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# Prasugrel inappropriate use in patients post-percutaneous coronary intervention (PCI): a single center study

## Abstract

Prasugrel is a thienopyridine that was approved by the US Food and Drug Administration in combination with aspirin for the reduction of thrombotic events as well as stent thrombosis in patients with acute coronary syndrome who undergo percutaneous coronary intervention. This retrospective study aims to assess the frequency of inappropriate use of prasugrel and to emphasize that prasugrel still needs more attention as inappropriate use may result in significant morbidity.

## Keywords

prasugrel, inappropriate use, coronary intervention, DAPT

## Background

The cornerstone in the management of acute coronary syndrome (ACS) is dual antiplatelet therapy (DAPT) including aspirin and P2Y12 inhibitors.[1] DAPT is most beneficial for patients undergoing percutaneous coronary intervention (PCI); it is known to reduce the occurrence of stent thrombosis and major cardiac events.[2-4] Clopidogrel is the most commonly used P2Y12 inhibitor. Limitations of clopidogrel include variable antiplatelet effect[5] and delayed onset of action.[3] This variability in the efficacy of clopidogrel paved the way for newer P2Y12 inhibitors such as prasugrel to be used in selective cases.

Prasugrel is a thienopyridine that was approved by the US Food and Drug Administration (FDA) in combination with aspirin for the reduction of thrombotic events as well as stent thrombosis in patients with ACS who undergo PCI. As prasugrel is a prodrug, it requires conversion to an active metabolite before binding to the P2Y12 receptor.[6] TRITON-TIMI 38 was a randomized clinical trial which compared prasugrel and clopidogrel in patients with ACS and concluded that prasugrel (in comparison to clopidogrel) has an early onset of action and provides significant inhibition of platelet aggregation in patients with ACS,[7,8] thereby significantly reducing rate of stent thrombosis and ischemic events in patient undergoing PCI. While there is an obvious benefit over clopidogrel, prasugrel is also associated with increased risk for major bleeding.[8] This risk of bleeding led to the conclusion that there is no net benefit of prasugrel in patients with previous stroke or transient ischemic attack (TIA), patients older than 75 years, and patients weighing <60 kg; it was concluded that it caused net harm.[8-10] For these reasons, use of prasugrel in such patient populations is a class III recommendation.[1]

This retrospective study aims to assess the frequency of inappropriate use of prasugrel and to emphasize that prasugrel still needs more attention as inappropriate use may result in significant morbidity.

## Methods

### Study design and patient population

This is a single center retrospective study to determine the inappropriate use of prasugrel in patients during the period between July 2014 and July 2015. Use of prasugrel in patients with history of cerebrovascular disease (CVA) or history of bleed or in patients who weigh <60 kg, or patient with age of ≥75 years was deemed as inappropriate. No exclusion criteria were applied. Marshall University's institutional review board approved the study.

### Endpoints

The primary study endpoint was the number of patients discharged to home on prasugrel. Secondary endpoints included patients prescribed prasugrel who had a history of CVA or bleed, weighed <60kg, or were of age ≥75 years.

### Data collection

Patient's clinical characteristics, demographics, as well as primary and secondary endpoints, were retrospectively collected from the patient's electronic medical records.

### Statistical analysis

Categorical variables were presented as percentages.

## Results

Duration of this study was July 2014 to July 2015. A total of 937 patients had PCI during this time; prasugrel was prescribed to 124 (12.3%). Prasugrel was inappropriately used in 18.5% (n=23) of patients. Of these patients, 4.8% (n=6) had a history of CVA, 1.6% (n=2) had a history of bleeding, 10.5% (n=13) were aged ≥75 years and 1.6% (n=2) weighed less than 60kg (Chart 1).

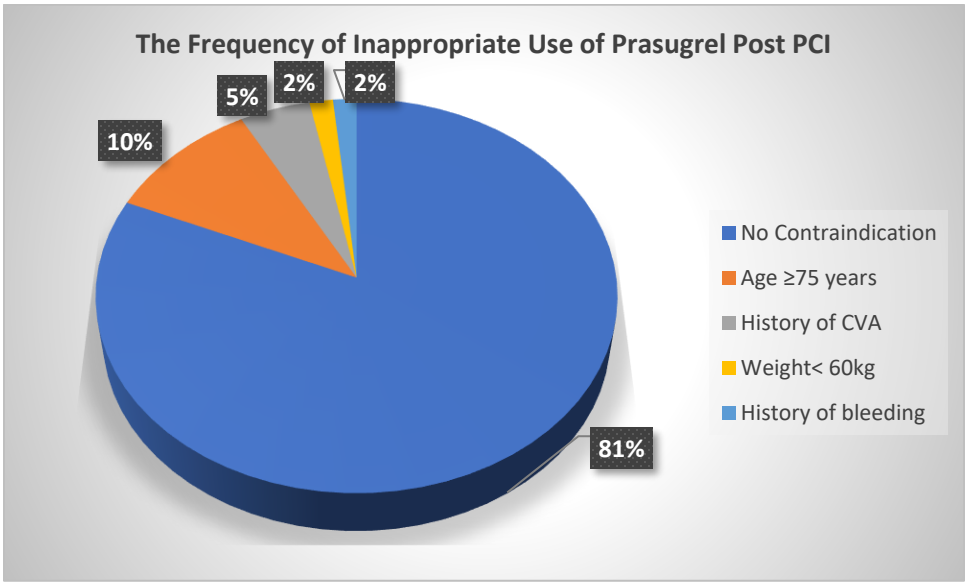


Chart 1 Frequency of inappropriate use of Prasugrel

Our data demonstrated that prasugrel was also used for patients who did not receive stents during their procedure; the incidence was calculated as 3.2% (n=4). Among patients who were prescribed prasugrel, 16.9% (n=21) presented with ST-elevation myocardial infarction, 24.2% (n=30) presented with non-ST elevation myocardial infarction, while 45.2% (n=56) patients had unstable angina and 13.7% (n=17) patients received prasugrel after elective PCI (Table 1).

| | Patient Discharge on Prasugrel (n=124) |
|---|---|
| **Age (≥75 years)** | 13 (10.5%) |
| **Male (n)** | 92 (74.2%) |
| **Female (n)** | 32 (25.8%) |
| **Weight/kg (<60)** | 2 (1.6%) |
| **TIA/Stroke (n)** | 6 (4.8%) |
| **HTN (n)** | 101 (81.5%) |
| **History of bleed** | 2 (1.6%) |
| **DM (n)** | 52 (41.9%) |
| **STEMI (n)** | 21 (16.9%) |
| **NSTEMI (n)** | 30 (24.2%) |
| **Unstable Angina (n)** | 56 (45.2%) |
| **Elective Procedure (n)** | 17 (13.7%) |
| **CAD (n)** | 74 (59.7%) |
| **Stent (n)** | 120 (96.8%) |
| **No stent (n)** | 4 (3.2%) |

Table 1: Demographics of patients who received prasugrel.

## Discussion

As stated in the 2016 update of the American College of Cardiology/American Heart Association DAPT guidelines prasugrel can only be used in place of clopidogrel in patients with ACS if the patient is not at an increased risk of bleeding; this is a Class IIB recommendation.[1] This recommendation was based on the findings of the TRITON–TIMI 38 trial, which concluded that prasugrel significantly decreases ischemic complications of ACS in patients undergoing PCI in comparison to clopidogrel.[11] The same study also found that prasugrel, when used as a part of DAPT in a patient with a history of cerebrovascular event, patients aged 75 or older, and those weighing <60 kg, had increased rate of fatal bleeding. The aim of our study was to report the prevalence of inappropriate use of prasugrel.

Our study demonstrates that the inappropriate use of prasugrel is significant and it affects a sizable portion of the patients requiring antiplatelet therapy. Secondly, we were able to deduce that the inappropriate use of prasugrel most frequently occurs when it is prescribed to patients aged >75 years; in our sample it was a staggering 10.5%. Alexopoulos et al., reported that age ≥ 75 years is a common inappropriate use of P2Y12 inhibitor (not limited to prasugrel).[12] It would be noteworthy to mention that the rate of bleeding requiring transfusion was found to be

significantly higher for patients receiving prasugrel inappropriately as compared with those receiving the drug under no contraindications.[13]

Alexopoulos et al. studied the Greek antiplatelet registry (GRAPE) and reported that 10.6% of the patients were inappropriately prescribed prasugrel on discharge.[12] In comparison to the GRAPE registry, our data shows that 18.5% patients were prescribed prasugrel inappropriately. Hira et al. studied PINNACLE national registry and found that 13.9% patients were inappropriately prescribed prasugrel while 4.4% patients were prescribed prasugrel for non-recommended indications;[14] the cumulative use was 18.3% which is consistent with findings of our study.

Variability in the prevalence of inappropriate use of prasugrel in the above-mentioned studies can be attributed to the difference in definition of "inappropriate use." Randomized studies that established the value of the P2Y12 inhibitors in the treatment of ACS patients undergoing PCI had excluded patients with many of the contraindications and special warnings mainly because of the accompanying increased risk of bleeding, without reporting on the prevalence of these characteristics in screened patients.[15] Such clinical research practice led to masking of valuable information about the population that is possibly affected the most by inappropriate use of prasugrel. Secondly, the definition of our study does not differentiate between non-recommended use or inappropriate use. Hence, our data reports a higher rate of inappropriate use.

Prasugrel was also used in patients who had an elective PCI, the proportion of such patients was 13.7% of our data. Use of prasugrel in this capacity has not been studied in detail.[16] Marchini et al. devised an algorithm for prasugrel use in 2010 but concluded that the use of prasugrel might be considered for patients where the coronary artery anatomy is "high-risk" and patients who have homozygous reduced-function CYP allele which renders clopidogrel hypo-responsive.[16] In 2012, TRIGGER-PCI study by Trenk et al. compared prasugrel and clopidogrel after elective PCI, and found that P2Y12 reaction unit (PRU) was significantly reduced in the prasugrel arm of the study. The study, however, could not demonstrate the benefit of prescribing prasugrel over clopidogrel in terms of endpoints which included cardiac death and myocardial infarction in six months.[17]

Damman et al. in 2014 reported that in respect to elective PCI, occurrence of mortality and bleeding was comparable between the clopidogrel group and the prasugrel group.[18] A recent randomized clinical trial by Hochholzer et al. "The ExcelsiorLOAD Trail" which compared P2Y12 inhibitors pharmacodynamics in peri interventional setting, reported that though prasugrel is more effective, the prasugrel arm of the study had a higher incidence of bleeding events.[19] Earlier in 2013, European Society of Cardiology recommended that prasugrel should only be used in high-risk patients who require elective stenting.[20] Use of prasugrel in elective PCI patients is still under debate and would need further studies to establish guidelines. Literature review reveals that prasugrel use is gradually increasing with time, but it is accompanied with its inappropriate use.[4,5] Therefore, physicians should use caution when prescribing prasugrel to patients undergoing PCI as inappropriate use may result in significant morbidity. Further studies assessing methods to overcome inappropriate prescribing of prasugrel would provide models for improvement.

The prasugrel package insert's black box warning recommends against its use in patient population with a history of cerebrovascular events, in patients aged 75 or older, and in patients weighing 60 kg or less. Despite these measures, evidence dictates that there has been an increase in the momentum of inappropriate or non-recommended use of prasugrel. Firstly, we strongly encourage caution in using prasugrel for patients who undergo elective PCIs. Prasugrel may have its benefits but judicious approach by the physician is warranted to avoid bleeding events. Secondly, it is also needful to emphasize that patients aged >75 are at significantly increased risk of morbidity and mortality, if there are prescribed prasugrel.

## Conclusions

According to our results, despite many years of FDA approval and well-known contraindications, prasugrel use in patients with known contraindications is not uncommon.

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