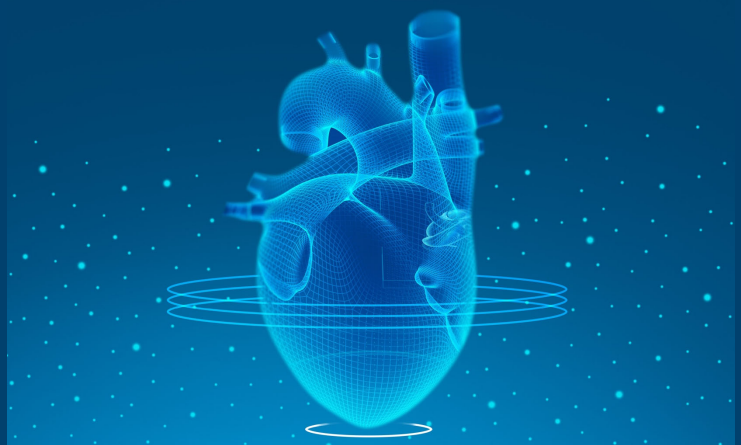
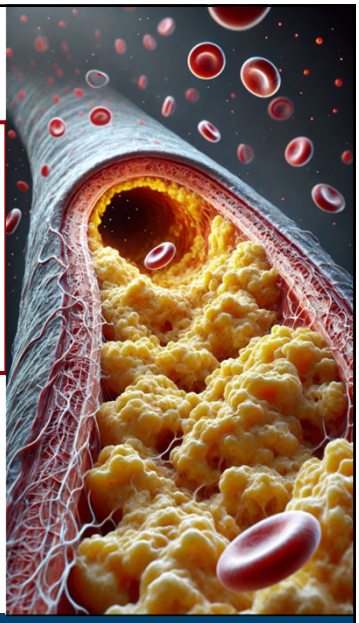
Minneapolis Heart Institute Foundation

GRAND ROUNDS



1

Demystifying the Evolving Evidence for Antiplatelet De-escalation in ASCVD



Matthew P. Lillyblad, PharmD, BCCCP, BCCP
Clinical Pharmacy Specialist, Senior- Cardiology and Critical Care
Abbott Northwestern Hospital, part of Allina Health

Minneapolis Heart Institute Foundation | GRAND ROUNDS

2

Relevant Financial Relationship Disclosures

- No current or recent financial relationships with pharmaceutical or other medical companies exist
- No potential conflicts of interest exist
- The use of medications outside of their FDA approved indication are included in this presentation

Minneapolis Heart Institute Foundation | GRAND ROUNDS

3

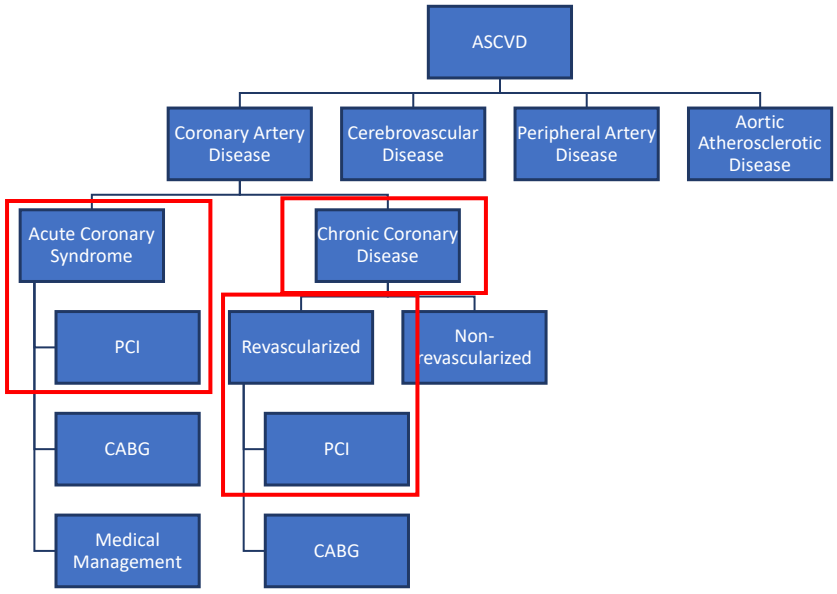
Objectives

- Describe the origin of traditional dual antiplatelet therapy durations
- Compare expected outcomes between de-escalation strategies for antiplatelet therapy in ASCVD
- Identify evidence-based strategies for antiplatelet de-escalation in ASCVD

Minneapolis Heart Institute Foundation | GRAND ROUNDS

4

Presentation Scope



5

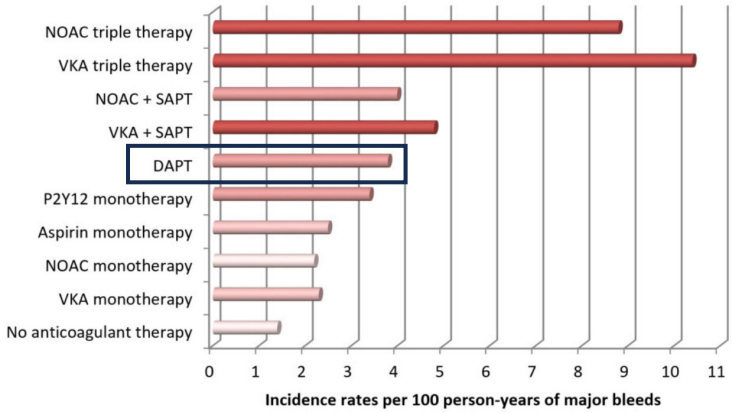
Background

- Antithrombotic therapy = cornerstone for CAD and ACS
- Dual antiplatelet therapy (DAPT) with ASA + P2Y12i = gold standard after PCI
  - ↓recurrent myocardial infarction
  - ↓stent thrombosis
- Newer generation P2Y12i further ↓ischemic events
- Primary limitation is ↑bleeding

6

Bleeding with DAPT

- Major bleeding
  - 1-10% @ 12 months in RCTs
  - 2.8-11% in observational studies
- Rates dependent on
  - Definitions
  - Potency of P2Y12i
  - Enrolled population risk
- Fatal bleeding relatively rare
  - PLATO = T0.3% vs. C0.3%
  - TRITON = P0.4% vs. C0.1%

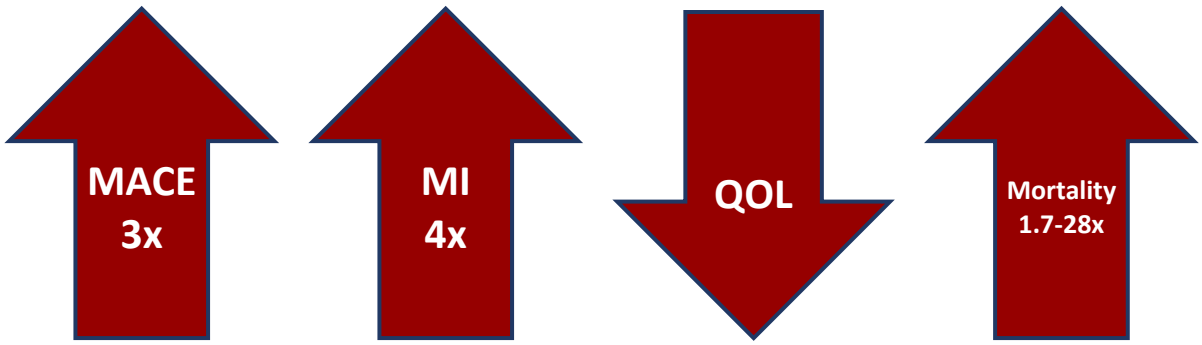


Minneapolis Heart Institute Foundation | GRAND ROUNDS

Rev Cardiovasc Med. 2022 Aug 15;23(8):286.
Nat Rev Cardiol. 2023 Dec;20(12):830-844.

7

Clinical Implications of Bleeding After PCI

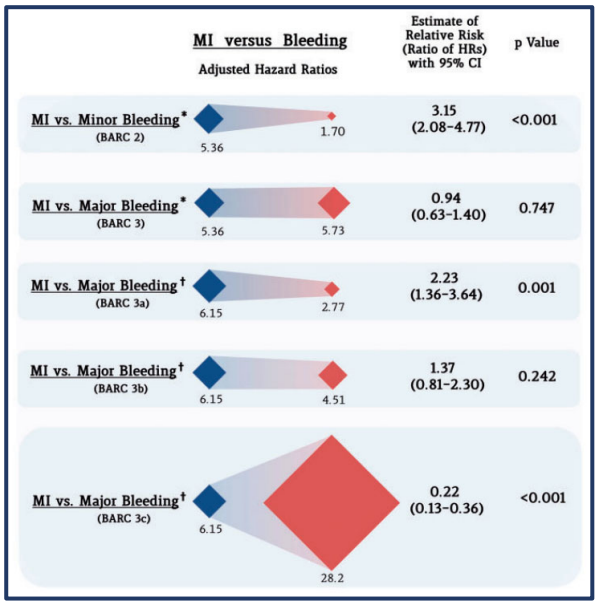


Minneapolis Heart Institute Foundation | GRAND ROUNDS

BMJ Open. 2019 Feb 20;9(2):e023337.
Circulation. 2006 Aug 22;114(8):774-82.

8

Impact of Recurrent MI vs. Bleeding on Mortality After ACS

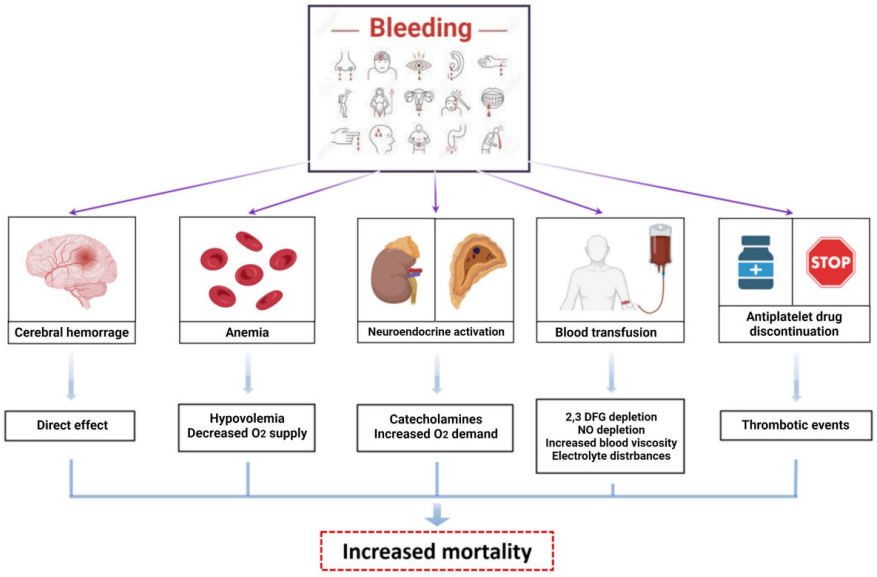


Minneapolis Heart Institute Foundation | GRAND ROUNDS

Eur Heart J. 2017 Mar 14;38(11):804-810.

9

Mechanism of Increased Mortality from Bleeding



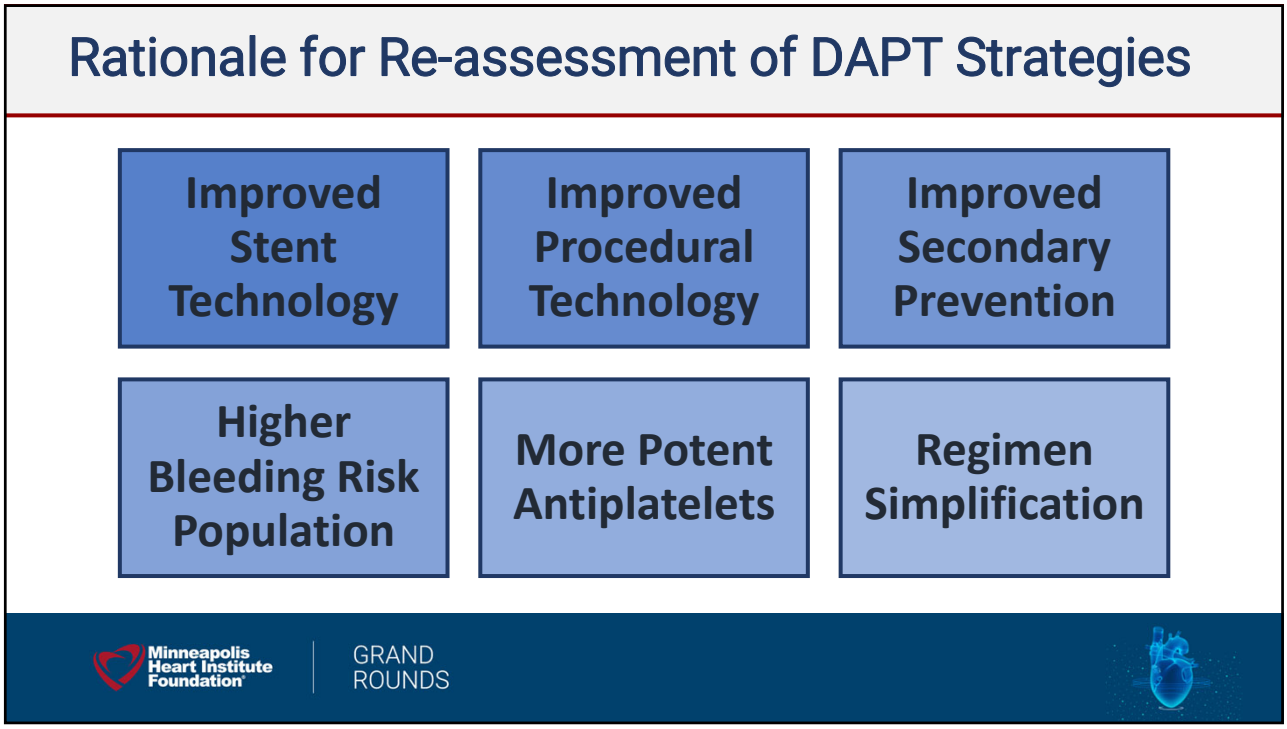
Minneapolis Heart Institute Foundation | GRAND ROUNDS

Rev Cardiovasc Med. 2022 Aug 15;23(8):286.

10

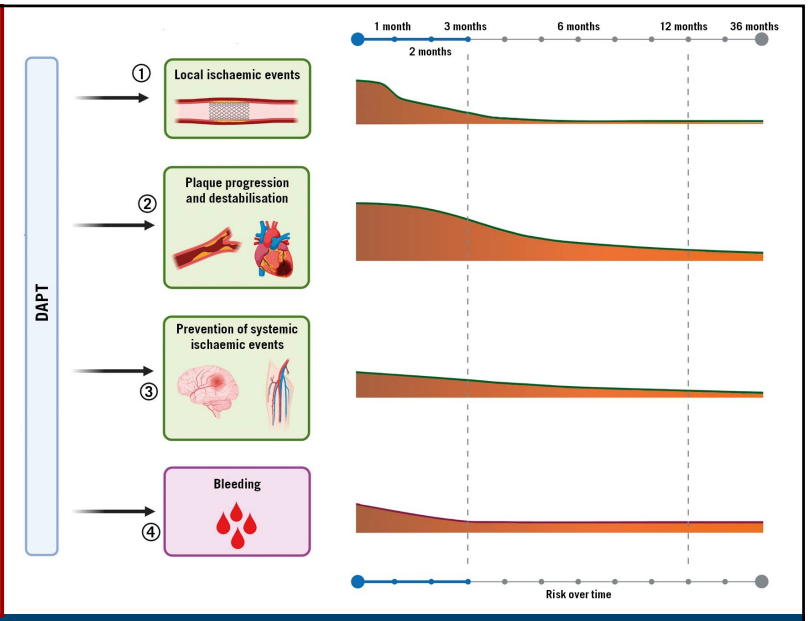

Preventing thrombosis
Avoiding Bleeding
Minneapolis Heart Institute Foundation
GRAND ROUNDS

11


Rationale for Re-assessment of DAPT Strategies
Improved Stent Technology
Improved Procedural Technology
Improved Secondary Prevention
Higher Bleeding Risk Population
More Potent Antiplatelets
Regimen Simplification
Minneapolis Heart Institute Foundation
GRAND ROUNDS

12

Thrombotic and Bleeding Outcomes After Coronary Stenting Over Time

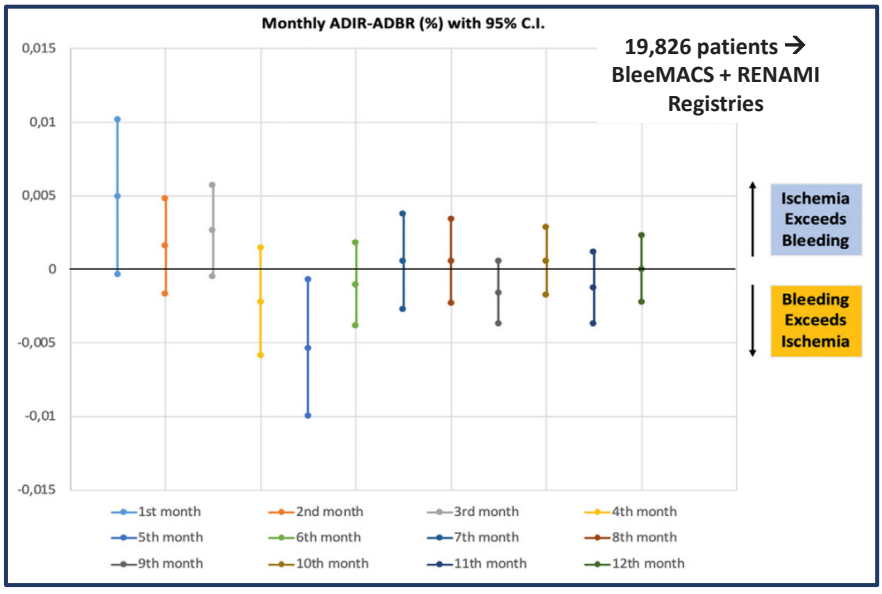


Minneapolis Heart Institute Foundation | GRAND ROUNDS

EuroIntervention. 2022 Apr 1;17(17):e1371-e1396.

13

Thrombotic and Bleeding Outcomes After Coronary Stenting Over Time



Minneapolis Heart Institute Foundation | GRAND ROUNDS

Am Heart J. 2020 Feb;220:108-115.

14

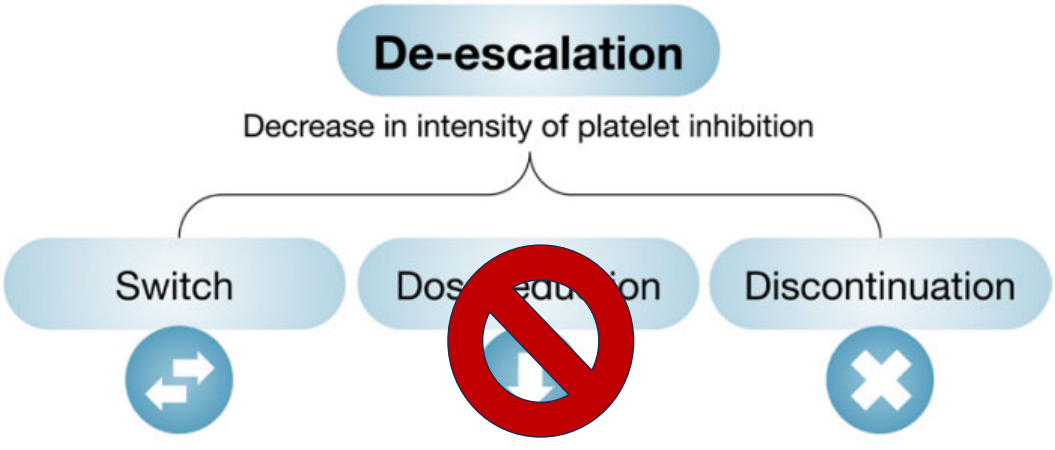
Factors Influencing Bleeding Risk with DAPT

- Patient specific baseline bleeding risk
- Number of antiplatelets/antithrombotics
- Potency of antiplatelets
- Duration of antiplatelets

Minneapolis Heart Institute Foundation | GRAND ROUNDS

15

Strategies for DAPT De-escalation



Minneapolis Heart Institute Foundation | GRAND ROUNDS

Circulation. 2023 Jun 20;147(25):1933-1944.

16

RCTs of DAPT De-escalation After PCI

EXCELLENT (2012)	RESET (2012)	OPTIMIZE (2013)	SECURITY (2014)	ISAR-SAFE (2015)	I-LOVE-IT 2 (2016)	NIPPON (2017)
TROPICAL (2017)	TOPIC (2017)	SMART DATE (2018)	DAPT STEMI (2018)	OPTIMA-C (2018)	GLOBAL LEADERS (2018)	SMART-CHOICE (2019)
REDUCE (2019)	POPular Genetics (2019)	TWILIGHT (2020)	TICO (2020)	One-Month DAPT (2021)	MASTER DAPT (2021)	TALOS-AMI (2021)
STOPDAPT-2 (2022)	SHARE (2024)	T-PASS (2024)	ULTIMATE DAPT (2024)			

Minneapolis Heart Institute Foundation | GRAND ROUNDS

17

Demystifying DAPT De-escalation……..

Minneapolis Heart Institute Foundation | GRAND ROUNDS

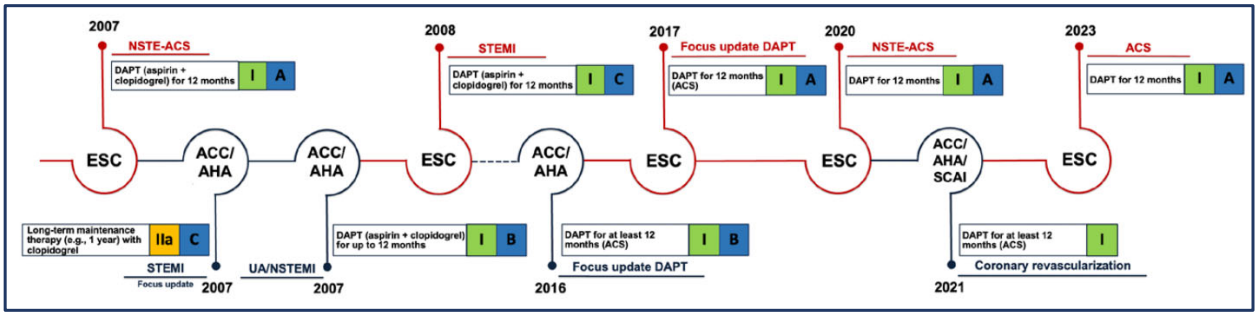
18

DAPT De-Escalation: Discontinuation (of ASA or P2Y12i)

Minneapolis Heart Institute Foundation | GRAND ROUNDS

19

Guideline Recommendations for DAPT Duration in ACS



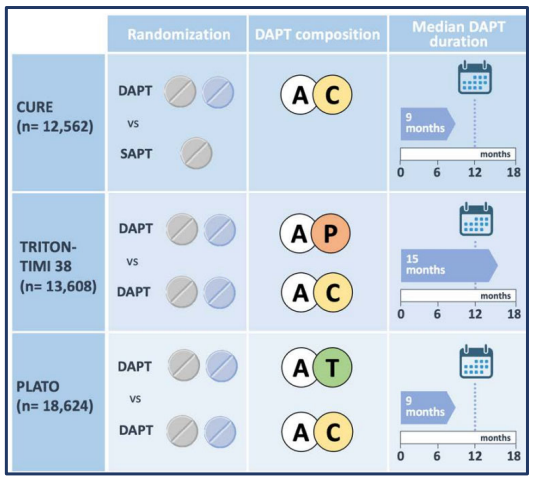
Minneapolis Heart Institute Foundation | GRAND ROUNDS

Circulation. 2024 Jul 23;150(4):317-335.

20

DAPT Durations in Landmark Clinical Trials

COR	LOE	RECOMMENDATIONS
Default Duration of DAPT		
1	A	1. In patients with ACS who are not at high bleeding risk, DAPT with aspirin and an oral P2Y12 inhibitor should be administered for at least 1 year to reduce MACE.[1-6]



Circulation. 2025 Apr;151(13):e771-e862.
Circulation. 2024 Jul 23;150(4):317-335.

21

CURE Investigators on DAPT Duration

"the exact duration of therapy cannot be deduced reliably from a trial with the design of CURE"

"the only way to reliably estimate the exact length of time that various treatments in any condition should be given is by prospectively randomizing patients to various durations of therapy."

Circulation. 2003 Feb25;107(7):966-72.

22

Core Tenants of DAPT Discontinuation

- Which agent?
- When?
- ACS vs. CCS
- Bleeding Risk

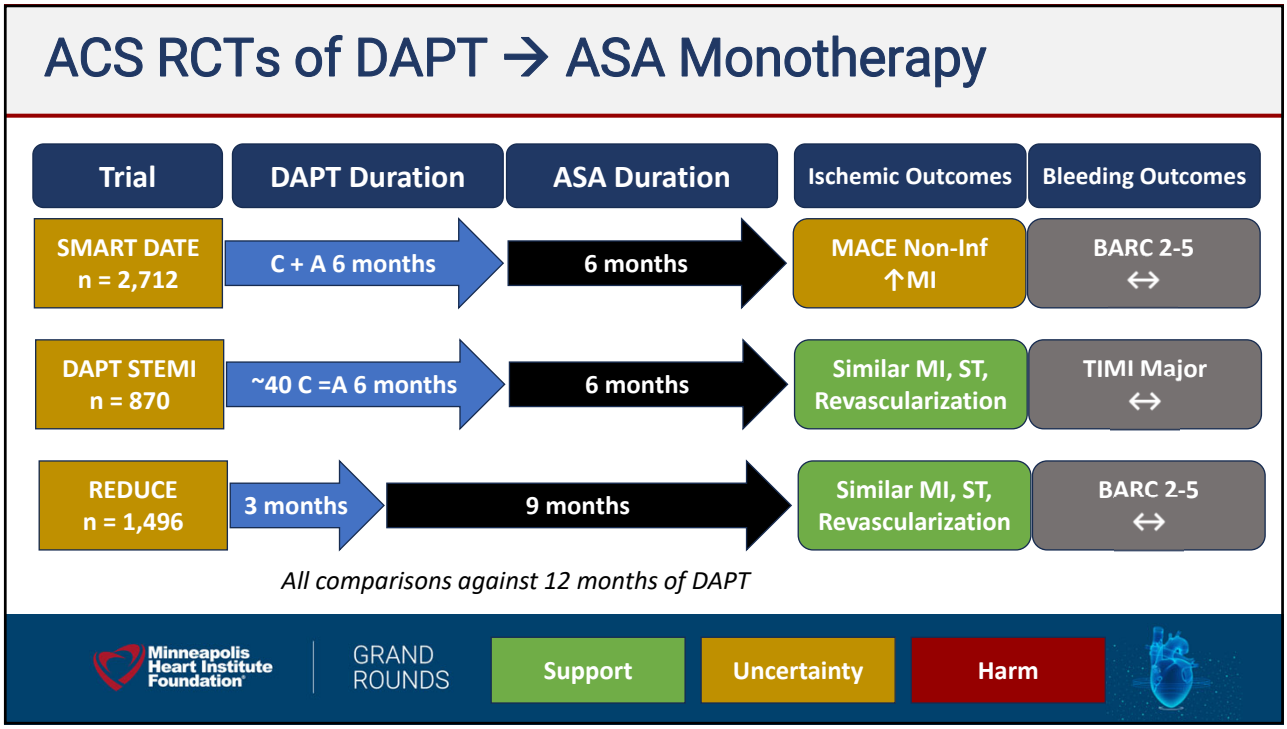
Minneapolis Heart Institute Foundation | GRAND ROUNDS

23

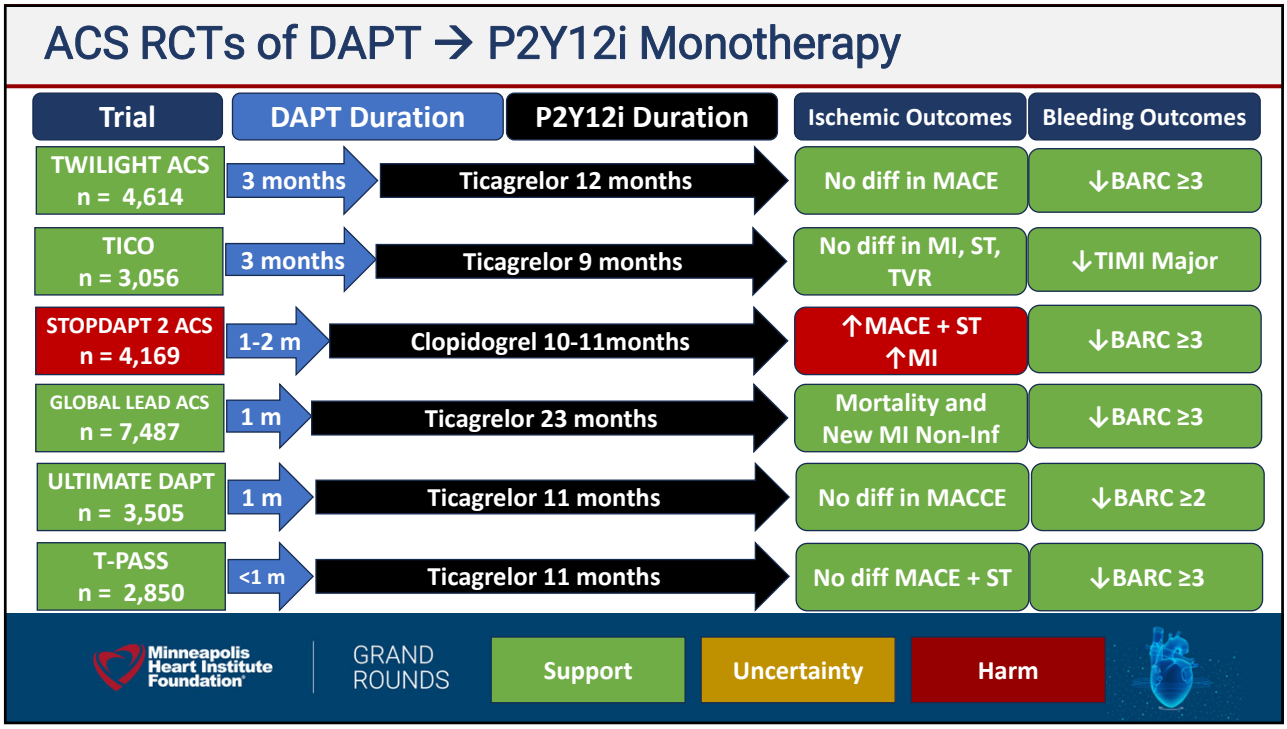
Abbreviated DAPT in RCTS of Acute Coronary Syndrome

Minneapolis Heart Institute Foundation | GRAND ROUNDS

24


ACS RCTs of DAPT → ASA Monotherapy
Trial
DAPT Duration
ASA Duration
Ischemic Outcomes
Bleeding Outcomes
SMART DATE n = 2,712
C + A 6 months
6 months
MACE Non-Inf ↑MI
BARC 2-5 ↔
DAPT STEMI n = 870
~40 C =A 6 months
6 months
Similar MI, ST, Revascularization
TIMI Major ↔
REDUCE n = 1,496
3 months
9 months
Similar MI, ST, Revascularization
BARC 2-5 ↔
All comparisons against 12 months of DAPT
Minneapolis Heart Institute Foundation
GRAND ROUNDS
Support
Uncertainty
Harm

25


ACS RCTs of DAPT → P2Y12i Monotherapy
Trial
DAPT Duration
P2Y12i Duration
Ischemic Outcomes
Bleeding Outcomes
TWILIGHT ACS n = 4,614
3 months
Ticagrelor 12 months
No diff in MACE
↓BARC ≥3
TICO n = 3,056
3 months
Ticagrelor 9 months
No diff in MI, ST, TVR
↓TIMI Major
STOPDAPT 2 ACS n = 4,169
1-2 m
Clopidogrel 10-11months
↑MACE + ST ↑MI
↓BARC ≥3
GLOBAL LEAD ACS n = 7,487
1 m
Ticagrelor 23 months
Mortality and New MI Non-Inf
↓BARC ≥3
ULTIMATE DAPT n = 3,505
1 m
Ticagrelor 11 months
No diff in MACCE
↓BARC ≥2
T-PASS n = 2,850
<1 m
Ticagrelor 11 months
No diff MACE + ST
↓BARC ≥3
Minneapolis Heart Institute Foundation
GRAND ROUNDS
Support
Uncertainty
Harm

26

Abbreviated DAPT in RCTs of Chronic Coronary Syndromes +/- Acute Coronary Syndrome

Minneapolis Heart Institute Foundation | GRAND ROUNDS

27

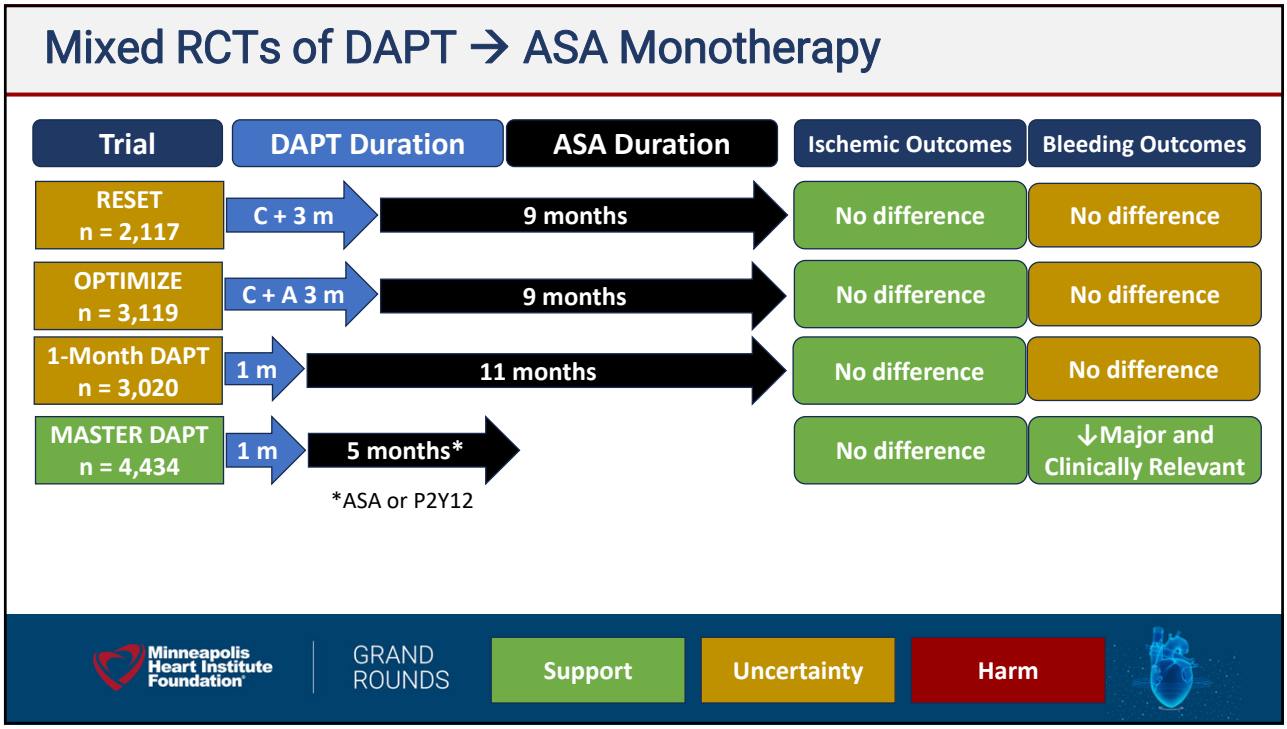
Mixed RCTs of DAPT → ASA Monotherapy

Trial	DAPT Duration	ASA Duration	Ischemic Outcomes	Bleeding Outcomes
EXCELLENT n = 1,443	C + A 6 months	6 months	No difference	No difference
NIPPON n = 3,773	C + A 6 months	6 months	No difference	No difference
OPTIMA-C n = 1,368	C + A 6 months	6 months	No difference	No difference
SECURITY n = 1,399	C + A 6 months	6 months	No difference	No difference
ISAR-SAFE n = 4,000	C + A 6 months	6 months	No difference	↓Any bleeding
I LOVE IT 2 n = 1,829	C + A 6 months	6 months	No difference	No difference

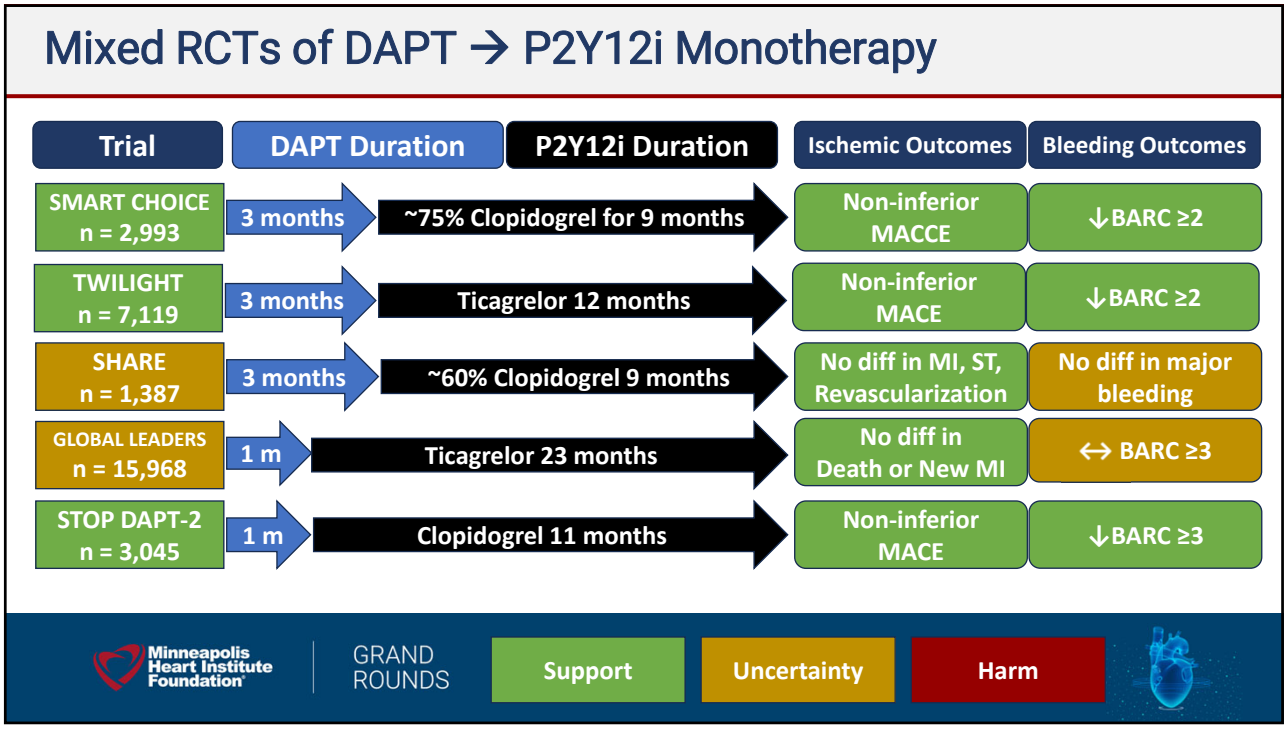
Minneapolis Heart Institute Foundation | GRAND ROUNDS

Support | Uncertainty | Harm

28


Mixed RCTs of DAPT → ASA Monotherapy
Trial
DAPT Duration
ASA Duration
Ischemic Outcomes
Bleeding Outcomes
RESET n = 2,117
C + 3 m
9 months
No difference
No difference
OPTIMIZE n = 3,119
C + A 3 m
9 months
No difference
No difference
1-Month DAPT n = 3,020
1 m
11 months
No difference
No difference
MASTER DAPT n = 4,434
1 m
5 months*
No difference
↓Major and Clinically Relevant
*ASA or P2Y12
Minneapolis Heart Institute Foundation
GRAND ROUNDS
Support
Uncertainty
Harm

29


Mixed RCTs of DAPT → P2Y12i Monotherapy
Trial
DAPT Duration
P2Y12i Duration
Ischemic Outcomes
Bleeding Outcomes
SMART CHOICE n = 2,993
3 months
~75% Clopidogrel for 9 months
Non-inferior MACCE
↓BARC ≥2
TWILIGHT n = 7,119
3 months
Ticagrelor 12 months
Non-inferior MACE
↓BARC ≥2
SHARE n = 1,387
3 months
~60% Clopidogrel 9 months
No diff in MI, ST, Revascularization
No diff in major bleeding
GLOBAL LEADERS n = 15,968
1 m
Ticagrelor 23 months
No diff in Death or New MI
↔ BARC ≥3
STOP DAPT-2 n = 3,045
1 m
Clopidogrel 11 months
Non-inferior MACE
↓BARC ≥3
Minneapolis Heart Institute Foundation
GRAND ROUNDS
Support
Uncertainty
Harm

30

DAPT De-Escalation: De-intensifying

Minneapolis Heart Institute Foundation | GRAND ROUNDS

31

Rationale for DAPT De-Intensifying

Prasugrel Bleeding

Table 3. Thrombolysis in Myocardial Infarction (TIMI) Bleeding End Points in the Overall Cohort at 15 Months.*

End Point	Prasugrel (N=6741)	Clopidogrel (N=6716)	Hazard Ratio for Prasugrel (95% CI)	P Value
	no. of patients (%)			
Non–CABG-related TIMI major bleeding (key safety end point)	146 (2.4)	111 (1.8)	1.32 (1.03–1.68)	0.03
Related to instrumentation	45 (0.7)	38 (0.6)	1.18 (0.77–1.82)	0.45
Spontaneous	92 (1.6)	61 (1.1)	1.51 (1.09–2.08)	0.01
Related to trauma	9 (0.2)	12 (0.2)	0.75 (0.32–1.78)	0.51
Life-threatening†	85 (1.4)	56 (0.9)	1.52 (1.08–2.13)	0.01
Related to instrumentation	28 (0.5)	18 (0.3)	1.55 (0.86–2.81)	0.14
Spontaneous	50 (0.9)	28 (0.5)	1.78 (1.12–2.83)	0.01
Related to trauma	7 (0.1)	10 (0.2)	0.70 (0.27–1.84)	0.47
Fatal‡	21 (0.4)	5 (0.1)	4.19 (1.58–11.11)	0.002
Nonfatal	64 (1.1)	51 (0.9)	1.25 (0.87–1.81)	0.23
Intracranial	19 (0.3)	17 (0.3)	1.12 (0.58–2.15)	0.74
Major or minor TIMI bleeding	303 (5.0)	231 (3.8)	1.31 (1.11–1.56)	0.002
Bleeding requiring transfusion§	244 (4.0)	182 (3.0)	1.34 (1.11–1.63)	<0.001
CABG-related TIMI major bleeding¶	24 (13.4)	6 (3.2)	4.73 (1.90–11.82)	<0.001

Ticagrelor Bleeding

Table 4. Safety of the Study Drugs.*

End Point	Ticagrelor Group	Clopidogrel Group	Hazard or Odds Ratio for Ticagrelor Group (95% CI)†	P Value
Primary safety end points — no./total no. (%)				
Major bleeding, study criteria	961/9235 (11.6)	929/9186 (11.2)	1.04 (0.95–1.13)	0.43
Major bleeding, TIMI criteria‡	657/9235 (7.9)	638/9186 (7.7)	1.03 (0.93–1.15)	0.57
Bleeding requiring red-cell transfusion	818/9235 (8.9)	809/9186 (8.9)	1.00 (0.91–1.11)	0.96
Life-threatening or fatal bleeding, study criteria	491/9235 (5.8)	480/9186 (5.8)	1.03 (0.90–1.16)	0.70
Fatal bleeding	20/9235 (0.3)	23/9186 (0.3)	0.87 (0.48–1.59)	0.66
Nonintracranial fatal bleeding	9/9235 (0.1)	21/9186 (0.3)		0.03
Intracranial bleeding	26/9235 (0.3)	14/9186 (0.2)	1.87 (0.98–3.58)	0.06
Fatal	11/9235 (0.1)	1/9186 (0.01)		0.02
Nonfatal	15/9235 (0.2)	13/9186 (0.2)		0.69
Secondary safety end points — no./total no. (%)				
Non–CABG-related major bleeding, study criteria	362/9235 (4.5)	306/9186 (3.8)	1.19 (1.02–1.38)	0.03
Non–CABG-related major bleeding, TIMI criteria	221/9235 (2.8)	177/9186 (2.2)	1.25 (1.03, 1.53)	0.03
CABG-related major bleeding, study criteria	619/9235 (7.4)	654/9186 (7.9)	0.95 (0.85–1.06)	0.32
CABG-related major bleeding, TIMI criteria	446/9235 (5.3)	476/9186 (5.8)	0.94 (0.82–1.07)	0.32
Major or minor bleeding, study criteria	1339/9235 (16.1)	1215/9186 (14.6)	1.11 (1.03–1.20)	0.008
Major or minor bleeding, TIMI criteria‡	946/9235 (11.4)	906/9186 (10.9)	1.05 (0.96–1.15)	0.33

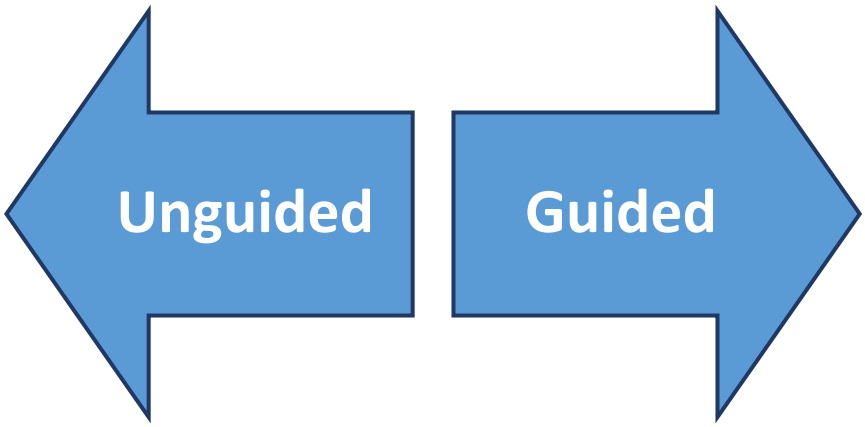
Minneapolis Heart Institute Foundation | GRAND ROUNDS

N Engl J Med. 2007 Nov 15;357(20):2001-15.

N Engl J Med. 2009 Sep 10;361(11):1045-57.

32

DAPT De-Intensifying



Minneapolis Heart Institute Foundation | GRAND ROUNDS

33

RCTs of DAPT Intensity Reduction: Unguided

Trial	HI-DAPT Duration	S-P2Y12i Duration	Ischemic Outcomes	Bleeding Outcomes
TOPIC n = 646	1 m	Clopidogrel for 11 months	No Difference	↓BARC ≥2 Bleeding
TALOS-AMI n =	1 m	Clopidogrel for 11 months	No Difference	↓BARC ≥2 Bleeding

Minneapolis Heart Institute Foundation | GRAND ROUNDS

Support | Uncertainty | Harm

34

RCTs of DAPT Switch: Guided

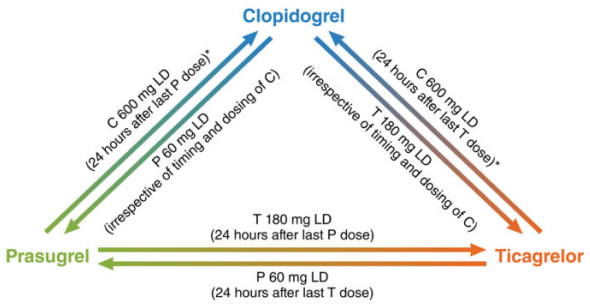
TROPICAL (n = 2,610)	POPular Genetics (n = 2.488)
• PFT guided (Multiplate) de-escalation at 2 weeks • Prasugrel → Clopidogrel • No difference in ischemic outcomes • No difference in bleeding outcomes	• Genotype-guided • Prasugrel or Ticagrelor if CYP2C19 LOF, otherwise clopidogrel • No difference in ischemic outcomes • Less BARC ≥2 bleeding

Minneapolis Heart Institute Foundation | GRAND ROUNDS

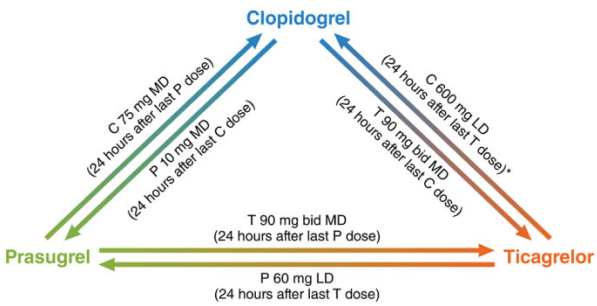
35

DAPT Transition Dosing

≤30 days from the index event



>30 days from the index event



Circulation. 2017 Nov 14;136(20):1955-1975.

Minneapolis Heart Institute Foundation | GRAND ROUNDS

36

Common Limitation Themes in De-escalation Studies

- Combination ACS and non-ACS populations
- Powered for bleeding outcomes
- Non-inferiority design for ischemic outcomes
- Selected patient population
- Low event rates in some studies
- Some generatability concerns

Minneapolis Heart Institute Foundation | GRAND ROUNDS

37

Risk Assessment for DAPT De-escalation

Minneapolis Heart Institute Foundation | GRAND ROUNDS

38

DAPT Duration in High Bleeding Risk Patients

Patients at HBR undergoing coronary stenting

PRECISE-DAPT score ≥ 25
- Age
- Haemoglobin
- Renal function
- White blood cells
- Prior bleeding

Or

HBR according to modified HBR-ARC definition
- Age
- Renal disease
- Liver disease
- Active cancer
- Anaemia
- Low platelet count
- Prior stroke or ICH
- Bleeding diathesis
- Prior bleeding or transfusion
- NSAID use

11 trials → 9006 HBR patients

Standard DAPT (6 months or more)

Short DAPT (3 months or less)

- 24% MCRB
- 20% Major bleed
- 21% CV death
- MACE (ACS and CCS)

Minneapolis Heart Institute Foundation | GRAND ROUNDS

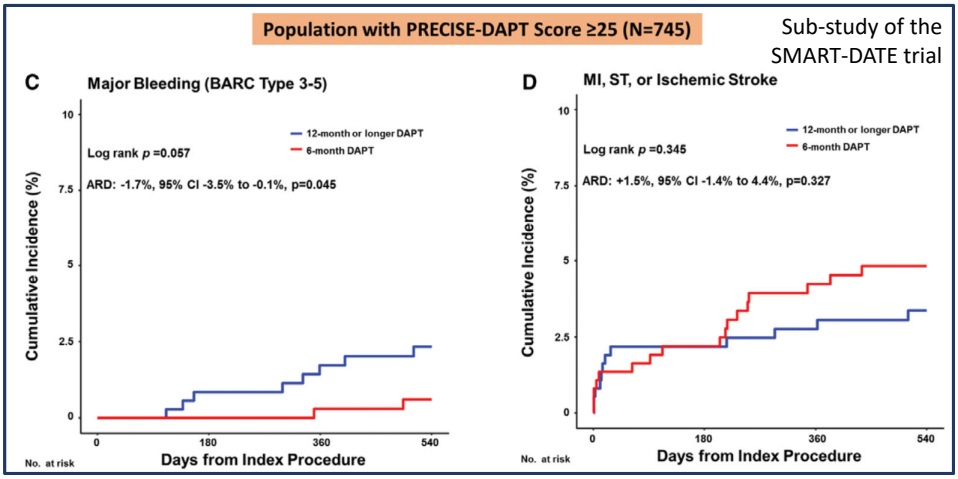
Eur Heart J. 2023 Mar 14;44(11):954-968.

39

Bleeding and Ischemic Outcomes in Patients with Low vs. High Bleeding Risk

Population with PRECISE-DAPT Score ≥25 (N=745)

Sub-study of the SMART-DATE trial

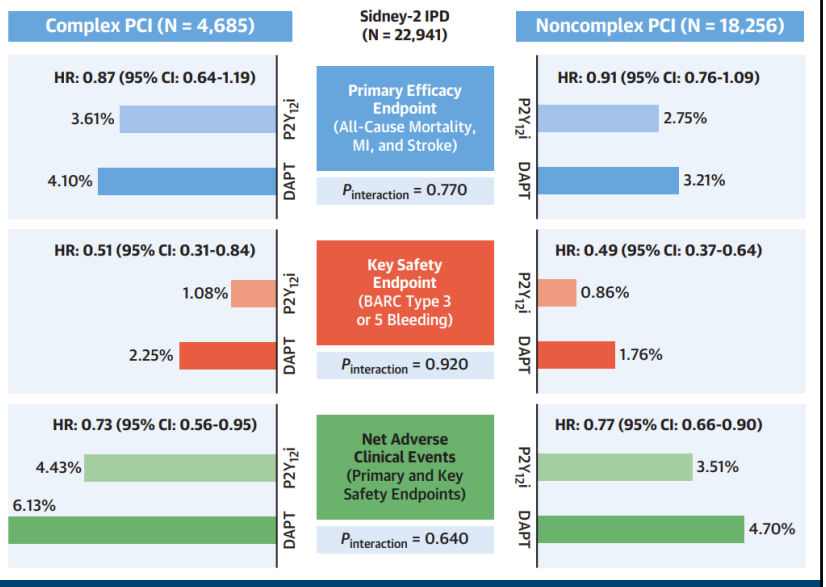


Minneapolis Heart Institute Foundation | GRAND ROUNDS

Circ Cardiovasc Interv. 2020 May;13(5):e008530.

40

DAPT vs. P2Y12i Monotherapy in High-Risk PCI



Minneapolis Heart Institute Foundation | GRAND ROUNDS

J Am Coll Cardiol. 2023 Feb 14;81(6):537-552.

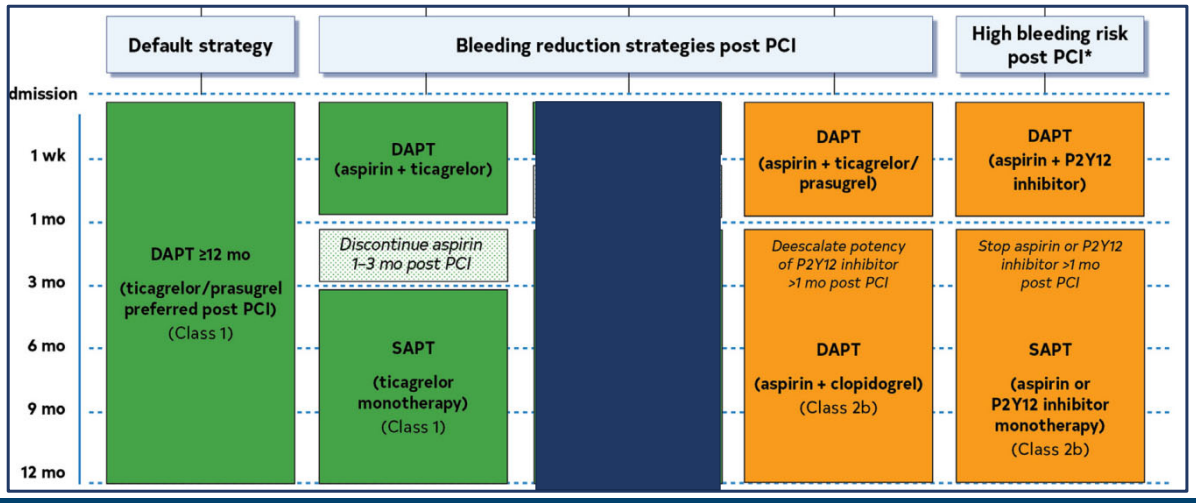
41

AHA/ACC Guideline Recommendations for DAPT De-escalation

Minneapolis Heart Institute Foundation | GRAND ROUNDS

42

AHA/ACC Guideline Recommendations for ACS PCI

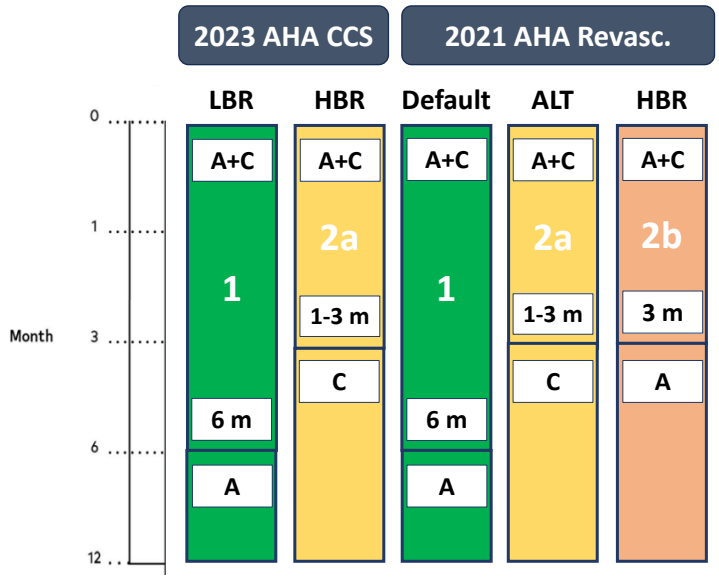


Minneapolis Heart Institute Foundation | GRAND ROUNDS

Circulation. 2025 Apr;151(13):e771-e862.

43

AHA/ACC Guideline Recommendations for CCS PCI



Minneapolis Heart Institute Foundation | GRAND ROUNDS

Circulation. 2023 Aug 29;148(9):e9-e119.

Circulation. 2022 Jan 18;145(3):e4-e17.

44

Final Take Aways

Minneapolis Heart Institute Foundation | GRAND ROUNDS

45

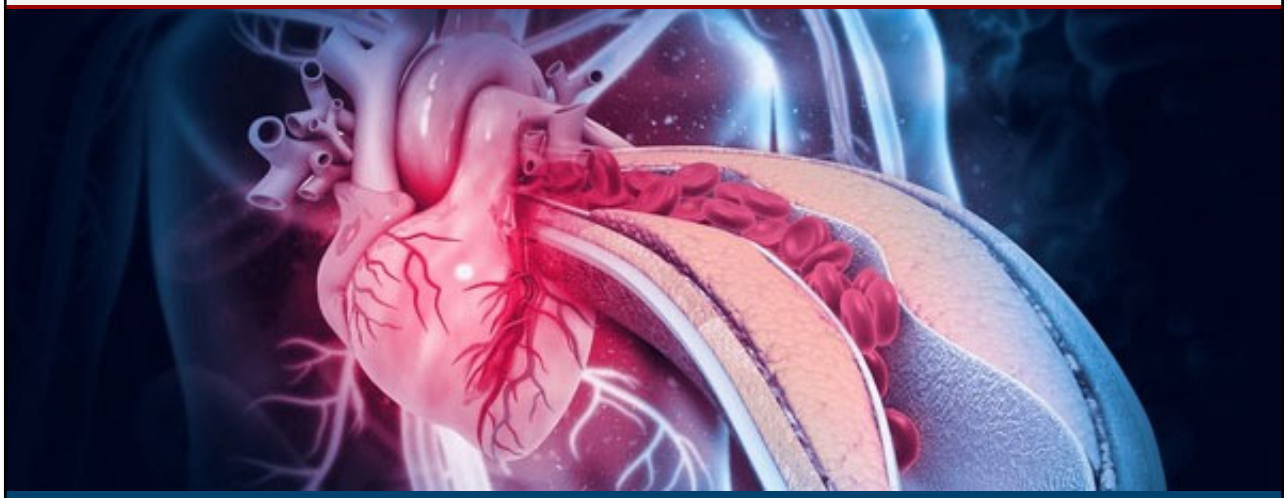
General Themes from the Literature as of 4/6/2025 @ 1159 PM

- Caution with aspirin monotherapy within 6 months
- If abbreviating DAPT in ACS, ideally use P2Y12i monotherapy
- If abbreviating in ACS, ticagrelor may allow for earlier (after 1 month)
- If longer DAPT is desired, consider reducing potency
- Genomic testing may be beneficial if you have concerns about clopidogrel monotherapy

Minneapolis Heart Institute Foundation | GRAND ROUNDS

46

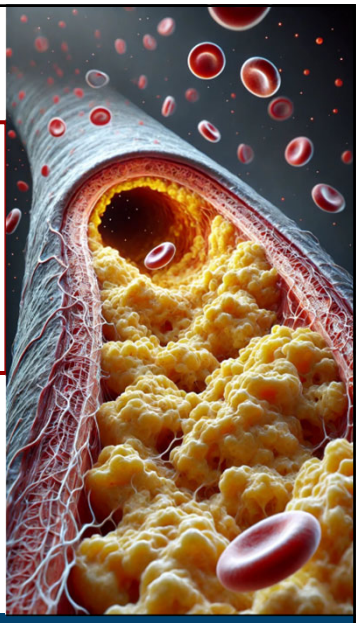
“Do Away with the Default”



Minneapolis Heart Institute Foundation | GRAND ROUNDS

47

Demystifying the Evolving Evidence for Antiplatelet De-escalation in ASCVD



Matthew P. Lillyblad, PharmD, BCCCP, BCCP
Clinical Pharmacy Specialist, Senior- Cardiology and Critical Care
Abbott Northwestern Hospital, part of Allina Health

Minneapolis Heart Institute Foundation | GRAND ROUNDS

48