Escalation and De-escalation Strategy for DAPT: Rationale and Evidence

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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.

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a) Consulting fee or honorarium from Abbott, 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;
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c) Federal agency: NIH

WHITE PAPER

STATE OF THE ART

International Expert Consensus on Switching Platelet $P2Y_{12}$ 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 $P2Y_{12}$ 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 $P2Y_{12}$ 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:

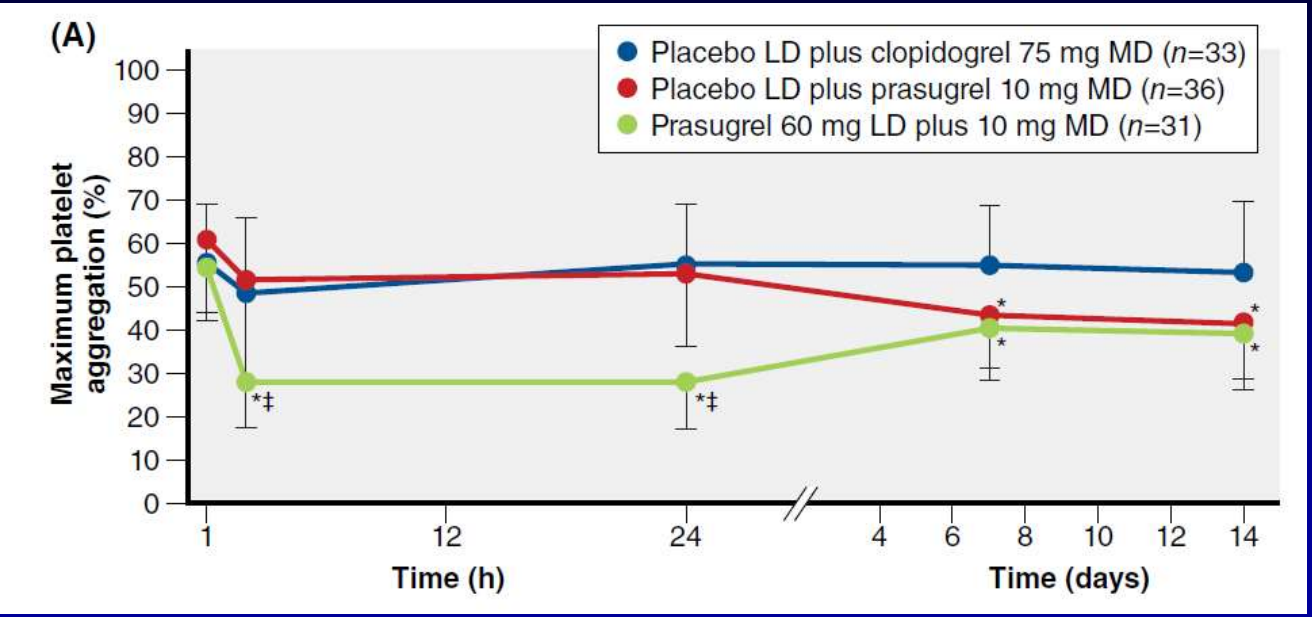
  a) patients presenting with an ACS undergoing PCI who may have been pretreated with clopidogrel at the time of clinical presentation

  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

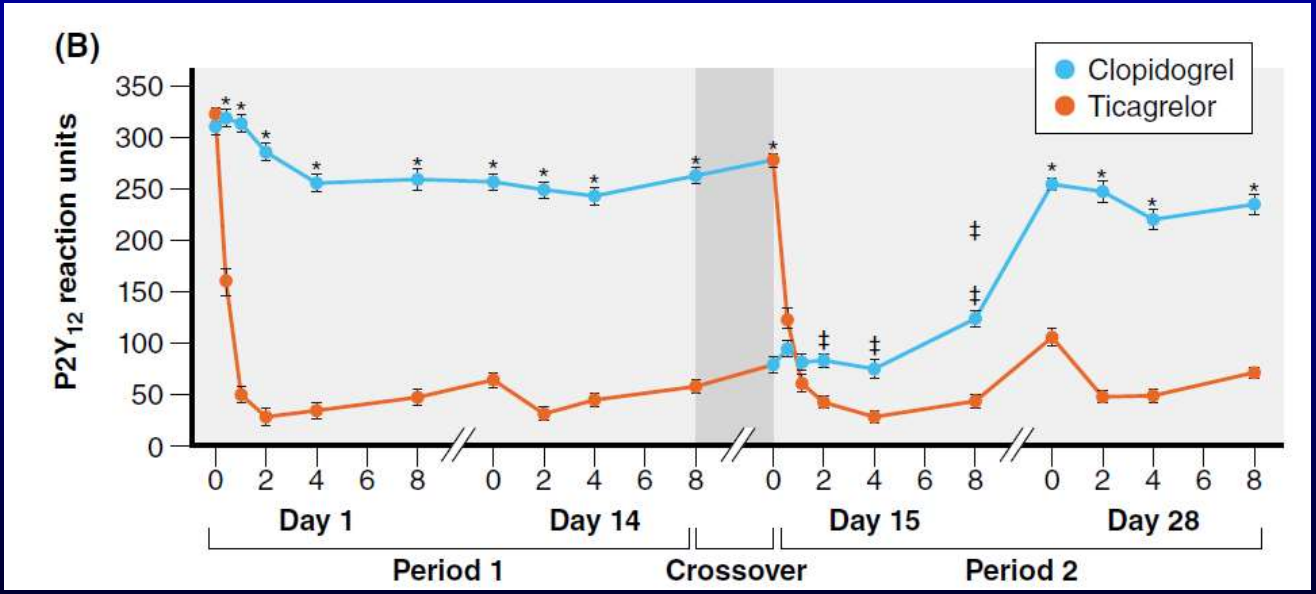
SWAP trial

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

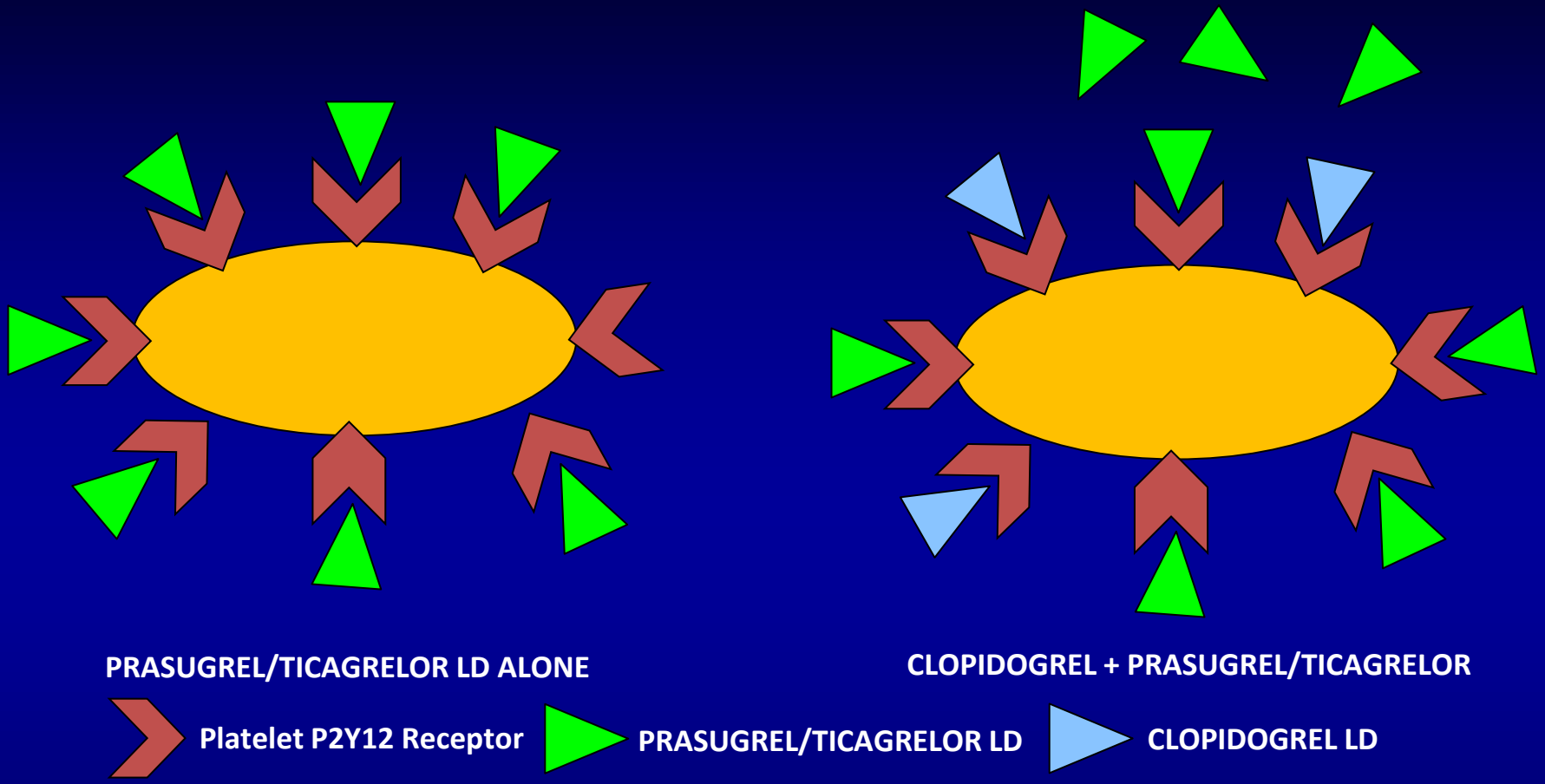


RESPOND trial

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



Biological hypothesis for $P2Y_{12}$-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, $P2Y_{12}$ 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 $P2Y_{12}$ 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 $P2Y_{12}$ receptors (e.g., from platelets newly entering the bloodstream). The extent of $P2Y_{12}$-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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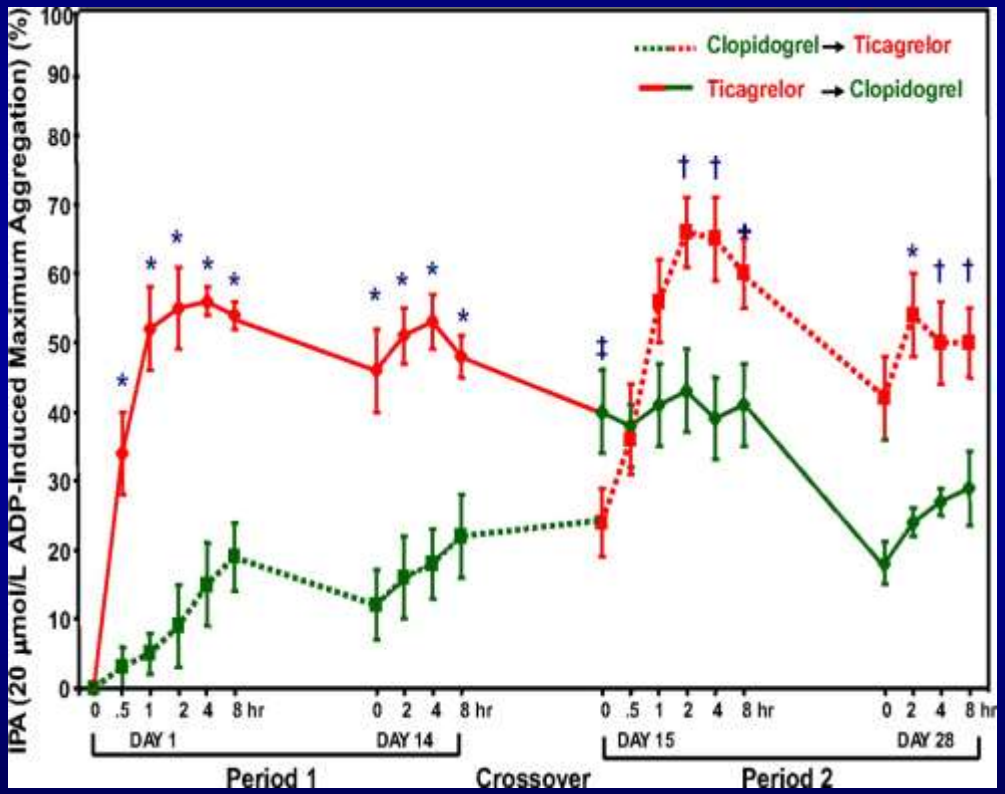
Expert Consensus Recommendations on Switching: *De-escalation*

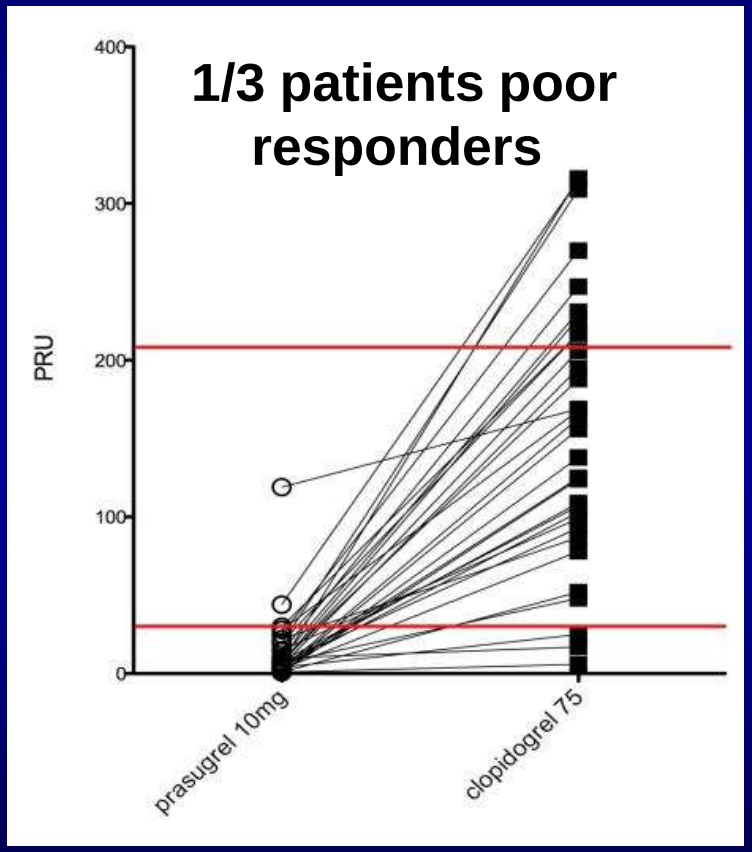
- **Overall, registry data indicate that the prevalence of in-hospital de-escalation ranges from 5% to 14% and from 5% to 8% after hospital discharge.**
- **Reduced costs associated with a generic formulation of clopidogrel and concerns about increased risk of bleeding with prasugrel and ticagrelor remain 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

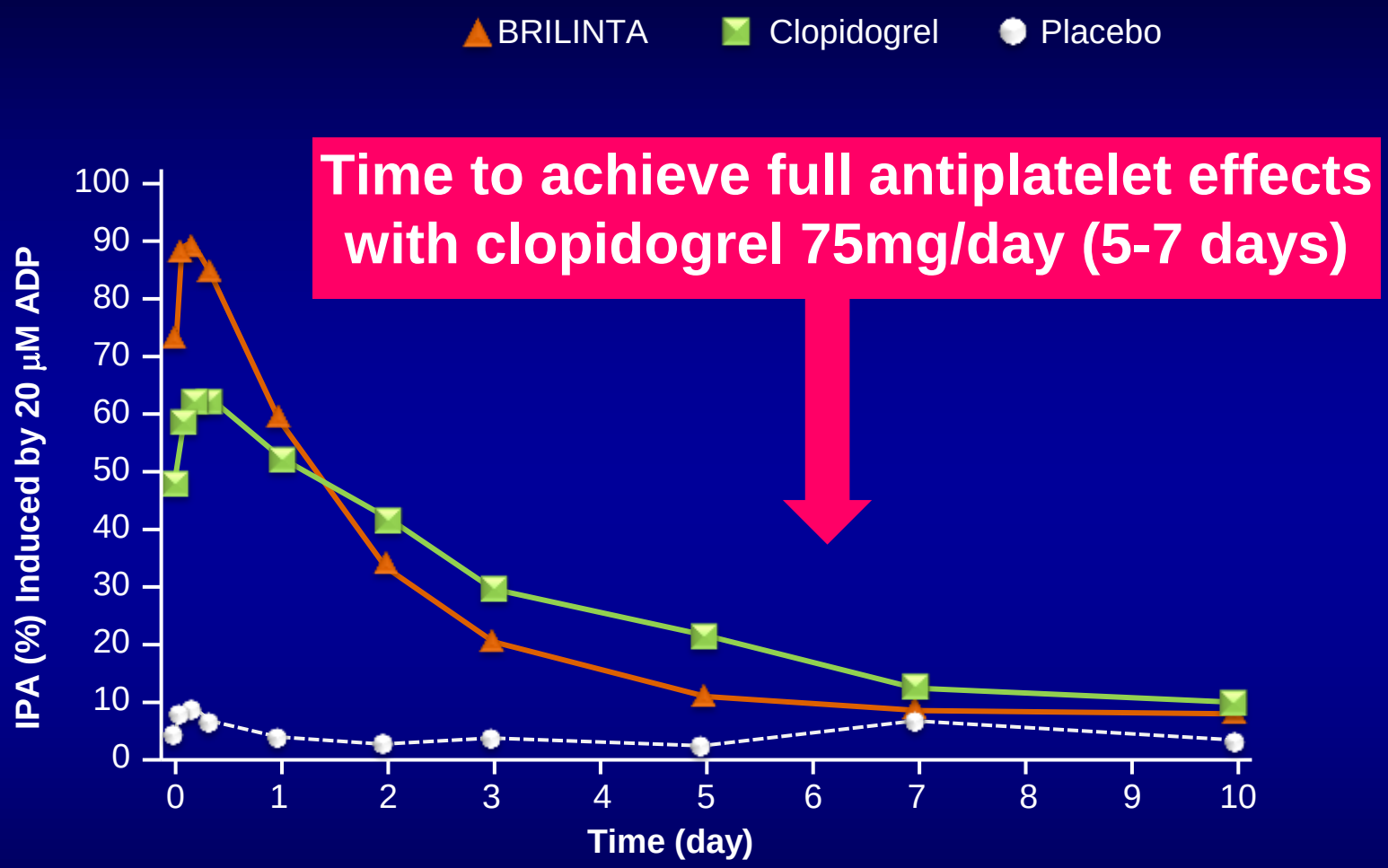


Gurbel P A et al.
Circulation 2010; 121:1188-99



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

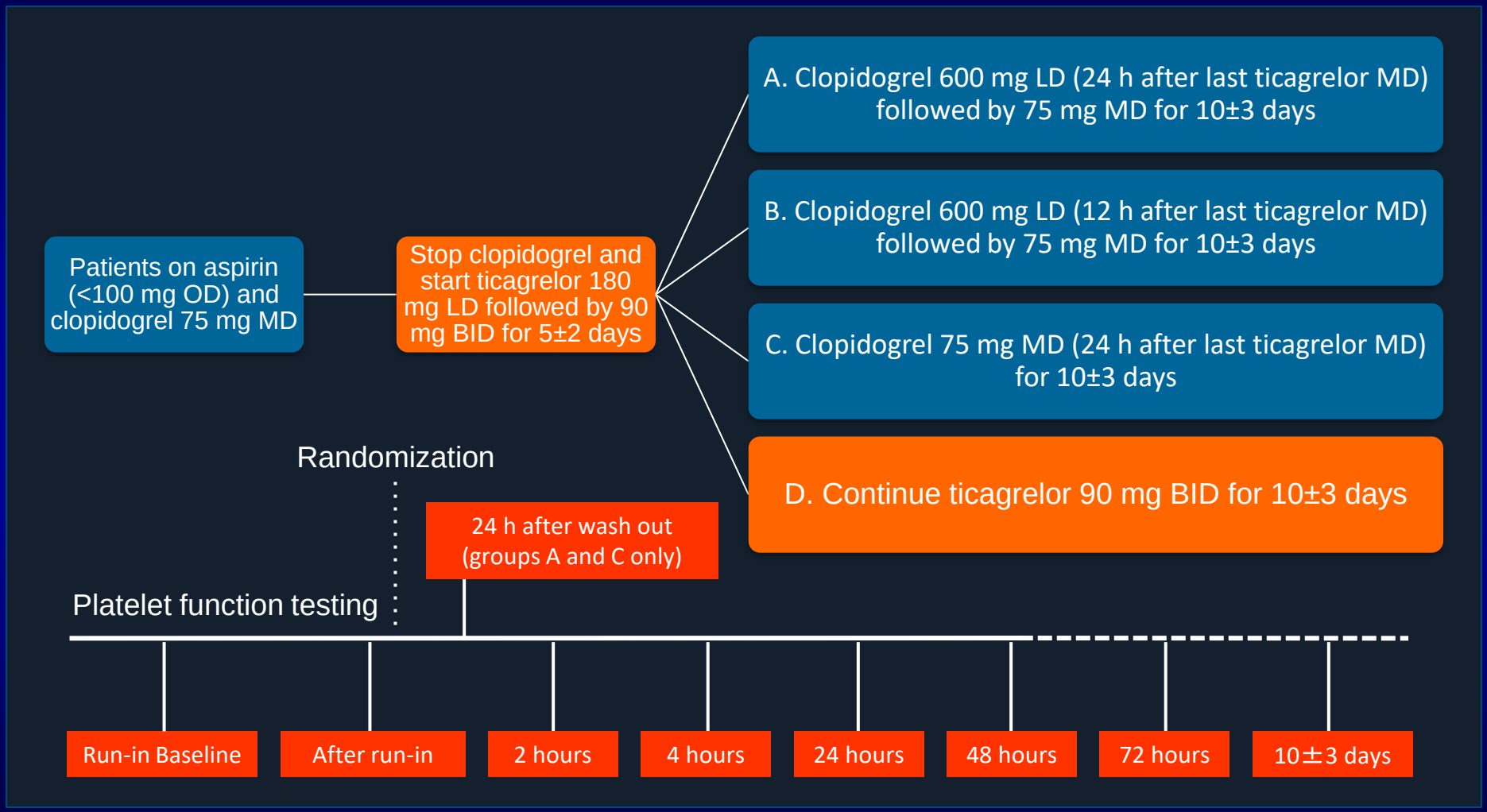
Ticagrelor Offset of IPA Over Time



IPA=inhibition of platelet aggregation.

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

SWAP-4: Ticagrelor to Clopidogrel



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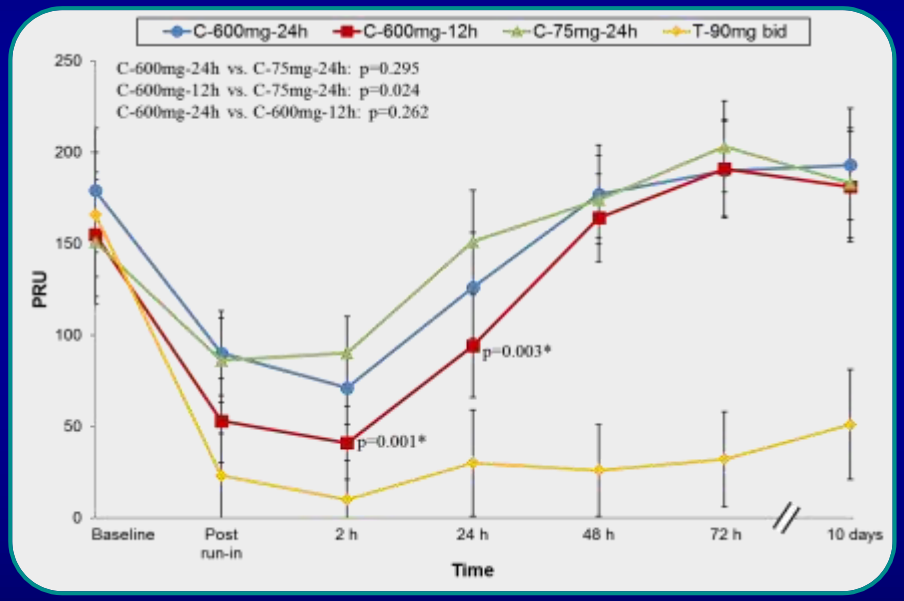
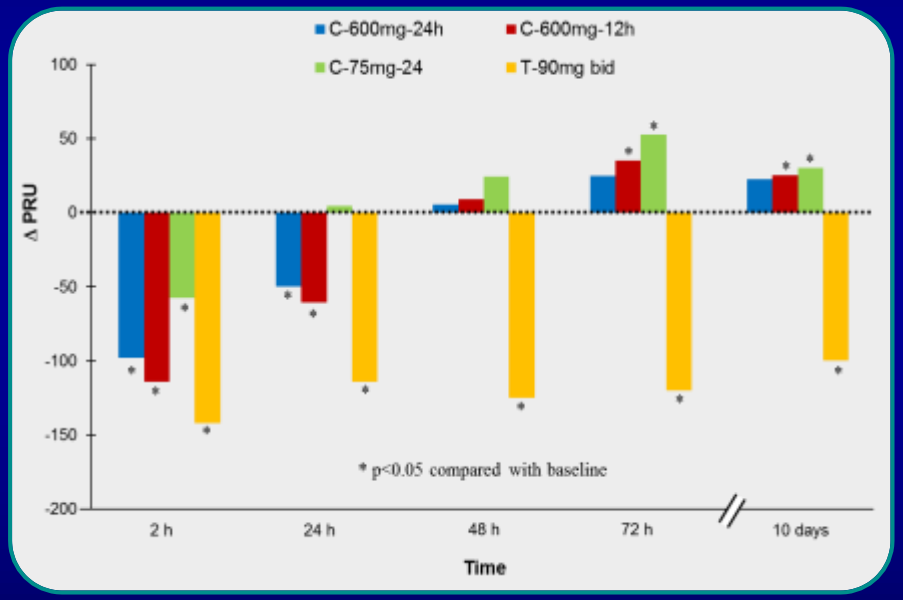
SWAP-4: Ticagrelor to Clopidogrel





Franchi F, Rollini F, & Angiolillo DJ. Circulation 2018

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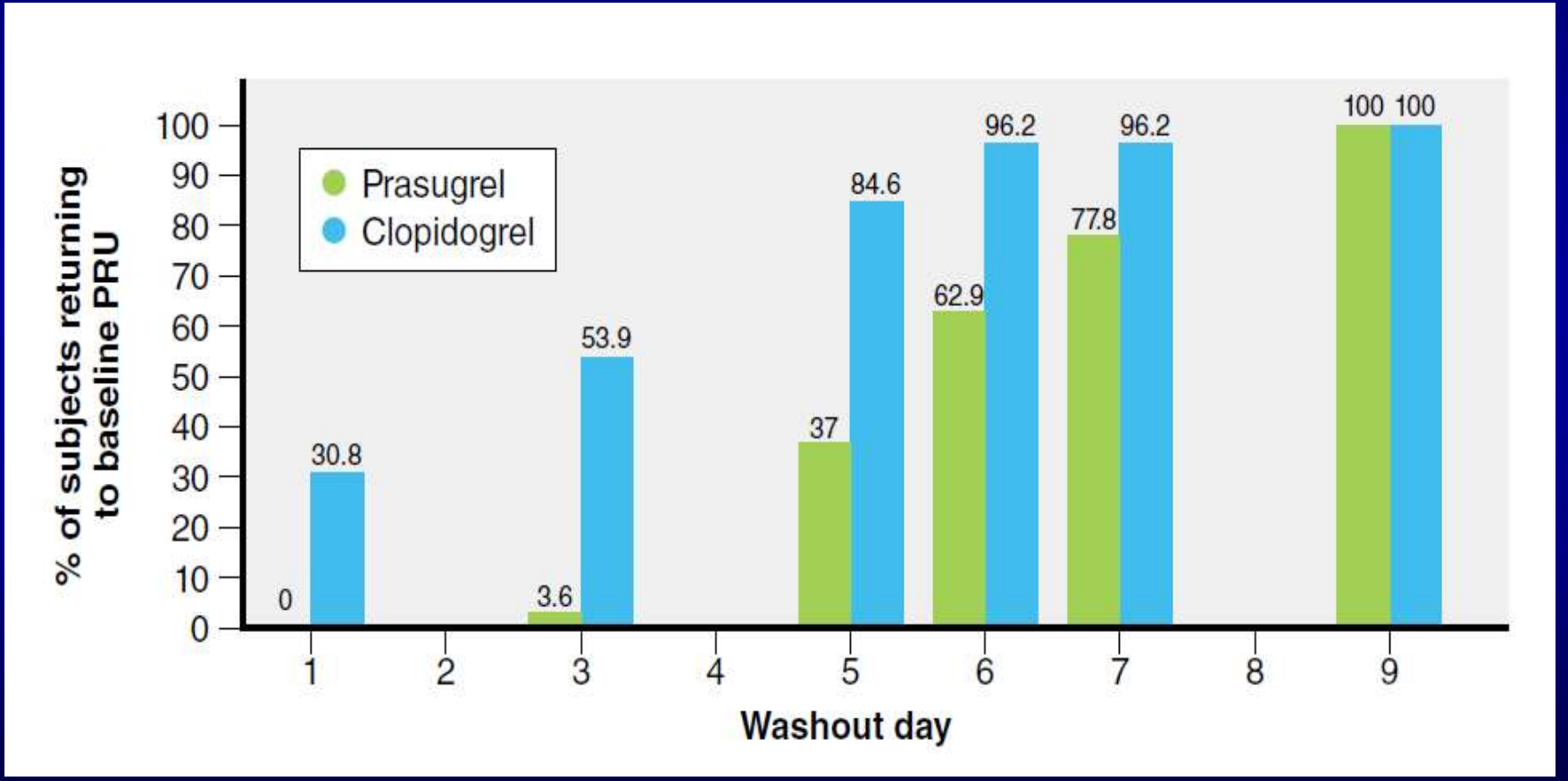
When de-escalating from ticagrelor to clopidogrel always give a 600 mg LD of clopidogrel 12-24 hours after last dose of ticagrelor in both the acute and chronic phase

Offset of antiplatelet effects of oral thienopyridines

RECOVERY trial



Adapted from Price MJ &Angiolillo DJ. J Am Coll Cardiol 2012;59:2338-4

Expert Consensus Recommendations on Switching

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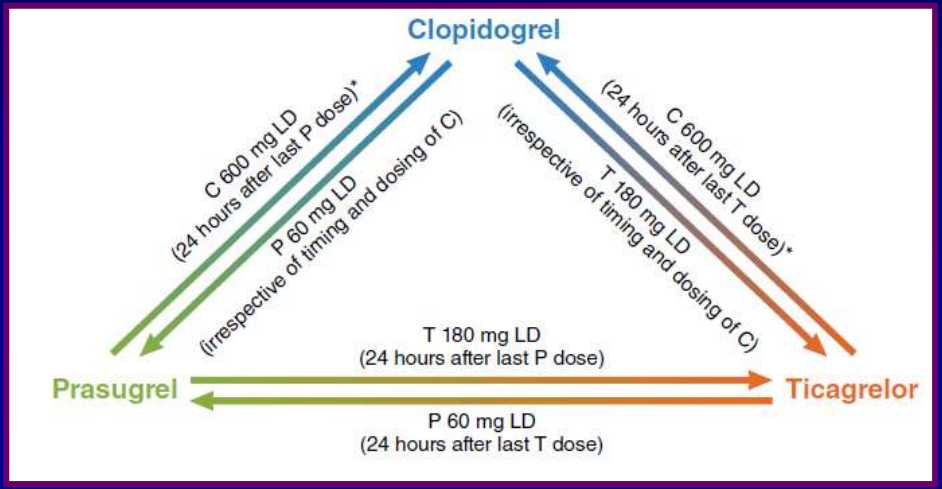
When de-escalating from prasugrel to clopidogrel:
Acute: 600mg LD 24 hours after last dose of prasugrel
Chronic: OK to switch with a 75mg MD 24 hours after last dose of prasugrel

Expert Consensus Recommendations on Switching

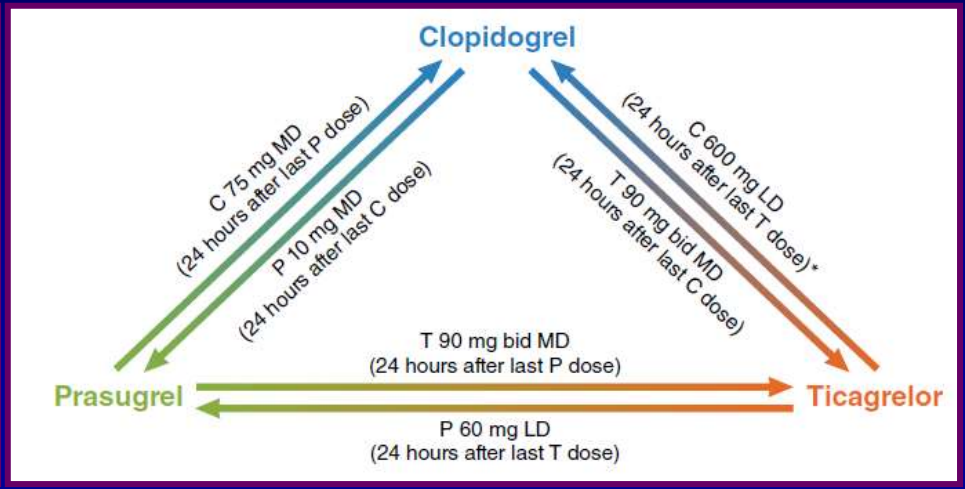
SWITCHING BETWEEN ORAL $P2Y_{12}$ INHIBITORS

Acute/Early 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.

Late/Very late phase



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.

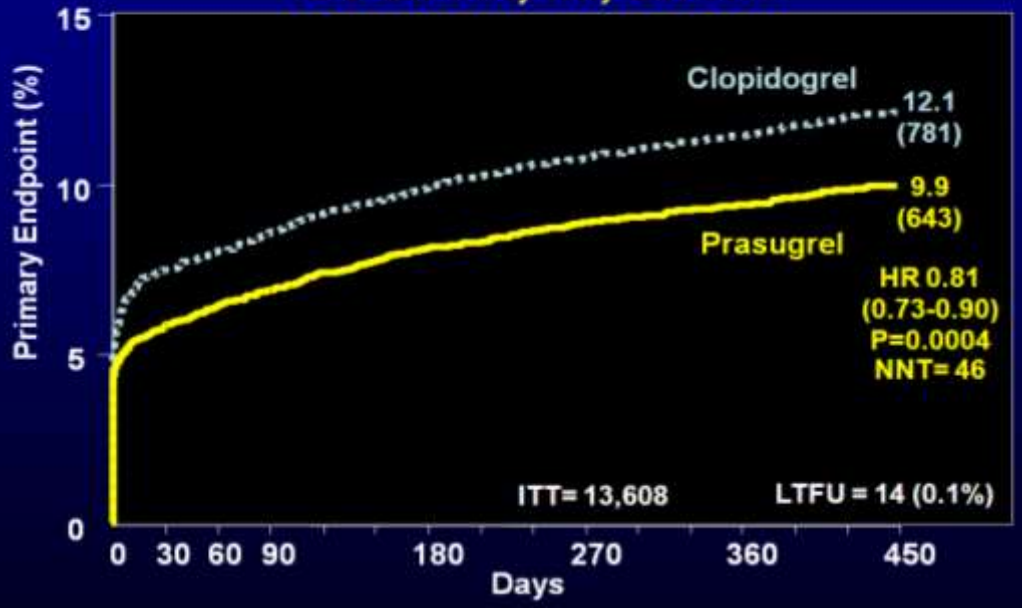
Angiolillo DJ et al. Circulation. 2017; 136:1955-75

Bleeding reduction strategies: De-escalation

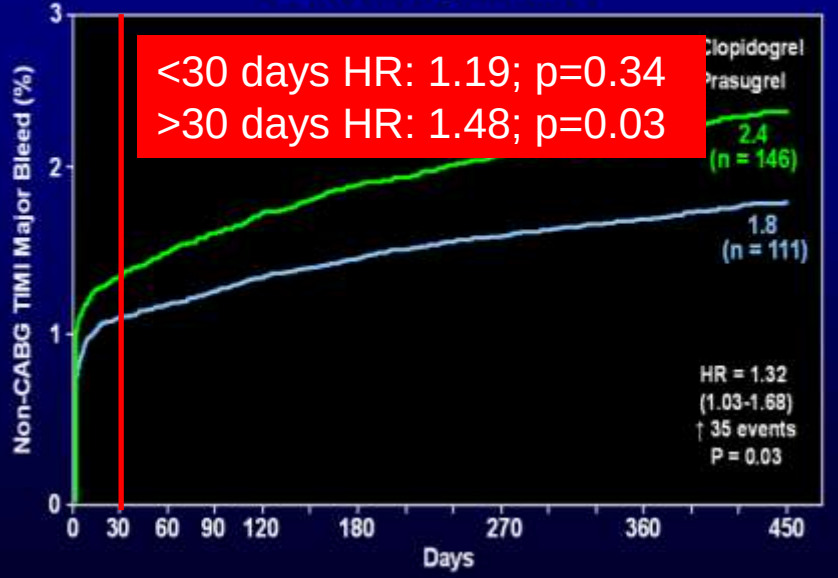
De-escalation (switching from prasugrel or ticagrelor to clopidogrel) as a strategy to reduce long-term bleeding events without a trade-off in ischemic protection

Angiolillo DJ, Rollini F, et al. Circulation. 2017

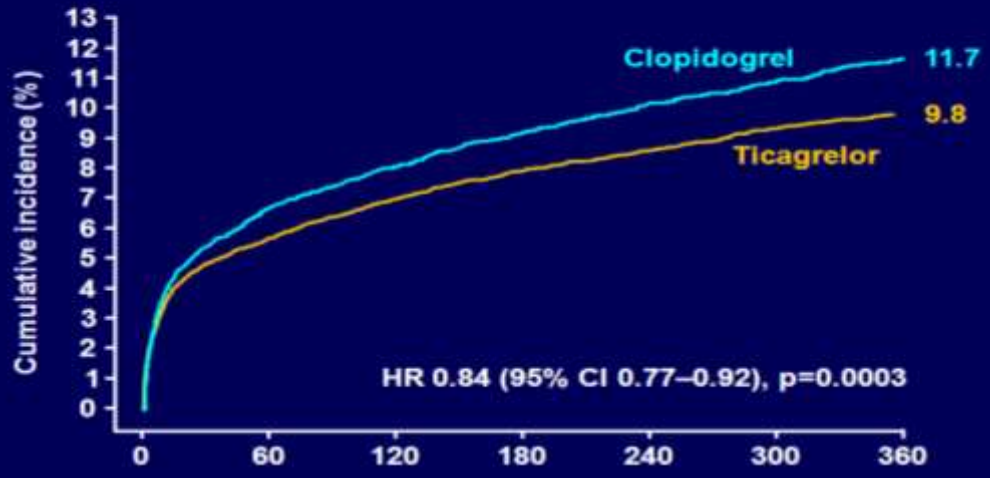
Primary Endpoint
CV Death, MI, Stroke



Non-CABG TIMI Major Bleed
All ACS Population

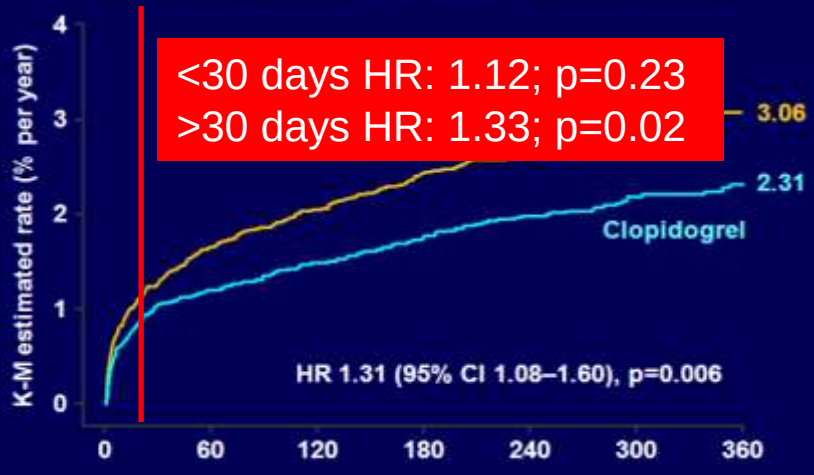


K-M estimate of time to first primary efficacy event (composite of CV death, MI or stroke)



Time to non-procedure-related PLATO major bleeding

Completeness of follow-up 99.97% = five patients lost to follow-up



De-escalation: Recent trial findings

- **Trial findings on the clinical impact of de-escalation:**

Early (discharge) post-ACS and Non-guided

- **SCOPE registry (observational): increased ischemic recurrences with no differences in bleeding.**

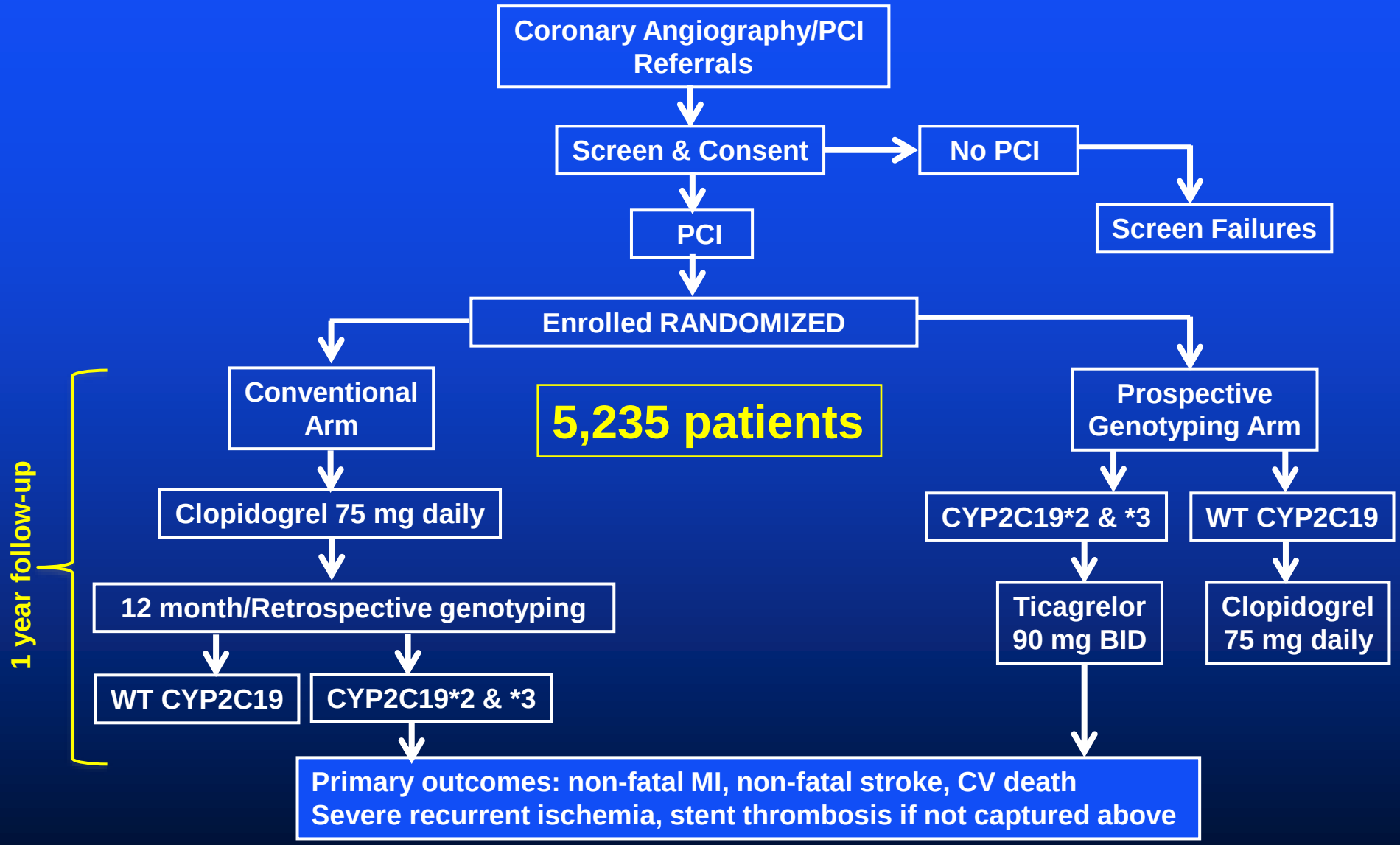
One-month post-ACS (low-risk) and Non-guided

- **TOPIC trial (randomized) : reduced bleeding, no increase in ischemic events**

One-week post-ACS (high-risk) and PFT-Guided

- **TROPICAL ACS trial (randomized): no increase in ischemic events, trend toward reduced bleeding**

TAILOR-PCI Study Design



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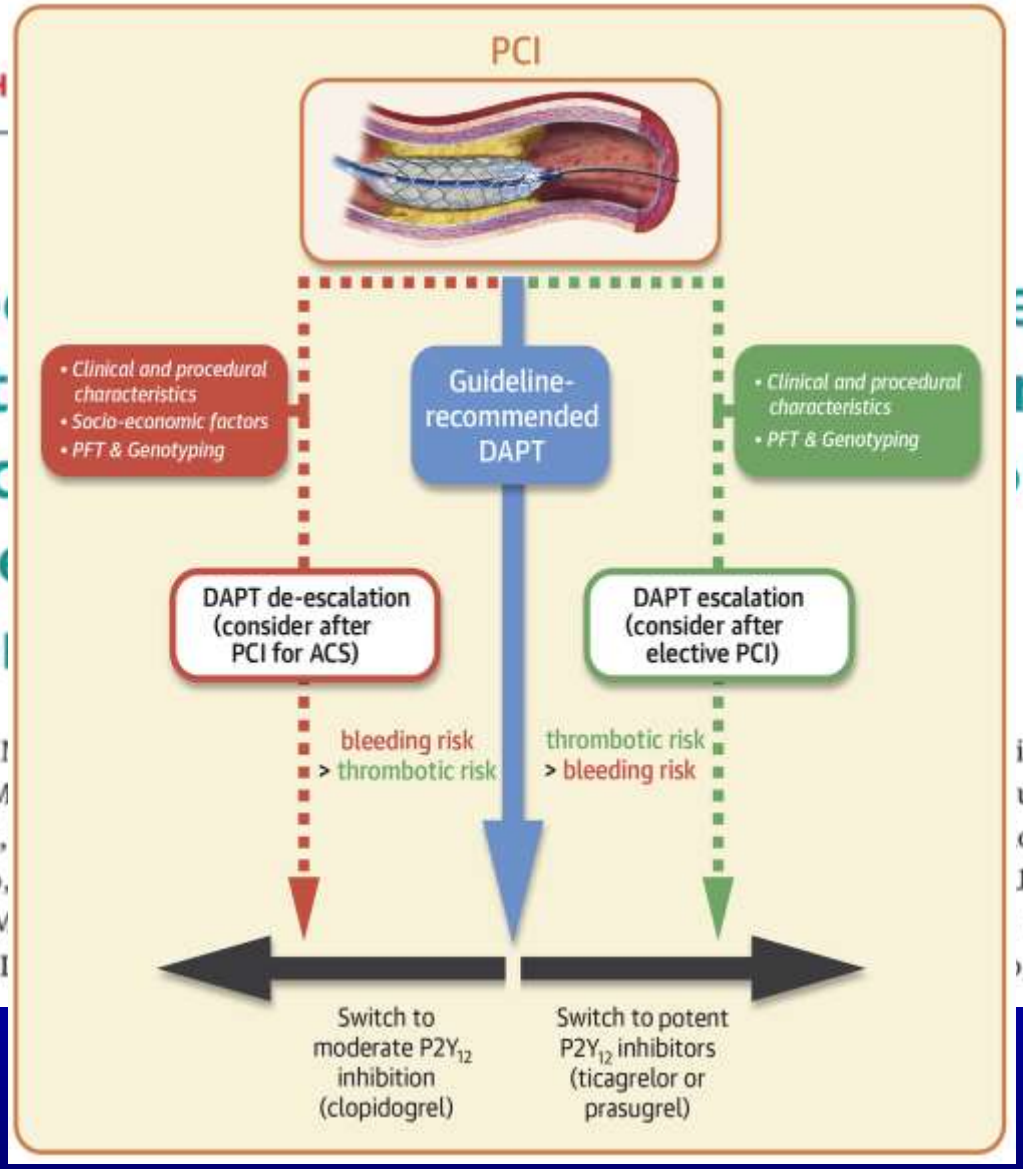

JACC Cardiovasc Interv. 2019 Jun 10. pii: S1936-8798(19)30831-3.
doi: 10.1016/j.jcin.2019.03.034. [Epub ahead of print]

Switching (de-escalation): CONCLUSIONS

- **De-escalation of $P2Y_{12}$ inhibition commonly occurs in clinical practice.**
- **Although « routine » de-escalation can not be recommended, de-escalation of $P2Y_{12}$ 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)**