Viewpoint: Paradoxical excess mortality in the PLATO trial should be independently verified

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Summary
The PLATO trial revealed excess all-cause (4.5%) and vascular (4.0%) mortality after experimental pyrimidine, ticagrelor, and even higher death rates (5.9% and 5.1%, respectively) after clopidogrel, which have never been seen in any previous acute coronary syndrome (ACS) trial. The Food and Drug Administration (FDA) conducted, and recently released the ticagrelor review outlining some paradoxical mortality patterns in PLATO, including the existence of alive patient, who initially was reported dead. The drug was recently approved in Europe, but repeatedly delayed in the USA. The objective of this viewpoint article was to evaluate extremely high death rates in PLATO by scrutinising FDA-released evidence, and comparing mortality patterns in recent ACS trials. These data were first presented as the analytical report submitted to the FDA on October 26, 2010. The available evidence suggest that mortality rates in PLATO, so as death benefit of ticagrelor over clopidogrel are extreme, despite incomplete follow-up, short duration of the trial, frequent preloading with clopidogrel, and gross mismatch between conventional average myocardial infarction rates but disproportionally frequent vascular fatalities, and heavily imbalanced sepsis-related deaths. In contrast to the overall PLATO results, the deaths rates in the USA were much lower (3.2% vs. 3.8%) not only favouring clopidogrel, but more importantly matching very well with identical rates in TRITON (3.2%), and one-year ACUITY (3.6%-3.9%) fatalities. Since the «play of chance» cannot explain these discrepancies due to excess death rates in both PLATO arms, and considering that study sponsor self-monitored sites in most countries, but not in the USA, the mortality data are questionable, and should be independently virified. It was concluded that excess mortality rates and delayed timing of the benefit onset in PLATO do not match with any recent ACS trial, and do not look natural. Reevaluation of the survival, especially driven from the several high-volume sponsor monitored sites in Eastern Europe may reveal discrepancies between those reported in PLATO and actual vital records. Future practice of self monitoring in pivotal indication-seeking clinical trials should be completely banned.

Keywords
Mortality, ticagrelor, clinical trial, outcomes, site monitoring

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Introduction

Ticagrelor (AZD6140, or Brilinta®) is an experimental oral antiplatelet agent, and a pioneer cyclopentyl-triazolo-pyrimidine, which is currently under regulatory scope in the USA for approval in post-ACS patients based predominantly on the positive results of the PLATelet Inhibition and Clinical Outcomes (PLATO) trial. However, there are some fundamental discrepancies, especially with regard to mortality rates, and outcome maturity patterns over time distinguishing PLATO from other recent acute coronary syndrome (ACS) trials. This viewpoint article summarises several major concerns based on reassessment of ticagrelor development including the PLATO trial results, retrospective data driven from similar ACS trials, and prior studies with ticagrelor. The paper represents the content of a report issued for the Food and Drug Administration (FDA) on October 26th, 2010, but solely reflects the viewpoint of the author, and has been subjected to peer review. The article does not necessarily reflect the views of the editors or publishers. Ticagrelor has been currently approved in Europe, but the decision was delayed for the second time in the USA.

Facts

Mortality rates in PLATO

All-cause mortality in the clopidogrel arm (5.9%) (1) was the highest ever reported in recent ACS trials. This happened despite 95% of antecedent aspirin use; 90% use of statins, 46% pretreatment with clopidogrel (1); massive (14.7%) incomplete follow-up (2); and relatively short (6–12 months) (1, 2) duration of PLATO. For the combination of dual antiplatelet agents (aspirin and clopidogrel), the closest but still lower deaths rates were reported only in the CURE (3) trial. The differences between the trials, which may affect mortality numbers are presented in ▶Table 1.

Obviously, PLATO patients were enrolled eight years after CURE, they smoked less, received much more aggressive blood pressure -, and lipid lowering control, and background aspirin therapy, but, most importantly, almost half of them were pretreated with clopidogrel (1), which was not allowed in CURE (3). In short, the paradoxical and unnatural rise of mortality numbers in PLATO trial does not match with historical rates, and lacks any obvious explanation (▶Fig. 1).

All trials with the exception of CURE and CHARISMA exhibit mortality rates below 4%. The higher rate in CHARISMA (4.8% for both arms) is probably due to a much longer follow-up (two years). Importantly, the USA mortality differs tremendously from overall PLATO mortality, and was 3.22% for clopidogrel (2) – identical to TRITON (3.2%) (4) – or 3.84% in USA for ticagrelor (2) – matching very well with one-year ACUITY fatalities (3.6–3.9%) (5). The death discrepancy of ≈1.5–2.0% between the USA, monitored by a 3rd party CRO (Clinical Research Organisation), versus self monitoring by a study sponsor (▶Fig. 2) in almost all other countries, raises concern that the mortality difference is not a play of chance, but this difference was entirely missed, and unaccounted by the ticagrelor secondary FDA review (2). These extra 200–250 fatalities are highly questionable, never seen in other recent ACS trials, but were desperately needed to show a significant mortality reduction (2, 6), and mandatory for ticagrelor's success as a trade-off for a woeful safety profile (7).

Prior evidence from antiplatelet trials with mortality benefit

Historically, there were only two anti-platelet trials which yielded significant mortality reduction. PLATO differs, since the mortality benefits of aspirin in ISIS-2 (8) (▶Fig. 3), or clopidogrel in COMMIT (9) (▶Fig. 4) were mild, achieved immediately, but most importantly, never grew beyond the initial qualifying coronary event.

Table 1: Comparisons between CURE and PLATO trials.

Trial (Enrollment)	CURE (1998–2000)	PLATO (2006–2009)
All-cause mortality in the clopidogrel+aspirin arm	5.7%	5.9%
Aspirin	66%	95%
Lipid-lowering	25%	90%
ACE inhibitor	37%	76%
Beta-blocker	59%	89%
Clopidogrel pretreatment Smoking	Disallowed 61%	46% 36%

In fact, the ISIS-2 patients were followed for up to four years, and there were no extra deaths prevented by aspirin despite much less aggressive hypertension control, and minimal use of lipid-lowering agents (10) compared to PLATO. Both trials beat placebo (8, 9) (▶Figs. 3, 4), while ticagrelor has been reported to be superior against the active comparator (clopidogrel); the benefit emerged late, and grows over time between three and nine months (2).

Mortality in PLATO versus TRITON STEMI cohort

Lack of early, but massively delayed (after 2–3 months) mortality prevention of ticagrelor has never been attributed to any drug in any ACS trial, and is totally different from TRITON as suggested by the entirely distinct survival patterns in STEMI patients. The fact that at two months "neutral" in terms of mortality prevention, prasugrel in TRITON exhibited some mortality benefit (▶Fig. 5), but "superior" ticagrelor in PLATO (▶Fig. 6) at the same two months yielded no extra benefit from clopidogrel despite 2.5 times larger sample size in this highest-risk ACS cohort is alarming and lacks any scientific explanation.

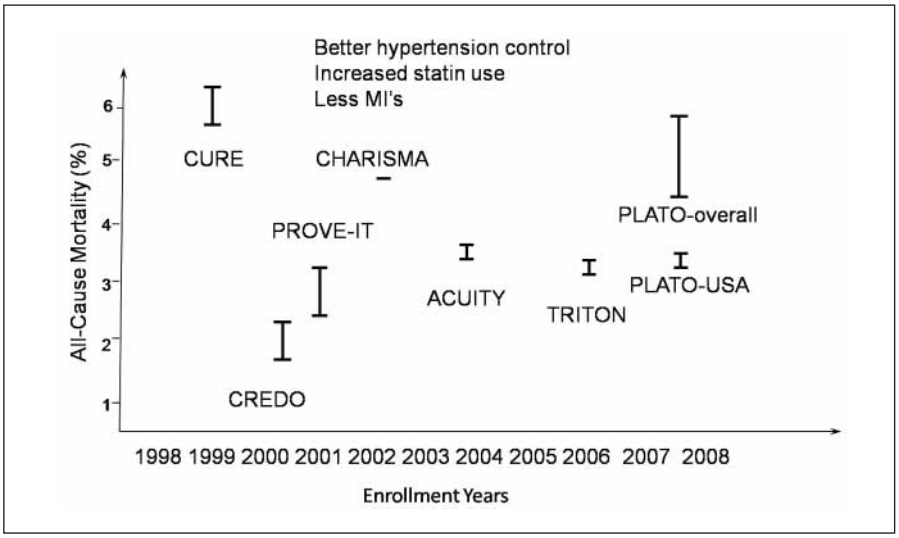

Figure 1: All-cause mortality rates in recent ACS trials.

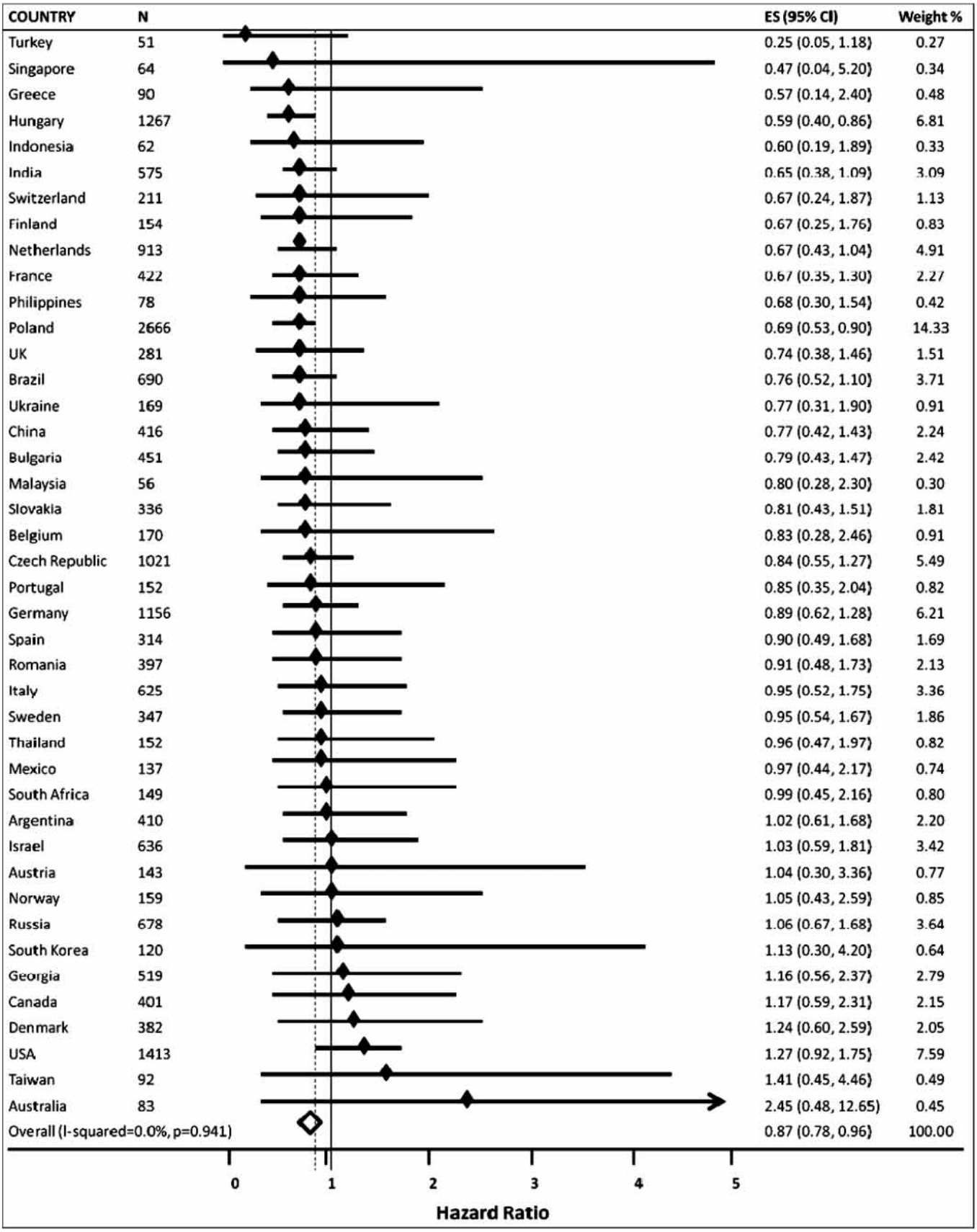

Figure 2: Distribution of outcomes in PLATO dependent of participating country.

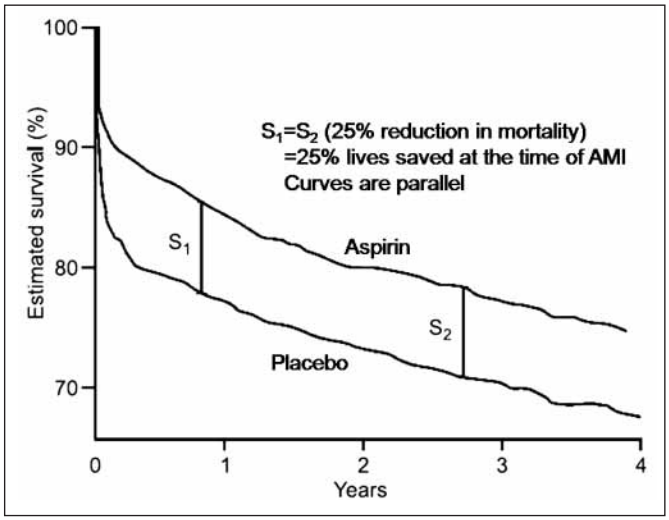

Figure 3: Kaplan-Meier curves maturity for mortality in ISIS-2 over four years after qualifying events.

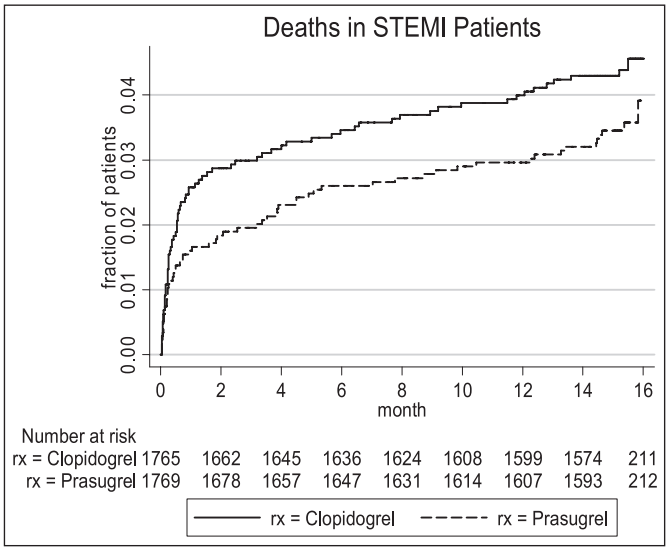

Figure 5: Mortality in the STEMI TRITON cohort.

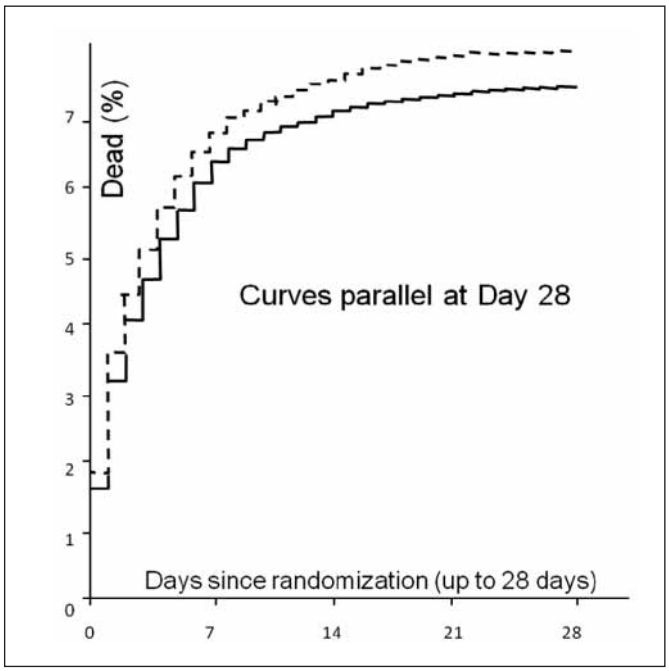

Figure 4: Kaplan-Meier curves maturity for mortality in COMMIT after qualifying myocardial infarction.

Poland and Hungary outcomes

There were 983 combined fatalities (5.28%) reported in PLATO (2), which is way above the recently reported mortality rates, raising the concern that these numbers should be independently verified. This is especially true since one "resurrected" patient has been already described in the FDA clinical review (2). In contrast to the heavily debated USA outcomes, two other countries deserve much more attention. In fact, Poland [0.69; 0.53–0.90] and Hungary [0.59; 0.40–0.86] have the narrowest hazard ratios (HR) for outcomes among all countries that participated in PLATO, and are the only two countries where the confidence intervals do not cross the median (▶Fig. 2). Poland and Hungary combined account for 21% of enrolled patients, but yielded astronomical 46% (n=69) of all endpoint events favouring ticagrelor (▶Table 2).

Patients from the highest-mortality sites in Poland and Hungary (▶Fig. 2) should be contacted by telephone or matched against active public records to verify their vital status. Direct, independent contact with study participants or their relatives is necessary to resolve this issue. The re-examination of PLATO electronic CRFs (Clinical Research Forms), hospital records, or other paperwork or computer files conducted by the FDA monitors in these countries was not sufficient. This is especially important since it was very easy to unblind the patients in PLATO, and the FDA review clearly indicates that "with so many groups having access to treatment codes", the Agency "was not reassured that the blind was properly maintained" (2).

Impact of myocardial infarction (MI) on mortality

The corresponding MI rate in PLATO's clopidogrel arm (6.9%) is indeed realistic, but, because of that, it is completely mismatched with so frequent vascular death (5.1%). What PLATO investigators are suggesting is that among MI patients treated with clopidogrel the death risk was 74% which is absurd especially considering extra reduction of sudden death (n=17), heart failure (n=11), and arrhythmia (n=8) in addition to vascular fatalities (2, 11) (▶Table 3). These extra-prevented deaths of cardiac origin leave no room whatsoever to explain vascular death benefit after ticagrelor, since they were re-

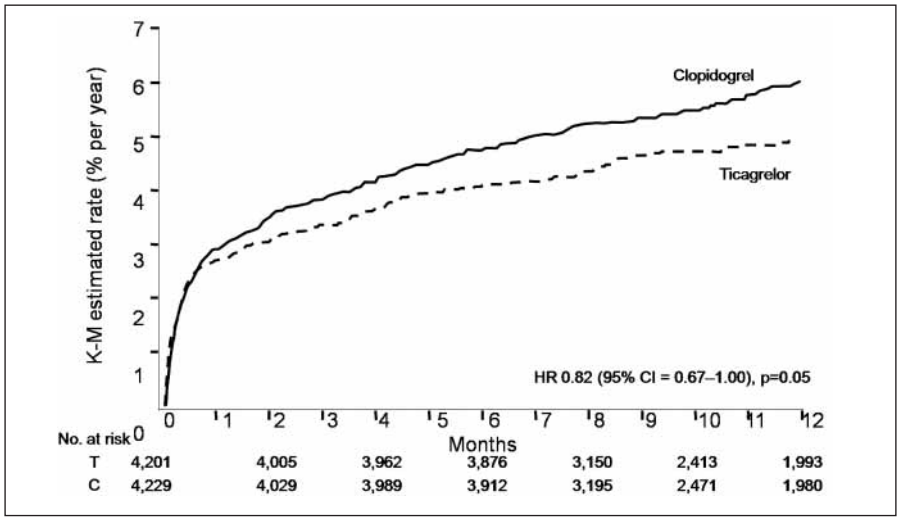

Figure 6: Mortality in the STEMI PLATO cohort.

Table 2: Polish and Hungarian outcomes in PLATO.

Characteristic	Randomised ticagrelor 90 mg bd N-9333	Treatment clopidogrel 75 mg od N-9291
Aortic dissection	1 (0.0%)	2 (0.0%)
Arterial embolism	0 (0.0%)	2 (0.0%)
Cancer	14 (0.2%)	17 (0.2%)
Cardiac arrhythmia	20 (0.2%)	28 (0.3%)
Death from bleeding (not related to trauma)	13 (0.1%)	15 (0.2%)
Endocarditis	0 (0.0%)	0 (0.0%)
Heart failure	51 (0.5%)	62 (0.7%)
Liver failure	0 (0.0%)	1 (0.0%)
Multiorgan failure	9 (0.1%)	14 (0.2%)
Myocardial infarction	89 (1.0%)	88 (0.9%)
Other coronary artery disease	4 (0.0%)	4 (0.0%)
Other non-vascular cause	8 (0.1%)	11 (0.1%)
Other vascular cause	44 (0.5%)	55 (0.6%)
Pneumonia	10 (0.1%)	8 (0.1%)
Pulmonary embolism	2 (0.0%)	8 (0.1%)
Renal failure	2 (0.0%)	5 (0.1%)
Respiratory failure	13 (0.1%)	12 (0.1%)
Ruptured aortic aneurysm	1 (0.0%)	0 (0.0%)
Sepsis	7 (0.1%)	23 (0.2%)
Stroke	20 (0.2%)	18 (0.2%)
Sudden death	60 (0.6%)	77 (0.8%)
Suicide	1 (0.0%)	1 (0.0%)
Trauma	3 (0.0%)	1 (0.0%)
Unstable angina	7 (0.1%)	8 (0.1%)
Valvular disease	0 (0.0%)	1 (0.0%)
Vascular death, sub-classification missing	0 (0.0%)	1 (0.0%)
Unknown	39 (0.4%)	58 (0.6%)

ported on top of already unbelievable 89 cardiovascular (CV) extra fatalities in the clopidogrel arm. Interestingly, by counting site-reported events, the primary outcome difference between ticagrelor and clopidogrel in PLATO was not significant (p=0.095 by *log* rank) (2). Less impressive benefit of ticagrelor was attributed to extra MIs adjudicated to the clopidogrel arm, shifting the HR from reported 0.84 (1) to much more neutral 0.94 (2), further diminishing overall ticagrelor benefit (if any). The fact that two (stroke and MI) out of three primary efficacy outcome measures yielded no benefit for ticagrelor, but that vascular death reduction favours ticagrelor so heavily is impossible to comprehend.

The comparison of the primary outcome endpoints in TRITON versus PLATO reveals a fundamental disproportion of events between trials, making the MI/CV death ratio in PLATO (►**Table 4**) unrealistic, and difficult to understand. Huge all-cause mortality rates, and gross reduction after ticagrelor (107 fewer events) also does not look natural, or at least random, since such massive benefit had never been observed in ACS trials.

Outcomes in PLATO-USA cohort

In contrast, the US sites were monitored by the third party CRO, Research Pharmaceutical Services (Fort Washington, PA, USA) potentially explaining the inverse benefit in the USA. The maturity patterns of Kaplan-Meier outcome curves (2) and distribution of events in the USA (2) (►Fig. 7) matched very well with previous evidence, while overall PLATO curves (1, 2) are paradoxical and unseen before.

Importantly, similar to the USA, sites in Russia and Georgia were also monitored by the third party CRO, Worldwide Clinical Trials (King of Prussia, PA, USA). Clopidogrel was superior to ticagrelor in both countries (►Fig. 2). The planned PEGASUS trial in stable coronary disease will be run by the TIMI investigators again (TIMI-54) (12), and this turn of events also challenges the

integrity of the PLATO trial results. Before clearing the mortality issue in PLATO, any more ticagrelor studies in the USA seem unethical, and PEGASUS should be put on hold until the excess mortality issue in PLATO clears.

Prior studies with ticagrelor

Also, it is critical to remember that Phase II studies with ticagrelor (DISPERSE [13] and DISPERSE-2 [14]) were run by the TIMI group with highly unfavourable results, including more deaths (13 vs. 4) (2) for ticagrelor (▶Table 5), while PLATO, with huge mortality benefit, was predominantly monitored by the study sponsor, while TIMI investigators were not involved.

Sepsis controversy

In addition to the MI/CV death risks ratio mismatch in the clopidogrel arm, the numbers for general infections and sepsis-related deaths make no sense whatsoever (see ▶Table 6 for details).

The data outlined in the table clearly suggest that more potent platelet inhibition with ticagrelor caused slightly more frequent risk for infections than those inflammatory events associated with clopidogrel which is perfectly understandable. However, the remarkable (>3 times) reduction of deaths reported after ticagrelor makes no sense, and should be independently verified as well.

Table 3: Causes of deaths in PLATO.

Country/Parameter	Poland	Hungary
Patients enrolled (n)	2,666	1,267
Reported events (n)	96/137	42/70
Events favouring ticagrelor (n)	41	28
Weight in PLATO (%)	14.33	6.81

Table 4: Primary endpoint component differences in TRITON and PLATO.

Outcome/Agent	Prasugrel	Ticagrelor
Vascular death (n)	–17	–89
Non-fatal myocardial infarction (n)	–122	–80?
Non-fatal stroke (n)	+1	+19
Total events (n)	–138	–150

Table 5: Efficacy of ticagrelor in phase II studies (DISPERSE and DISPERSE-2 combined).

Outcome (%)	Ticagrelor (n=663)	Clopidogrel (n=327)
CV death/MI/stroke	3.9	4.9
CV death	1.8	1.2
MI	2.4	4.3
Stroke	0.3	0.3
Death	1.96 (n=13)	1.2 (n=4)

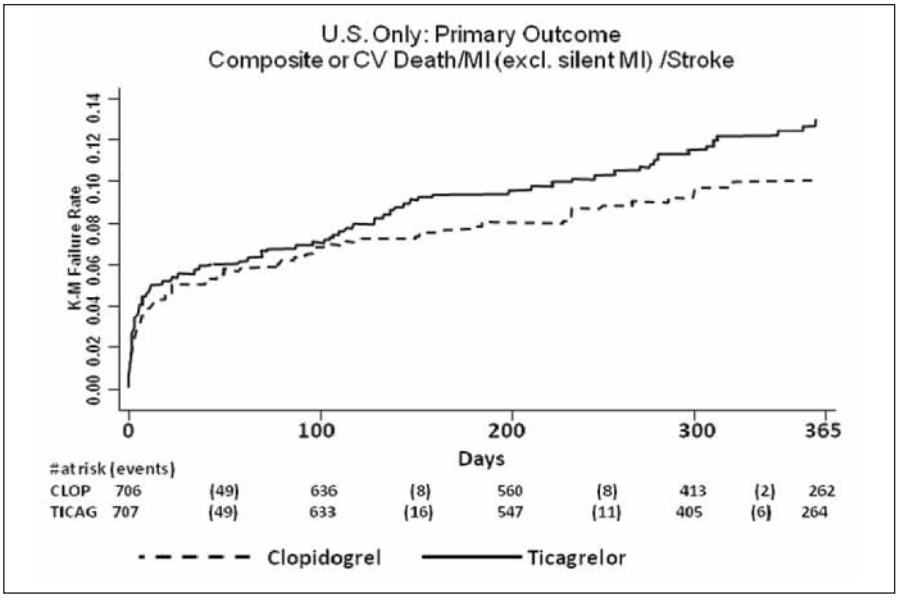

Figure 7: The outcome patterns in the PLATO-US cohort. (Reprinted from R. Fiorentino, Clin Rev).

Trial/Duration	Monitoring	Mortality
CHARISMA – 2 years	C5	Identical (4.8%)
PROVE-IT – 2 years	TIMI	2.2% vs. 3.2%
ACUITY – 1 year	CRF	3.7% – 3.9%
TRITON – 6–15 months	TIMI	3.0% – 3.2%
Short-term one-month trials		
CURRENT	OASIS	Identical CV deaths (1.9%)
CHAMPION-PCI	Study Sponsor	Identical (0.9%)
CHAMPION-PLATFORM	Study Sponsor	1.5% vs.1.7%
PLATO – 6–12 months	Study Sponsor	4.5% vs. 5.9%
PLATO – 6–12 months	3rd party CRO in the USA	3.2% – 3.8%

Table 6: Distribution of infections and sepsis-related deaths in PLATO, dependent on treatment assignment.

Impressions

The death rates in PLATO in general, and mortality benefit of ticagrelor in particular seem paradoxical and unnatural, requiring independent vital status verification in top enrolling sites in Poland and Hungary, especially those with unusually high reported mortality independently from randomisation codes. The differences in mortality for 3rd party CRO, and sponsor self-monitoring are presented in ▶Table 7.

PLATO mortality rates are unlikely to be caused by a play of chance considering the overall large sample size, high numbers in both arms (15, 16), and the following concerns:

A. The previously unseen high death rates after clopidogrel and ticagrelor, and further unseen magnitude of death reduction reported after ticagrelor;
B. The unseen pattern of delayed (until after two months) but growing late mortality benefit despite short duration, frequent clopidogrel pretreatment, and incomplete follow-up.
C. Volunteering the hypothesis that aspirin dose affects PLATO outcomes at the time of active regulatory submission may represent an attempt to shift attention from real problems with other sponsor-monitored countries like Poland or Hungary to the USA;
D. The USA mortality data, not monitored by the PLATO sponsor, but 3rd party CRO matched very well with prior evidence;
E. Eliminating TIMI from conducting, and most importantly monitoring PLATO;
F. Desperation to show mortality benefit of ticagrelor despite opposite phase 2 results to achieve a reasonable trade-off for the unfavourable safety.
G. Failure of the parent compound (cangrelor) (17), and rolofylline (18) to improve outcomes. Lack of efficacy for rolofylline in heart failure (18) also challenges the adenosine-related mechanism of potential ticagrelor mortality benefit in PLATO (6, 19), since both agents may similarly exert their effects via modulation of adenosine receptors.
H. Lack of regional outcome differences in TRITON (20).

In summary, the above evidence suggests that PLATO mortality numbers are paradoxical, and should be independently verified. Regulators should completely ban sponsors from site self-monitoring, especially in indication-seeking studies.

Table 7: Site monitoring and mortality in recent ACS trials.

Symptom/Infection	Ticagrelor	Clopidogrel
Upper respiratory	947 (10.25%)	882 (9.6%)
Heart	15 (0.16%)	9 (0.1%)
Lungs	233 (2.52%)	245 (2.67%)
Urinary tract	184 (2.0%)	161 (1.8%)
Viral	466 (5.05%)	415 (4.52%)
Bacterial	506 (5.48%)	492 (5.36%)
Sepsis-related deaths	7 (0.1%)	23 (0.2%)

Disclosure

Dr. Serebruany is listed as an inventor for the US patent application: Treating cardiac arrhythmias, heart failure, peripheral artery disease and stroke with cyclopentyl-triazolo-pyrimidine or derivative thereof (USN 61/253,829) assigned to Heart*Drug*™ Research LLC. He received funding for research studies with clopidogrel, and consultant fees from both clopidogrel and ticagrelor manufacturers.

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