

Contemporary and Future P2Y12 Inhibitors Strategies

Switching Strategy with Contemporary P2Y12 Inhibitors: Escalation and De-escalation



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Presenter Disclosure Information

Name: Dominick J Angiolillo

Within the past 12 months, the presenter or their spouse/partner have had a financial interest/arrangement or affiliation with the organization listed below.

Received payment as an individual for:

- a) Consulting fee or honorarium from Amgen, Aralez, AstraZeneca, Bayer, Biosensors, Boehringer Ingelheim, Bristol-Myers Squibb, Chiesi, Daiichi-Sankyo, Eli Lilly, Haemonetics, Janssen, Merck, PhaseBio, PLx Pharma, Pfizer, Sanofi, and The Medicines Company;
- b) Honorarium for participation in review activities (DSMB member) from CeloNova.
- c) Honorarium from the American Board of Internal Medicine (Interventional Cardiology Subspecialty Exam Writing Committee Member) and American College of Cardiology (Associate Editor JACC Cardiovasc Interventions)

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- a) Grant support industry: from Amgen, AstraZeneca, Bayer, Biosensors, CeloNova, CSL Behring, Daiichi-Sankyo, Eisai, Eli-Lilly, Gilead, Idorsia, Janssen, Matsutani Chemical Industry Co., Merck, Novartis, Osprey Medical, and Renal Guard Solutions.
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- c) Federal agency: NIH

Expert Consensus Recommendations on Switching

SWITCHING BETWEEN ORAL P2Y₁₂ INHIBITORS

- Escalation (Switching From Clopidogrel to Prasugrel or Ticagrelor)
- De-escalation (Switching From Prasugrel or Ticagrelor to Clopidogrel)
- Change (Switching Between Prasugrel and Ticagrelor)

SWITCHING BETWEEN INTRAVENOUS AND ORAL P2Y₁₂ INHIBITORS

- Bridge (Switching from Oral P2Y₁₂ Inhibitors to Cangrelor)
- Transition (Switching from Cangrelor to Oral P2Y₁₂ Inhibitors)

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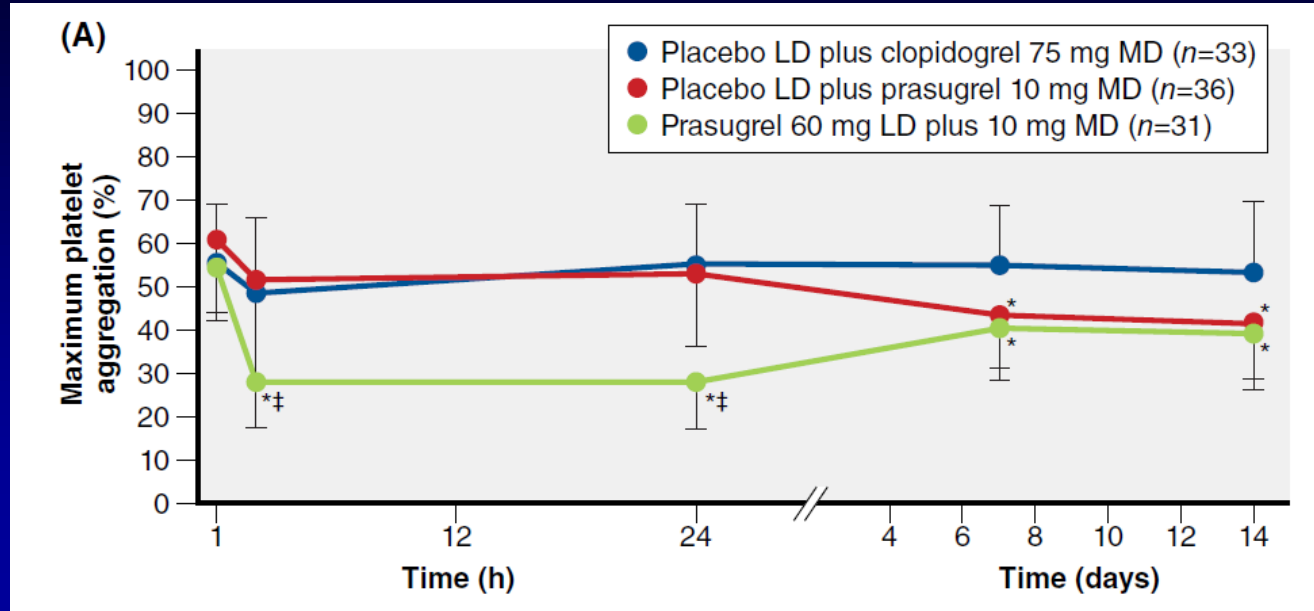
Expert Consensus Recommendations on Switching: Escalation

- Registry data shows that the prevalence of escalation varies from 5% to 50%, depending on the clinical setting and the period of observation.
- Escalating from clopidogrel to prasugrel or ticagrelor therapy commonly occurs in:
 - a) patients presenting with an ACS undergoing PCI who may have been pretreated with clopidogrel at the time of clinical presentation
 - b) occurrence of an ACS while on clopidogrel (“therapeutic failure”).
- To date, most data on escalation therapy derive from subgroup analyses of large clinical trials, registries, and PD studies.
- In PLATO, patients pre-treated with clopidogrel were eligible for randomization (~50% of patients) and switched with a ticagrelor 180mg LD. Consistent benefit on primary efficacy endpoint and no safety concerns (best evidence available).
- In TRITON-TIMI 38, patients pre-treated with clopidogrel were not eligible for randomization.

Key PD studies on Escalation

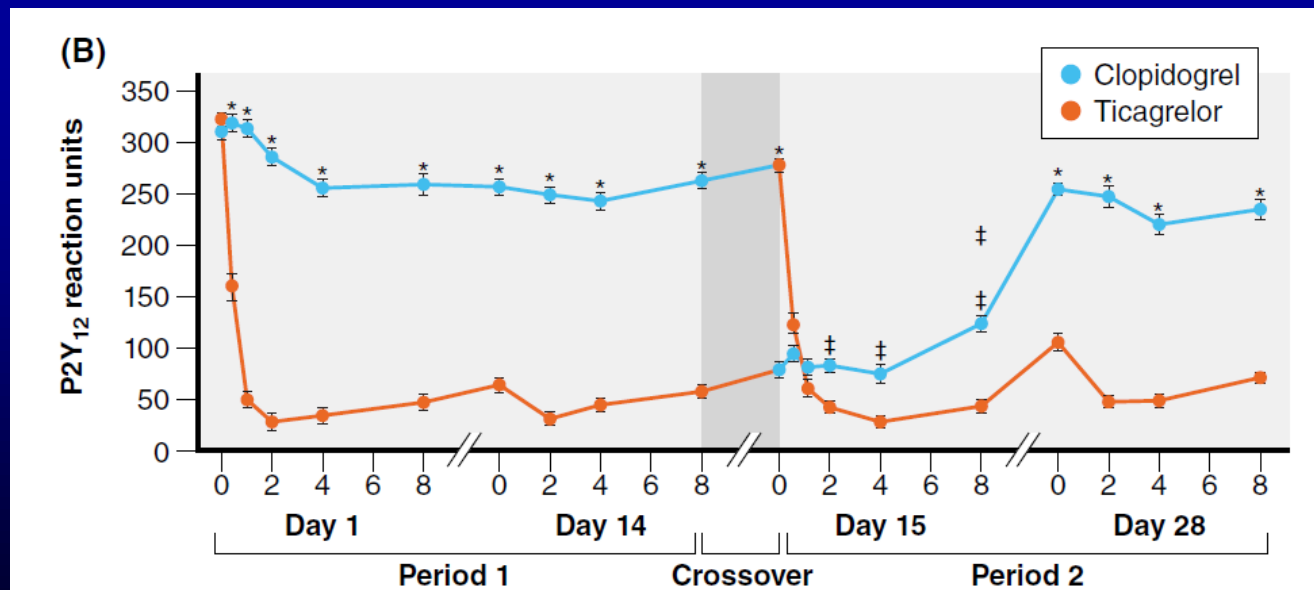
SWAP trial

Adapted from Angiolillo DJ et al.
J Am Coll Cardiol 2010;56:1017-23

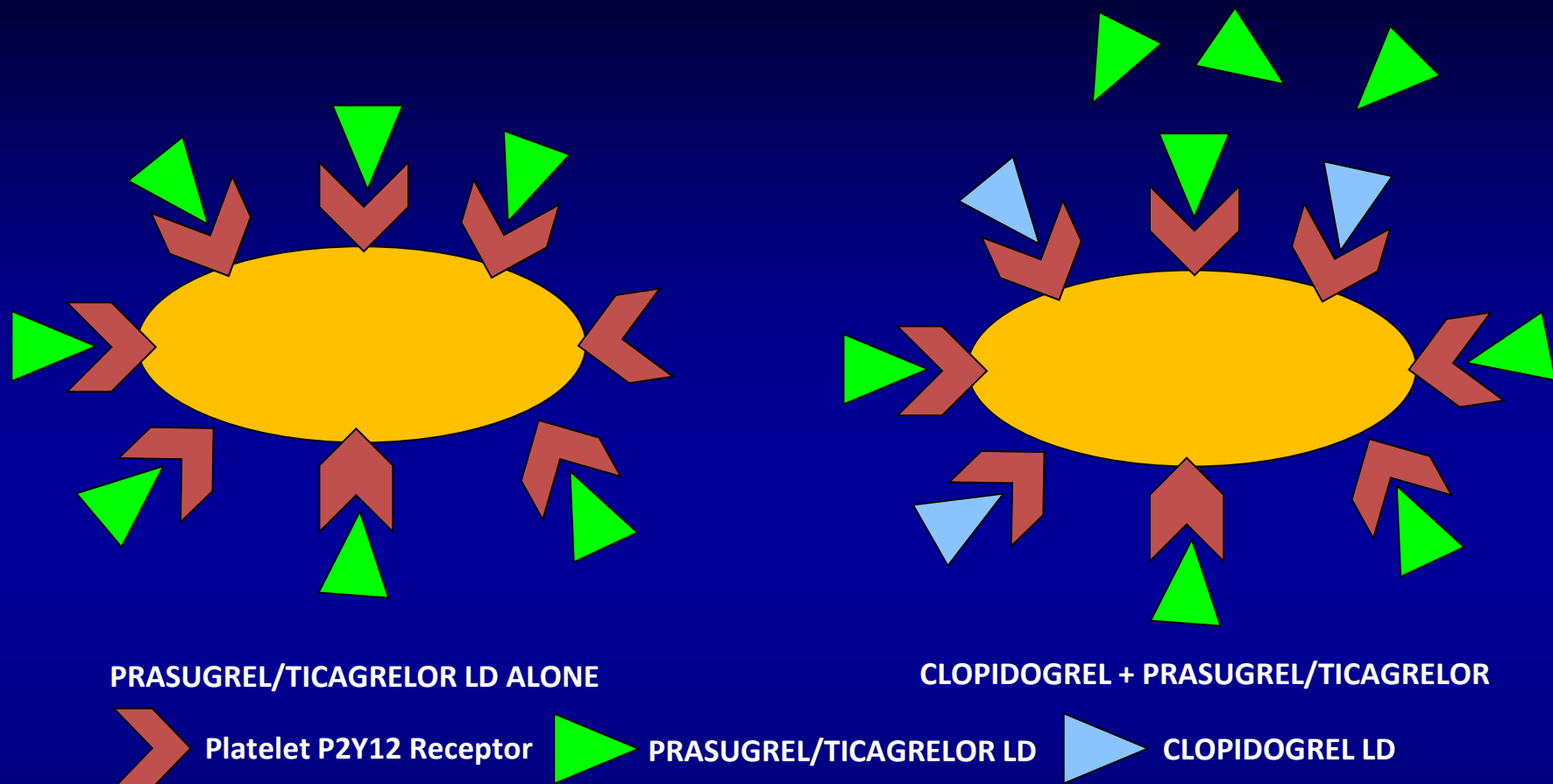


RESPOND trial

Adapted from Gurbel PA et al.
Circulation 2010;121:1188-99



Biological hypothesis for P2Y₁₂-receptor occupancy after administration of a loading dose of prasugrel or ticagrelor, with or without previous exposure to clopidogrel



Adapted from Rollini F et al. *Nat Rev Cardiol.* 2016;13:11–27.

After administration of a clopidogrel LD, P2Y₁₂ receptors are only partially occupied. Therefore, the administration of a LD of prasugrel or ticagrelor to a patient already treated with clopidogrel would lead to blockade of the remaining uninhibited P2Y₁₂ receptors. When all the receptors have been occupied, the remaining molecules of the active metabolite of prasugrel do not bind to any receptor and are immediately hydrolysed. The remaining molecules of ticagrelor, which do not bind to any receptor, remain in the bloodstream for 6-12 hours (ticagrelor half-life) until they bind with unoccupied P2Y₁₂ receptors (e.g., from platelets newly entering the bloodstream). The extent of P2Y₁₂-receptor occupancy when prasugrel or ticagrelor is added to clopidogrel is similar to that resulting from therapy with prasugrel or ticagrelor alone.

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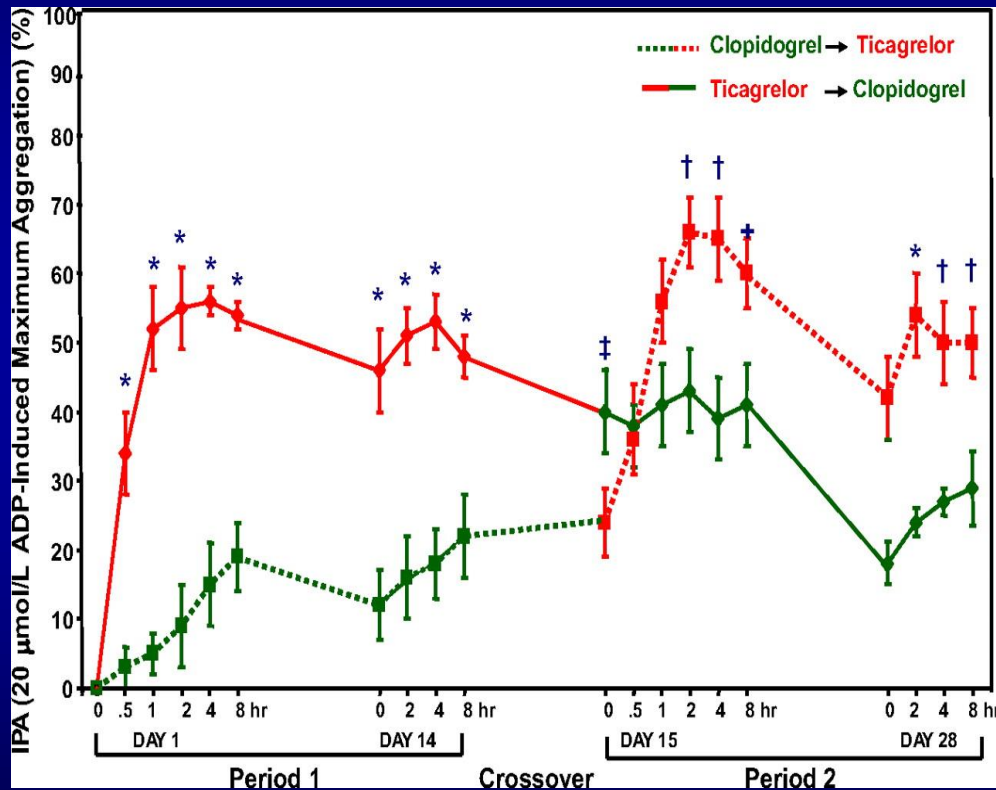
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Expert Consensus Recommendations on Switching: De-escalation

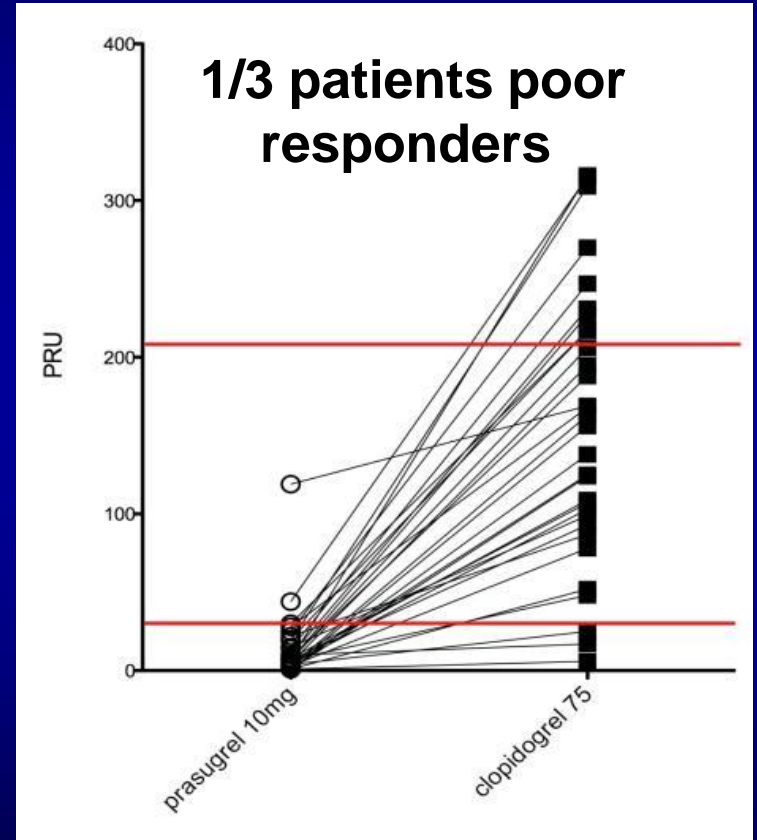
- **Overall, registry data indicate that the prevalence of in-hospital de-escalation ranges from 5% to 14% and from 5% to 8% after hospital discharge.**
- **Reduced costs associated with a generic formulation of clopidogrel and concerns about increased risk of bleeding with prasugrel and ticagrelor remain the most important reasons for de-escalation.**
- **Non-bleeding side effects such as dyspnea also represent a potential reason for interrupting ticagrelor therapy.**
- **PD studies consistently show an increase in platelet reactivity. Binding properties and offset important for defining how to switch.**

PD Effects of De-escalation from Ticagrelor or Prasugrel to Clopidogrel

De-escalation inevitably leads to an increase in platelet reactivity and HPR rates



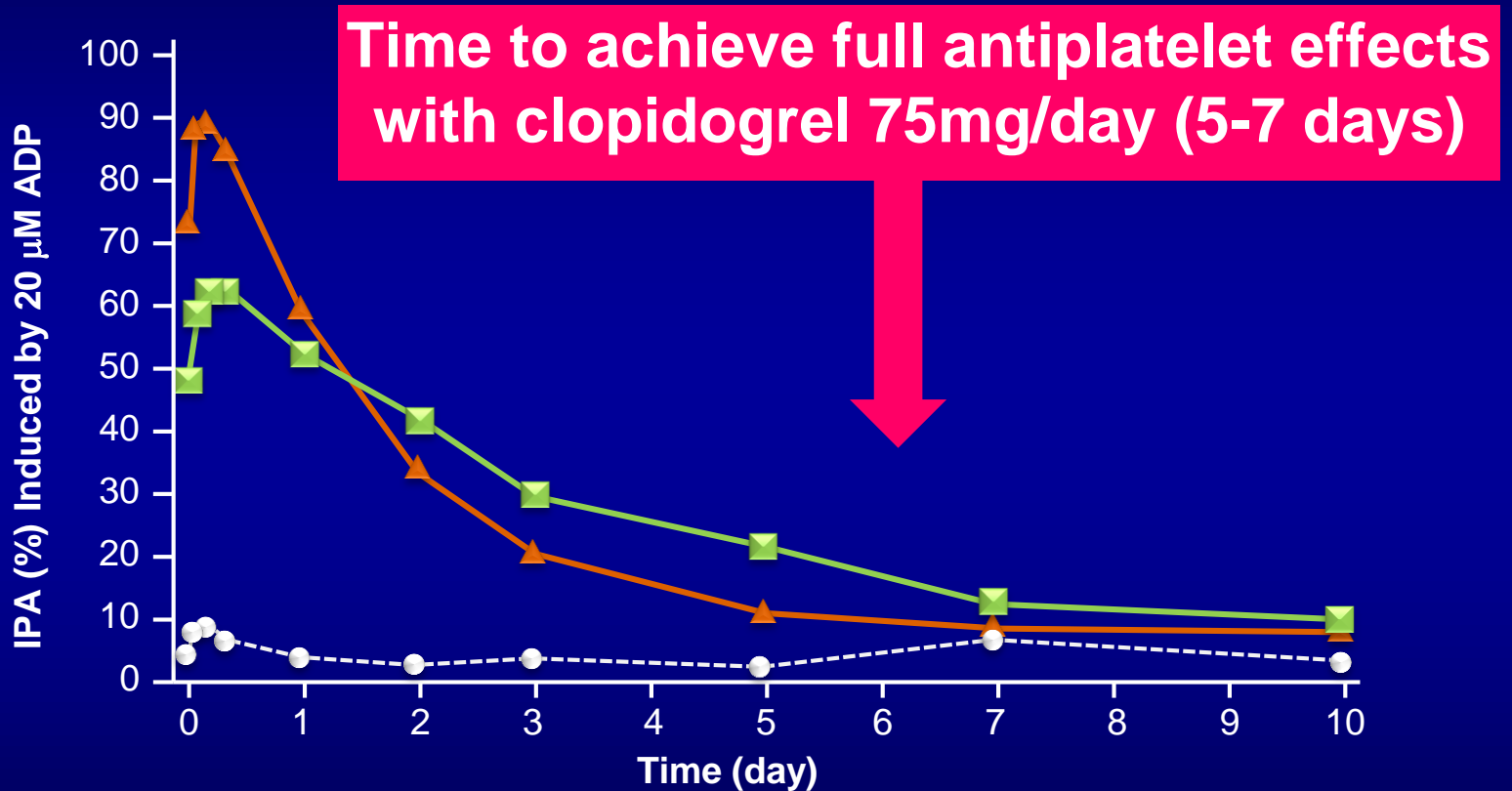
Gurbel P A et al.
Circulation 2010; 121:1188-99



Kerneis M et al.
JACC Cardiovasc Interv. 2013;6:158-165

Ticagrelor Offset of IPA Over Time

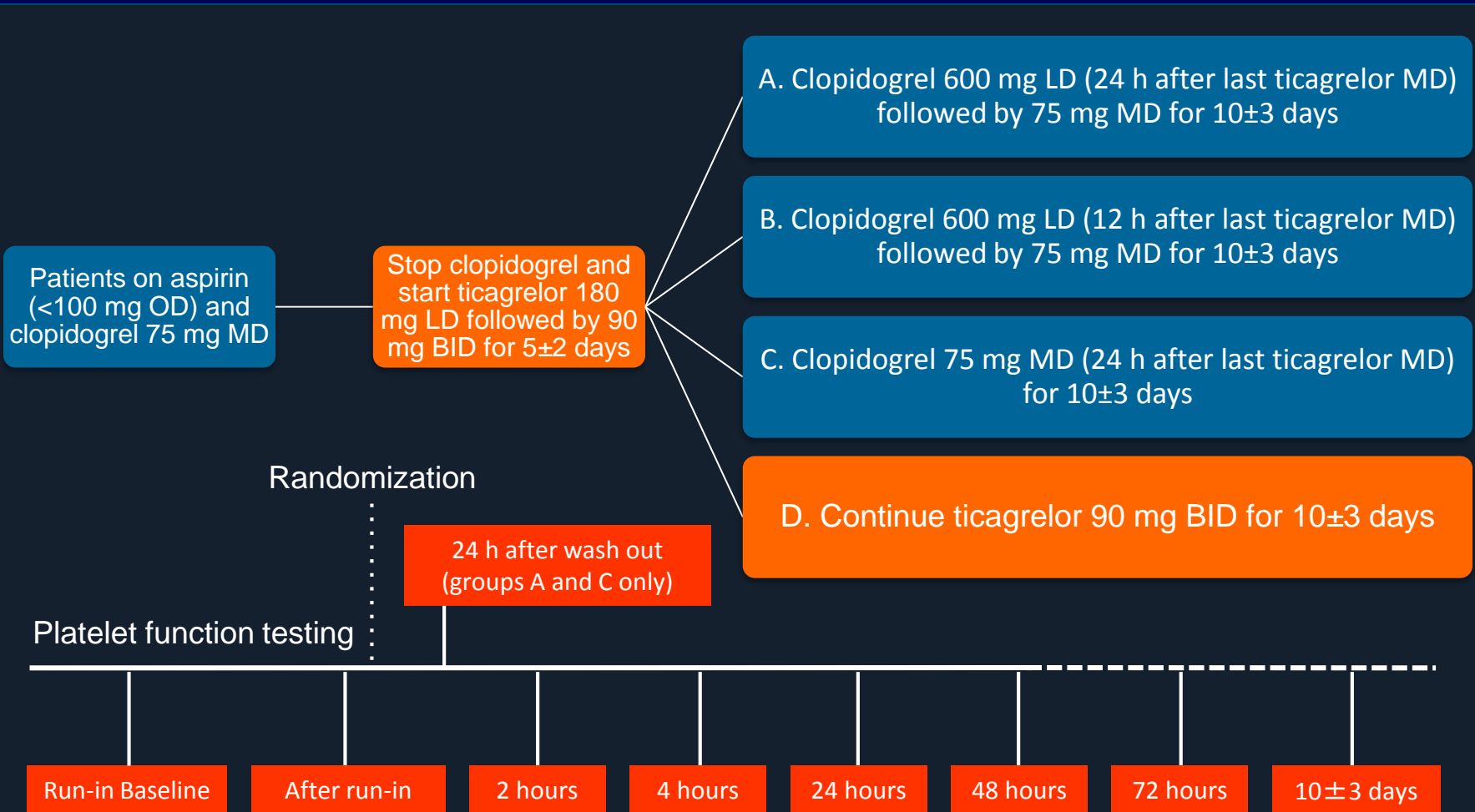
▲ BRILINTA ■ Clopidogrel ● Placebo



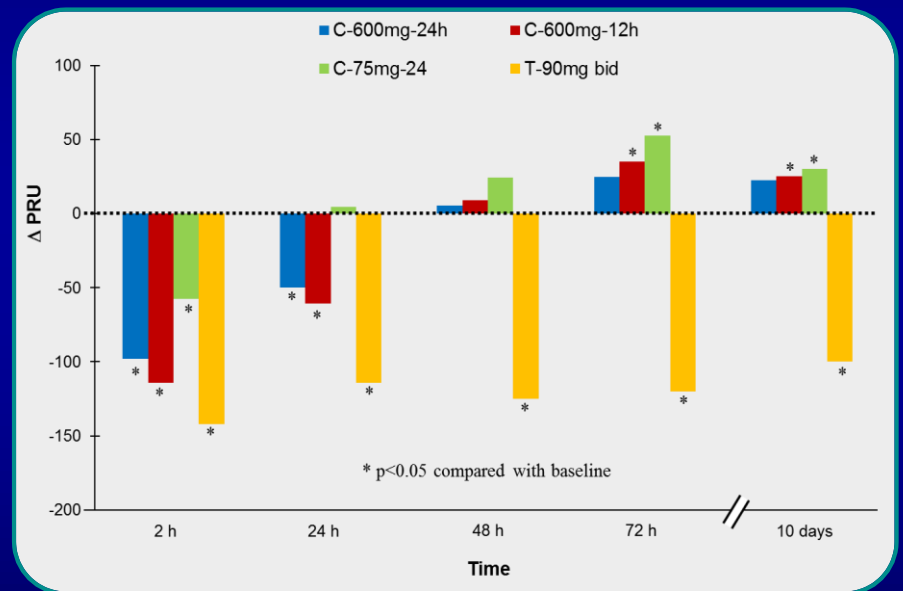
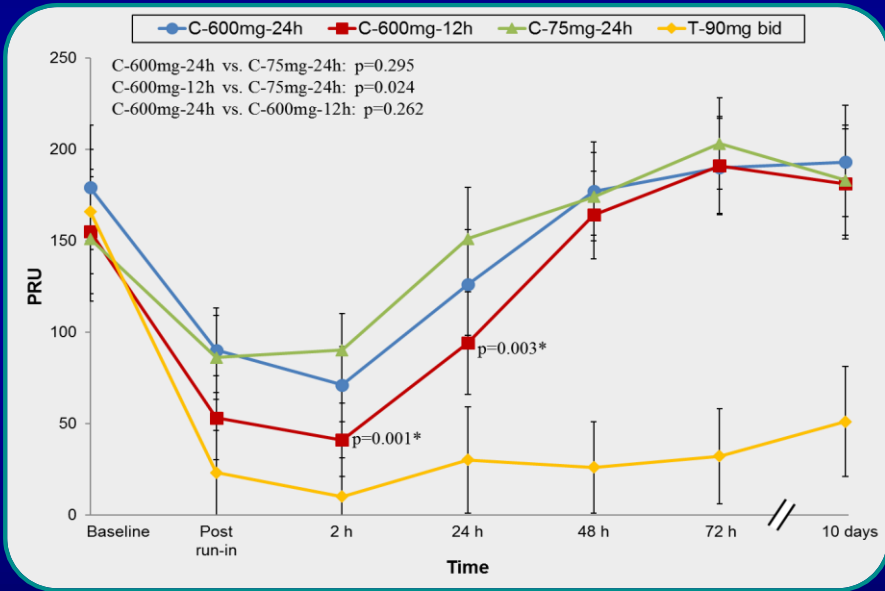
IPA=inhibition of platelet aggregation.

Gurbel et al. *Circulation*. 2009;120(25):2577-2585.

SWAP-4: Ticagrelor to Clopidogrel



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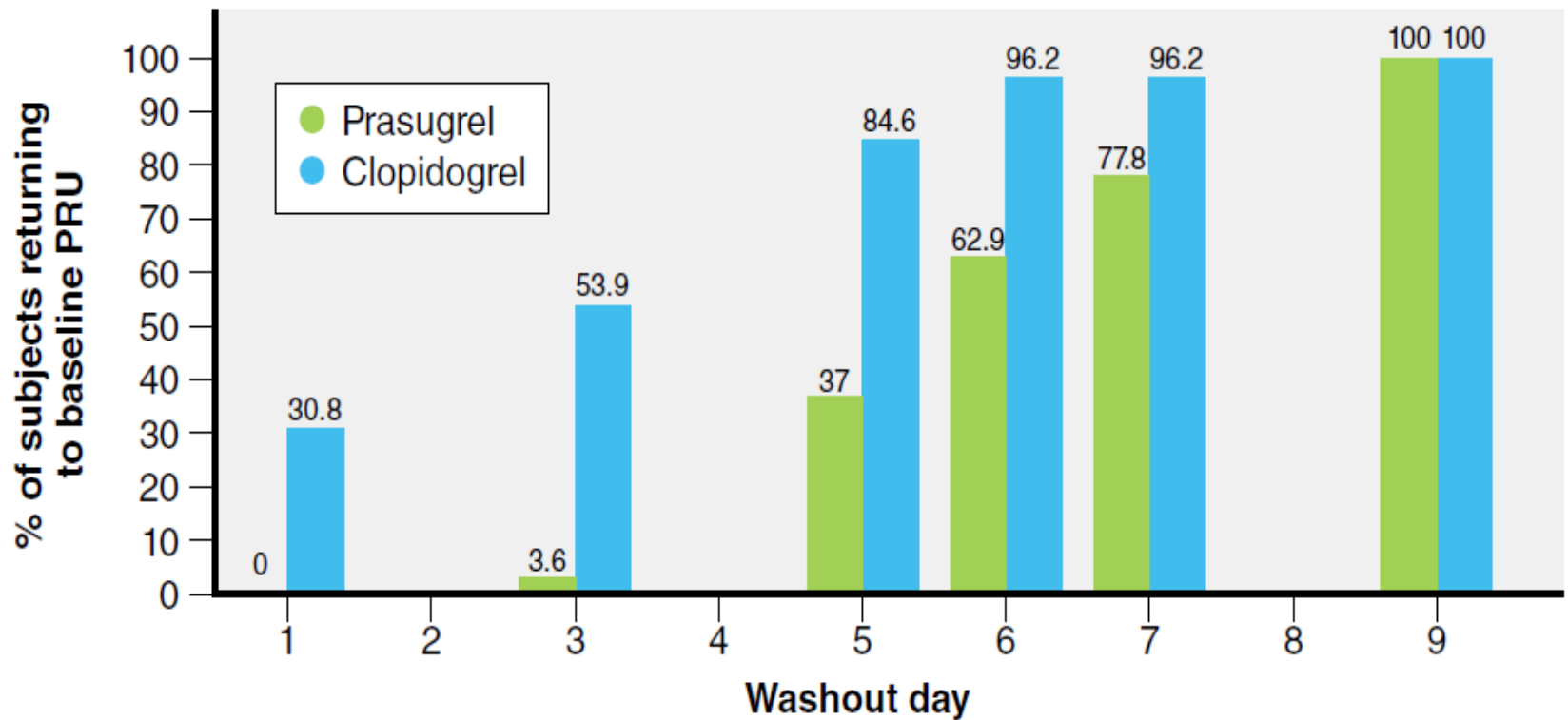
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When de-escalating from ticagrelor to clopidogrel always give a 600 mg LD of clopidogrel 12-24 hours after last dose of ticagrelor in both the acute and chronic phase

Offset of antiplatelet effects of oral thienopyridines

RECOVERY trial



Expert Consensus Recommendations on Switching

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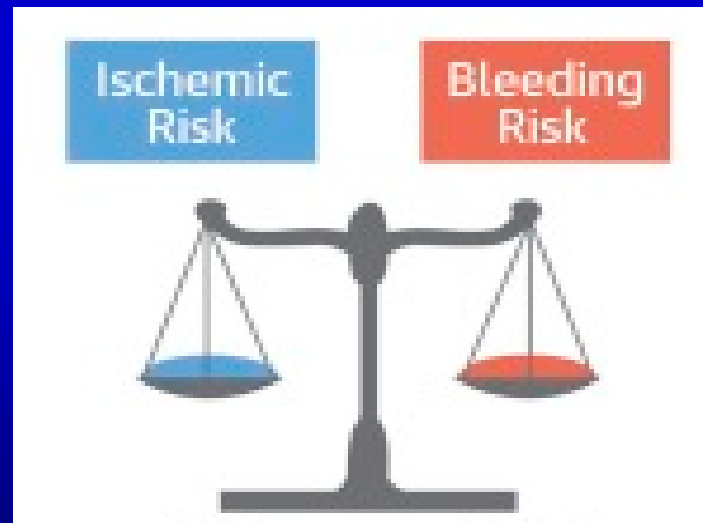
When de-escalating from prasugrel to clopidogrel:

Acute: 600mg LD 24 hours after last dose of prasugrel

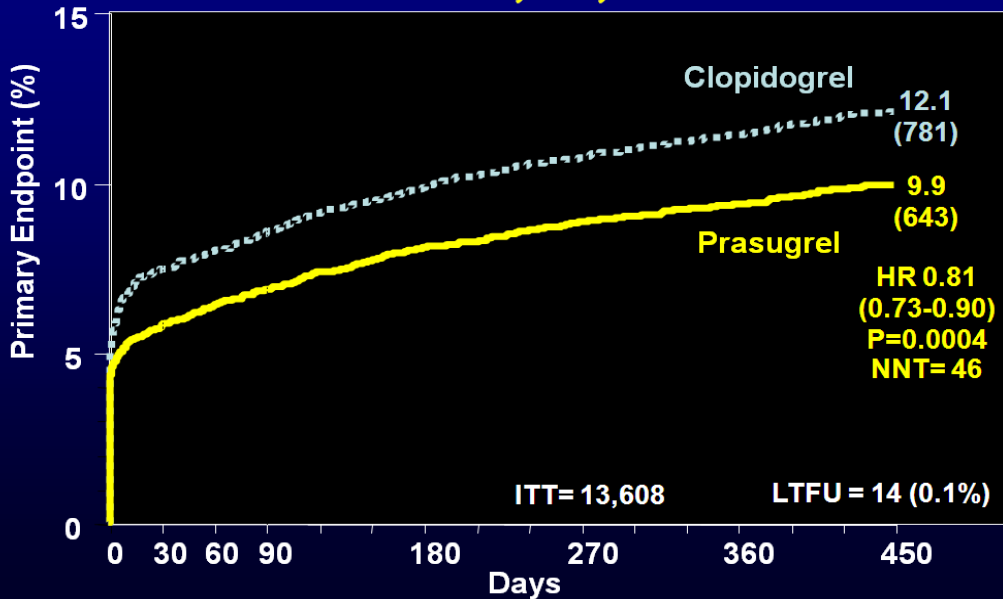
Chronic: OK to switch with a 75mg MD 24 hours after last dose of prasugrel

Bleeding reduction strategies: De-escalation

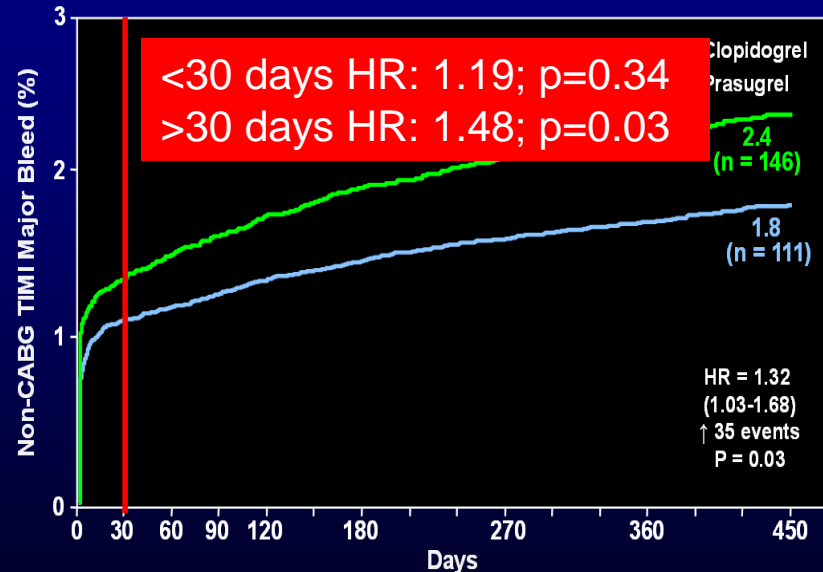
De-escalation (switching from prasugrel or ticagrelor to clopidogrel) as a strategy to reduce long-term bleeding events without a trade-off in ischemic protection



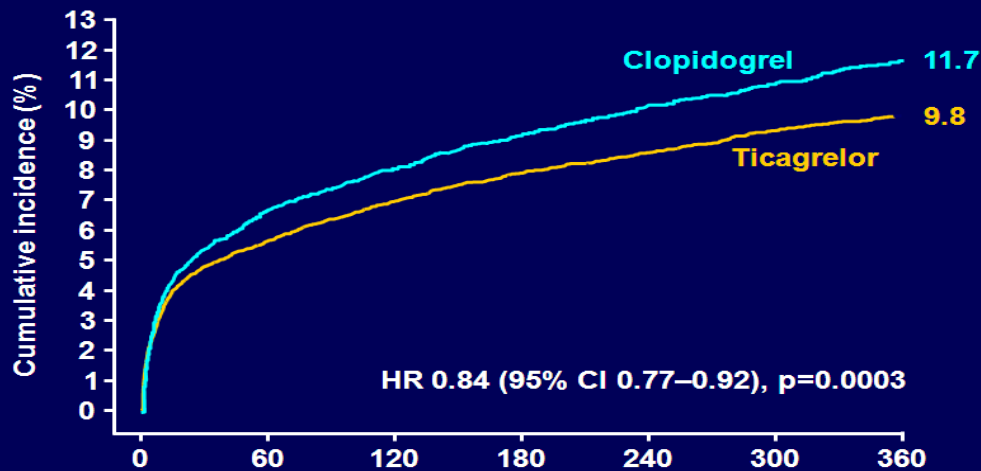
Primary Endpoint CV Death, MI, Stroke



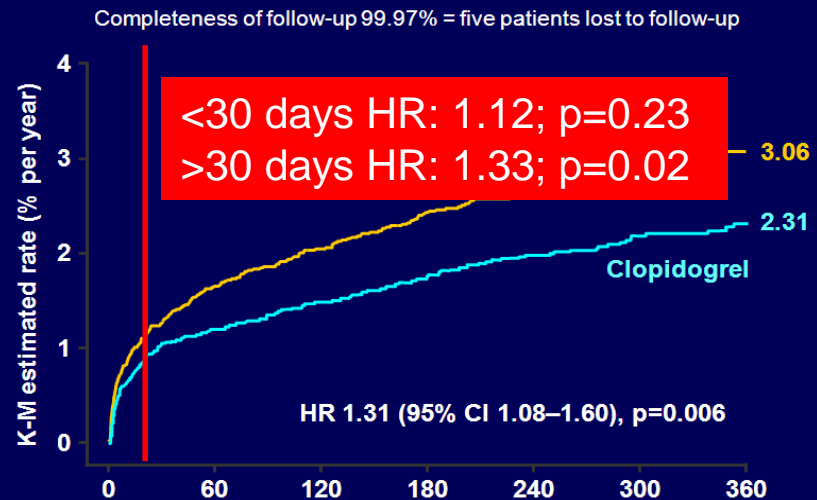
Non-CABG TIMI Major Bleed All ACS Population



K-M estimate of time to first primary efficacy event (composite of CV death, MI or stroke)



Time to non-procedure-related PLATO major bleeding



Expert Consensus Recommendations on Switching: De-escalation

- **Conflicting findings have been observed on the clinical impact of de-escalation:**
 - **SCOPE registry (observational; early de-escalation): increased ischemic recurrences with no differences in bleeding**
 - **TOPIC trial (randomized; one-month de-escalation; non guided): reduced bleeding, no increase in ischemic events**
 - **TROPICAL ACS trial (randomized; 1 week de-escalation; guided by PFT): no increase in ischemic events, trend toward reduced bleeding**

Switching (de-escalation): CONCLUSIONS

- **De-escalation of P2Y₁₂ inhibition commonly occurs in clinical practice.**
- **Although « routine » de-escalation can not be recommended, de-escalation of P2Y₁₂ inhibiting therapy is a reasonable approach to reduce the risk of bleeding in selected patients requiring DAPT.**
- **Tips for practice:**
 - **Avoid early (<30 days) switch**
 - **Identify patients at high risk of bleeding/low ischemic risk**
 - **Consider testing to identify good responders to clopidogrel**
 - **Use recommended switching regimens (be aware of DDI)**
- **Stay tuned for *Updated International Consensus Document on Guided De-escalation* (Co-chairs: D. Sibbing and D.J. Angiolillo)**

International Expert Consensus on Switching Platelet P2Y₁₂ Receptor–Inhibiting Therapies

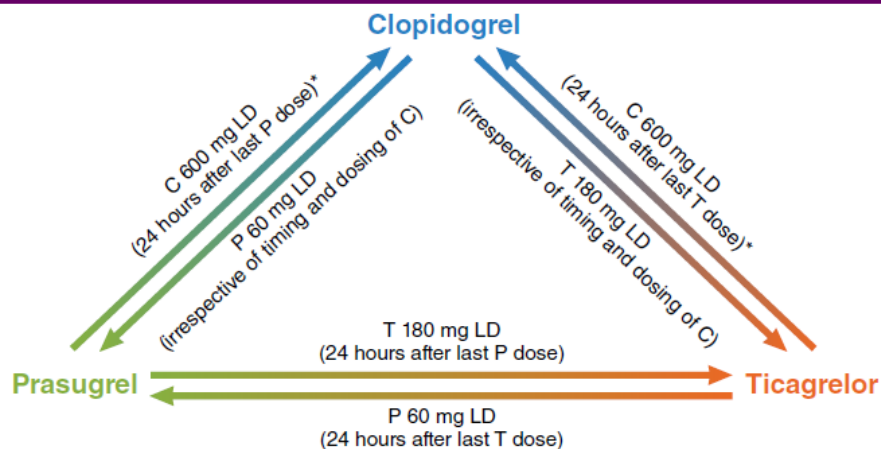
Dominick J. Angiolillo, Fabiana Rollini, Robert F. Storey, Deepak L. Bhatt, Stefan James, David J. Schneider, Dirk Sibbing, Derek YF So, Dietmar Trenk, Dimitrios Alexopoulos, Paul A. Gurbel, Willibald Hochholzer, Leonardo De Luca, Laurent Bonello, Daniel Aradi, Thomas Cuisset, Udaya S. Tantry, Tracy Y. Wang, Marco Valgimigli, Ron Waksman, Roxana Mehran, Gilles Montalescot, Francesco Franchi, Matthew J. Price

Circulation. 2017; 136:1955-1975

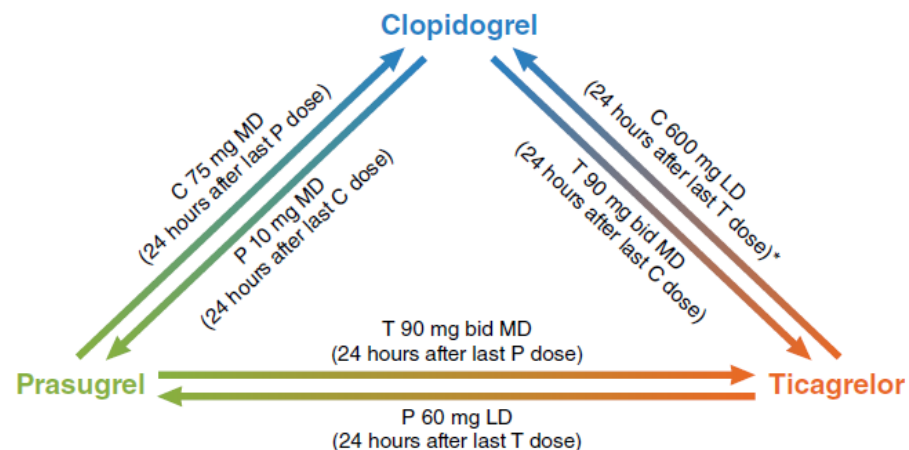
Expert Consensus Recommendations on Switching

SWITCHING BETWEEN ORAL P2Y₁₂ INHIBITORS

Acute/Early Phase



Late/Very late phase



In the acute/early phase (≤ 30 days from the index event), switching should occur with the administration of a loading dose (LD) in most cases, with the exception of patients who are de-escalating therapy because of bleeding or bleeding concerns, in whom a maintenance dose (MD) of clopidogrel (C) should be considered. Timing of switching should be 24 hours after the last dose of a given drug, with the exception of when escalating to prasugrel (P) or ticagrelor (T), when the LD can be given regardless of the timing and dosing of the previous clopidogrel regimen.

*Consider de-escalation with clopidogrel 75-mg MD (24 hours after last prasugrel or ticagrelor dose) in patients with bleeding or bleeding concerns.

In the late/very late phase (> 30 days from the index event), switching should occur with the administration of an MD 24 hours after the last dose of a given drug, with the exception of patients changing from ticagrelor to prasugrel therapy, for whom an LD should be considered.

De-escalation from ticagrelor to clopidogrel should occur with administration of an LD 24 hours after the last dose of ticagrelor (but in patients in whom de-escalation occurs because of bleeding or bleeding concerns, an MD of clopidogrel should be considered).

*Consider de-escalation with clopidogrel 75-mg MD (24 hours after last prasugrel or ticagrelor dose) in patients with bleeding or bleeding concerns.