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CONTEMPORARY REVIEW

Review of the Ticagrelor Trials Evidence Base

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- Narrative review of 22 **RCTs** with ≥400 participants each
- Endpoints: **ischemic** and **bleeding** outcomes of **ticagrelor** across major indications
- Settings: ACS, stroke/TIA, PAD, stable CAD, elective PCI, CABG
- Compared with **clopidogrel** across mentioned settings

Pharmacology & Mechanism

- Ticagrelor: **reversible** P2Y12 inhibitor, direct-acting (**no hepatic activation, not susceptible to CYP2C19 polymorphism**)
- **Faster** onset (~30 min) vs clopidogrel (~2 hrs), greater potency, less response variability
- Associated with **Dyspnea** and slightly increased **bleeding**
- Increases extracellular adenosine which although acts as a cardioprotective agent, may cause dyspnea and bradycardia

History of Ticagrelor

- **2009 –** PLATO Trial: Shows ticagrelor superior to clopidogrel in ACS for reducing CV death, MI, and stroke
- **2011 –** Approved by **FDA** and EMA for ACS patients (with or without PCI)
- **2013–2017 –** PEGASUS (post-MI long term use), EUCLID (PAD): modest or neutral results
- **2016–2020**
  - SOCRATES, THALES trials (Stroke/TIA), THEMIS (diabetes + CAD)
  - ATLANTIC, DUBIUS: timing strategies (no added benefit from early loading)
- **2020–2024**
  - Focus on de-escalation (TALOS-AMI) and aspirin-free strategies (TWILIGHT, TICO).
  - Recognition of bleeding risks, adherence issues, and diminishing marginal benefits in low-risk populations

Ticagrelor in ACS

- Decreased CV death/MI/stroke by 10% compared to Clopidogrel

- Similar overall major bleeding

- **Limitations:**

- Increased non-CABG bleeding and dyspnea
- higher bleeding/discontinuation in elderly (Subgroup analyses)
- Lower compliance and early discontinuation (cost, side effects, tolerability, BD use)
- Clopidogrel remains widely used in low-risk or frail patients
- Benefit shrinks as baseline risk falls

ACS Trials- Summary

Indication	Trial	Ischemic Event	Major Non-CABG Bleeding Event	Treatment
ACS/MI	**PLATO** [NCT00391872]			Ticagrelor+ASA vs. clopidogrel+ASA in ACS
	PHILO [NCT01294462]			Ticagrelor+ASA vs. clopidogrel+ASA in ACS in Japanese, South Korean, and Taiwanese patients
	TICAKOREA [NCT02094963]			Ticagrelor+ASA vs. clopidogrel+ASA in ACS in South Korean patients
	TREAT [NCT02298088]		*	Ticagrelor+ASA vs. clopidogrel+ASA in fibrinolytic -treated STEMI
	POPular AGE [NCT02317198]			Ticagrelor+ASA vs. clopidogrel+ASA in elderly NSTE -ACS
	PRAGUE -18 [NCT02808767]		*	Ticagrelor+ASA vs. prasugrel+ASA in acute MI treated with primary PCI
	ISAR-REACT 5 [NCT01944800]		*	Ticagrelor+ASA vs. prasugrel+ASA in ACS with planned invasive management
	ATLANTIC [NCT01347580]			Ticagrelor pre-hospital administration vs. catherization lab administration in STEMI
	DUBIUS [NCT02618837]		*	Ticagrelor pretreatment before angiography vs. no pretreatment in NSTE-ACS

*Represents data for Major Bleeding rather than Major Non -CABG Bleeding
#Primary endpoint evaluated saphenous vein graft patency/occlusion rather than traditional cardiovascular ischemic events (e.g., cardiovascular death, MI, stroke)

Key
- Significantly better outcome with ticagrelor
- Not statistically inferior or different
- Numerically worse with ticagrelor (>1% absolute difference); not statistically inferior or different
- Significantly worse outcome with ticagrelor

CABG

- Ticagrelor + ASA improved 1-year vein graft patency vs ASA alone in one study (DACAB)
- Mixed results: some graft benefit, but no clear clinical advantage
- There is no enough evidence to support routine use in CABG

Indication	Trial	Ischemic Event	Major Non-CABG Bleeding Event	Treatment
CABG	**DACAB** [NCT02201771]	#		Ticagrelor+ASA vs. ticagrelor vs. ASA in elective CABG in Chinese patients
	TiCAB [NCT01755520]		*	Ticagrelor vs. ASA in elective CABG
	POPular-CABG [NCT02352402]	#		Ticagrelor+ASA vs. ASA in elective CABG

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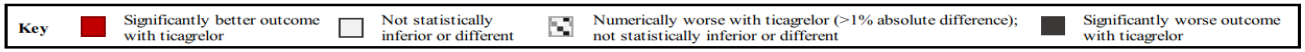

Stroke / High-Risk TIA

- Ticagrelor + aspirin DAPT decreased stroke/death compared to ASA alone (THALES trial)
- Ticagrelor monotherapy ≈ ASA for stroke/MI/death
- More risk of severe intracranial bleeding

Clinical Use Summary:

- Clopidogrel + aspirin (21–90 days) preferred in most with low bleeding risk if started within 12–24 hrs
- Ticagrelor + aspirin (30 days) reasonable in CYP2C19 LOF carriers

Indication	Trial	Ischemic Event	Major Non-CABG Bleeding Event	Treatment
TIA/Stroke	**SOCRATES** [NCT01994720]		*	Ticagrelor+ASA vs. ASA in mild/moderate risk stroke and high -risk transient ischemic attack
	THALES [NCT03354429]		*	Ticagrelor+ASA vs. ASA in mild/moderate risk stroke and high -risk transient ischemic attack

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Peripheral Artery Disease

- No difference in CV death, MI, or stroke
- No difference in acute limb events or major bleeding

- Not approved by FDA for PAD
- Clopidogrel remains standard antiplatelet agent in PAD

Indication	Trial	Ischemic Event	Major Non-CABG Bleeding Event	Treatment
PAD	**EUCLID** [NCT01732822]		 *	Ticagrelor vs. clopidogrel in symptomatic PAD

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Stable CAD & Elective PCI

- **ALPHEUS** trial (high-risk elective PCI):
  - Ticagrelor vs clopidogrel → no difference in peri-procedural MI or myocardial injury
  - ↑ minor bleeding and ↑ dyspnea with ticagrelor
- Ticagrelor offers no added ischemic benefit in stable CAD undergoing elective PCI
- Higher bleeding risk and poorer tolerability
- Clopidogrel remains the preferred agent in this setting

Indication	Trial	Ischemic Event	Major Non-CABG Bleeding Event	Treatment
Elective PCI	**ALPHEUS** [NCT02617290]		 *	Ticagrelor+ASA vs. clopidogrel+ASA in high -risk elective PCI

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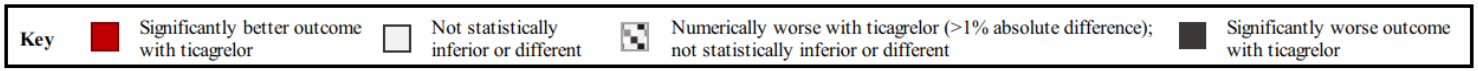

Secondary/Long-Term Prevention

- **PEGASUS-TIMI 54** (prior MI, 1–3 yrs):
  - Ticagrelor 60 mg BID + aspirin ↓ CV death/MI/stroke by ~1.3% (ARR)
  - ↑ TIMI major bleeding (~1.2%); no excess fatal or intracranial bleeding
  - Net benefit in high-risk, low-bleeding-risk patients
- **THEMIS** (stable CAD + diabetes, no prior MI):
  - Modest ischemic reduction (ARR ~0.8%)
  - ↑ major bleeding including intracranial hemorrhage
  - Overall net clinical benefit neutral
- Consider long-term ticagrelor only in select high-risk patients (e.g., prior MI, diabetes)
- Avoid in those with high bleeding risk or without prior ischemic events

Indication	Trial	Ischemic Event	Major Non-CABG Bleeding Event	Treatment
Secondary Prevention	**PEGASUS** [NCT01225562]		 *	Ticagrelor+ASA vs. ASA in patients with a history of MI
	THEMIS [NCT01991795]		 *	Ticagrelor+ASA vs. ASA in patients with CAD and diabetes

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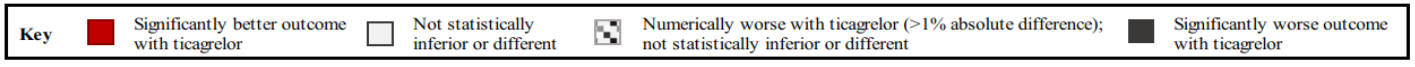

De-escalation, a new trend

- **ASA + Ticagrelor to ASA + Clopidogrel after 1 months:**
  - ↓ composite of ischemia + bleeding, mainly by reducing bleeding
- **ASA + Ticagrelor to Ticagrelor after 3 months (compared to continued DAPT)**:
  - ↓ BARC 2–5 bleeding (~40%) without ↑ ischemic events

Indication	Trial	Ischemic Event	Major Non-CABG Bleeding Event	Treatment
De-escalation	**TALOS-AMI** [NCT02018055]		*	Ticagrelor+ASA vs. de-escalation to clopidogrel+ASA in acute MI in South Korean patients
Aspirin Withdrawal	**GLOBAL LEADERS** [NCT02018055]		*	Ticagrelor+ASA (1 month) followed by ticagrelor (23 months) vs. ticagrelor or clopidogrel+ASA (12 months) followed by ASA (12 months) in ACS and CAD
	TWILIGHT [NCT02270242]		*	Ticagrelor+ASA for 3 months followed by ticagrelor for 12 months vs. ticagrelor+ASA for 12 months in high-risk PCI
	TICO [NCT02494895]		*	Ticagrelor+ASA for 3 months followed by ticagrelor monotherapy vs. ticagrelor+ASA for 12 months in ACS in South Korean patients

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Take-Home Points

- Most benefit seen in:
  - High-risk ACS
  - Selected stroke/TIA cases
  - De-escalation after ACS(ASA free approach)
- Neutral or negative balance in:
  - Stable CAD
  - PAD
  - Elective PCI
  - CABG
- Current factors limiting benefit:
  - ↑ bleeding risk, dyspnea, BID dosing, cost
  - Poor adherence and early discontinuation common

Thanks for your attention