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IN PERSPECTIVE
Educational Papers

Comparison of 1-month vs. 12-month dual antiplatelet therapy after implantation of drug-eluting stents in patients with acute coronary syndrome: the ULTIMATE-DAPT trial

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Evidence before this study

The 2023 ESC guidelines assigned to 12-month dual antiplatelet therapy (DAPT) the single class I recommendation on DAPT in patients with acute coronary syndrome (ACS) after drug-eluting stent (DES) implantation. However, evidence exists that various DAPT de-escalation strategies are preferable to 12-month DAPT, which has sparked ongoing debate.[1,2] Several randomized clinical trials (RCTs) and individual patient data (IPD) meta-analysis investigated the efficacy and safety of $P2Y_{12}$ inhibitor monotherapy after 1–3 months of DAPT.

The GLOBAL LEADERS trial, encompassing all-comer patients, found no clear superiority on death or Q-wave myocardial infarction (MI) between a 1-month DAPT followed by ticagrelor monotherapy and standard 12-month DAPT followed by aspirin after DES implantation. The bleeding risk was reduced in ACS (1.95% vs. 2.68%) but not chronic coronary syndrome patients (2.13% vs. 1.62%) with 1-month DAPT,[3,4] which contributed to foster additional research efforts with $P2Y_{12}$ inhibitor monotherapy. The GLOBAL LEADERS Adjudication Sub-StudY (GLASSY), which, unlike the parent trial, implemented a central adjudication of events, confirmed the potential of lower bleeding and similar fatal or non-fatal ischaemic risks with ticagrelor monotherapy than standard DAPT.[5]

The TWILIGHT study, which included selected high-risk patients including ACS, showed that after 3 months of DAPT, ticagrelor monotherapy was safer [Bleeding Academic Research Consortium (BARC) 3 or 5 bleeding 1% vs. 2%] and similarly effective [major adverse cardiovascular events (MACE) endpoint: a composite of all-cause death, non-fatal MI, or non-fatal stroke; *P* for non-inferiority <0.001] compared with standard additional 12-month DAPT.[6]

The SIDNEY-2 Collaboration, involving over 38,000 patients, supported $P2Y_{12}$ inhibitor monotherapy for reducing BARC type 3 or 5 bleeding events by 44% [hazard ratio (HR) 0.56; 95% confidence interval (CI): 0.41–0.75] and demonstrated its non-inferiority for MACE compared to standard DAPT, with notable benefits for bleeding in ACS patients (*P* for interaction 0.51)[7] and those undergoing complex percutaneous coronary intervention (PCI).[8]

While these findings hold true for ticagrelor in ACS patients in a more recent IPD analysis, they may not be applicable when clopidogrel is used.[9]

Trial description

The ULTIMATE-DAPT trial was designed to test whether antiplatelet monotherapy with ticagrelor alone vs. ticagrelor plus aspirin reduces the incidence of clinically relevant bleeding without increasing the risk of major adverse cardiovascular and cerebrovascular events (MACCEs) in ACS patients following DES who have completed a 1-month course of DAPT with aspirin plus ticagrelor. The ULTIMATE-DAPT was a prospective, multicentre, randomized, controlled trial.

Patients were initially randomized to intravascular ultrasound (IVUS)-guided ($n = 1753$) or angiography-guided ($n = 1752$) PCI for index ACS event and received DAPT with ticagrelor (90 mg b.i.d.) and aspirin (100 mg q.d.) for 30 days. If they had no ischaemic or bleeding events at the end of 30 days, they were randomized to continuing DAPT for 12 months total ($n = 1700$) or stopping aspirin and switching to ticagrelor + placebo ($n = 1700$).[10]

Patient population

In total, 3400 patients were randomized. Their median age was 63, 26% of the patients were females, 31.6% had diabetes, and 7% had chronic kidney disease (CKD), whereas severe CKD was an exclusion criterion, together with chronic oral anticoagulation, stroke within 3 months or any permanent neurologic deficit, and prior intracranial bleed, previous coronary artery bypass graft (CABG), or any planned surgery within 90 days. Overall, 40% of patients had unstable angina,

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32% non–ST-segment elevation myocardial infarction (NSTEMI), and 28% STEMI.

Other notable features/characteristics

- Chinese race: 88%.
- Median duration of DAPT in the abbreviated therapy group: 28 days [interquartile range (IQR) 25–33].
- Median duration of DAPT in the standard therapy group: 365days (IQR 365–365).
- Number of diseased vessels: one-vessel disease (70%), two-vessel disease (23%).
- During follow-up, a reduction in ticagrelor from 90 to 60 mg b.i.d. was required in 0.8% of patients.

Principal findings

Assessed between 1 and 12 months.

The primary effectiveness endpoint

Bleeding Academic Research Consortium (BARC) 2, 3, or 5 bleeding for ticagrelor + placebo vs. ticagrelor + aspirin was 2.1% vs. 4.6% (HR 0.45, 95% CI 0.30–0.66, $P < 0.0001$).

The primary safety endpoint

Major adverse cardiovascular or cerebrovascular events (cardiac death, MI, ischaemic stroke, definite stent thrombosis, and clinically driven target vessel revascularization) were 3.6% vs. 3.7% ($P < 0.0001$ for non-inferiority, $P = 0.89$ for superiority).

Key secondary outcomes for ticagrelor + placebo vs. ticagrelor + aspirin

- All-cause mortality: 0.7% vs. 0.8%, $P = 0.84$.
- Spontaneous MI: 0.9% vs. 0.7%, $P = 0.29$.
- Repeat revascularization: 2.4% vs. 2.4%, $P = 0.95$.
- Stent thrombosis: 0.3% vs. 0.3%, $P = 0.96$.

Trial interpretation

The advent of ULTIMATE-DAPT marks a pivotal moment in interventional cardiology, reinforcing and building upon results from prior landmark trials and IPD analysis such as GLOBAL LEADERS, TWILIGHT, and the SIDNEY-2 Collaboration.[3–7,9] The trial is a relatively large-scale, randomized, placebo-controlled, double-blind investigation comparing ticagrelor monotherapy to ticagrelor plus aspirin in ACS patients following a month of standard DAPT.[10] Ticagrelor plus placebo slashes clinically relevant bleeding events by over 50% compared to ticagrelor plus aspirin (HR 0.45, 95% CI 0.30–0.66), with a notable decrease in secondary bleeding endpoints. Remarkably, this reduction in bleeding risk does not compromise ischaemic outcomes; MACCE rates remain comparable between groups (HR 0.98, 95% CI 0.69–1.39; $P = 0.89$ for superiority, $P < 0.0001$ for non-inferiority), reaffirming the safety and efficacy of ticagrelor monotherapy. However, ULTIMATE-DAPT suffered from some limitations. The inclusion of target vessel revascularization in MACCE is contentious, given its significant contribution to ischaemic events. With ischaemic event rates lower than anticipated, exclusion of target vessel revascularization would render the study underpowered. Moreover, the broader geographical generalizability of these findings may be questioned. Despite the multicentric nature of the study, 98.7% of participants were from China and Pakistan, with only 44 (1.3%) patients from Europe. However, insights gleaned from previous trials like GLOBAL LEADERS provide support for the generalizability of ULTIMATE-DAPT's findings and render robustness to the findings.

Look, and you will see; look again, and you will see more. Today, with all compelling evidence supporting the efficacy of ticagrelor monotherapy in reducing bleeding risk without compromising ischaemic outcomes, the time is ripe for guideline updates on both sides of the ocean. As we move forward, let us heed the call to embrace these transformative findings and usher in a new era of precision medicine in cardiovascular care.

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