

CVCT Forum 2012



HEART FAILURE TRIALISTS WORKSHOP
Learning from Recent Trials and Shaping the Future of
Heart Failure

Japanese Regulatory Viewpoint

Yuki ANDO

Senior Scientist for Biostatistics

Biostatistics Group/Center for Product Evaluation

Pharmaceuticals and Medical Devices Agency

Disclosure & Disclaimer

- Disclosure
 - I have no potential conflicts of interest to report.
- Disclaimer
 - This is not an official PMDA guidance or policy statement.
 - No official support or endorsement by the PMDA is intended or should be inferred.

Clinical development in Japan

- Transition of Japanese drug development
 - From: domestic clinical development in Japan
 - To: global drug development
- Three major types of clinical development strategies in Japan or multiple countries including Japan
 - Single-country development
 - Bridging development to which foreign clinical trial data are extrapolated
 - Global development with confirmatory global clinical trials
- Optimal strategy should be employed in consideration of ethnic factors in disease characteristics and clinical environment.

Development of HF drug in Japan

- Difference between Japan and western countries
 - Underlying disease in heart failure
 - Ischemic heart disease (West) or dilated cardiomyopathy (J)
 - Dosage of drugs for heart failure and underlying disease
 - E.g., β -blocker, ARB (lower dose in Japan)
- Clinical data for efficacy and safety of heart failure drugs in Japanese patients should be sufficient.
 - Especially for the recommended dose for Japanese
- Ethnic difference is associated with difficulty in using foreign data and participating global clinical trials.

Japanese guidance document

- Guideline on clinical evaluation of heart failure drugs
 - Publication: 29 March 2011
 - Enforcement: 1 April 2012
- Background
 - Necessity of reflecting the latest knowledge of pharmaceutical medicine
 - Further understanding of HF and transition of purpose of treatment for HF to “improvement of survival and QOL of patients”
 - Necessity of providing trial endpoints for HF clinical trials in Japan, based on different background from western countries

Acute heart failure

- Purpose of treatment
 - Improvement of short-term prognosis, subjective and objective symptoms, hemodynamics, and QOL
- Trial endpoint
 - Primary endpoint: success of rescue, mortality and morbidity, subjective symptoms
 - Secondary endpoint: improvement of hemodynamics, QOL, etc.
 - Importance of investigation of not only short-term mortality but long term mortality (not worsen, more than 6 months)
- Possibility of conducting domestic confirmatory clinical trials in Japan
 - Trial size will be relatively small for investigating short-term outcome and follow-up period is also relatively short.

Chronic heart failure

- Purpose of treatment
 - Improvement of mortality, morbidity, and QOL
- Trial endpoint
 - Primary endpoint: mortality, morbidity (for Japanese study, in light of lower mortality from HF in Japan) in most cases, and subjective symptoms
 - Secondary endpoint: QOL, exercise tolerance, hemodynamics, etc.
- Possibility of participating in global clinical trials for investigating mortality
 - It is difficult to conduct large-scale confirmatory trial for mortality in Japan.
 - Careful consideration of ethnic difference and recommended dose for Japanese patients is needed.

Endpoint of HF clinical trial

- Importance of improvement of symptom such as relief of dyspnea or improvement of QOL in HF patients are well-recognized in Japan.
 - Drug for improvement of symptoms may possibly be useful unless it worsen mortality.
- So far it is difficult to reach consensus on how to measure and evaluate subjective endpoint.
 - Collected clinical trial data with possible variables may be potential evidence for validation but need careful review.
- Seeking possible surrogate endpoints is also a consideration.
 - E.g., biomarkers such as BNP, diagnostic imaging, improvement of serious arrhythmia or fluid volume

Thank you for your attention.

- Information

- Email: ando-yuki@pmda.go.jp

- PMDA Homepage (English)

- <http://www.pmda.go.jp/english/index.html>