

Chapter 14. Drugs for Heart Failure

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I. INTRODUCTORY REMARKS

Heart failure (HF) has reached epidemic proportions in the U.S. with nearly 5 millions individuals afflicted with this condition. Despite major advances in the treatment of this condition, both pharmacological and non-pharmacological, HF is responsible for more than 250 000 deaths per year in the US alone. Furthermore, this condition is associated with significant morbidity with almost 1 million hospital admissions each year. Because of this, the management of HF is associated with an annual cost of more than 24 billion dollars. These statistics clearly illustrates that novel therapies, both pharmacological and non-pharmacological, are still required to improve the prognosis of these patients. Unfortunately, the development of new HF drugs is complicated by a lack of established surrogate markers as reliable as blood pressure in hypertension or cholesterol concentrations in dyslipidemia.

II. PHASE II STUDY TO EVALUATE THE EFFECTIVENESS AND SAFETY OF NEW HEART FAILURE DRUGS

II.1. Outline of a typical development plan

This phase generally begins with open, single-blind or double-blind studies comparing various dosages of a new agent in addition to or compared to an established treatment. Frequently, these dosages are derived from the hypertension literature, because these dosages have been proven to be safe and effective. These studies are generally conducted in a limited number of centers.

Results of these pilot studies are vital for appropriate design of key studies, since these small initial trials then lead to large dose-finding multicenter, controlled trials. These studies are generally conducted using a parallel design and compare the investigational drug with placebo or an active-control, depending if it is expected to be used in addition to current treatment or as an alternative to an established treatment. For example, angiotensin receptor blockers (ARBs) were initially compared to angiotensin-converting enzyme (ACE) inhibitors because they were expected to provide a superior clinical benefit through a more complete inhibition of the effects of the renin-angiotensin-aldosterone system, while being better tolerated because they do not cause an accumulation of bradykinin. Oppositely, when experimental data demonstrated that bradykinin accumulation could positively influence the evolution of HF, the addition of an ARB in patients already receiving an ACE inhibitor was investigated with positive results. These dose-finding studies will generally involve patients with HF of moderate to severe symptoms of New York Heart Association (NYHA) II-IV. Asymptomatic patients are usually excluded (NYHA functional class I). End points commonly consist of vital signs, exercise tolerance, hemodynamic measurements, echocardiographic measurements, neurohormone concentrations and patient's assessment of well-being.

The potential for drug interactions with commonly used cardiovascular drugs with a high potential for interaction (warfarin, digoxin) and other drugs known to affect the metabolism of commonly used drugs (cimetidine, rifampin) may also be investigated, but these investigations are generally conducted in healthy or hypertensive patients and, unfortunately, only rarely in HF patients. Because the pharmacokinetics of some agents vary between healthy individuals and patients with HF, it is possible that the importance of a drug interaction could vary between these two patient populations and it would be therefore preferable to evaluate drug interactions of interest in the HF patient population also.

II.2. Short-term studies

II.2.A. Objectives

Evaluate both the short-term efficacy, generally through hemodynamic monitoring, neurohormonal measurements and functional class, and the safety of the agent.

II.2.B. Primary endpoints

Because there is no established surrogate marker to evaluate the efficacy of drugs in HF, endpoints vary greatly in short term studies, but generally consist of either:

- a. Hemodynamic measurements (filling pressures, cardiac index, systemic vascular resistance, blood pressure, heart rate)
- b. Improvement in symptoms or functional class
- c. Improvement in exercise capacity (peak oxygen consumption, sub maximal exercise tolerance or 6 minutes walk test).
- d. Measurements of neurohormones: catecholamines, brain natriuretic peptide (BNP), others.
- e. Echocardiographic or Magnetic Resonance Imaging (MRI) parameters: left ventricular (LV) dimensions, volumes, LV ejection fraction (LVEF), and degree of mitral regurgitation.
- f. Patients' perception of dyspnoea and well-being.

II.2.C. Secondary endpoints

In these initial phase II studies, secondary endpoints will consist of the incidence of adverse drug effects (safety and tolerability) and mortality, cardiovascular events (CV mortality, myocardial infarction, stroke and cause-specific hospitalizations). The impact of the agent under investigation on quality of life may also be evaluated.

II.2.D. Exploratory endpoints

Relationship between dose, efficacy, and adverse effects. Drug withdrawal and rebound effects.

II.2.E. Study design

A least one randomized, double-blinded, parallel-group design, using multiple centers is generally conducted. Patients can be randomized to different doses of the investigated drug versus placebo or an active control, usually with a dose-ranging design. Patients should be receiving an optimal medical therapy at proven or maximally tolerated doses at the beginning of the study; they should be maintained on this regimen throughout the duration of the study. The drug titration period will depend on the agent being investigated and the need to monitor for vital signs, electrolytes, renal and liver function tests. Maintenance phase should be of at least 3 months duration, but no longer than 6 months. At the end of the study, the patients should be withdrawn from the investigational drug based on a pre-established schedule. If the drug is planned to be on the market in a near future, an open label extension phase can be offered to the patient.

Concomitant therapy

Unless contraindicated, all patients should be on optimal medical therapy (both agents and doses) consisting of agents from the following class of agents:

- a. ACE inhibitors or ARBs
- b. Beta-blockers
- c. Spironolactone (in NYHA class III-IV patients)
- d. Diuretics, usually
- e. Digoxin

II.2.F. Planned sample

In these initial trials, the sample size will depend on the end points measured. Typically the smaller initial trials will include approximately 50 to 100 patients, whereas the larger dose-finding trial can include up to a few hundred patients.

II.2.G. Study population

Patients with symptomatic, chronic HF

II.2.H. Specific inclusion criteria

- a. Adults (at least 18 years of age)
- b. Left ventricular ejection fraction $\leq 40\%$ (or 35%), measured in the last 6 months.
- c. NYHA class II-IV symptoms.
- d. Stable symptoms: duration of stability varies according to study (4 days-3 months, except studies of decompensated HF)
- e. Stable medical regimen ≥ 1 month (except diuretics)

II.2.I. Specific exclusion criteria

- a. Inability to provide informed consent
- b. Unstable angina, myocardial infarction or coronary revascularisation within the last 6 weeks-3 months.
- c. Planned cardiac surgery (within 3-6 months).
- d. Significant valvular disease.
- e. Systolic blood pressure < 90 mmHg (except in studies of cardiogenic shock).
- f. Uncontrolled hypertension (blood pressure systolic > 170 mm Hg or diastolic > 105 mm Hg).
- g. Heart rate < 60 bpm for agent causing significant bradycardia.
- h. Advanced heart block without pacemaker.
- i. Significant renal insufficiency (definition varies between trials and the nature of the drug studied).
- j. Significant non-cardiac co-morbidities or laboratory abnormalities.
- k. Pregnancy and women of childbearing potential unless a safe contraception method is used.
- l. A potentially reversible cause of HF (e.g. thyrotoxicosis or uncontrolled supraventricular arrhythmia).
- m. Known drug or alcohol misuse, poor compliance with treatment or any other serious systemic disease that might complicate management and reduce life expectancy.
- n. Administration of any investigational drug within the preceding 30 days.

II.2.J. Tools for assessing endpoints

Primary endpoints

- a. Echocardiography or MRI
- b. Exercise stress test with or without O_2 consumption measurements
- c. Right heart catheter
- d. Blood samples
- e. Visual analog scale (for symptoms' self-evaluation)

Secondary endpoints

- a. Emergency room visits log
- b. Discharge summary: cause & number of hospital admission
- c. Death certificate
- d. Quality of life questionnaire

The measure of the endpoints will be performed according:

- a. Review of the Case Report forms for all clinical events, including queries of the patient's clinical chart if needed
- b. Standardized method of evaluation: Core laboratory for consistency of data: echocardiography, MRI, blood samples (neuro-hormones, BNP, etc.), and exercise stress test.

II.2.K. Specific criteria for early withdrawal and discontinuation

- a. Patient's request/consent withdrawal
- b. Pregnancy

- c. Serious adverse effects
- d. When, in the opinion of the physician, continuation of the therapy is not in the best interest of the patient.

II.2.L. Data analysis method

The analysis of efficacy variables is based on the intention-to-treat principle, which includes all randomized patients. The specific statistical analyses will vary according to the types of variables measured and end points evaluated. All statistical tests are two-sided and statistical significance is generally established with a p value ≤ 0.05 . Multiple statistical methods can be used for the primary and secondary end points.

II.3. Long-term studies

At the end of the randomized phase, it is usual for patients completing short-term studies to be offered an extension phase with open-label follow-up. The objective of this prolongation is to provide data on tolerability and safety during long-term use. The study drug may be continued for as long as it is felt to be clinically beneficial, until the agent is available on the market.

III. PHASE III STUDY TO EVALUATE THE EFFECTIVENESS AND SAFETY OF NEW DRUGS FOR HEART FAILURE

III.1. Outline of a typical development plan

Whereas phase II studies generally focus on surrogate markers of efficacy, phase III trials are specifically designed to evaluate the impact of the drug under investigation on clinical outcomes, mainly death and hospitalization. This phase generally includes at least one large multicenter double-blind, randomized placebo or active control trial of patients with symptomatic HF (NYHA functional class II-IV). Patients with NYHA functional class I are generally excluded because of their lower risk of cardiovascular events. For patients in NYHA II, a criteria for potential instability is often required (ex. hospital admission for HF within 6-12 months or use of diuretics). The follow-up of these studies should be of at least 6 months, preferably 12 months, but can be extended to several years.

III.2. Short-term studies

The design for phase III trials in HF is similar to that described above for phase II trials. Sometimes, multiple doses or regimens are explored.

III.3. Long-term studies

III.3.A. Objectives

To evaluate the long-term efficacy and safety of a given treatment compared with optimal medical management.

III.3.B. Primary endpoints

Mortality (total, cardiovascular), or a combination of mortality and morbidity (which generally consists of cardiovascular hospitalizations or episodes of worsening HF) is usually used.

III.3.C. Secondary endpoints

Secondary endpoints for phase III trials will consist of any of the previously mentioned endpoints not included in the primary endpoints or any components of a combined end point. In addition, drug safety and tolerance is reported as a secondary endpoint. Furthermore, the following can also constitute secondary endpoints: ischemic events (myocardial infarction, angina, need for revascularisation), changes in neurohormones or inflammatory markers levels, exercise tolerance, quality of life or changes in

echocardiographic (or MRI) parameters (left ventricular dimensions, LV ejection fraction [LVEF], ventricular volumes, degree of mitral regurgitation, etc...).

III.3.D. Exploratory endpoints

Exploratory analyses are generally limited to any sub-group analysis not prospectively defined.

III.3.E. Study design

Phase III study are usually multicenter, randomized, double-blinded placebo-controlled or active-controlled studies.

Concomitant therapy

Optimal medical treatment as described for the phase II in section II.2.E.

III.3.F. Planned sample

In phase III trials, the sample size is calculated based on the number of events expected in the population studied during the course of the trial and the expected reduction on these events rate with the new treatment. Usually, several thousand patients are planned to be enrolled.

III.3.G. Study population

As described for phase II studies in the section II.2.G.

III.3.H. Specific inclusion criteria

The inclusion criteria are generally the same as those used for the phase II.

III.3.I. Specific exclusion criteria

The exclusion criteria are generally the same as those used for the phase II. In addition, patients awaiting a cardiac transplantation are often excluded.

III.3.J. Tools for assessing endpoints

Primary endpoints

- a. Clinical end-points committee (CEC): an independent CEC is usually formed to review every event occurring during the course of the study, with blind adjudication.

Secondary end points

- a. Discharge summary (cause & duration of hospitalization)
- b. Worsening HF: chest X-Ray, BNP level, IV diuretic used or number of unplanned HF clinic visits.

The measurement of endpoints is performed as described for the phase II studies in the section II.2.J.

III.3.K. Specific criteria for early withdrawal and discontinuation

These criteria are generally the same as those discussed for phase II trials in section II.2.K.

III.3.L. Data analysis method

The data analysis is performed in an intention to treat fashion although an “on treatment” analysis is sometimes performed retrospectively in some cases (e.g. high rate of withdrawal).

IV. PHASE III STUDY TO EVALUATE THE EFFECTIVENESS AND SAFETY OF NEW DRUGS FOR HEART FAILURE IN SPECIAL POPULATIONS

The majority of HF trials have previously focused on patients with depressed left ventricular systolic function (ex. LVEF < 40%), probably because they have a poorer prognosis than patients with symptomatic HF and

preserved systolic function. Nevertheless, this preserved HF group represents almost a third of all HF patients, but has not been studied extensively. With the aging of the population and the prevalence of diabetes, which has reached epidemic proportions, this group will increase dramatically. Thus, efforts have been put forward lately to study more carefully HF patients with preserved systolic function. Unfortunately, the diagnosis is often difficult, since dyspnoea is often multifactorial (including participation of cardiac causes, hypertension and pulmonary disease). Furthermore, there is a lack of consensus on the criteria to define and investigate this entity. Fortunately, a potential surrogate marker could help differentiate between shortness of breath of pulmonary or cardiac origin, the BNP, which is a hormone secreted mainly by the ventricle in response to stretch.

IV.1. Outline of a typical development plan

Similar to phase III study as outlined in section III.1, except for the inclusion criteria.

IV.2. Long term studies

IV.2.A. Objectives

As described for phase III studies in section III.3.A.

IV.2.B. Primary endpoints

As described for phase III studies in section III.3.B.

IV.2.C. Secondary endpoints

As described for phase III studies in section III.3.C.

IV.2.D. Study design

As described for phase III studies in section III.3.E.

Concomitant therapy

Optimal medical treatment is unknown in this patients' group, and usually relies on the treatment of concomitant illnesses (ex. ischemia, dyslipidemia, diabetes, hypertension, etc.).

IV.2.E. Planned sample

As for phase III trials of HF patients with systolic dysfunction, the sample size is calculated based on the number of events expected in the population studied during the course of the study and the expected reduction on these events rate with the new treatment. Unfortunately, since HF with preserved systolic function has not been fully studied, assumptions on prognosis and number of events are currently difficult to assess.

IV.2.F. Study population

- a. Preserved LV systolic function (EF > 40%)
- b. Others, as outline for phase II studies in section II.2.G.

IV.2.G. Specific inclusion criteria

The inclusion criteria are similar to those described for phase II studies in section II.2.H.

IV.2.H. Specific exclusion criteria

The exclusion criteria are similar to those described for phase II studies in section II.2.I.

IV.2.I. Tools for assessing endpoints

The tools to assess and measure the endpoints are usually the same as those used during the phase III in section III.3.J.

IV.2.J. Specific criteria for early withdrawal and discontinuation

Usually the same as those discussed for phase II trials in section II.2.K.

IV.2.K. Data analysis method

Usually the same as those used for the phase III in section III.3.L., but special emphasis should be put on the number of events needed (see above).

V. PHASE IV STUDIES

Phase IV studies are usually large-scale, open-label postmarketing surveillance trials. These studies take place once the FDA or EMEA has approved the agent. The goal is to evaluate if the safety and efficacy of the agent evaluated in controlled studies is maintained in a large population. These usually include patients from subgroups potentially at higher risk for adverse events. Physicians systematically document their observations concerning patients with HF on case report forms. This trial design is rarely used in the HF population.

V.1. Outline of a typical development plan

Similar to phase II and III studies outlined above.

V.2. Short-term study

V.2.A. Objectives

The goal is to find if the safety and efficacy of the pharmacological agent as evaluated in controlled studies is maintained in a large population. The duration is usually 6 months.

V.2.B. Primary endpoints

Similar to phase II and III studies outlined in section II.2.B. and III.3.B. In addition, global tolerability is rated among specific subgroups of patients: genders, age and co-morbidities. Quality of life questionnaire can also be included.

V.2.C. Secondary endpoints

Similar to phase II and III studies outlined in sections II.2.C. and III.3.C.

V.2.D. Study design

Randomized, active-controlled, open-label study

Concomitant therapy

As described in the phase II outline in section II.2.E.

V.2.E. Planned sample

While for antihypertensive drugs several thousand patients are usually necessary, the study of drugs indicated for HF usually include smaller cohorts. The number of patients enrolled in these trials have been as small as 50 and, generally, is limited to no more than a few hundred patients.

V.2.F. Study population

As described in the phase II studies outlined in section II.2.G.

V.2.G. Specific inclusion criteria

As described in the phase II studies outlined in section II.2.H.

V.2.H. Specific exclusion criteria

As described in the phase II studies outlined in section II.2.I.

V.2.I. Tools for assessing endpoints

- a. Tolerability questionnaire
- b. Blood samples
- c. Exercise tolerance test

Measure of endpoints

As described in the phase II outlined in section II.2.J.

V.2.J. Specific criteria for early withdrawal and discontinuation

As described in the phase II outlined in section II.2.K.

V.2.K. Data analysis method

As described in the phase II outlined in section II.2.L.

V.3. Long-term studies

V.3.A. Objectives

The goal is to compare the effects of drug A and drug B on clinical outcome. The duration may be up to 5 years. The only example of a phase IV study in patients with HF is the recently published COMET (Carvedilol Or Metoprolol European Trial). Since beta-blockers have been shown to reduce mortality in HF patients with systolic dysfunction, they aimed to compare the effects of carvedilol and metoprolol on clinical outcome, in patients who were on background treatment with diuretics and ACE inhibitors. The methods of the COMET trial will be used as an example of phase IV study.

V.3.B. Primary endpoints

The primary end points of the COMET study were all-cause mortality and the composite end point of all-cause mortality or all-cause admission.

V.3.C. Secondary endpoints

Similar to the ones described for phase III trial.

V.3.D. Study design

Randomized, active-controlled, open-label or double-blind study (COMET).

Concomitant therapy

- a. On stable HF treatment with ACE inhibitors for ≥ 4 weeks unless contraindicated.
- b. On treatment with diuretics (≥ 40 mg of furosemide or equivalent) for at least 2 weeks.
- c. Digitalis, ARBs, or other vasodilators could be used at the discretion of the investigators.

V.3.E. Planned sample

The COMET study was planned as an event-driven parallel-group survival study to compare carvedilol and metoprolol with respect to all-cause mortality. A total of 1020 fatal events were needed to detect a risk reduction of 20% with at least 80% power with an overall type I error of 0.05.

V.3.F. Study population

Eligible patients were men or women with symptomatic chronic HF (New York Heart Association [NYHA] class II–IV),

V.3.G. Specific inclusion criteria

- a. At least one cardiovascular admission during the previous 2 years.
- b. LV ejection fraction ≤ 0.35 , measured within the previous 3 months or left-ventricular end diastolic diameter ≥ 6.0 cm and a fractional shortening $< 20\%$ measured by echocardiography.

V.3.H. Specific exclusion criteria

- a. A recent change of treatment, current treatment with diltiazem or verapamil, amiodarone (>200 mg per day) or class-I antiarrhythmic drugs.
- b. Patients with unstable angina, myocardial infarction, or coronary revascularisation or stroke within the previous 2 months.
- c. Uncontrolled hypertension (blood pressure systolic >170 mm Hg or diastolic >105 mm Hg).
- d. Hemodynamically significant valvular disease.
- e. Symptomatic and sustained ventricular arrhythmias within the past 2 months not adequately treated with antiarrhythmic drugs or defibrillator.
- f. Pregnancy, women with childbearing potential on inadequate contraception.
- g. Known drug or alcohol misuse, poor compliance with treatment.
- h. Any other serious systemic disease that might complicate management and reduce life expectancy.
- i. Patients in whom there was a contraindication to use of β -blockers, such as resting heart rate < 60 bpm, sick sinus syndrome, bifascicular block, second or third degree atrioventricular block unless treated with a pacemaker, sitting systolic blood pressure < 85 mm Hg, history of asthma or chronic obstructive pulmonary disease, peripheral arterial disease with symptoms at rest, or unstable insulin-dependent diabetes mellitus.

V.3.I. Tools for assessing primary endpoints

As described in the phase III outlined in section III.3.J.

Measure of end points

As described in the phase III outlined in section III.3.J.

V.3.J. Specific criteria for early withdrawal and discontinuation

As described in the phase II outlined in section II.2.K.

V.3.K. Data analysis method

Analysis was done by intention to treat.

V.4. Comments

Although the phase IV study design is common in clinical research focusing on hypertension, it is infrequently conducted in the HF population. Only one large phase IV study including patients with HF has been published, which is described in detail above.

VI. EXAMPLES OF LANDMARK WELL DESIGNED TRIALS

Phase II studies

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Phase III studies

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Phase III –Special population (HF with preserved LVEF)

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Phase IV

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VII. SUGGESTED READINGS

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6. Seminar in new drug development: <http://www.fda.gov/cder/learn/CDERLearn/default.htm>