Important New Evidence Service

In Partnership with The Centre for Medicines Optimisation at Keele University

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Cardiovascular disease: Supporting decisions about prolonged use of dual antiplatelet therapy after a myocardial infarction

Recently, the extended use of dual antiplatelet therapy (DAPT) with ticagrelor in combination with aspirin was recommended by NICE as an option to prevent atherothrombotic events in patients who had a myocardial infarction (MI) and who are at high risk of a further event. However, for antiplatelet therapy there is a trade-off between a reduced risk of further cardiovascular (CV) events and an increased risk of bleeding. A team of academics has developed and validated prognostic models estimating the potential benefits and risk of harms of extended DAPT. Their findings have also been used to create a web-based tool to provide personalised risk predictions to aid shared decisions about whether to prolong DAPT.

Pasea L, Chung S, Pujades-Rodriguez M et al. Personalising the decision for prolonged dual antiplatelet therapy: development, validation and potential impact of prognostic models for CV events and bleeding in myocardial infarction survivors. European Health Journal. 2017. ehw683. doi: 10.1093/eurheartj/ehw683

What do we know already?

- People who survive for a year since their last acute myocardial infarction (MI) continue to be at a high risk of a further major CV event. Mortality and the risk of major bleeding are also high. A recent study of data from 4 developed countries found the cumulative 3-year risk of mortality following an MI to be between 20% and 30%.
- The 2013 NICE guidance on MI (CG172) recommends the use of DAPT with aspirin plus a second antiplatelet (such as clopidogrel, ticagrelor or prasugrel) for 12 months after an MI. The choice of the second antiplatelet is guided by the type of MI the person has had and how the acute MI was managed (see guideline for recommendations). After 12 months, aspirin can be continued indefinitely.
- More recently, the PEGASUS-TIMI 54 trial investigated the longer-term use of ticagrelor and found that extending DAPT beyond 12 months reduced the risk of CV mortality, stroke or MI by 16% at 3 years compared with aspirin alone, although the risk of major bleeding doubled.
- The findings of this trial informed NICE technology appraisal guidance, published late last year, recommending extended DAPT with ticagrelor plus aspirin as an option for preventing atherothrombotic events in adults who had an MI and who are at high risk of a further event. Treatment with ticagrelor, which for this indication is used at a lower 60 mg dose twice daily, can continue for up to 3 years. There are limited data to support the efficacy and safety of treatment beyond this period.

What does this evidence add?

- This new study has developed and validated prognostic models for major CV and bleeding events using clinical data from the electronic health records of a cohort of patients in England at 12 months after their last acute MI (i.e. the point at which discussions about whether to prolong DAPT would take place.) These 'real-world' data indicated that the CV event rate was much higher than seen in the PEGASUS-TIMI 54 trial placebo arm.
- They then applied the relative risks from PEGASUS-TIMI 54 to estimate the potential benefits and risk of harms of prolonged DAPT. The greatest benefit was seen in highest risk patients, in whom for every 10,000 people treated per year, 249 CV events (CV death, MI or stroke) were prevented, although this came at a price of 134 additional major bleeds. People at the lowest risk benefited less, with 28 CV events prevented per 10,000 people treated and an additional 9 major bleeds.

- A web-based tool (https://farr-data-lab.shinyapps.io/caliber-prolonged_dapt_benefits_harms_risks/) presents personalised risk predictions based on the multiple prognostic factors identified, which included biomarkers, antithrombotic prescriptions, medical history, smoking status and demographics.
- The study has some important limitations. The researchers did not know which type of coronary stent was used in patients who underwent percutaneous coronary intervention (PCI), which is an important predictor of prognosis after an acute MI. In addition, the investigators used relative risks from the ticagrelor study. It is therefore not clear if the same risks and benefits apply to other antiplatelets that could be used, such as clopidogrel (*although only ticagrelor has a specific licensed indication for use as extended DAPT*). However, these findings highlight the continued high CV risk for patients surviving 12 months after a heart attack, and the online tool may be a useful new resource to use when discussing whether to prolong DAPT.

Study details

Study Population for development and validation of models

- The study used data from the CALIBER (ClinicAl research using LInked Bespoke and Electronic health Records) database, that contains primary-care, secondary-care, disease registry and mortality data, and includes approximately 2 million patients in England.
- The investigators studied people who survived at least 1 year after their last acute MI (combined n for development and validation cohorts = 18,307); the mean age was approximately 70 years and around two-thirds were male. Data were collected between 2000 and 2010, before the launch of ticagrelor and while prolonged DAPT was rare in the UK (only around 3% of patients in the cohort were receiving prolonged DAPT using clopidogrel in addition to aspirin).
- The last acute MI was a non-ST-elevation myocardial infarction (NSTEMI) in approximately 31% of people, a ST-elevation myocardial infarction (STEMI) in 17% and the subtype was unspecified in around 52%. At 1-year post-MI, approximately one-sixth of people had a history of atrial fibrillation and approximately one-quarter had heart failure.

Results

- The authors developed prognostic models providing estimates of major CV event and bleeding risks for patients 12 months after an MI. They identified 20 prognostic factors for inclusion in their CV event model and 18 prognostic factors for inclusion in the bleeding models. For the CV event model, the primary end point related to the potential benefit of prolonged DAPT was a composite of CV death, MI or ischaemic / unspecified stroke. Three bleeding end points assessed the risks of prolonged therapy:
    - fatal or hospitalised bleeding
    - 'CALIBER' major bleeding (a composite of fatal bleeding, intracranial bleeding, hospitalised bleeding with length of stay exceeding 14 days and bleeding requiring transfusion)
    - fatal or intracranial bleeding.

  All-cause mortality was also reported.
- The prognostic models for CV and bleeding events were well-calibrated. Notably, much higher event rates were observed in this 'real-world' study cohort compared to the placebo group in the PEGASUS-TIMI 54 trial for CV events (16.5% versus 9.0%) and for major bleeding (1.7% versus 1.3%).
- Based on the results of the PEGASUS-TIMI 54 trial, the investigators estimated that for every 10,000 people with the highest risk treated with prolonged DAPT, 249 CV events may be prevented per year and 134 major bleeding events caused. The benefits and risks were less in the lowest risk groups, in which 28 CV events may be prevented and 42 major bleeding events caused per 10,000 people treated per year. The authors comment that a potential net benefit of DAPT was observed in most patients, even when avoiding bleeding was considered twice as important as preventing CV events, although the magnitude of benefit should also be considered.
- The authors noted that patient characteristics of the cohorts changed from baseline (i.e. at acute MI discharge) to 1-year post-MI, with increased heart failure and renal disease, and a reduction in smoking rates. This highlights the importance of using up-to-date patient characteristics for clinical decision-making.

Level of evidence:
Level 2 (limited quality patient-oriented evidence) according to the SORT criteria.

Study funding:
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