patients with previous MI and additional risk factors that make this subgroup more prone to recurrent events and death, particularly in terms of CV mortality (Figure 2).

While current guidelines[5] also recommend the combination of low-dose rivaroxaban and aspirin for event prevention based on the findings of the COMPASS trial[99], the pre-specified significance thresholds for cardiovascular mortality and all-cause mortality were not met, thus leaving unanswered the question whether the COMPASS-like regimen may be an alternative

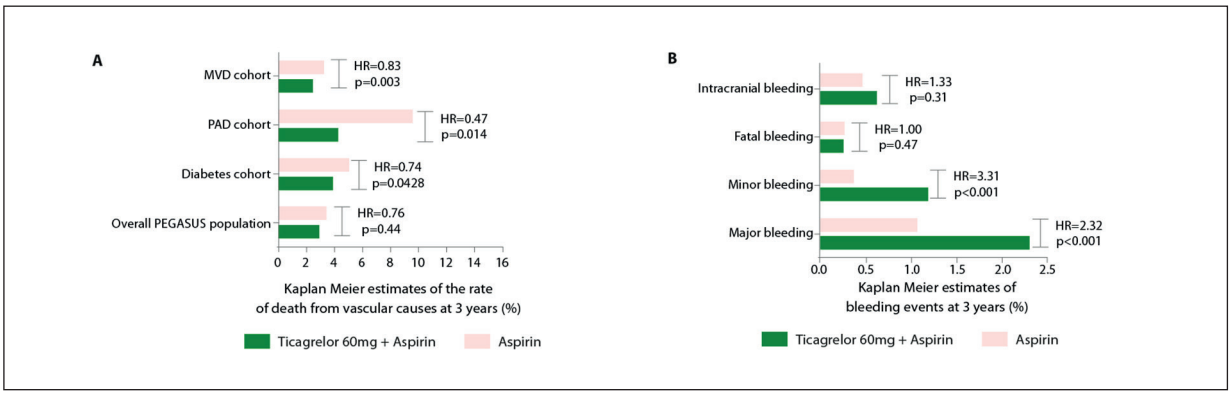

Figure 2. Cardiovascular protective benefit of ticagrelor in patients with previous MI (1 to 3 years) and at least one of the following additional high-risk features: age of 65 years or older, diabetes mellitus requiring medication, a second previous spontaneous MI, multivessel coronary artery disease, or chronic renal dysfunction. Mortality benefit (panel **A**) and bleeding risk (panel **B**). The percentages are Kaplan–Meier estimates of the rate of the end point at 3 years. Graphical elaboration of previously published data in [23,45,96,98]. HR, hazard ratio; MVD, multivessel disease; PAD, peripheral artery disease.

option to the PEGASUS-TIMI-like regimen in conferring cardio-protection in patients at high-risk of ischemic events without a high bleeding risk. Pending further research on comparative studies between long-term DAPT with ticagrelor or treatment with low-dose factor Xa inhibitors on top of aspirin, evidence stemming from real-world studies and/or registries may provide guidance on the generalizability of the PEGASUS-TIMI and COMPASS trials to routine clinical practice[100-102].

Discussion

Prevention of coronary thrombosis and its acute and chronic sequelae is of paramount clinical relevance when managing patients with ACS and CCS[5] with recurrent ischemic events and mortality being primary treatment goals. Owing to the evolving nature of patients with CCS, characterized by a broad spectrum of clinical presentations and prior medical history, as well as the advances in therapeutic and surgical management of ACS, a greater attention to the rate of hard clinical outcomes, the improvement of the long-term prognosis, and reduction of residual risk of recurrent events is increasingly reported among cardiologists. The seminal findings from the PLATO[19] and PEGASUS-TIMI 54[23] trials and their related subgroup analyses provided evidence that accomplishing clinically meaningful reduction in cardiovascular mortality is feasible in the setting of ACS and CCS across a broad range of high-risk patient populations and is associated with increased major but not fatal or intracranial bleeding. Definition of the benefits and risks to be expected in real life is of great relevance and has great potential in confirming the generalizability of the evidence from randomized trials to clinical practice. With respect to ticagrelor, the evidence stemming from national registries and observational studies may translate the earlier findings in PLATO and PEGASUS-TIMI 54 populations, whose strict eligibility criteria and risk definition assessment do not fully acknowledge the current knowledge of the natural history of CAD, into contemporary practice. A prospective study performed on more than 45,000 patients enrolled in the SWEDHEART registry showed a 15% reduction in the risk of the primary outcome [11.7% *vs.* 22.3%, adjusted HR: 0.85 (95% confidence interval: 0.78-0.93)] and a 17% reduction in the risk of death [5.8% *vs.* 12.9% (adjusted HR: 0.83 (0.75-0.92)] in patients treated with ticagrelor compared with those receiving clopidogrel[103]. Further evidence of the benefit of ticagrelor on mortality was also reported in a real-world STEMI population in a case-control study examining all patients with STEMI included in the Cardio-STEMI SANREMO registry[104]. Significant lower rates of unadjusted cardiac hospital death occurred in the ticagrelor group (0.7% *vs.* 5.4%; $p = 0.024$) compared with the clopidogrel group and a greater unadjusted survival at 1 year after STEMI was reported in those treated with ticagrelor *vs.* clopidogrel (97.8% *vs.* 87.8%; $p =$

0.024)[104]. There was no difference in Bleeding Academic Research Consortium bleeding and in the unadjusted incidence of hospital major adverse cardiovascular events (MACE; cardiac death, myocardial infarction, or stroke)[104]. In patients with ACS balancing ischemic benefit with bleeding risk is of outmost relevance, particularly in patients treated with PCI. Therefore, there is an ongoing debate on the ability of ticagrelor, compared with clopidogrel, to be associated with better outcomes in routine clinical practice. An earlier systematic analysis carried out on 23,714 patients[105] who were revascularized by PCI found that ticagrelor and clopidogrel were comparable in terms of efficacy. The use of ticagrelor was associated with a significantly higher rate of minor and major bleeding when compared with clopidogrel. Nevertheless, as stated by Guan et al[105], life-threatening bleeding (odds ratio, OR: 1.00, 95% CI: 0.79-1.27; p=0.98) was not significantly different between these two antiplatelet drugs. Of note, Guan et al[105] reported no differences in all-cause mortality, MACEs, MI, stroke, and stent thrombosis between ticagrelor and clopidogrel in contrast to the findings stemmed from a recent direct pairwise meta-analysis by Navarese et al[25]. Finally, a retrospective cohort study including 62,580 propensity score-matched patients reported that the use of ticagrelor, compared with clopidogrel, was not associated with a statistically significant difference in the risk of net clinical adverse events (defined as recurrent MI, revascularization, ischemic stroke, hemorrhagic stroke, and gastrointestinal bleeding) at 12 months[106]. This outcome represents the numerical difference between ischemic events avoided and excess bleeding events[107] and it can be relevant to both clinicians and patients in shared decision making. Overall, further real-world evidence guiding clinicians in selecting the appropriate $P2Y_{12}$ inhibitor for a high-risk patient group, like that represented by those revascularized by PCI, is urgently needed.

Furthermore, by taking advantage of the Cardio-STEMI SANREMO registry, a recent study[108] also clarified how many real-world patients meet the PEGASUS-TIMI54 criteria and the extent to which these criteria predict a patient's risk and prognosis. To date, about 70% of the patients hospitalized for STEMI met the PEGASUS-TIMI 54 criteria and were identified by having a significantly lower 4-year survival and being at increased risk of mortality; importantly, in such patients, treatment with ticagrelor proved to be effective in improving 4-year survival and lowering mortality rates compared with other antiplatelet agents[108]. Further evidence on the use of ticagrelor 60 mg in real-life patients after MI has also been provided in a recent Italian prospective observational study[101]. In most cases, patients with more than two risk factors were deemed eligible to receive ticagrelor 60 mg twice daily and almost seven patients in ten (66.7%) were patients with recurrent events; importantly, PEGASUS criteria for eligibility to prolonged DAPT as per PEGASUS study design, such as MVD, age >65 years and diabetes were also found to be the eligibility criteria for prescribing prolonged DAPT with ticagrelor[90]. The applicability in real-life of the PEGASUS-TIMI54 trial was explored in the analysis of the EYESHOT (EmploYEd antithrombotic therapies in patients with acute coronary Syndromes HOspitalized in iTaly) registry that provided meaningful insights on the current management and treatment of patients with previous MI referring to cardiologists[100]. Overall, it has been suggested that, by virtue of their ease of use, the PEGASUS-TIMI 54 inclusion criteria, along with the DAPT score and the PRECISE-DAPT score, may be useful tools to support clinical decision-making about the duration of DAPT[109]. While deaths averted provide a measure of health gain and improved prognosis, cost-effectiveness studies are useful to monitor the feasibility of the evidence gathered in randomized trials in the current practice routine where reimbursement-related issues may have an impact on treatment selection. Interestingly, ticagrelor was found to be cost-effective compared with clopidogrel in preventing downstream morbidity and mortality associated with ACS[109] and to yield a cost-effectiveness ratio providing higher value for high- risk patients including those with >1 previous MI, MVD, diabetes, renal dysfunction, and PAD[110].

Conclusions

Ticagrelor is an effective and well-tolerated option to attain a meaningful and clinically relevant reduction in cardiovascular mortality in both acute and chronic settings (Figure 3) across a broad range of high-risk patient subpopulations with an acceptable payoff in terms of bleeding risk.

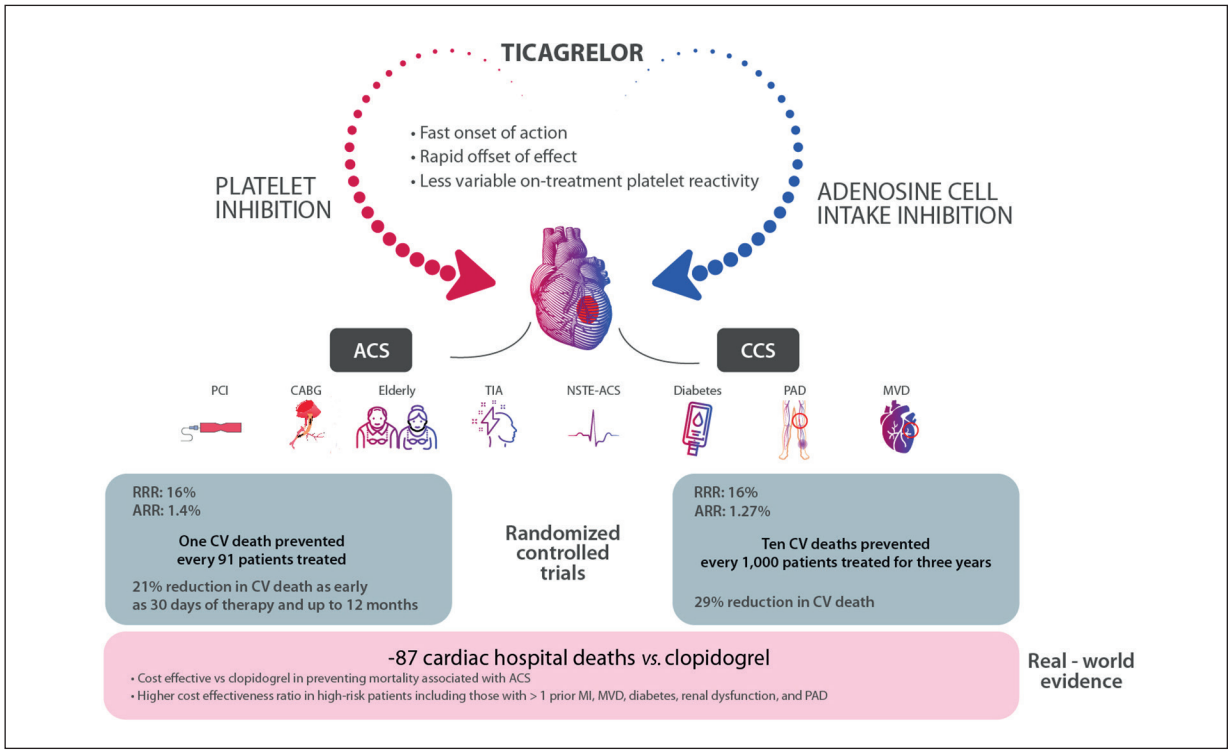

Figure 3. Benefit of ticagrelor in patients with ACS and CCS. ACS, acute coronary syndrome; ARR, absolute risk reduction; CABG, coronary artery bypass graft; CCS, chronic coronary syndrome; CV, cardiovascular; MI, myocardial infarction; MVD, multivessel disease, NSTE-ACS, acute coronary syndromes without ST-segment elevation; PCI, percutaneous coronary intervention; PAD, peripheral artery disease; RRR, relative risk reduction; TIA, transient ischemic attack.

Conflict of Interest

The Authors declare that they have no conflict of interests.

Acknowledgements

Writing and editing assistance, including preparation of a draft manuscript under the direction and guidance of the authors, incorporation of author feedback, and manuscript submission, was provided by EDRA, with the helpful support of Chiara Degirolamo, Ph.D, and supported by an unconditioned grant from AstraZeneca.

Declaration of Funding

This work was carried out thanks to an unrestricted educational grant from AstraZeneca to EDRA. The authors did not receive any direct or indirect funding.

Declaration of Financial/Other Relationships

AstraZeneca did not have any role in the design, planning, or execution of the review. The terms of the financial support from AstraZeneca included freedom for the authors to reach their own conclusions, and an absolute right to publish the results of this work, irrespective of any conclusions reached.

Authors' Contribution

All authors contributed equally to this work. All authors take responsibility for the integrity of the work as a whole and have given their approval for this version to be published.

References

1) World Health Organization. Global Status Report on Noncommunicable Diseases 2014. World Health Organization; 2014.
2) Benjamin EJ, Muntner P, Alonso A, Bittencourt MS, Callaway CW, Carson AP, Chamberlain AM, Chang AR, Cheng S, Das SR, Delling FN, Djousse L, Elkind MSV, Ferguson JF, Fornage M, Jordan LC, Khan SS, Kissela BM, Knutson KL, Kwan TW, Lackland DT, Lewis TT, Lichtman JH, Longenecker CT, Loop MS, Lutsey PL, Martin SS, Matsushita K, Moran AE, Mussolino ME, O'Flaherty M, Pandey A, Perak AM, Rosamond WD, Roth GA, Sampson UKA, Satou GM, Schroeder EB, Shah SH, Spartano NL, Stokes A, Tirschwell DL, Tsao CW, Turakhia MP, VanWagner LB, Wilkins JT, Wong SS, Virani SS; American Heart Association Council on Epidemiology and Prevention Statistics Committee and Stroke Statistics Subcommittee. Heart Disease and Stroke

Statistics-2019 Update: A Report From the American Heart Association. Circ 2019; 139: e56-e528.

3) Bauters C, Tricot O, Meurice T, Lamblin N, CORONOR Investigators. Long-term risk and predictors of cardiovascular death in stable coronary artery disease: the CORONOR study. Coron Artery Dis 2017; 28: 636-641.
4) Ain DL, Jang I. Natural history of coronary atherosclerosis did contemporary medical therapy change the course? Coron Artery Dis 2015; 26: 463-465.
5) Knuuti J, Wijns W, Saraste A, Capodanno D, Barbato E, Funck-Brentano C, Prescott E, Storey RF, Deaton C, Cuisset T, Agewall S, Dickstein K, Edvardsen T, Escaned J, Gersh BJ, Svitil P, Gilard M, Hasdai D, Hatala R, Mahfoud F, Masip J, Muneretto C, Valgimigli M, Achenbach S, Bax JJ, ESC Scientific Document Group. 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes. Eur Heart J 2020; 41: 407-477.
6) Ford ES, Ajani UA, Croft JB, Critchley JA, Labarthe DR, Kottke TE, Giles WH, Capewell S. Explaining the decrease in U.S. deaths from coronary disease, 1980-2000. N Engl J Med 2007; 356: 2388-2398.
7) Jernberg T, Hasvold P, Henriksson M, Hjelm H, Thuresson M, Janzon M. Cardiovascular risk in post-myocardial infarction patients: nationwide real-world data demonstrate the importance of a long-term perspective. Eur Heart J 2015; 36: 1163-1170.
8) Abu-Assi E, López-López A, González-Salvado V, Redondo-Diéguez A, pena-Gil C, Bouzas-Cruz N, Rapoiseiras-Roubin S, Abumuaileq RR, Garcia-Acuna JM, Gonzalez-Juanatey JR. The Risk of Cardiovascular Events After an Acute Coronary Event Remains High, Especially During the First Year, Despite Revascularization. Rev Esp Cardiol (Engl Ed) 2016; 69: 11-18.
9) Varenhorst C, Hasvold P, Johansson S, Janzon M, Albertsson P, Leosdottir M, Hambraeus K, James S, Jernberg T, Svennblad B, Lagerqvist B. Culprit and Nonculprit Recurrent Ischemic Events in Patients With Myocardial Infarction: Data From SWEDEHEART (Swedish Web System for Enhancement and Development of Evidence-Based Care in Heart Disease Evaluated According to Recommended Therapies). J Am Heart Assoc 2018; 7: e007174.
10) Ilardi F, Ferrone M, Avvedimento M, Servillo G, Gargiulo G. Complete Revascularization in Acute and Chronic Coronary Syndrome. Cardiol Clin 2020; 38: 491-505.
11) Timmis A, Rapsomaniki E, Chung SC, Pujades-Rodriguez M, Moayyeri A, Stogiannis D, Shah AD, Pasea L, Denaxas S, Emmas C, Hemingway H. Prolonged dual antiplatelet therapy in stable coronary disease: comparative observational study of benefits and harms in unselected versus trial populations. BMJ 2016; 353: i3163.
12) Lindholm D, James SK, Bertilsson M, Becker RC, Cannon CP, Giannitsis E, Harrington RA, Himmelmann A, Kontny F, Siegbahn A, Steg PG, Storey RF, Velders MA, Weaver WD, Wallentin L, PLATO Investigators. Biomarkers and coronary lesions predict outcomes after revascularization in non-ST-elevation acute coronary syndrome. Clin Chem 2016; 63: 573-584.
13) Klingenberg R, Aghlmandi S, Raber L, Gencer B, Nanchen D, Heg D, Carballo S, Rodondi N, Mach F, Windecker S, Juni P, vonEckardstein A, Matter CM, Luscher TF. Improved risk stratification of patients with acute coronary syndromes using a combination of hsTnT, NT-proBNP and hsCRP with the GRACE score. Eur Heart J Acute Cardiovasc Care 2018; 7: 129-138.
14) Miao B, Hernandez AV, Alberts MJ, Mangiafico N, Roman YM, Coleman CI. Incidence and Predictors of Major Adverse Cardiovascular Events in Patients With Established Atherosclerotic Disease or Multiple Risk Factors. J Am Heart Assoc 2020; 9: e014402.
15) Sorbets E, Fox KM, Elbez Y, Danchin N, Dorian P, Ferrari R, Ford I, Greenlaw N, Kalra PR, Parma Z, Shalnova S, Tardif JC, Tendera M, Zamorano JL, Vidal-Petiot E, Steg PG; on behalf of the CLARIFY investigator. Long-term outcomes of chronic coronary syndrome worldwide: insights from the international CLARIFY registry. Eur Heart J 2020; 41: 347-355.
16) Kalbacher D, Waldeyer C, Blankenberg S, Westermann D. Beyond conventional secondary prevention in coronary artery disease—what to choose in the era of CANTOS, COMPASS, FOURIER, ODYSSEY and PEGASUS-TIMI 54? A review on contemporary literature. Ann Transl Med 2018; 6: 323.
17) Gargiulo G, Valgimigli M, Capodanno D, Bittl JA. State of the art: duration of dual antiplatelet therapy after percutaneous coronary intervention and coronary stent implantation – past, present and future perspectives. EuroIntervention 2017; 13: 717-733.
18) Tersalvi G, Biasco L, Cioffi GM, Pedrazzini G. Acute Coronary Syndrome, Antiplatelet Therapy, and Bleeding: A Clinical Perspective. J Clin Med 2020; 9: 2064.
19) Wallentin L, Becker RC, Budaj A, Cannon CP, Emanuelsson H, Held C, Horrow J, Husted S, James S, Katus H, Mahaffey KW,Scirica BM, Skene A, Steg PG, Storey RF, Harrington RA, PLATO Investigators. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. N Engl J Med 2009; 361: 1045-1057.
20) Wiviott SD, Braunwald E, McCabe CH, Montalescot G, Ruzyllo W, Gottlieb S, Neumann FJ, Ardissino D, De Servi S, Murphy SA, Riesmeyer J, Weerakkody G, Gibson CM, Antman EM, TRITON-TIMI 38 Investigators. Prasugrel versus clopidogrel in patients with acute coronary syndromes. N Engl J Med 2007; 357: 2001-2015.

21) Udell JA, Bonaca MP, Collet JP, Lincoff AM, Kereiakes DJ, Costa F, Lee CW, Mauri L, Valgimigli M, Park SJ, Montalescot G, Sabatine MS, Braunwald E, Bhatt DL. Long-term dual antiplatelet therapy for secondary prevention of cardiovascular events in the subgroup of patients with previous myocardial infarction: a collaborative meta-analysis of randomized trials. Eur Heart J 2016; 37: 390-399.

22) Mauri L, Kereiakes DJ, Yeh RW, Driscoll-Shempp P, Cutlip DE, Steg PG, Normand SL, Braunwald E, Wiviott SD, Cohen DJ, Holmes DR, Krucoff MW, Hermiller J, Dauerman HL, Simon DI, Kandzari DE, Garratt KN, Lee DP, Pow TK, Ver Lee P, Rinaldi MJ, Massaro JM, DAPT Study Investigators. Twelve or 30 months of dual antiplatelet therapy after drug-eluting stents. N Engl J Med 2014; 371: 2155-2166.

23) Bonaca MP, Bhatt DL, Cohen M, Steg PG, Storey RF, Jensen EC, Magnani G, Bansilal S, Fish MP, Im K, Bengtsson O, Oude Ophuis T, Budaj A, Theroux P, Ruda M, Hamm C, Goto S, Spinar J, Nicolau JC, Kiss RG, Murphy SA, Wiviott SD, Held P, Braunwald E, Sabatine MS, PEGASUS-TIMI 54 Steering Committee and Investigators. Long-term use of ticagrelor in patients with prior myocardial infarction. N Engl J Med 2015; 372: 1791-1800.

24) CAPRIE Steering Committee. A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). Lancet 1996; 348: 1329-1339.

25) Navarese EP, Khan SU, Kołodziejczak M, Kubica J, Buccheri S, Cannon CP, Gurbel PA, De Servi S, Budaj A, Bartorelli A, Trabattoni D, Ohman EM, Wallentin L, Roe MT, James S. Comparative Efficacy and Safety of Oral P2Y12 Inhibitors in Acute Coronary Syndrome: Network Meta-Analysis of 52 816 Patients From 12 Randomized Trials. Circ 2020;142: 150-160.

26) Wang D, Yang XH, Zhang JD, Li R, Jia M, Cui X. Compared efficacy of clopidogrel and ticagrelor in treating acute coronary syndrome: a meta-analysis. BMC Cardiovascular Dis 2018; 18: 217.

27) Valgimigli M, Bueno H, Byrne RA, Collet JP, Costa F, Jeppsson A, Jüni P, Kastrati A, Kolh P, Mauri L, Montalescot G, Neumann FJ, Petricevic M, Roffi M, Steg PG, Windecker S, Zamorano JL, Levine GN; ESC Scientific Document Group; ESC Committee for Practice Guidelines (CPG); ESC National Cardiac Societies. 2017 ESC focused update on dual antiplatelet therapy in coronary artery disease developed in collaboration with EACTS: The Task Force for dual antiplatelet therapy in coronary artery disease of the European Society of Cardiology (ESC) and of the European Association for Cardio-Thoracic Surgery (EACTS). Eur Heart J 2018; 39: 213-260.

28) Doost Hosseiny A, Moloi S, Chandrasekhar J, Farshid A. Mortality pattern and cause of death in a long-term follow-up of patients with STEMI treated with primary PCI. Open Heart 2016; 3: e000405.

29) Rapsomaniki E, Thuresson M, Yang E, Blin P, Hunt P, Chung SC, Stogiannis D, Pujades-Rodriguez M, Timmis A, Denaxas SC, Danchin N, Stokes M, Thomas-Delecourt F, Emmas C, Hasvold P, Jennings E, Johansson S, Cohen DJ, Jernberg T, Moore N, Janzon M, Hemingway H. Using big data from health records from four countries to evaluate chronic disease outcomes: a study in 114 364 survivors of myocardial infarction. Eur Heart J Qual Care Clin Outcomes 2016; 2: 172-183.

30) Gulizia MM, Colivicchi F, Abrignani MG, Ambrosetti M, Aspromonte N, Barile G, Caporale R, Casolo G, Chiuini E, Di Lenarda A, Faggiano P, Gabrielli D, Geraci G, La Manna AG, Maggioni AP, Marchese A, Massari FM, Mureddu GF, Musumeci G, Nardi F, Panno AV, Pedretti RFE, Piredda M, Pusineri E, Riccio C, Rossini R, di Uccio FS, Urbinati S, Varbella F, Zito GB, De Luca L, ESC Scientific Document Group; Faculty for approval of the Consensus Document. Consensus Document ANMCO/ANCE/ARCA/GICR-IACPR/GISE/SICOA: Long-term Antiplatelet Therapy in Patients with Coronary Artery Disease. Eur Heart J Suppl. 2018; 20(Suppl F): F1-F74.

31) Fanaroff AC, Roe MT, Clare RM, Lokhnygina Y, Navar AM, Giugliano RP, Wiviott SD, Tershakovec AM, Braunwald E, Blazing MA. Competing Risks of Cardiovascular Versus Noncardiovascular Death During Long-Term Follow-Up After Acute Coronary Syndromes. J Am Heart Assoc 2017; 6: e005840.

32) Blazing MA, Giugliano RP, Cannon CP, Musliner TA, Tershakovec AM, White JA, Reist C, McCagg A, Braunwald E, Califf RM. Evaluating cardiovascular event reduction with ezetimibe as an adjunct to simvastatin in 18 144 patients after acute coronary syndromes: final baseline characteristics of the IMPROVE-IT study population. Am Heart J 2014; 168: 205-212.e1.

33) Daly CA, De Stavola B, Sendon JL, Tavazzi L, Boersma E, Clemens F, Danchin N, Delahaye F, Gitt A, Julian D, Mulcahy D, Ruzyllo W, Thygesen K, Verheugt F, Fox KM; Euro Heart Survey Investigators. Predicting prognosis in stable angina—results from the Euro heart survey of stable angina: prospective observational study. BMJ 2006; 332: 262-267.

34) Bhatt DL, Steg PG, Ohman EM, Hirsch AT, Ikeda Y, Mas JL, Goto S, Liau CS, Richard AJ, Rother J, Wilson PW, REACH Registry Investigators. International prevalence, recognition, and treatment of cardiovascular risk factors in outpatients with atherothrombosis. JAMA 2006; 295: 180-189.

35) Ibanez B, James S, Agewall S, Antunes MJ, Bucciarelli-Ducci C, Bueno H, Caforio ALP, Crea F, Goudevenos JA, Halvorsen S, Hindricks G, Kastrati A, Lenzen MJ, Prescott E, Roffi M, Valgimigli M, Varenhorst C, Vranckx P, Widimský P, ESC Scientific Document Group. 2017 ESC Guidelines

for the management of acute myocardial infarction in patients presenting with ST-segment elevation: The Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). Eur Heart J 2018; 39: 119-177.

36) Collet JP, Thiele H, Barbato E, Barthélémy O, Bauersachs J, Bhatt DL, Dendale P, Dorobantu M, Edvardsen T, Folliguet T, Gale CP, Gilard M, Jobs A, Jüni P, Lambrinou E, Lewis BS, Mehilli J, Meliga E, Merkely B, Mueller C, Roffi M, Rutten FH, Sibbing D, Siontis GCM; ESC Scientific Document Group. 2020 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. Eur Heart J 2021; 42: 1289-1367.

37) Berg DD, Wiviott SD, Braunwald E, Guo J, Im K, Kashani A, Gibson CM, Cannon CP, Morrow DA, Bhatt DL, Mega JL, O'Donoghue ML, Antman EM, Newby LK, Sabatine MS, Giugliano RP. Modes and timing of death in 66 252 patients with non-ST-segment elevation acute coronary syndromes enrolled in 14 TIMI trials. Eur Heart J 2018; 39: 3810-3820.

38) Jang WJ, Ahn SG, Song YB, Choi SH, Chun WJ, Oh JH, Cho SW, Kim BS, Yoon JH, Koo BK, Yu CW, Jang YS, Tahk SJ, Kim HS, Gwon HC, Lee SY, Hahn JY. Benefit of Prolonged Dual Antiplatelet Therapy After Implantation of Drug-Eluting Stent for Coronary Bifurcation Lesions: Results From the Coronary Bifurcation Stenting Registry II. Circ Cardiovasc Interv 2018; 11: e005849.

39) D'Ascenzo F, Bertaina M, Fioravanti F, Bongiovanni F, Raposeiras-Roubin S, Abu-Assi E, Kinnaird T, Ariza-Solé A, Manzano-Fernández S, Templin C, Velicki L, Xanthopoulou I, Cerrato E, Rognoni A, Boccuzzi G, Omedè P, Montabone A, Taha S, Durante A, Gili S, Magnani G, Autelli M, Grosso A, Blanco PF, Garay A, Quadri G, Varbella F, Queija BC, Paz RC, Fernández MC, Pousa IM, Gallo D, Morbiducci U, Dominguez-Rodriguez A, Valdés M, Cequier A, Alexopoulos D, Iñiguez-Romo A, Gaita F, Rinaldi M, Lüscher TF. Long versus short dual antiplatelet therapy in acute coronary syndrome patients treated with prasugrel or ticagrelor and coronary revascularization: Insights from the RENAMI registry. Eur J Prev Cardiol 2020; 27: 696-705.

40) Palmerini T, Bruno AG, Gilard M, Morice MC, Valgimigli M, Montalescot G, Collet JP, Della Riva D, Bacchi-Reggiani ML, Steg PG, Diallo A, Vicaut E, Helft G, Nakamura M, Généreux P, Vahl TP, Stone GW. Risk-Benefit Profile of Longer-Than-1-Year Dual-Antiplatelet Therapy Duration After Drug-Eluting Stent Implantation in Relation to Clinical Presentation. Circ Cardiovasc Interv 2019; 12: e007541.

41) Schüpke S, Neumann FJ, Menichelli M, Mayer K, Bernlochner I, Wöhrle J, Richardt G, Liebetrau C, Witzenbichler B, Antoniucci D, Akin I, Bott-Flügel L, Fischer M, Landmesser U, Katus HA, Sibbing D, Seyfarth M, Janisch M, Boncompagni D, Hilz R, Rottbauer W, Okrojek R, Möllmann H, Hochholzer W, Migliorini A, Cassese S, Mollo P, Xhepa E, Kufner S, Strehle A, Leggewie S, Allali A, Ndrepepa G, Schühlen H, Angiolillo DJ, Hamm CW, Hapfelmeier A, Tölg R, Trenk D, Schunkert H, Laugwitz KL, Kastrati A; ISAR-REACT 5 Trial Investigators; ISAR-REACT 5 Trial Investigators. Ticagrelor or prasugrel in patients with acute coronary syndromes. N Engl J Med 2019; 381: 1524-1534.

42) Yeh RW, Kereiakes DJ, Steg PG, Windecker S, Rinaldi MJ, Gershlick AH, Cutlip DE, Cohen DJ, Tanguay JF, Jacobs A, Wiviott SD, Massaro JM, Iancu AC, Mauri L, DAPT Study Investigators. Benefits and risks of extended duration dual antiplatelet therapy after PCI in patients with and without acute myocardial infarction. J Am Coll Cardiol 2015; 65: 2211.

43) Yusuf S, Zhao F, Mehta SR, Chrolavicius S, Tognoni G, Fox KK, Clopidogrel in Unstable Angina to Prevent Recurrent Events Trial Investigators. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. N Engl J Med 2001; 345: 494-502.

44) Bhatt DL, Fox KA, Hacke W, Berger PB, Black HR, Boden WE, Cacoub P, Cohen EA, Creager MA, Easton JD, Flather MD, Haffner SM, Hamm CW, Hankey GJ, Johnston SC, Mak KH, Mas JL, Montalescot G, Pearson TA, Steg PG, Steinhubl SR, Weber MA, Brennan DM, Fabry-Ribaudo L, Booth J, Topol EJ, CHARISMA Investigators Clopidogrel and aspirin versus aspirin alone for the prevention of atherothrombotic events. N Engl J Med 2006; 354: 1706-1717.

45) Dellborg M, Bonaca MP, Storey RF, Steg PG, Im KA, Cohen M, Bhatt DL, Oude Ophuis T, Budaj A, Hamm C, Spinar J, Kiss RG, Lopez-Sendon J, Kamensky G, Van de Werf F, Ardissino D, Kontny F, Montalescot G, Johanson P, Bengtsson O, Himmelmann A, Braunwald E, Sabatine MS. Efficacy and safety with ticagrelor in patients with prior myocardial infarction in the approved European label: insights from PEGASUS-TIMI 54. Eur Heart J Cardiovasc Pharmacother 2019; 5: 200-206.

46) Ariotti S, Gargiulo G, Valgimigli M. Long-Term Use of Ticagrelor in Patients with Coronary Artery Disease. Curr Cardiol Rep 2017; 19: 2.

47) Gargiulo G, Moschovitis A, Windecker S, Valgimigli M. Developing drugs for use before, during and soon after percutaneous coronary intervention. Exp Opin Pharmacother 2016; 17: 803-818.

48) Armstrong D, Summers C, Ewart L, Nylander S, Sidaway JE, van Giezen JJ. Characterization of the adenosine pharmacology of ticagrelor reveals therapeutically relevant inhibition of equilibrative nucleoside transporter 1. J Cardiovasc Pharmacol Ther 2014; 19: 209-219.

49) Aungraheeta R, Conibear A, Butler M, Kelly E, Nylander S, Mumford A, Mundell SJ. Inverse agonism at the P2Y12 receptor and ENT1 transporter blockade contribute to platelet inhibition by ticagrelor. Blood 2016; 128: 2717-2728.

50) Cattaneo M, Schulz R, Nylander S. Adenosine-mediated effects of ticagrelor: evidence and potential clinical relevance. J Am Coll Cardiol 2014; 63: 2503-2509.

51) Nylander S, Femia EA, Scavone M, Berntsson P, Asztély AK, Nelander K, Löfgren L, Nilsson RG, Cattaneo M. Ticagrelor inhibits human platelet aggregation via adenosine in addition to P2Y12 antagonism. J Thromb Haemost 2013; 11: 1867-1876.

52) van Giezen JJ, Sidaway J, Glaves P, Kirk I, Björkman JA. Ticagrelor inhibits adenosine uptake in vitro and enhances adenosine-mediated hyperemia responses in a canine model. J Cardiovasc Pharmacol Ther 2012;17: 164-172.

53) Bonello L, Laine M, Kipson N, Mancini J, Helal O, Fromonot J, Gariboldi V, Condo J, Thuny F, Frere C, Camoin-Jau L, Paganelli F, Dignat-George F, Guieu R. Ticagrelor increases adenosine plasma concentration in patients with an acute coronary syndrome. J Am Coll Cardiol 2014; 63: 872-877.

54) Ariotti S, Ortega-Paz L, van Leeuwen M, Brugaletta S, Leonardi S, Akkerhuis KM, Rimoldi SF, Janssens G, Gianni U, van den Berge JC, Karagiannis A, Windecker S, Valgimigli M; HI-TECH Investigators. Effects of Ticagrelor, Prasugrel, or Clopidogrel on Endothelial Function and Other Vascular Biomarkers: A Randomized Crossover Study. JACC Cardiovasc Interv 2018; 11: 1576-1586.

55) Ticagrelor Summary of product characteristics. Last version May 2021. Available at: https://www.ema.europa.eu/en/documents/product-information/brilique-epar-product-information_en.pdf.

56) Steg PG, Harrington RA, Emanuelsson H, Katus HA, Mahaffey KW, Meier B, Storey RF, Wojdyla DM, Lewis BS, Maurer G, Wallentin L, James SK; PLATO Study Group. Stent thrombosis with ticagrelor versus clopidogrel in patients with acute coronary syndromes: an analysis from the prospective, randomized PLATO trial. Circ 2013; 128: 1055-1065.

57) Cannon CP, Harrington RA, James S, Ardissino D, Becker RC, Emanuelsson H, Husted S, Katus H, Keltai M, Khurmi NS, Kontny F, Lewis BS, Steg PG, Storey RF, Wojdyla D, Wallentin L, PLATelet inhibition and patient Outcomes Investigators. Comparison of ticagrelor with clopidogrel in patients with a planned invasive strategy for acute coronary syndromes (PLATO): a randomised double-blind study. Lancet 2010; 375: 283-293.

58) James SK, Roe MT, Cannon CP, Cornel JH, Horrow J, Husted S, Katus H, Morais J, Steg PG, Storey RF, Stevens S, Wallentin L, Harrington RA, PLATO Investigators. Ticagrelor versus clopidogrel in patients with acute coronary syndromes intended for non-invasive management: substudy from prospective randomised PLATelet inhibition and patient Outcomes (PLATO) trial. BMJ 2011; 342: d3527.

59) Erdem G, Bakhai A, Taneja AK, Collinson J, Banya W, Flather MD. Rates and causes of death from non-ST elevation acute coronary syndromes: ten year follow-up of the PRAIS-UK registry. Int J Cardiol 2013; 168: 490-494.

60) Chan MY, Sun JL, Newby KL, Shaw LK, Lin M, Peterson ED, Califf RM, Kong DF, Roe MT. Long-term mortality of patients undergoing cardiac catheterization for ST-elevation and non-ST-elevation myocardial infarction. Circ 2009; 119: 3110-3117.

61) Lindholm D, Varenhorst C, Cannon CP, Harrington RA, Himmelmann A, Maya J, Husted S, Steg PG, Cornel JH, Storey RF, Stevens SR, Wallentin L, James SK. Ticagrelor vs. clopidogrel in patients with non-ST-elevation acute coronary syndrome with or without revascularization: results from the PLATO trial. Eur Heart J 2014; 35: 2083-2093.

62) Husted S, James S, Becker RC, Horrow J, Katus H, Storey RF, Cannon CP, Heras M, Lopes RD, Morais J, Mahaffey KW, Bach RG, Wojdyla D, Wallentin L, PLATO study group. Ticagrelor versus clopidogrel in elderly patients with acute coronary syndromes: a substudy from the prospective randomized PLATelet inhibition and patient Outcomes (PLATO) trial. Circ Cardiovasc Qual Outcomes 2012; 5: 680-688.

63) Szummer K, Montez-Rath ME, Alfredsson J, Erlinge D, Lindahl B, Hofmann R, Ravn-Fischer A, Svensson P, Jernberg T. Comparison Between Ticagrelor and Clopidogrel in Elderly Patients With an Acute Coronary Syndrome: Insights From the SWEDEHEART Registry. Circ 2020; 142: 1700-1708.

64) James SK, Pieper KS, Cannon CP, Storey RF, Becker RC, Steg PG, Wallentin L, Harrington RA, PLATO study group. Ticagrelor in patients with acute coronary syndromes and stroke: interpretation of subgroups in clinical trials. Stroke. 2013; 44: 1477-1479.

65) Angiolillo DJ, Bernardo E, Sabate M, Jimenez-Quevedo P, Costa MA, Palazuelos J, Hernandez-Antolin R, Moreno R, Escaned J, Alfonso F, Banuelos C, Guzman LA, Bass TA, Macaya C, Fernandez-Ortiz A. Impact of platelet reactivity on cardiovascular outcomes in patients with type 2 diabetes mellitus and coronary artery disease. J Am Coll Cardiol 2007; 50: 1541-1547.

66) Angiolillo DJ, Shoemaker SB, Desai B, Yuan H, Charlton RK, Bernardo E, Zenni MM, Guzman LA, Bass TA, Costa MA. Randomized comparison of a high clopidogrel maintenance dose in patients with diabetes mellitus and coronary artery disease: results of the optimizing antiplatelet therapy in diabetes mellitus (OPTIMUS) study. Circ 2007; 115: 708-716.

67) Gargiulo G, Windecker S, da Costa BR, Feres F, Hong MK, Gilard M, Kim HS, Colombo A, Bhatt DL, Kim BK, Morice MC, Park KW, Chieffo A, Palmerini T, Stone GW, Valgimigli M. Short term versus long term dual antiplatelet therapy after implantation of drug eluting stent in patients with

or without diabetes: systematic review and meta-analysis of individual participant data from randomised trials. BMJ 2016; 355: i5483.

68) James S, Angiolillo DJ, Cornel JH, Erlinge D, Husted S, Kontny F, Maya J, Nicolau JC, Spinar J, Storey RF, Stevens SR, Wallentin L; PLATO Study Group. Ticagrelor vs. clopidogrel in patients with acute coronary syndromes and diabetes: a substudy from the PLATelet inhibition and patient Outcomes (PLATO) trial. Eur Heart J 2010; 31: 3006-3016.

69) Held C, Asenblad N, Bassand JP, Becker RC, Cannon CP, Claeys MJ, Harrington RA, Horrow J, Husted S, James SK, Mahaffey KW, Nicolau JC, Scirica BM, Storey RF, Vintila M, Ycas J, Wallentin L. Ticagrelor versus clopidogrel in patients with acute coronary syndromes undergoing coronary artery bypass surgery: results from the PLATO (Platelet Inhibition and Patient Outcomes) trial. J Am Coll Cardiol 2011; 57: 672-684.

70) James S, Budaj A, Aylward P, Buck KK, Cannon CP, Cornel JH, Harrington RA, Horrow J, Katus H, Keltai M, Lewis BS, Parikh K, Storey RF, Szummer K, Wojdyla D, Wallentin L. Ticagrelor versus clopidogrel in acute coronary syndromes in relation to renal function: results from the Platelet Inhibition and Patient Outcomes (PLATO) trial. Circ 2010; 122: 1056-1067.

71) Patel MR, Becker RC, Wojdyla DM, Emanuelsson H, Hiatt WR, Horrow J, Husted S, Mahaffey KW, Steg PG, Storey RF, Wallentin L, James SK. Cardiovascular events in acute coronary syndrome patients with peripheral arterial disease treated with ticagrelor compared with clopidogrel: Data from the PLATO Trial. Eur J Prev Cardiol 2015; 22: 734-742.

72) Steg PG, James S, Harrington RA, Ardissino D, Becker RC, Cannon CP, Emanuelsson H, Finkelstein A, Husted S, Katus H, Kilhamn J, Olofsson S, Storey RF, Weaver WD, Wallentin L, PLATO Study Group. Ticagrelor versus clopidogrel in patients with ST-elevation acute coronary syndromes intended for reperfusion with primary percutaneous coronary intervention: A Platelet Inhibition and Patient Outcomes (PLATO) trial subgroup analysis. Circ 2010; 122: 2131-2141.

73) Becker RC, Bassand JP, Budaj A, Wojdyla DM, James SK, Cornel JH, French J, Held C, Horrow J, Husted S, Lopez-Sendon J, Lassila R, Mahaffey KW, Storey RF, Harrington RA, Wallentin L. Bleeding complications with the P2Y12 receptor antagonists clopidogrel and ticagrelor in the PLATelet inhibition and patient Outcomes (PLATO) trial. Eur Heart J 2011; 32: 2933-2944.

74) Roffi M, Patrono C, Collet JP, Mueller C, Valgimigli M, Andreotti F, Bax JJ, Borger MA, Brotons C, Chew DP, Gencer B, Hasenfuss G, Kjeldsen K, Lancellotti P, Landmesser U, Mehilli J, Mukherjee D, Storey RF, Windecker S; ESC Scientific Document Group. 2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: Task Force for the Management of Acute Coronary Syndromes in Patients Presenting without Persistent ST-Segment Elevation of the European Society of Cardiology (ESC). Eur Heart J 2016; 37: 267-315.

75) Motovska Z, Hlinomaz O, Miklik R, Hromadka M, Varvarovsky I, Dusek J, Knot J, Jarkovsky J, Kala P, Rokyta R, Tousek F, Kramarikova P, Majtan B, Simek S, Branny M, Mrozek J, Cervinka P, Ostransky J, Widimsky P; PRAGUE-18 Study Group. Prasugrel Versus Ticagrelor in Patients With Acute Myocardial Infarction Treated With Primary Percutaneous Coronary Intervention: Multicenter Randomized PRAGUE-18 Study. Circ 2016; 134: 1603-1612.

76) Jneid H. Ticagrelor or prasugrel in acute coronary syndromes. The winner takes it all? N Eng J Med 2019; 381: 1582-1585.

77) Tarantini G, Mojoli M, Varbella F, Caporale R, Rigattieri S, Andò G, Cirillo P, Pierini S, Santarelli A, Sganzerla P, Cacciavillani L, Babuin L, De Cesare N, Limbruno U, Massoni A, Rognoni A, Pavan D, Belloni F, Cernetti C, Favero L, Saia F, Fovino LN, Masiero G, Roncon L, Gasparetto V, Ferlini M, Ronco F, Rossini R, Canova P, Trabattoni D, Russo A, Guiducci V, Penzo C, Tarantino F, Mauro C, Corrada E, Esposito G, Marchese A, Berti S, Martinato M, Azzolina D, Gregori D, Angiolillo DJ, Musumeci G; DUBIUS Investigators; Italian Society of Interventional Cardiology. Timing of Oral P2Y12 Inhibitor Administration in Patients With Non-ST-Segment Elevation Acute Coronary Syndrome. J Am Coll Cardiol 2020; 76: 2450-2459.

78) Gargiulo G, Esposito G, Avvedimento M, Nagler M, Minuz P, Campo G, Gragnano F, Manavifar N, Piccolo R, Tebaldi M, Cirillo P, Hunziker L, Vranckx P, Leonardi S, Heg D, Windecker S, Valgimigli M. Cangrelor, Tirofiban, and Chewed or Standard Prasugrel Regimens in Patients With ST-Segment-Elevation Myocardial Infarction: Primary Results of the FABOLUS-FASTER Trial. Circ 2020; 142: 441-454.

79) Alexopoulos D, Pappas C, Sfantou D, Xanthopoulou I, Didagelos M, Kikas P, Ziakas A, Tziakas D, Karvounis H, Iliodromitis E. Cangrelor in Ticagrelor-Loaded STEMI Patients Undergoing Primary Percutaneous Coronary Intervention. J Am Coll Cardiol 2018; 72: 1750-1751.

80) Franchi F, Rollini F, Rivas A, Wali M, Briceno M, Agarwal M, Shaikh Z, Nawaz A, Silva G, Been L, Smairat R, Kaufman M, Pineda AM, Suryadevara S, Soffer D, Zenni MM, Bass TA, Angiolillo DJ. Platelet Inhibition With Cangrelor and Crushed Ticagrelor in Patients With ST-Segment-Elevation Myocardial Infarction Undergoing Primary Percutaneous Coronary Intervention. Circ 2019; 139: 1661-1670.

81) Angiolillo DJ, Rollini F, Storey RF, Bhatt DL, James S, Schneider DJ, Sibbing D, So DYF, Trenk D, Alexopoulos D, Gurbel PA, Hochholzer W, De Luca L, Bonello L, Aradi D, Cuisset T, Tan-

try US, Wang TY, Valgimigli M, Waksman R, Mehran R, Montalescot G, Franchi F, Price MJ. International Expert Consensus on Switching Platelet P2Y12 Receptor-Inhibiting Therapies. Circ 2017; 136: 1955-1975.

82) Roe MT, Ohman EM, TRILOGY ACS Investigators. Prasugrel versus clopidogrel for acute coronary syndromes. N Engl J Med 2013; 368: 188-189.

83) Morrow DA, Braunwald E, Bonaca MP, Ameriso SF, Dalby AJ, Fish MP, Fox KA, Lipka LJ, Liu X, Nicolau JC, Ophuis AJ, Paolasso E, Scirica BM, Spinar J, Theroux P, Wiviott SD, Strony J, Murphy SA; TRA 2P–TIMI 50 Steering Committee and Investigators. Vorapaxar in the secondary prevention of atherothrombotic events. N Engl J Med 2012; 366: 1404-1413.

84) Capodanno D, Gargiulo G, Buccheri S, Giacoppo D, Capranzano P, Tamburino C. Meta-Analyses of Dual Antiplatelet Therapy Following Drug-Eluting Stent Implantation: Do Bleeding and Stent Thrombosis Weigh Similar on Mortality? J Am Coll Cardiol 2015; 66: 1639-1640.

85) Gargiulo G, Windecker S, Vranckx P, Gibson CM, Mehran R, Valgimigli M. A Critical Appraisal of Aspirin in Secondary Prevention: Is Less More? Circulation 2016; 134: 1881-1906.

86) Giacoppo D, Matsuda Y, Fovino LN, D'Amico G, Gargiulo G, Byrne RA, Capodanno D, Valgimigli M, Mehran R, Tarantini G. Short dual antiplatelet therapy followed by P2Y12 inhibitor monotherapy vs. prolonged dual antiplatelet therapy after percutaneous coronary intervention with second-generation drug-eluting stents: a systematic review and meta-analysis of randomized clinical trials. Eur Heart J 2021; 42: 308-319.

87) Gargiulo G, Goette A, Tijssen J, Eckardt L, Lewalter T, Vranckx P, Valgimigli M. Safety and efficacy outcomes of double vs. triple antithrombotic therapy in patients with atrial fibrillation following percutaneous coronary intervention: a systematic review and meta-analysis of non-vitamin K antagonist oral anticoagulant-based randomized clinical trials. Eur Heart J 2019; 40: 3757-3767.

88) Gargiulo G, Cannon CP, Gibson CM, Goette A, Lopes RD, Oldgren J, Korjian S, Windecker S, Esposito G, Vranckx P, Valgimigli M. Safety and efficacy of double vs. triple antithrombotic therapy in patients with atrial fibrillation with or without acute coronary syndrome undergoing percutaneous coronary intervention: a collaborative meta-analysis of non-vitamin K antagonist oral anticoagulant-based randomized clinical trials. Eur Heart J Cardiovasc Pharmacother 2021; 7: f50-f60.

89) Gargiulo G, Esposito G. Consolidating the value of the standardised ARC-HBR definition. EuroIntervention 2021; 16: 1126-1128.

90) Corpataux N, Spirito A, Gragnano F, Vaisnora L, Galea R, Svab S, Gargiulo G, Zanchin T, Zanchin C, Siontis GCM, Praz F, Lanz J, Hunziker L, Stortecky S, Pilgrim T, Räber L, Capodanno D, Urban P, Pocock S, Heg D, Windecker S, Valgimigli M. Validation of high bleeding risk criteria and definition as proposed by the academic research consortium for high bleeding risk. Eur Heart J 2020; 41: 3743-3749.

91) Ueki Y, Bär S, Losdat S, Otsuka T, Zanchin C, Zanchin T, Gragnano F, Gargiulo G, Siontis GCM, Praz F, Lanz J, Hunziker L, Stortecky S, Pilgrim T, Heg D, Valgimigli M, Windecker S, Räber L. Validation of the Academic Research Consortium for High Bleeding Risk (ARC-HBR) criteria in patients undergoing percutaneous coronary intervention and comparison with contemporary bleeding risk scores. EuroIntervention 2020; 16: 371-379.

92) Bhatt DL, Eagle KA, Ohman EM, Hirsch AT, Goto S, Mahoney EM, Wilson PWF, Albers MJ, D'Agostino R, Liau CS, Mas JL, Rother J, Smith SC, Salette G, Contant CF, Massaro JM, Steg PG, REACH Registry Investigators. Comparative determinants of 4-year cardiovascular event rates in stable outpatients at risk of or with atherothrombosis. JAMA 2010; 304: 1350-1357.

93) Johansson S, Rosengren A, Young K, Jennings EM. Mortality and morbidity trends after the first year in survivors of acute myocardial infarction: a systematic review. BMC Cardiovasc Disord 2017; 17: 53.

94) Bonaca MP, Bhatt DL, Braunwald E, Cohen M, Steg PG, Storey RF, Held P, Jensen EC, Sabatine MS. Design and rationale for the Prevention of Cardiovascular Events in Patients With Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin-Thrombolysis in Myocardial Infarction 54 (PEGASUS-TIMI 54) trial. Am Heart J 2014; 167: 437-444.e5.

95) Bonaca MP, Storey RF, Theroux P, Steg PG, Bhatt DL, Cohen MC, Im K, Murphy SA, Magnani G, Ophuis TO, Rudah M, Parkhomenko A, Isaza D, Kamensky G, Goudev A, Montalescot G, Jensen EC, Johanson P, Braunwald E, Sabatine MS. Efficacy and Safety of Ticagrelor Over Time in Patients With Prior MI in PEGASUS-TIMI 54. J Am Coll Cardiol 2017; 70: 1368-1375.

96) Bonaca MP, Bhatt DL, Storey RF, Steg PG, Cohen M, Kuder J, Goodrich E, Nicolau JC, Parkhomenko A, López-Sendón J, Dellborg M, Dalby A, Špinar J, Aylward P, Corbalán R, Abola MTB, Jensen EC, Held P, Braunwald E, Sabatine MS. Ticagrelor for Prevention of Ischemic Events After Myocardial Infarction in Patients With Peripheral Artery Disease. J Am Coll Cardiol 2016; 67: 2719-2728.

97) Lee SY, Hong MK, Shin DH, Kim JS, Kim BK, Ko YG, Choi D, Jang Y, Kim HS, Valgimigli M, Colombo A, Gilard M, Palmerini T, Stone GW. Association Between Duration of Dual Antiplatelet Therapy and Angiographic Multivessel Disease on Outcomes in Patients Treated With Newer-Generation Drug-Eluting Stents. Circ Cardiovasc Interv 2016; 9: e004256.

98) Bansilal S, Bonaca MP, Cornel JH, Storey RF, Bhatt DL, Steg PG, Im K, Murphy SA, Angiolillo DJ, Kiss RG, Parkhomenko AN, Lopez-Sendon J, Isaza D, Goudev A, Kontny F, Held P, Jensen EC, Braunwald E, Sabatine MS, Oude Ophuis AJ. Ticagrelor for Secondary Prevention of Atherothrombotic Events in Patients With Multivessel Coronary Disease. J Am Coll Cardiol 2018; 71: 489-496.

99) Eikelboom JW, Connolly SJ, Bosch J, Dagenais GR, Hart RG, Shestakovska O, Diaz R, Alings M, Lonn EM, Anand SS, Widimsky P, Hori M, Avezum A, Piegas LS, Branch KRH, Probstfield J, Bhatt DL, Zhu J, Liang Y, Maggioni AP, Lopez- Jaramillo P, O'Donnell M, Kakkar AK, Fox KAA, Parkhomenko AN, Ertl G, Stork S, Keltai M, Ryden L, Pogosova N, Dans AL, Lanas F, Commerford PJ, Torp-Pedersen C, Guzik TJ, Verhamme PB, Vinereanu D, Kim JH, Tonkin AM, Lewis BS, Felix C, Yusoff K, Steg PG, Metsarinne KP, Cook Bruns N, Misselwitz F, Chen E, Leong D, Yusuf S; COMPASS Investigators. Rivaroxaban with or without aspirin in stable cardiovascular disease. N Engl J Med 2017; 377: 1319-1330.

100) De Luca L, Piscione F, Colivicchi F, Lucci D, Mascia F, Marinoni B, Cirillo P, Grosseto D, Mauro C, Calabrò P, Nardi F, Rossini R, Geraci G, Gabrielli D, Di Lenarda A, Gulizia MM; EYESHOT Post-MI Investigators. Contemporary management of patients referring to cardiologists one to three years from a myocardial infarction: The EYESHOT Post-MI study. Int J Cardiol 2018; 273: 8-14.

101) Cesaro A, Taglialatela V, Gragnano F, Moscarella E, Fimiani F, Conte M, Barletta V, Monda E, Limongelli G, Severino S, Cirillo P, Calabrò P. Low-Dose Ticagrelor in Patients With High Ischemic Risk and Previous Myocardial Infarction: A Multicenter Prospective Real-World Observational Study. J Cardiovasc Pharmacol 2020; 76: 173-180.

102) Darmon A, Sorbets E, Ducrocq G, Elbez Y, Abtan J, Popovic B, Ohman EM, Röther J, Wilson PF, Montalescot G, Zeymer U, Bhatt DL, Steg PG; REACH Registry Investigators. Association of Multiple Enrichment Criteria With Ischemic and Bleeding Risks Among COMPASS-Eligible Patients. J Am Coll Cardiol 2019; 73: 3281-3291.

103) Sahlén A, Varenhorst C, Lagerqvist B, Renlund H, Omerovic E, Erlinge D, Wallentin L, James SK, Jernberg T. Outcomes in patients treated with ticagrelor or clopidogrel after acute myocardial infarction: experiences from SWEDEHEART registry. Eur Heart J 2016; 37: 3335-3342.

104) Vercellino M, Sànchez FA, Boasi V, Perri D, Tacchi C, Secco GG, Cattunar S, Pistis G, Mascelli G. Ticagrelor versus clopidogrel in real-world patients with ST elevation myocardial infarction: 1-year results by propensity score analysis. BMC Cardiovasc Disord 2017; 17: 97.

105) Guan W, Lu H, Yang K. Choosing between ticagrelor and clopidogrel following percutaneous coronary intervention. A systematic review and Meta-Analysis (2007–2017). Med (Baltimore) 2018; 97: e12978.

106) You SC, Rho Y, Bikdeli B, Kim J, Siapos A, Weaver J, Londhe A, Cho J, Park J, Schuemie M, Suchard MA, Madigan D, Hripcsak G, Gupta A, Reich CG, Ryan PB, Park RW, Krumholz HM. Association of ticagrelor vs clopidogrel with net adverse clinical events in patients with acute coronary syndrome undergoing percutaneous coronary intervention. JAMA 2020; 324: 1640-1650.

107) Bates ER. Net adverse clinical events with antiplatelet therapy in acute coronary syndromes. JAMA 2020; 324: 1613-1615.

108) Sanchez F, Boasi V, Vercellino M, Tacchi C, Cannarile P, Pingelli N, Perri D, Gomez L, cattunar S, Mascelli G. Risk definition and outcomes with the application of the PEGASUS-TIMI 54 trial inclusion criteria to a "real world" STEMI population: results from the Italian "CARDIO-STEMI SANREMO" registry. BMC Cardiovasc Disord 2021; 21: 144.

109) Liew D, De Abreu Lourenço R, Adena M, Chim L, Aylward P. Cost-effectiveness of 12-month treatment with ticagrelor compared with clopidogrel in the management of acute coronary syndromes. Clin Ther 2013; 35: 1110-1117.e9.

110) Magnuson EA, Li H, Wang K, Vilain K, Shafiq A, Bonaca MP, Bhatt DL, Cohen M, Steg PG, Storey RF, Braunwald E, Sabatine MS, Cohen DJ, PEGASUS-TIMI 54 Trial Investigators. Cost-Effectiveness of Long-Term Ticagrelor in Patients With Prior Myocardial Infarction: Results From the PEGASUS-TIMI 54 Trial. J Am Coll Cardiol 2017; 70: 527-538.