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European Medicines Agency talks to doctors and industry about revising trial design

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The European Medicines Agency (EMA) has discussed its concept paper for evaluating trial results on treatments for acute coronary syndromes with doctors and drug companies. The conclusions are published today in *European Heart Journal: Acute Cardiovascular Care*.

Ahead of updating its internal guidance, the EMA requested a meeting of the Cardiovascular Round Table (CRT), an independent forum established by the European Society of Cardiology (ESC). The meeting was attended by clinicians, regulators, and scientists from academia and the pharmaceutical industry. Regulators included members of the Cardiovascular Working Party of the EMA and the US Food and Drug Administration (FDA).

Lead author Professor Héctor Bueno said: "The EMA had produced proposals on updating the 'Note for Guidance on Acute Coronary Syndrome' and wanted feedback from academia and industry. So they asked if the CRT would meet to discuss the issue and come up with recommendations."

The group's first recommendation was that trials should use troponin to diagnose myocardial infarction (MI). To establish consistency and facilitate interpretation of data across clinical trials, MI should be defined using the latest guideline on the universal definition of MI.

It was agreed that trials evaluating medicines for acute coronary syndromes (ACS) should include patients with ST-segment elevation

myocardial infarction (STEMI) and patients with non-STEMI (NSTEMI). In certain situations the populations should be studied separately. For example, medicines used during primary percutaneous coronary intervention should be assessed in STEMI alone.

Professor Bueno said: "Scientists often prefer narrow and 'clean' populations but industry seeks marketing authorisation for a broader population. Subgroup analysis can be done as a second step. The discussion showed why there can different views on the optimal trial design because the aims may be different."

Similarly, it was recommended that trials should not focus on high, intermediate or low risk patients but should include patients at all levels of risk. Trials should be designed so that information is collected to enable calculation of the Global Registry of Acute Coronary Events (GRACE) risk score for each patient. Subgroup analysis according to risk can then be conducted as a second step.

"For approval, EU regulators recommend a trial design that includes patients with different clinical profiles and risks, who are in different settings and geographies within the EU," said Professor Bueno. "They want robust, well conducted clinical trials with a clear benefit/risk analysis of the study population and results that could be extrapolated to a broader population treated in day-to-day clinical practice."

The choice of primary endpoint was a hot topic. The historical endpoint is a composite of cardiovascular (CV) death, MI and stroke. But the majority of participants advocated the combination of CV and MI as the primary endpoint for evaluating drugs in patients with ACS. Stroke should be included in the composite primary endpoint only when a drug is suspected to have an impact on strokes, for example anticoagulants.

All-cause death must be recorded for safety and is therefore a key

secondary efficacy endpoint. "Any divergence between the trend for cardiovascular death and all-cause death can be a red flag for a safety issue," said Professor Bueno.

Regardless of trial design, regulators expect background therapy to reflect the current standard of care recommended by guidelines. However, they acknowledged that the availability of drugs and interventions may vary between and within EU countries. As a minimum, the standard of care at regional level should be followed. The comparator drug could be placebo or an active comparator depending on the standard of care and the intended indication.

The challenges of evaluating of novel therapies like gene therapy, antibodies, cell therapy, and RNA-based therapies were highlighted. These included limited trial size and choice of the primary endpoint.

Professor Bueno said: "This was a rich discussion and we hope the conclusions help the three parties agree an approach to designing clinical trials in ACS that promotes the discovery of new treatments."

More information: Report of the European Society of Cardiology Cardiovascular Round Table regulatory workshop update of the evaluation of new agents for the treatment of acute coronary syndrome: Executive summary. *European Heart Journal: Acute Cardiovascular Care*. DOI: 10.1177/2048872616649859

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