Viewpoint: Reversible nature of platelet binding causing transfusion-related acute lung injury (TRALI) syndrome may explain dyspnea after ticagrelor and elinogrel

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Summary
There may be a universal mechanism explaining dyspnea after ticagrelor and elinogrel, namely, transfusion-related acute lung injury (TRALI). Indeed, recent clinical trials with ticagrelor (DISPERSE, DISPERSE-II, and PLATO), and elinogrel (INNOVATE PCI) revealed double-digit rates of dyspnea after novel reversible antiplatelet agents. In contrast, dyspnea is not associated with conventional non-reversible agents such as aspirin, or thienopyridines (ticlopidine, clopidogrel, or prasugrel) suggesting distinct mechanism of shortness of breath after ticagrelor and elinogrel. The adenosine hypothesis has been offered to explain such adverse association. However, despite obvious similarity between ticagrelor and adenosine molecules, the chemical structure of elinogrel is entirely different. In fact, ticagrelor is a cyclopentyl-triazolo-pyrimidine, while elinogrel is a quinazolinone. Since both agents cause dyspnea, the adenosine hypothesis is no longer valid. In contrast, the reversible nature of platelet inhibition attributable to both ticagrelor and elinogrel causing premature cell ageing, apoptosis, impaired turnover due to sequestration of overloaded, exhausted platelets in the pulmonary circulation are among potential autoimmune mechanism(s) resulting in the development of a TRALI-like reaction, and frequent dyspnea. Despite expected benefit for better bleeding control, further development of reversible antithrombins is severely limited due to the existence of a potentially universal serious adverse event, such as TRALI-syndrome with dyspnea as a predominant clinical manifestation. Since TRALI is an established number one contributor to mortality after blood transfusions, ticagrelor death “benefit” in PLATO is challenged further.

Keywords
Ticagrelor, elinogrel, adenosine, TRALI, dyspnea, reversibility

Dyspnea is a common reason for seeking medical advice, and often requires patient admission to the emergency department (1). In US dyspnea is not only considered a serious adverse event, but also holds a heavy economic burden of an average $6,958 affiliated costs per single outpatient visit (2). Whilst the association between treatment with conventional antithrombotic agents and dyspnea is not new, and few anecdotal reports are available; however, the associated incidence of shortness of breath is extremely rare. In fact, dyspnea does not appear to represent a safety concern for the current oral antiplatelet therapy. Indeed, therapy with aspirin, clopidogrel, or prasugrel does not cause dyspnea unless there is an underlying disease associated with the shortness of breath. Importantly, most package inserts for antiplatelet agents do not even mention dyspnea as a potential adverse reaction; moreover, the vast majority of pertinent clinical trials do not describe dyspnea in their safety/adverse events sections of the primary publications.

In contrast, recent randomised evidence suggests that novel P2Y12 platelet inhibitors, namely, ticagrelor and elinogrel are causing dyspnea. Recently approved ticagrelor, in a 100–400 mg daily caused a dose-dependent 10–20% incidence of dyspnea in both Phase 2 DISPERSE, and DISPERSE-2 trials (3–5). This adverse association was later confirmed in the large Phase 3 PLATO trial, in which dyspnea was the most prominent side effect of 180 mg/daily ticagrelor when compared to 75 mg/daily clopidogrel (hazard ratio [HR]=1.84; confidence interval [CI]=1.68–2.02; p<0.001) (6). In addition, recent Phase 2 study INNOVATE-PCI with elinogrel, (7) another experimental antiplatelet agent revealed similar to ticagrelor problem such as difficulty to breath. In contrast to the very reasonable and low rate of dyspnea after clopidogrel (4.3%), elinogrel caused dyspnea in an alarming 12.1–15.4% of patients (8). Importantly, association of both ticagrelor and elinogrel with dyspnea has been not only an unpleasant, but an unexpected surprise, raising woeful concerns about the adequacy of early drug development. Obviously, Phase 2 studies are not designed to “discover” such crucial safety issues, which should be noted much earlier. Importantly, another reversible P2Y12 blocker, canegrelor has also been associated with increased dyspnea rates (1.4%) compared to the placebo group (0.5%), with 37 patients and 14 patients, re-
spectively (p = 0.002), in the CHAMPION-PLATFORM trial (9). In contrast, personal communications with the BRIDGE investigators (10) revealed that cangrelor did not cause dyspnea when used in heart surgery patients, probably due to the lower cangrelor daily dose. Since no full verifiable data are available at this time, any speculations seem premature. Still, the most likely explanation of such a difference is a shorter exposure of platelets to intravenous cangrelor, in contrast to chronic oral administration of ticagrelor or elinogrel. As with each autoimmune disorder, transfusion-related acute lung injury (TRALI) syndrome requires long-term contact of the drug with primed platelets with repeated cycles of onset and offset binding to trigger the “two-hit event”, which may be less damaging for the intravenous agent such as cangrelor.

Before the INNOVATE PCI trial data with elinogrel became available, the reason(s) explaining why ticagrelor caused dyspnea had been heavily debated. Ticagrelor does not belong to the thienopyridines, but is a carbocyclic nucleoside, representing a “first-in-class” cyclopentyl-triazolo-pyrimidine (11). Therefore, a distinct chemical structure of ticagrelor may be responsible for such adverse association allowing generation of a hypothesis suggesting that the mechanism of ticagrelor action is via promoting adenosine (12). Indeed, comparing these two molecules reveals their striking similarity (Fig. 1A and B). As a potential precursor of adenosine, ticagrelor apparently may lose propylsulfate and benzodifluoride residuals after oral digestion, ultimately increasing blood adenosine content. Since ticagrelor does not require hepatic metabolism (13), the adenosine pathway appears to be a reasonable consideration. Moreover, some of the benefits as well as side effects of ticagrelor are similar to those of adenosine (12). However, the adenosine hypothesis was severely challenged when elinogrel, another reversible antiplatelet agent, similar to ticagrelor caused double-digit rates of dyspnea in the INNOVATE-PCI trial. Since the chemical structure of elinogrel is entirely different from that of adenosine (Fig. 1C), there should be some other common feature linking ticagrelor and elinogrel with dyspnea. It seems that the cornerstone of such adverse association is a reversible nature of drug binding to the P2Y12 platelet receptors. There are few indirect facts supporting such a new hypothesis. First, conventional irreversible agents, such as aspirin, thienopyridines, or platelet GP IIb/IIIa inhibitors do not usually cause dyspnea. Second, we do not have any experience in using reversible antiplatelet agents beyond the few data generated in clinical trials so far. Finally, it is entirely unclear what the impact of drug pharmacokinetics, the repeated receptor occupancy followed by drug release during onset or offset of binding, and especially unbinding on platelet survival, life span, or apoptosis, is. Obviously, such “exhausted” platelets may be considered as foreign, triggering a systemic autoimmune response. Some theoretical considerations supporting such a hypothesis are outlined below.

Platelet life and death is regulated by Bcl-2 family proteins. Specifically, platelets depend on Bcl-x(L) for survival. Bcl-x(L) maintains platelet viability by restraining the killer protein Bak. When Bak is unleashed, it triggers classical intrinsic apoptosis by causing mitochondrial damage, and leading to caspase activation and phosphatidylserine exposure. Resulting platelet apoptosis can be blocked by caspase inhibitors, or by genetic deletion of Bak and its close relative Bax proteins (14). It is entirely unclear how repeated reversible platelet inhibition of activation-dependent receptors impacts delicate balance of Bcl-2 proteins. Most likely after ticagrelor or elinogrel intake platelets are destructed by the repeated daily cycle of binding and unbinding, causing cell damage, resulting in these damaged cells to be considered “foreign” by the own immune system, potentially resulting in a systemic autoimmune response. Since platelets are, by default, genetically programmed to die by apoptosis, aged or destructed platelets are primed for cell death (15). Perturbations in the platelet apoptosis leading to changes in their life span in vivo after reversible antiplatelet agents may play a key role in TRALI syndrome development and associated dyspnea.

TRALI is a major cause of morbidity after blood transfusion and is the leading cause of transfusion-associated mortality reported to the US FDA (16, 17). It has a reported incidence of one in 5,000 blood products transfused but is likely to be significantly more common due to under-recognition and underreporting (18). TRALI is suggested to be a “two hit” event. The “first hit” is
underlying sequestration and priming of neutrophils in the pulmonary compartment. The “second hit” is the transfusion of either human leukocyte antibodies or aged blood products which results in activation of the primed neutrophils and finally in pulmonary edema and associated dyspnea. Several mechanisms are under scrutiny. The first suggested mechanism is that soluble mediators accumulating during storage of erythrocytes and platelets may play a role, including bioactive lipids or soluble CD40-ligand (19). These soluble factors are known to cause lung injury in the presence of a “first hit”. Importantly, patients with coronary artery disease exhibit high plasma levels of soluble CD40 ligand (20, 21), while the platelets destructed by reversible binding may serve as “a first hit” in TRALI development. Another proposed mechanism involves the aged blood cells per se. During storage, blood cells undergo numerous changes in their biochemical and structural condition and acquire pro-inflammatory properties, sometimes collectively referred to as the “cell storage lesion” triggering further pulmonary edema and shortness of breath (22). Importantly, exclusive transfusion of platelet concentrates per se may cause TRALI, presumably by triggering cell membrane lipid transformation during storage (23). Presently, there is no golden standard for the diagnosis of TRALI, which relies on a high index of suspicion and on excluding other types of transfusion reactions. Moreover, the current definitions of TRALI are heavily dependent on clinical symptoms, rather than on certain laboratory findings (24), making a precise diagnosis difficult.

In short, most experts agree that TRALI requires an immune priming step followed by addition of a blood component dominated by neutrophils interacting with platelets and the lung endothelium (25). Therefore, TRALI-like syndrome may represent a universal mechanism responsible for dyspnea observed after ticagrelor and/or elinogrel. Unless this issue is cleared and convincingly denied, severe restrictions should be enforced for further development of reversible antithrombins. Importantly, these limitations may be true not only for antplatelet agents, but for anticoagulants as well. In fact, REG1 (Regado Bioscience, Basking Ridge, NJ, USA), an investigational reversible anticoagulant, has been associated in addition to severe and unclear “allergic reactions” with some dyspnea (0.9%) in contrast to ‘no dyspnea’ reported after heparin in the RADAR trial (26).

There is an ongoing trend of fundamental flows in early development of antithrombins. Indeed, platelet and coagulation studies are important, but only after the general safety profile of drug candidates has been confirmed. Last but not least, if the adenosine theory of ticagrelor benefit is now challenged, it is entirely unclear by which mechanisms “Treating Cardiac Arrhythmias, heart failure, peripheral artery disease and stroke with cyclopropyl-triazolo-pyrimidine or derivative thereof” (USN 61/253,829) assigned to HeartDrug™ manufacturers. Importantly, this limitation may be true not only for antplatelet agents, but for anticoagulants as well. In fact, REG1 (Regado Bioscience, Basking Ridge, NJ, USA), an investigational reversible anticoagulant, has been associated in addition to severe and unclear “allergic reactions” with some dyspnea (0.9%) in contrast to ‘no dyspnea’ reported after heparin in the RADAR trial (26).

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In conclusion, the concept of reversible binding for oral chronic antiplatelet agents has been presently challenged. Despite potential advantage in better bleeding control during heart surgery, drug reversibility holds clear risks for autoimmune TRALI-like complications with clinical manifestation such as dyspnea. Since these drugs are planned to be predominantly used in outpatients, dyspnea is considered a serious adverse event requiring immediate medical attention, and TRALI is an established number one death risk after blood transfusion, the future of broad chronic use for the reversible agents is uncertain. Importantly, the present viewpoint outlines a reasonable hypothesis which is not based on specific research with regard to the drugs under discussion. However, this topical issue requires urgent unbiased investigation.

Conflicts of interest
VLS is listed as an inventor for the U.S. Patent Application “Treating Cardiac Arrhythmias, heart failure, peripheral artery disease and stroke with cyclopropyl-triazolo-pyrimidine or derivative thereof” (USN 61/253,829) assigned to HeartDrug™. He received funding for research studies with clopidogrel, and consultant fees from the clopidogrel, ticagrelor, and elinogrel manufacturers.

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