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

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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 worldwide¹. 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 possible³. Greater knowledge of the natural history of CAD 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 intertwined⁴. 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 practice⁵. 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 dysfunction⁶.
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\textsuperscript{7,18}. Dual antiplatelet therapy (DAPT) with aspirin and an oral P\textsubscript{2}\text{Y}_{12} inhibitor is the cornerstone of antithrombotic therapy after MI and/or percutaneous coronary intervention (PCI)\textsuperscript{9}, 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)\textsuperscript{9}. DAPT can influence the residual thrombotic risk\textsuperscript{16}, reduce ischemic recurrences in patients with ACS\textsuperscript{20,30}, in clinically stable patients undergoing PCI\textsuperscript{31} or those who have had coronary stenting\textsuperscript{22}, as well as lower ischemic relapse in those with a history of MI\textsuperscript{23,24}. Among oral P\textsubscript{2}\text{Y}_{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\textsuperscript{25}. Ticagrelor has been acknowledged to have more rapid onset as well as more significant platelet inhibition function in patients with ACS\textsuperscript{30} and is an alternative strategy in treating patients with clopidogrel intolerance or resistance\textsuperscript{26} and a valuable option for patients with CCS and a history of MI\textsuperscript{27}.

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 utmost 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. 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. 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.

The risk of a recurrent CV event or death is the highest in the first year after an ACS event and continues to increase for at least 5 years. 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 with one in five individuals experiencing an event in that time period. 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. 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. 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. 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. 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).

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. 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. 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). 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 P2Y12 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, whose in-hospital mortality rates vary between 4% and 12%, and patients with NSTE-
and whose cumulative incidence of CV death is approximately 2.67% at 1 year after the event\(^2\). 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\(^2\). 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\(^1\). Clinical guidelines recommended 12-month (or longer) duration of DAPT after PCI for patients with STEMI\(^3\) and NSTEMI\(^4\) 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\(^5,6\). Recent data from the Coronary Bifurcation Stenting Registry II\(^7\) and RENAMI registry\(^8\) 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\(^9\) and real-life ACS patients undergoing PCI and stent implantation\(^10\). 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\(^9\). Nevertheless, a recent meta-analysis\(^10\) 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\(^1\).

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\(^12,20,41\) 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 MACCE 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 P2Y₁₂ 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)⁹ as well as the TRITON-TIMI 38 (TRial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet InhibitionN with Prasugrel-Thrombolysis In Myocardial Infarction 38) trial²⁰.

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 months⁹. 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%³⁵. It has been estimated that such mortality benefit translates to one CV death prevented every 91 patients treated with ticagrelor³⁵.

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 characteristics³⁶. 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 population³⁵,⁵⁷.

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 strategies³⁷. 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 strategies³⁸.

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%-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 days⁶¹.

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-
Aiming a P2Y₁₂ inhibitor⁶². 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, respectively⁶².

A recent large observational study⁶³ from the SWEDHEART 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 reported⁶⁵-⁶⁷ to have higher on-treatment platelet reactivity and worse clinical outcomes when taking aspirin and clopidogrel. Therefore, whether the potent P2Y₁₂ 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 significance⁶⁸. Moreover, cardioprotective effects of ticagrelor were observed in patients with levels of HbA₁c ≥ 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 clopidogrel⁶⁹. 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 P2Y₁₂ 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 bleeding⁶⁹. 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, with peripheral artery disease (PAD) and STEMI. 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. 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 P2Y12 inhibition (preferably with ticagrelor) in the absence of contraindications as soon as the diagnosis is confirmed.

In last few years, new evidence on head-to-head comparison of ticagrelor and prasugrel has emerged. The PRAGUE-18 trial, 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. 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
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 arm (86.1%)). The most recent guidelines in 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 P2Y12 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 P2Y12 inhibitor pre-treatment in cases of NSTE-ACS has also been provided by the recent DU-BIUS trial77. Overall, this recommendation will determine that most patients with NSTE-ACS undergoing PCI will be P2Y12 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 P2Y12 inhibitor to limit drug-drug interactions and potential risks of a variable time-window with inadequate platelet inhibition at the end of cangrelor infusion78-81.

**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 trials12,14,82,83 and depending on the relative contribution of ischemic and bleeding events on mortality84. 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 challenging17,85,86. This assessment is particularly difficult when considering that a variable but not negligible proportion of patients are at HBR87-91. 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 events92,93.

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) trial125,94. 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%)\(^{25}\). 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\(^{31}\). 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\(^{35}\).

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\(^{31}\). 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\(^{46}\). Furthermore, when yearly long-term effects of ticagrelor were also analyzed, a sustained benefit without late waning in efficacy was observed\(^{45}\). 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\(^{36}\). 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.

Discussion

Prevention of coronary thrombosis and its acute and chronic sequelae is of paramount clinical relevance when managing patients with ACS and CCS 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 PLATO99 and PEGASUS-TIMI 5423 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 clopidogrel103. 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 registry104. 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 =
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)\textsuperscript{104}. In patients with ACS balancing ischemic benefit with bleeding risk is of utmost 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\textsuperscript{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\textsuperscript{105} life-threatening bleeding (odds ratio, OR: 1.00, 95% CI: 0.79-1.27; \textit{p}=0.98) was not significantly different between these two antiplatelet drugs. Of note, Guan et al\textsuperscript{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\textsuperscript{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\textsuperscript{106}. This outcome represents the numerical difference between ischemic events avoided and excess bleeding events\textsuperscript{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\textsubscript{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\textsuperscript{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\textsuperscript{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\textsuperscript{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\textsuperscript{100}. 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 taly) registry that provided meaningful insights on the current management and treatment of patients with previous MI referring to cardiologists\textsuperscript{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\textsuperscript{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\textsuperscript{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\textsuperscript{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 sub-populations with an acceptable payoff in terms of bleeding risk.
Conflict of Interest
The Authors declare that they have no conflict of interests.

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