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The multiplication of loaves and fishes approach: a critic to *double* anti-thrombotics or to *double* number of ischaemic events?

We thank Dr Galli and colleagues for their interest in our meta-analysis.[1,2]

We agree that a very short duration of triple antithrombotic therapy (TAT) after percutaneous coronary intervention (PCI) may expose patients with an indication to oral anticoagulation (OAC) to higher ischaemic risk as previously reported and commented upon.[3,4] The proposed strategy of delaying dual therapy (DAT) onset by some weeks (e.g. 1 month) in OAC patients undergoing PCI seems a reasonable compromise and is being tested against a still relatively short TAT duration of 3-month DAPT in the @@@Management of High Bleeding Risk Patients Post Bioresorbable Polymer Coated Stent Implantation With an Abbreviated vs. Standard DAPT Regimen (MASTER-DAPT) Study.[5]

Our current meta-analysis integrates the previous ones by clarifying the role of clinical presentation (acute or chronic coronary syndrome, ACS or CCS) on safety and efficacy of DAT vs. TAT[1] and the novel message is that the small, yet potentially clinically relevant, ischaemic risks associated with very short TAT does not seem to be confined to ACS patients only.

We respectfully disagree that our primary analysis should have excluded ACS who did not receive index PCI from the AUGUSTUS. As clarified in a previous response letter,[6] the rationale for including all study participants from AUGUSTUS, firstly, comes from the need to respect the randomization process while avoiding arbitrary selection of a post-randomization subgroups, which randomization was not stratified for. We did exclude patients with ACS without PCI in a sensitivity analysis, which confirmed the absence of interaction between clinical presentation and ischaemic or bleeding endpoints and which should not be misinterpreted as suggested by the authors. Subgroup analysis interpretation should be[7,8] based on the presence or absence of significant heterogeneity across strata (ACS and CCS) instead of superiority statistics within each stratum (e.g. PCI population or dabigatran doses).

Secondly, Galli *et al.* statement that ACS without PCI comprises patients who cannot experience stent thrombosis (ST) is not accurate. Galli *et al.* may want to value the fact that even patients who did not receive PCI or stent implantation at the time of the qualifying event may still be exposed to the risk of ST because of stenting procedures performed before the qualifying visit. Indeed, 2 of the overall 32 definite/probable ST cases observed during the study occurred in patients allocated to DAT who received stent implantation prior to the qualifying event and were therefore allocated in the ACS no PCI stratum.[6] We assume Galli *et al.* do not fundamentally disagree with this approach considering that they also included all AUGUSTUS patients in a prior meta-analysis focusing on ST risks.[9]

The point raised on the ST definition is an interesting one. We simply opted for the primary ST definition for each of the four included trials, consisting of definite ST for three studies and definite or probable ST for AUGUSUTUS. The statement that the Academic Research Consortium-2 recommends against the use of definite or probable ST is not precise (the consortium recommends against the use of possible ST due its low specificity). We again assume Galli *et al.* would agree with this approach considering that they also included definite or probable ST in the same prior meta-analysis.[9] It would have been desirable to use a consistent ST definition across trials but the rates of definite ST in patients with or without ACS have not been published for the AUGUSUTUS trial.

Galli *et al.* are also invited to read more carefully our manuscript regarding the apparent inconsistency on ST risk in this compared to our prior meta-analysis, as we wrote: 'Due to missing information on ACS or SCAD presentation, the present analysis excluded 41 (0.4%) among the 10 234 originally included patients across the four selected trials, which explains the apparently inconsistent findings on ST in this compared with a prior meta-analysis'.[1]

We pre-specified to pool both dabigatran doses for the RE-DUAL PCI and run sensitivity analyses for each of the employed dabigatran regimens.[3] This approach respects the RE-DUAL trial design and has been used also by other authors,[10] including Galli *et al.*[9] The tactic of using both doses separately in the same pooled analysis is highly questionable due to the duplication of the control group population, which is a mere artefact. RE-DUAL PCI included 981 patients in the TAT group and acuity of clinical presentation was known for 980 (475 ACS and 505 CCS) in whom a total of 29 myocardial infarction (MI) events occurred (16 in ACS and 13 in CCS) and were included in the present analysis. With the authors' approach, which follows the 'multiplication of loaves and fishes' principle, the TAT group now comprises as many as 1743 patients (844 ACS and 899 CCS) in whom a total of 51 MI events has apparently occurred (27 in ACS and 24 in CCS), which is obviously a pure fabrication and does not correspond to reality. We assume Galli *et al.* would agree with this approach considering that they also recently applied the same.[9]

Finally, testing each dabigatran dose separately against the TAT group further introduces serious biases in the analysis due to different patient eligibility towards the two tested dabigatran regimens across participating regions. In RE-DUAL PCI, all patients in the USA and non-elderly patients in other countries were randomly assigned to the 110-mg DAT, the 150-mg DAT, or TAT in a 1:1:1 ratio. Elderly patients outside the USA were randomly assigned to the 110-mg DAT or TAT in a 1:1 ratio; they were not eligible to be assigned to the 150-mg DAT, in accordance with the recommendations of the dabigatran label in those countries.

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