THE NORTHERN HOSPITAL

TICAGRELOR

"The Strawberry Thief" Indigo-discharged and block-printed cotton, 1883, William Morris & Co.

"The Spring of this year was like Winter, cold and wet, the wine blossom terrible, and the harvest bad..."

Heinrich Bullinger, 1570.

Within the span of recorded Human civilization, going back to the Third millennium B.C, lies a most enigmatic period known as the "Little Ice Age". This was a period of unusual

cold where average global temperatures fell as much as 2 degrees Celsius. This may not seem like much however in the finely balanced ecosystems of planet Earth this had devastating effects. The period is not well defined, nor is there a general agreeance amoung climate scientists as to when it began and when it finished. In its broadest definition, the period 1300 - 1850 is taken as the Little Ice Age; it follows a period known as the "Medieval Warming Period" of roughly 900 - 1300 A.D and preceded the present period of warming that began in the late 19th century that increasingly appears to be caused directly by Human activity. But some climate scientists limit the period to its most severe, roughly the years 1500 - 1850, with the apogee in the year 1680.

We do not have direct records of temperatures during these times, however for the severest winters there are abundant historical descriptions of unprecedentedly arid summers and the harshest of winters. By the 1570s the first hints of a natural disaster on a truly global scale - including Europe, Russia, China and the Americas were apparent. By the end of the Sixteenth century descriptions began to appear of Mediterranean harbours covered with ice, "frost fairs" being annually held on frozen-solid rivers on the Thames, the Danube and the Rhine. Birds literally dropped from the skies, frozen to death. Crops repeatedly failed leading to unprecedented periods of famine in Europe. Most believed that the disaster was due to the wrath of God. Bishop Marco Antonio Martinengo recorded in his diary, 18th May 1590, "God shows us his anger, by sending us eternal winter, cold which we feel at home, wrapped even in out thickest furs". The Dutch chronicler Wouter Jacobszoon, grimly recorded in 1572, "God has abandoned us".

Scientists have been accumulating abundant and arresting indirect evidence, that confirms plummeting average temperatures, from such methods as ice-core drillings and dendrochronology. One fascinating piece of historical evidence comes in the form of wine harvest dates. Owing to a lack of reliable and comprehensive data on grain harvests it is difficult to directly correlate crop failures with temperature. However wine was an especially precious commodity and harvest dates for grapes were meticulously kept, as well as records for quality, prices, and amounts. It may seem surprising that such meticulous records were kept for wine, until it is appreciated that until well into the Nineteenth century wine was not simply the luxury item that it is considered today. Before the sterilizing effect of boiling water on microorganisms was known, the only known way to ensure a healthy water supply was by adding alcohol to it. As salt was the great preserver of food, alcohol was the preserver of drinking water. Wine was a part of everyday consumption, and it was often used as payment for services rendered. Any hike in wine prices created almost as much social unrest as that caused by a hike in bread prices. Medieval men, women and even children were rarely completely sober!

The timing of the grape harvest was critical. Once grapes are ripe they become prey to thieves and birds, as well as rot, mould and frost. The vintners therefore aim to harvest as early as possible, as soon as the grapes are properly ripe. When ripe the grape has just the right amount of sugar to create a wine with delectate aromas and taste. If harvested too early wine will not have the optimal taste. In colder weather, without sunshine the time to ripen takes longer. In this situation the vintner must weigh the risk of harvesting too early with consequent too little sugar and too much acid or harvesting too late running the risk of rot and loss from birds. Harvest dates therefore can give scientists a surprisingly accurate impression of weather for any given year. The best

documentation of medieval wine dates, not surprisingly, comes from France, and the best of all from Burgundy and regions around Paris. Before about 1570 the grape harvest would reliably commence around September 21. But between 1571 and 1620 it had become on average ten days later; on the 1st of October. It was clear that the winters were becoming harsher and longer. In the especially cold year of 1573 the harvest began on 16th of October. In the years 1581 and 1587 harvest took place at the end of October. The trend to later and later dates of the wine harvest over the last decades of the Sixteenth century attests to the increasing severity of the winters of those years.

The actual cause of the Little Age is unknown. For most that lived through it there was little doubt that it was caused by the displeasure of God. To the more enlightened it was due to astronomical influences, an idea that actually correlates with some Twenty first century theories that blame reduced solar activity, as confirmed by markedly reduced sunspot activity recordings for the period, as the reason.

When we prescribe the agent ticagrelor for patients presenting with acute coronary syndromes in the Emergency Department we are faced with a dilemma as complex as the timing of a medieval grape harvest during the Little Ice Age. If we go to early, we may compromise those who require urgent coronary artery bypass graft surgery - if we go too late we risk further thrombosis with an adverse outcome!

"Winter Landscape with Ice Skaters", oil on canvas, c. 1608, Hendrick Avercamp. Rijksmuseum, Amsterdam.

TICAGRELOR

*In the ED or Cath-lab setting, ticagrelor can be administered to unwell patients who cannot sit up or to patients who have difficulty swallowing tablets - by using a newly developed **oro-dispersible** formulation. This tablet is placed on the tongue, where it readily dissolves, then can be easily swallowed.*

Introduction

Ticagrelor (trade name in Australia, "**Brilinta**") is an oral **antiplatelet agent** used in the treatment of **acute coronary syndromes**.

It is the currently preferred option (in combination with **aspirin**) **for patients with ACS (with or without ST-segment elevation), requiring early/ emergent PCI.**

Ticagrelor has a number of advantages over the previously favored *clopidogrel* including:

1. A more **rapid onset** of action.

2. A more **pronounced** (> 80% inhibition) anti-platelet effect

3. Has greater efficacy in combination with aspirin compared to the combination of clopidogrel and aspirin

4. Ticagrelor has a *more consistent* antiplatelet response in patients.

   - Some patients (up to 30 % by some reports) are **non-responders to clopidogrel.** [6]

5. Less complications:

   - It has a reduced rate of vascular complications with no increase in overall major bleeding compared to clopidogrel.

6. Since ticagrelor binds reversibly, the recovery of platelet function *does not depend on replacement of platelets.*

7. As its antiplatelet action is of shorter duration than either clopidogrel or prasugrel, the duration of the risk of increased bleeding following ticagrelor's discontinuation is also shorter and it may be used in closer proximity to surgery.

A rare but important adverse effect is that of conduction delays/ bradyarrhythmias, especially (but not exclusively) in patients who already have these abnormalities. In these patients there is a risk of ventricular pause/ standstill. For this group of patients clopidogrel is preferred.

Recently an orodispersible formulation has become available, which can be placed on the tongue, allowed to dissolve, then swallowed. This formulation is particularly useful in the emergent setting in the ED or Cath-Lab where unwell patients are unable to sit up and take the regular film coated formulation with water - or for patients in general who cannot easily swallow tablets.

History

Ticagrelor was approved for use in the European Union in December 3, 2010.

It was approved by the US Food and Drug Administration on July 20, 2011.

Ticagrelor's brady-arrhythmic potential was investigated in a sub-study of the PLATO trial, which concluded that the effects were transient and not clinically significant beyond the acute initiation phase. Since then, however there have been emerging reports of **ticagrelor associated high-degree heart block**, requiring **drug discontinuation** and in some cases pacemaker insertion.

Chemistry

Ticagrelor is a member of the chemical class known as the **cyclo-pentyl-triazolo-pyrimidines**

Of note it has some structural similarities to **adenosine** - this could explain its occasional adenosine - like side effects - (**See Appendix 1 & 2 below**).

Physiology

Extracellular adenosine has a half-life of just several seconds due to rapid cellular uptake via:

1. Sodium independent equilibrative nucleoside transporters (ENTs)

    - ENTs are ubiquitous, present on erythrocytes as well as the liver, heart, spleen, kidneys, lungs, intestines, and brain

And

2. Sodium dependent concentrative nucleoside transporters (CNTs).

    - CNTs are found primarily in the liver, kidneys, and small intestine.

The adenosine receptors (or P1 receptors) are a class of purinergic G protein-coupled receptors with adenosine as endogenous ligand. There are four known types of adenosine receptors in humans: A1, $A2_A$, $A2_B$ and A3.

Three adenosine receptor subtypes A1, $A2_A$, and A3 have cardiac expression with agonism resulting in bradycardia, coronary vasodilatation, and activation of multifaceted cardio-protective mechanisms, respectively.

Classification

The classes of antiplatelet drugs include:

1. Irreversible cyclooxygenase inhibitors:

    Aspirin acts by irreversibly acetylating COX-1, whereas other NSAIDs reversibly acetylate both COX-1 and COX-2, which prevents synthesis of TXA_2, a key factor in the platelet aggregation process.

    - Aspirin
    - Triflusal (Disgren)

2. Adenosine diphosphate (ADP) receptor inhibitors:

    Thienopyridines impair platelet aggregation by blocking the interaction of ADP with its receptor.

    - Clopidogrel (Plavix)
    - Prasugrel (Effient)
    - **Ticagrelor** (Brilinta)

- Ticlopidine (Ticlid)

3. Phosphodiesterase inhibitors:

   Phosphodiesterase inhibitors (PI) are thought to act by blocking the decomposition of cAMP, which inhibits calcium release during platelet activation.

   - Cilostazol (Pletal)

4. Glycoprotein IIB/IIIA inhibitors (intravenous use only):

   Glycoprotein IIb–IIIa antagonists block the IIb–IIIa fibrinogen receptors, which are involved in the final step of the platelet aggregation pathway.

   - Abciximab (ReoPro)
   - Eptifibatide (Integrilin)
   - Tirofiban (Aggrastat)

5. Adenosine reuptake inhibitors:

   - Dipyridamole (Persantine)

6. Thromboxane inhibitors:

   - Thromboxane synthase inhibitors
   - Thromboxane receptor antagonists
     - ♥ Terutroban

Preparation

Ticagrelor as:

Tablets: standard release (‘film coated”) formulation:

- 90 mg

Tablets: Oral dispersible formulation:

- 90 mg

Mechanism of Action

Ticagrelor is an oral platelet aggregation inhibitor.

It is a **selective** and **reversibly** binding **adenosine diphosphate (ADP) receptor antagonist** that acts on the **$P2Y_{12}$ - ADP-receptor**

It can prevent ADP mediated platelet activation and aggregation.

$P2Y_{12}$ belongs to the Gi class of a group of G protein-coupled (GPCR) purinergic receptors and is a chemoreceptor for adenosine diphosphate (ADP). The P2Y family has several receptor subtypes with different pharmacological selectivity, which overlaps in some cases, for various adenosine and uridine nucleotides. This receptor is involved in platelet aggregation.

Since ticagrelor binds reversibly, the recovery of platelet function *does not depend on replacement of platelets.*

The active metabolite of the thienopyridines (**clopidogrel, prasugrel) *irreversibly*** binds to the platelet P2Y12 receptor and inhibits platelet aggregation for the life of the platelet.

Clopidogrel and prasugrel are given *once* daily.

Ticagrelor is *reversible* and requires twice-daily dosing.

As its antiplatelet action is of shorter duration than either clopidogrel or prasugrel, the duration of the risk of increased bleeding following ticagrelor's discontinuation is also shorter and it may be used in closer proximity to surgery.

Pharmacodynamics

Ticagrelor has a **more rapid onset** of antiplatelet effect compared to clopidogrel.

Peak time of action: [7]

- 1.5 hours (ticagrelor)
- 2.5 hours (metabolite)

It has a **faster rate of offset** of antiplatelet effect as compared to clopidogrel

Peak inhibition of platelet aggregation (around 90%) at about **2 hours** following a loading dose of **180 mg**.

Pharmacokinetics

Absorption:

- Absorption of ticagrelor is rapid
- The mean absolute bioavailability of ticagrelor is estimated to be around 36%.

Distribution:

- The steady state volume of distribution of ticagrelor is 87.5 L.
- Ticagrelor and its active metabolite are extensively bound to human plasma protein (> 99.0%).
- It is unknown if ticagrelor crosses the human placenta.
- It is unknown if ticagrelor is distributed into human breast milk.

Metabolism and excretion:

- Ticagrelor is metabolized in the liver via the CYP450 - 3A4 enzyme.

  The ticagrelor metabolite (AR-C124910XX) has antiplatelet activity.

- Elimination half-life:

  - ♥ Ticagrelor: 6.9 hours
  - ♥ Ticagrelor metabolite: 8.6 hours

Indications

Principle indications in the **ED** include:

ACS (with or without ST-segment elevation), (**given together with aspirin**)

- Ticagrelor with aspirin is more effective than clopidogrel with aspirin in preventing cardiovascular events in patients with ACS

If the patient is considered to be a **high probability for needing CAGS** then ticagrelor should be withheld - ideally CAGS is not undertaken until **5 days** after ceasing ticagrelor.

Where uncertainty exists - ticagrelor may be withheld until the **coronary angiogram has been done** and the need for CAGS has been definitively determined.

Contraindications/ Precautions

These include:

1. Severe active bleeding or disease states with an increased risk of severe bleeding:
   - e.g. bleeding disorders, severe hepatic disease.
2. Other drugs that can affect the clotting process may increase the risk of bleeding
   - Avoid combinations where possible or monitor closely.

3. Weight < **60 kilograms**:

   - There is an increased the risk of bleeding.

4. Asthma/ COPD:

   - Ticagrelor may cause **dyspnoea** in these patients, (a relative contra-indication).

     The mechanism for this effect has not been elucidated.

5. Caution with concurrent treatment with strong inhibitors of the CYP450 - 3A4 enzyme:

   - Ticagrelor concentrations may increase, thus increasing the risk of bleeding.

6. Contraindicated in moderate to severe liver impairment (ticagrelor is mostly eliminated via the liver).

7. Contraindicated in known hypersensitivity to ticagrelor.

8. Contraindicated in those with a history of intracranial haemorrhage.

9. **Conduction delays/ bradyarrhythmias**

10. Surgery:

    The risk must be weighed between cardiovascular events (including stent thrombosis) from stopping antiplatelet agents against bleeding risk if continued.

    It may be safe to continue antiplatelet agents before **minor** surgery with low risk of bleeding, e.g. dental procedures, cataract surgery or some dermatological procedures.

    It may be necessary to reduce the antiplatelet effect before **surgery with a high bleeding risk**, e.g. CABG

    For patients with coronary stents, consider delaying elective surgery until dual antiplatelet treatment is no longer required; consult patient's cardiologist before stopping antiplatelet agents.

    If antiplatelet effect is **not wanted,** stop clopidogrel > 5 days before, prasugrel > 7 days before and **ticagrelor 5 days before planned surgery**.

Pregnancy

There is no definitive human data currently available.

The Australian Medicines Handbook gives it a category B1 classification. [2]

Category B1 drugs are those drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed. Studies in animals have not shown evidence of an increased occurrence of fetal damage

There is very limited information available following the use of ticagrelor during pregnancy.

A single case report of maternal use of ticagrelor during pregnancy described the delivery of a healthy but small for gestational age term neonate.

However, due to potential serious adverse effects, such as bleeding, consider an alternative medicine with more safety information during pregnancy.

Consultation with a haematologist for further advice is recommended.

Breast feeding

Avoid in breast feeding, (insufficient data).

Animal studies have suggested that ticagrelor is excreted into breast milk.

However, published human data describing the use of ticagrelor during breastfeeding have not been located.

Due to potential severe adverse effects, such as bleeding in the breastfed infant, consider an alternative therapy if possible.

Adverse Effects

1. **Bleeding** is the principal adverse effect:
    - Though the incidence of **total** major bleeding is similar to clopidogrel, the rate of major intracranial haemorrhage is higher with ticagrelor.
2. Creatinine levels may increase during treatment with ticagrelor. The mechanism has not been elucidated
3. Dyspnea by an unknown mechanism.
4. Allergic skin reactions (uncommon).
5. **Conduction delays/ bradyarrhythmias (see above)**
    - **This is an uncommon, but important adverse effect.**

The exact mechanism of ticagrelor-induced brady-arrhythmia is uncertain, but **inhibition of adenosine reuptake** has been proposed as likely due to structural similarities between ticagrelor and adenosine.

In the setting of acute coronary extracellular adenosine concentrations are amplified by the ischaemia and myocardial cellular reuptake is blunted. Ticagrelor can aggravate this situation resulting in **enhanced agonism** of **adenosine A1 receptors**, resulting in negative chronotropy and dromotropy (i.e reduced conduction velocity).

This is more likely in ACS patients with pre-existing conduction delays or bradyarrhythmias, or those taking medications that predispose to these conditions, however , there are reports of conduction delays/ bradyarrhythmias occurring even in those with normal ECGs (see case report below).

Clopidogrel appears less likely to cause this effect.

Dosing

Adults: [2]

- **Loading dose 180 mg.**

Then

- **90 mg twice a day.**

Take with **low-dose** aspirin (75 - 150 mg) once daily.

For patients with conduction delays or bradyarrhythmias, ticagrelor should not be given. Clopidogrel may be given instead in these situations.

Administration advice: Regular film coated versus orodispersible formulations:

Recently an orodispersible formulation has become available, which can be placed on the tongue, allowed to dissolve, then swallowed. This formulation is particularly useful in the emergent setting in the ED or Cath-Lab where unwell patients are unable to sit up and take the regular film coated formulation with water - or for patients in general who cannot easily swallow tablets.

Ticagrelor orodispersible tablets:

- Ticagrelor orodispersible tablets ("Brilinta" brand) may be used as an alternative to Brilinta film-coated tablets for patients who have difficulty swallowing the tablets in particular those patients lying flat, and unable to sit up to swallow.

The tablet should be **placed on the tongue**, where it will **rapidly disperse** in saliva.

It can then be swallowed (with or without water).

Ticagrelor film coated tablets (crushed with water for patients who cannot swallow tablets):

If the **orodispersible** formation is not available - and the patient cannot swallow tablets - Ticagrelor film coated tablets ("Brilinta" brand) can be **crushed** using a mortar and pestle or a similar device.

Adding approximately 100 mL of water to the mortar - crushing device and stir for approximately 1 minute before transferring the dispersion to a dosing cup and administer.

Add another 100 mL of water to the mortar - crushing device and stir for approximately ½ minute to ensure that all the remaining powder is dispersed before transferring this to the dosing cup. Stir the contents of the dosing cup again for approximately ½ minute and administer the remaining water/ dispersed tablet.

Nasogastric tube administration:

- The **orodispersible tablet** can be dispersed in water and administered via a nasogastric tube (CH8 or greater). It is important to flush the nasogastric tube through with water after administration of the mixture to ensure delivery of the total dose.

Or

- For administration of the **film coated tablets** via a nasogastric tube (CH8 or greater), crush the tablets as stated above and use approximately 50 mL of water to disperse the crushed powder before withdrawing the dispersion into a suitable syringe.

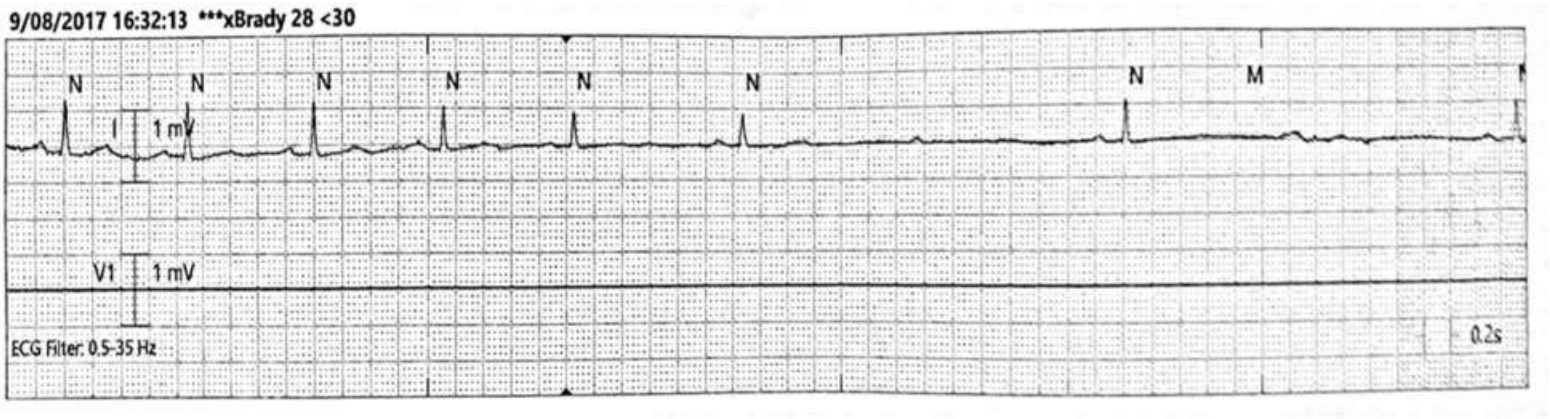
  Then administer the full contents of the syringe via the nasogastric tube.

  Add another 50 mL to the mortar/ crushing device and stir for approximately ½ minute to ensure that all the remaining powder is dispersed, before withdrawing the dispersion into the syringe and administering via the nasogastric tube.

  Refill the syringe with approximately 25 mL of water and shake before flushing any remaining contents from the nasogastric tube into the stomach.

Appendix 1

Case report:



Ventricular pauses, following a loading dose of 180 mg of ticagrelor. [8]

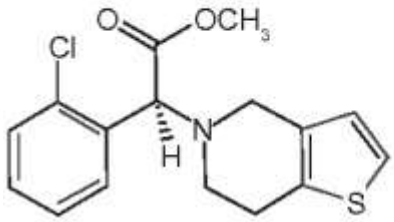
A 59-year-old female presented with an NSTEACS and received an oral loading dose of ticagrelor 180 mg following PCI to her mid-left circumflex coronary artery.

Three hours later, four pauses were observed on telemetry over a 20 minute period, the longest being 18.5 seconds in duration. Her baseline ECG was normal

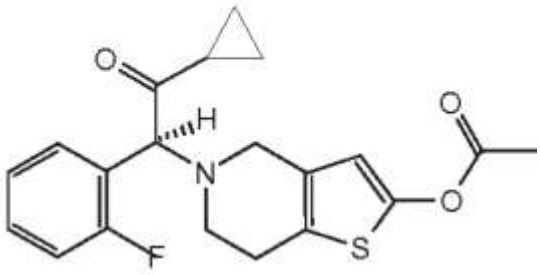
Ticagrelor was ceased and clopidogrel commenced in place. No arrhythmic events were recorded on loop recorder interrogation following ticagrelor discontinuation.

Appendix 2: *The Chemical Structure of Ticagrelor*

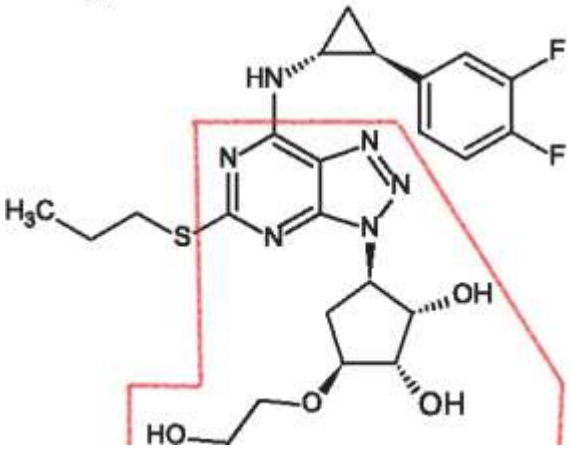
Clopidogrel:



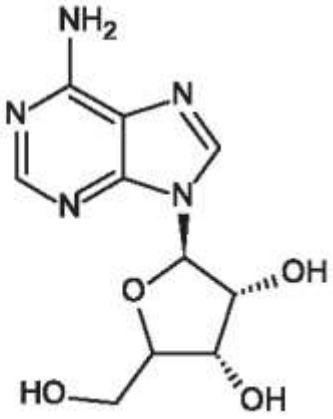
Prasugrel:



Ticagrelor:



Adenosine:

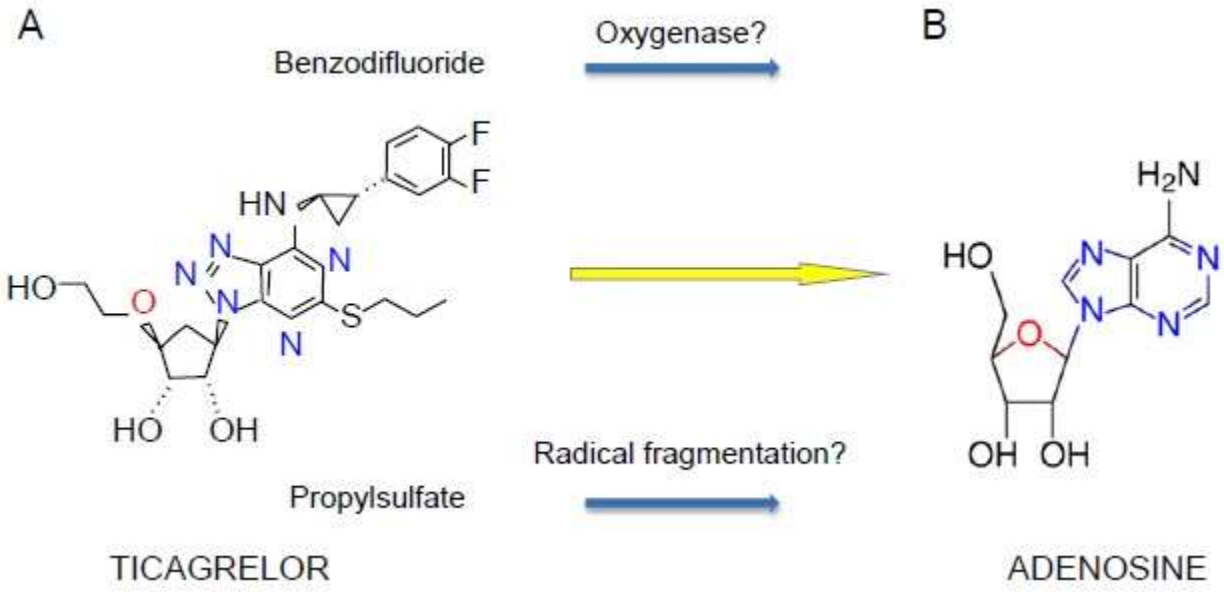


The chemical structure of ticagrelor is very similar to that of adenosine, (James J Nawarskas. Critical appraisal of ticagrelor in the management of acute coronary syndrome. Therapeutics and Clinical Risk Management dx.doi.org/10.2147/TCRM.S19835).

It is theorized that ticagrelor loses two key structures after oral administration, i.e, propyl sulfate and benzodifluoride, by either oxygenase and/or radical fragmentation pathways.

In this sense, ticagrelor is effectively a precursor of adenosine because, after the loss of these structures, the resulting compound is essentially adenosine.

Ticagrelor also inhibits uptake of adenosine by erythrocytes during ACS. The mechanism for this is thought to be inhibition of the sodium-independent equilibrative nucleoside transporters subtype 1.



Potential interplay between ticagrelor (A) and adenosine (B).

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