Acute Myocardial Infarction: Questions and Decisions

Infarto agudo de miocardio: sobre interrogantes y decisiones

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Two recent communications challenged concepts widely accepted by the cardiology community. The first questions whether interventions with proven efficacy in heart failure with reduced ejection fraction (HFrEF) should necessarily be effective in ventricular dysfunction after acute myocardial infarction (AMI). The second raises the question about the usefulness of indicating beta-blockers (BBs) to all patients after AMI in the absence if HF and, by extension, in ischemic heart disease in the absence of angina.

Discussing how these results impact on clinical practice is as interesting as answering certain questions that may or may not justify the findings.

EMPACT-MI trial

The EMPACT-MI (1) trial evaluated the effect of empagliflozin in post-AMI patients with rEF or signs of HF.

The trial included 6522 post-AMI patients within 14 days after hospitalization (follow-up of 18 months) who were randomized to placebo or empagliflozin. The study showed no difference in the composite end point of readmission for HF or death from any cause.

Several questions arise from this finding.

Why was there no effect despite the unquestionable efficacy of effective interventions in ventricular dysfunction following myocardial infarction?

One might conclude that the question is inappropriate, because there was an effect on rehospitalizations, and that, although gliflozins demonstrated a reduction in mortality in chronic HF, it was a secondary endpoint. However, several meta-analyses have confirmed the reduction in cardiovascular mortality and all-cause mortality. (2)

Is the lack of effect due to having selected a low-risk population?

The low risk is apparent from two considerations:

- In the original sample size calculation, the authors estimated that 3313 patients were needed to be included, a number that had to be increased to 5000, based on the low event rate (6.6%/year for death from any cause or HF rehospitalization).
- When the endpoints of this study are compared with those of gliflozins in chronic HF, (3-4) (Table 1), again it becomes evident that the post-AMI study included a much lower risk population.

Were the inclusion criteria incorrect?

This does not seem to be the case: 60% had EF < 45% and associated congestion, 20% had only EF <45%, and the rest had signs of congestion requiring treatment.

In addition, other risk criteria (Table 2) associated with poor outcomes after AMI were included.

Why did these risk criteria not translate into worse clinical outcomes with a higher event rate?

It is likely that the initially calculated risk was high, but that it could include transient conditions that later resolved spontaneously with treatment.

- The probable involved mechanisms include recovery of myocardium at risk (stunning), associated with the high rate of reperfusion.
- ventricular remodeling
- resolution of the inflammatory state characteristic of the acute phase.

Is there another intervention whose benefit, applicable only to the distant post-AMI period, suggests recovery of myocardial function?

In patients with previously normal EF, and EF < 40% after AMI, the indication for implantable cardioverter-defibrillator should be postponed until day 40 after the acute episode, and only after persistent dysfunction has been proven.

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	EMPACT-MI (1)	DAPA-HF (3)	EMPEROR-Reduced (4)
CV death / HFH (%)	5.7	15.6	21
HFH (%)	3.4	9.8	15.5
Overall mortality (%)	3.8	9.5	10.7

AMI: acute myocardial infarction; CV: cardiovascular; HFH: heart failure hospitalization

Table 1. Annual incidence rate of major events in the placebo group of the empagliflozin trial after AMI (EMPACT-MI) and gliflozin studies in chronic heart failure (DAPA-HF and EMPEROR-Reduced). (1,3,4)

Inclusion criteria

- AMI within 14 days after admission
- recent EF < 45 % or symptoms of congestion (requiring treatment)
- Additional factors (at least one of the following) :
  - >65 years
  - recent EF<35%
  - history of AMI, atrial fibrillation or diabetes
  - glomerular filtration rate < 60 mL/min/1.73 m^2
  - elevated BNP / uric acid levels
  - elevated pulmonary artery pressure
  - three-vessel coronary artery disease
  - peripheral artery disease
  - absence of reperfusion strategy

AMI: acute myocardial infarction; BNP: brain natriuretic peptide; EF: ejection fraction

Table 2. Inclusion criteria in the EMPACT-MI trial (1)

Why did these presumably transient conditions not affect the beneficial effect of other interventions such as neurohormonal blockade with BBs or converting enzyme inhibitors?

These interventions evaluated against placebo might have generated a favorable scenario facilitating the recovery of the hemodynamic condition.

For example, the rate and success of reperfusion strategy is likely to be significantly higher today than when these studies were conducted, resulting in a larger area of potentially salvageable peri-infarct ischemic myocardium.

Does the result of the EMPACT-MI trial in post-AMI patients call into question the effect of gliflozins in chronic HF?

Clearly not. The clinical trials are compelling in terms of reducing the rate of the composite endpoint of death/rehospitalization for HF in patients with reduced or preserved EF with signs of congestion.

In AMI patients with EF < 40%, should gliflozins be indicated at discharge or during outpatient care?

Administration at discharge is probably associated with higher compliance. After discharge, the indication is a feasible option after confirming that the EF is < 40%. In this case, outpatient visits must be systematically scheduled for the following two weeks. This proposal has demonstrated a benefit that extends beyond the indication of gliflozins, resulting also in a global strategy that reduces rehospitalizations.

REDUCE-AMI trial

This open-label, pragmatic randomized study (5) nested in an observational cohort in 3 countries compared treatment with BBs (bisoprolol, 5 mg or metoprolol, 100 mg) versus no treatment with BBs in 5020 AMI patients with preserved EF (≥ 50%) within 7 days after hospitalization, during a mean follow-up of 3.5 years.

There was no difference in the incidence of the primary endpoint, a composite of death from any cause or new AMI.

The following clinically relevant questions may affect decision-making:

Is the result of the study sufficiently definitive to rule out the use of BB in patients with AMI and an EF ≥ 50%?

The open design, the diagnosis of AMI obtained directly from the population-based registry database, and crossovers (18% of patients discontinued BB and 14% of patients who were untreated received them) are limiting factors that may affect the interpretation of the negative result.

Again, is the lack of effect due to the inclusion of a low-risk population?

The trial design initially estimated an endpoint incidence (death from any cause or AMI) of 7.2%/year. During the study, as the actual incidence was less than 3%/year, the sample size was recalculated to 5000 patients. Death from any cause was approximately 1.2 %/year, clearly very low. The study was underpowered.

Is preserved EF a sufficient criterion to select a low-risk population not amenable to BB treatment?

Other factors beyond EF affect the outcome after AMI. In the REDUCE-AMI, age (65 years), diabetes in only 13% of the patients, previous AMI in 7%, atrial fibrillation in <1%, ST-segment elevation in only 33% of the cases and one-vessel disease in 55% of patients are low-risk variables. Under other conditions, AMI patients may be at higher risk even when EF is > 50%.

How can the results of this trial be put into practice?

In AMI patients with reduced EF, the indication for BB is well-established. In those with preserved EF, and until new information becomes available, the decision to indicate BB is based on the associated conditions that determine the patient's overall risk.

Has this study solved the problem of indicating BB in AMI patients with preserved ventricular function?

Definitely not. Further ongoing studies will bring the definitive answer.

Conflicts of interest

None declared.

(See authors' conflict of interests forms on the web).

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