J-MELODIC

利尿薬のクラス効果に基づいた慢性心不全に対する効果的薬物療法の確立に関する多施設共同臨床研究

試験概要　：

利尿薬が投与されている慢性心不全例の予後・ＱＯＬ，左心機能が
短時間作用型の利尿薬（フロセミド）と長時間作用型の利尿薬（アゾセミド）で
異なるかを比較検討する多施設共同臨床研究

主任研究者：
兵庫医科大学　内科学　循環器内科　増山　理

対象：
利尿薬が投与されている慢性心不全症例

試験デザイン：
前向き無作為オープン比較試験

参加施設：全国２６施設（２００８年３月現在　五十音順）
秋田組合総合病院，秋田県立脳血管研究センター，
秋田大学医学部附属病院，尼崎中央病院，医誠会病院，茨木医誠会病院，
大阪大学医学部附属病院，大阪南医療センター，大阪労災病院，
川崎病院，関西労災病院，近畿大学医学部附属病院，熊本託麻台病院，
国立循環器病センター，湖東総合病院，宝塚市立病院，町立津南病院，
寺元記念病院，名古屋市立大学病院，奈良県立医科大学附属病院，
東宝塚さとう病院，兵庫医科大学病院，平鹿総合病院，藤原記念病院，
本荘第一病院，和歌山医科大学病院

http://j-melodic.com/

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添付資料６

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Study 1 of 41 for search of: congestive heart failure, diuretics
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Comparison of Long- and Short-Acting **Diuretics** in **Congestive Heart Failure**

This study is currently recruiting participants.
Verified by Hyogo College of Medicine, June 2007

Sponsors and Collaborators:	**Hyogo College of Medicine** Ministry of Health, Labour and Welfare
Information provided by:	Hyogo College of Medicine
ClinicalTrials.gov Identifier:	NCT00355667

Purpose

The purpose of this study is to compare therapeutic effects of furosemide, a short-acting loop **diuretic**, and azosemide, a long-acting one, in patients with **heart failure**, and to test our hypothesis that long-acting **diuretics** are superior to short-acting types in **heart failure**.

Condition	Intervention	Phase
Congestive Heart Failure	Drug: furosemide Drug: azosemide	Phase IV

MedlinePlus related topics: Heart Failure

ChemIDplus related topics: Furosemide Azosemid

U.S. FDA Resources

Study Type: Interventional
Study Design: Treatment, Randomized, Open Label, Active Control, Parallel Assignment, Efficacy Study
Official Title: Japanese Multicenter Evaluation of Long- Versus Short-Acting **Diuretics** in **Congestive Heart Failure**

Further study details as provided by Hyogo College of Medicine:

Primary Outcome Measures:

- unplanned admission to hospital for **congestive heart failure**. [Time Frame: 2 years]

Secondary Outcome Measures:

- all cause mortality [Time Frame: 2 years]
- worsening of the symptoms (that is defined by either a decrease by <1 Mets in the SAS questionnaire score or an increase by >I class in the NYHA functional class for at least 3 months as compared with the baseline) [Time Frame: 2 years]

- an increase in brain natriuretic peptide (BNP) by > 30% of the value at the randomization in patients with BNP < 200 pg/ml at the randomization [Time Frame: 2 years]
- a need for modification of the treatment for **heart failure** (changes in oral medicine for at least one month or addition of intravenous drug(s) for at least 4 hours) [Time Frame: 2 years]

Estimated Enrollment: 300
Study Start Date: June 2006
Estimated Study Completion Date: March 2010

Detailed Description:

The mortality and morbidity of heart failure are still high despite emerging evidences that have shown beneficial effects of ACE inhibitor, beta-blocker, ARB, and aldosterone receptor antagonist. Diuretics are the most prescribed in heart failure patients in attenuating symptoms due to fluid retention, and diuretics are recommended as essential medicines in patients with heart failure symptoms and/or fluid retention. However, the effects of a long-term administration of diuretics on morbidity and mortality have not been adequately assessed in the prospective clinical study, and the retrospective analysis did not necessarily indicate the diuretic-induced improvement of mortality. McCurley et al demonstrated the adverse effects of furosemide in a tachycardia-induced heart failure model (J Am Coll Cardiol 2004; 44: 1301-1307). Yoshida et al. demonstrated that the administration of furosemide did not improve mortality rate, while the administration of azosemide, a long-acting loop diuretic, improved mortality rate in a hypertensive heart failure model (Cardiovasc Res 2005; 68: 118-127). If the effects on mortality and/or morbidity of heart failure patients are different among classes of diuretics, we should choose a class to provide better prognosis. Thus, we designed a multicenter prospective study, J-Melodic (Japanese Multicenter Evaluation of LOng- versus short-acting Diuretics In Congestive heart failure) to obtain a clinical evidence about the effects of diuretics in heart failure.

Comparison: Congestive heart failure patients matched with the following conditions will be recruited: (1) clinical diagnosis of heart failure based on a slight modification of the Framingham criteria within 6 months before the entry, (2) twenty years or older, (3) NYHA II or III, (4) loop diuretic (s) is (are) administered currently, (5) no change in baseline therapy and symptoms of heart failure within a month. After screening for eligibility and obtaining written informed consent, patients will be randomized to either azosemide or furosemide treatment in a 1:1 ratio. In any arms, patients are treated with standard therapy including digitalis, mineralocorticoid receptor blockers, ACE inhibitors, ARB, beta-blockers, and calcium channel blockers. Patients discontinued taking previous loop diuretic(s) and were directly rolled over to one of the two arms with either azosemide 30-60 mg/day or furosemide 20-40 mg/day, without a placebo run-in period. The dose of each diuretic will be appropriately adjusted according to symptoms of each patient, and patients will be maintained for the rest of the study. Thereafter, patients are reviewed every 2 to 8 weeks. The planned minimum follow-up period for each patient is 2 years, and electrocardiography, chest X-ray and blood sample will be conducted at the study entry and every 12 months after the randomization.

The primary outcome is a composite of cardiovascular death and unplanned admission to hospital for congestive heart failure. The secondary outcomes are listed as follows: all cause mortality; worsening of the symptoms [that is defined by either a decrease by (1) 1 Mets in the SAS questionnaire score or an increase by (2) I class in the NYHA functional class for at least 3 months as compared with the baseline]; an increase in brain natriuretic peptide (BNP) by more than 30% of the value at the randomization in patients with BNP less than 200 pg/ml at the randomization; unplanned admission to hospital for congestive heart failure, or a need for modification of the treatment for heart failure (changes in oral medicine for at least one month or addition of intravenous drug(s) for at least 4 hours).

Eligibility

Ages Eligible for Study: 20 Years and older
Genders Eligible for Study: Both
Accepts Healthy Volunteers: No

Criteria

Inclusion Criteria:

- Clinical diagnosis of heart failure based on a slight modification of the Framingham criteria as previously described within 6 months before the entry

- Current status of heart failure is NYHA II or III.
- Currently, loop diuretic(s) is (are) administered.
- No change in baseline therapy and symptoms of heart failure within a month

Exclusion Criteria:

- Current symptomatic hypotension
- Hypertension that has not been controlled to the satisfaction of the investigator
- Hemodynamically significant (in the investigators opinion) LV outflow tract obstruction (due to either aortic stenosis or ventricular hypertrophy)
- Acute coronary syndrome
- Primary pulmonary hypertension or pulmonary hypertension not due to LV dysfunction
- Serious cerebrovascular disease
- Acute myocardial infarction within the last 3 months
- Patients who require intravenous inotropes
- Cerebrovascular accident within the last 3 months
- Percutaneous coronary intervention or open heart surgery within the last 3 months
- On the waiting list for percutaneous coronary intervention or open heart surgery
- Serum creatinine > 2.5 mg/dl
- Serious liver disease
- Any change in cardiovascular drug therapy within a month prior to randomization
- History of chronic obstructive pulmonary disease or restrictive lung disease
- Diabetes mellitus that has not been well controlled (fasting blood glucose>200 mg/dl、HbA1c > 8%)
- Any life-threatening acute disease
- Patients with implantable cardiac defibrillator
- Other diseases likely to cause death or serious disability during the period of the study
- Patients unable to walk without personal aid

Contacts and Locations

Please refer to this study by its ClinicalTrials.gov identifier: NCT00355667

Contacts

Contact: Takeshi Tsujino, MD, PhD	+81-798-45-6553	ttsujino@hyo-med.ac.jp
Contact: Tohru Masuyama, MD, PhD	+81-798-45-6553	masuyama@hyo-med.ac.jp

Locations

Japan, Hyogo

The Hospital of Hyogo College of Medicine — Recruiting

Nishinomiya, Hyogo, Japan, 663-8501

Contact: Takeshi Tsujino, MD, PhD +81-798-45-6553 ttsujino@hyo-med.ac.jp

Contact: Tohru Masuyama, MD, PhD +81-798-45-6553 masuyama@hyo-med.ac.jp

Principal Investigator: Tohru Masuyama, MD, PhD

Sponsors and Collaborators

Hyogo College of Medicine

Ministry of Health, Labour and Welfare

Investigators

Principal Investigator: Tohru Masuyama, MD, PhD Cardiovascular Division, Hyogo College of Medicine

More Information

J-MELODIC home page (in Japanese) This link exits the ClinicalTrials.gov site

Publications:

Yoshida J, Yamamoto K, Mano T, Sakata Y, Nishio M, Ohtani T, Hori M, Miwa T, Masuyama T. Different effects of long- and short-acting loop diuretics on survival rate in Dahl high-salt heart failure model rats. Cardiovasc Res. 2005 Oct 1;68(1):118-27.

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ClinicalTrials.gov Identifier: NCT00355667

Health Authority: Japan: Ministry of Health, Labor and Welfare

Keywords provided by Hyogo College of Medicine:
diuretics
furosemide
azosemide
congestive heart failure

Study placed in the following topic categories:
Heart Failure
Azosemid
Heart Diseases
Furosemide

Additional relevant MeSH terms:

Heart Diseases	Therapeutic Uses
Diuretics	Physiological Effects of Drugs
Heart Failure	Cardiovascular Diseases
Membrane Transport Modulators	Cardiovascular Agents
Molecular Mechanisms of Pharmacological Action	Sodium Potassium Chloride Symporter Inhibitors
Natriuretic Agents	Pharmacologic Actions

ClinicalTrials.gov processed this record on March 31, 2008

UMIN-CTR　試験情報の閲覧

ＵＭＩＮ試験ＩＤ：UMIN000000528

試験名：　利尿薬のクラス効果に基づいた慢性心不全に対する効果的薬物療法の確立に関する多施設共同臨床研究

登録日：　2006/11/23 15:05:59

更新日：　2007/06/08 15:12:04

基本情報 (Basic information)		
項目(Item)	日本語(Japanese)	英語(English)
試験名 (Official scientific title of the study)	利尿薬のクラス効果に基づいた慢性心不全に対する効果的薬物療法の確立に関する多施設共同臨床研究	Japanese Multicenter Evaluation of LOng-versus short-acting Diuretics In Congestive heart failure
試験簡略名 (Title of the study (Brief title))	J-MELODIC	J-MELODIC
試験実施地域 (Region)	日本/Japan	

対象疾患(Condition)		
項目(Item)	日本語(Japanese)	英語(English)
対象疾患名 (Condition)	うっ血性心不全	congestive heart failure
疾患区分1 (Classification by specialty)	循環器内科学/Cardiology	
疾患区分2 (Classification by malignancy)	がん以外/Others	
ゲノム情報の取扱い (Genomic information)	いいえ/NO	

目的(Objectives)		
項目(Item)	日本語(Japanese)	英語(English)

目的1 (Narrative objectives1)	日本における慢性心不全症例は200−250万人に至ると推測される。わが国では海外で行われた大規模臨床試験の結果をもとに、心不全診療に関するガイドラインが作成され、心不全診療の最適化が図られている。しかし、いまだに慢性心不全症例の10年生存率は30%程度に過ぎない。心不全治療の最大の目的は生命予後およびQOLの改善である。かかる観点から作成された日本および欧米の心不全治療ガイドラインにおいて、利尿薬は心不全患者に対して積極的に投与すべき基本治療薬のひとつである。実際、わが国において利尿薬は慢性心不全患者の約70%の患者に投与されている。ACE阻害薬、β遮断薬など他の心不全基本治療薬の効果は欧米の大規模試験により確認されている。しかし、利尿薬の生命予後改善効果に関するエビデンスは無い。むしろ、最近の心不全モデル動物を用いた実験で、短時間作用型利尿薬は生命予後を悪化させる可能性が示された(J Am Coll Cardiol 2004; 44: 1301-1307)。また、我々は心不全モデル動物実験により、長時間作用型利尿薬と短時間作用型利尿薬では予後改善効果が異なる、すなわち生存率改善効果は短時間作用型利尿薬に比し長時間作用型利尿薬で優れていることを明らかにした(Cardiovasc Res 2005; 68: 118-127)。短時間作用型利尿薬では交感神経やレニン・アンジオテンシン系が反射性に活性化されたが、長時間作用型ではこれらが回避されており、予後改善効果に結びついたと考えられた。そこで本臨床研究では、慢性心不全症例を対象とし、長時間作用型利尿薬アゾセミドと短時間作用型利尿薬フロセミドの効果を、前向き無作為オープン比較試験により検討する。また、神経体液性因子や生理学的検査指標の推移を比較検討し、両者の間に有効性において差異が存在する場合には、その機序を明らかにする。現在、わが国で心不全症例に投与されている利尿薬の80%が短時間作用型利尿薬である。動物実験で示された長時間作用型利尿薬の優位性が本臨床試験でも示された場合、日本・欧米の慢性心不全治療ガイドラインにおける基本治療薬の部分を大きく変え、現在わが国において100万人以上で投与されている短時間作用型利尿薬は今後長時間作用型利尿薬に変更すべきであることが推奨されることになる。	The mortality and morbidity of heart failure are still high despite emerging evidences that have shown beneficial effects of ACE inhibitor, beta-blocker, ARB, and aldosterone receptor antagonist. Diuretics are the most prescribed in heart failure patients in attenuating symptoms due to fluid retention, and diuretics are recommended as essential medicines in patients with heart failure symptoms and/or fluid retention. However, the effects of a long-term administration of diuretics on morbidity and mortality have not been adequately assessed in the prospective clinical study, and the retrospective analysis did not necessarily indicate the diuretic-induced improvement of mortality. McCurley et al demonstrated the adverse effects of furosemide in a tachycardia-induced heart failure model (J Am Coll Cardiol 2004; 44: 1301-1307). Yoshida et al. demonstrated that the administration of furosemide did not improve mortality rate, while the administration of azosemide, a long-acting loop diuretic, improved mortality rate in a hypertensive heart failure model (Cardiovasc Res 2005; 68: 118-127). If the effects on mortality and/or morbidity of heart failure patients are different among classes of diuretics, we should choose a class to provide better prognosis. Thus, we designed a multicenter prospective study, J-Melodic (Japanese Multicenter Evaluation of LOng- versus short-acting Diuretics In Congestive heart failure) to obtain a clinical evidence about the effects of diuretics in heart failure. The purpose of this study is to compare therapeutic effects of furosemide, a short-acting loop diuretic, and azosemide, a long-acting one, in patients with heart failure, and to test our hypothesis that long-acting diuretics are superior to short-acting types in heart failure.
目的2 (Basic objectives2)	有効性/Efficacy	
目的2 -その他詳細 (Basic objectives - Others)		
試験の性質1 (Trial characteristics_1)	検証的/Confirmatory	
試験の性質2 (Trial characteristics_2)	説明的/Explanatory	
試験のフェーズ (Developmental phase)	第IV相/Phase IV	

評価 (Assessment)		
項目(Item)	日本語(Japanese)	英語(English)
主要アウトカム評価項目 (Primary outcomes)	心不全症状の悪化による、入院または心血管死	A composite of cardiovascular death and unplanned admission to hospital for congestive heart failure.
副次アウトカム評価項目 (Key secondary outcomes)	1、全死亡 2、ＱＯＬの変化（3ヶ月以上にわたるSAS 1Mets以上の低下ないしNYHA I度以上の悪化） 3、ＢＮＰの上昇（割付前に200 pg/ml以上の患者で、割付前より30%以上の上昇）(ランダム化の1年後、2年後に評価する) 4、心不全症状の悪化により、以下のいずれかの処置が必要となった場合 a)入院 b)すでに用いている、試験薬あるいは併用薬の中止・減量・増量（1ヶ月以上持続した場合） c) 併用可能薬・試験薬（現在服用していないもの）・試験薬が属するクラス（利尿薬）の他の薬剤（併用不可能薬）いずれかを「心不全治療」目的で新規追加（追加後1ヶ月以上経過した場合）、静注投与用抗心不全薬の4時間以上の投与	1. All cause mortality 2. Worsening of the symptoms [that is defined by either a decrease by (a) 1 Mets in the SAS questionnaire score or an increase by (b) I class in the NYHA functional class for at least 3 months as compared with the baseline] 3. An increase in brain natriuretic peptide (BNP) by more than 30% of the value at the randomization in patients with BNP more than or equal to 200 pg/ml at the randomization. 4. Unplanned admission to hospital for congestive heart failure, or a need for modification of the treatment for heart failure (changes in oral medicine for at least one month or addition of intravenous drug(s) for at least 4 hours).

基本事項 (Base)		
項目(Item)	日本語(Japanese)	英語(English)
試験の種類 (Study type)	介入/Interventional	

試験デザイン (Study design)		
項目(Item)	日本語(Japanese)	英語(English)
基本デザイン (Basic design)	並行群間比較/Parallel	
ランダム化 (Randomization)	ランダム化/Randomized	
ランダム化の単位 (Randomization unit)	個別/Individual	
ブラインド化 (Blinding)	オープンだが測定者がブラインド化されている/Open -but assessor(s) are blinded	
コントロール (Control)	実薬・標準治療対照/Active	
層別化 (Stratification)	はい/YES	
動的割付 (Dynamic allocation)	はい/YES	

試験実施施設の考慮 (Institution consideration)	
ブロック化 (Blocking)	
割付コードを知る方法 (Concealment)	中央登録/Central registration

介入 (Intervention)		
項目(Item)	日本語(Japanese)	英語(English)
群数 (No. of arms)	2	
介入の目的 (Purpose of intervention)	治療・ケア/Treatment	
介入の種類 (Type of intervention)	医薬品/Medicine	
介入1 (Interventions/ Control_1)	選択基準をみたす慢性心不全患者３００例を対象とし、２群（１：１の割合）に無作為に割付を行い、そのうちの1群をアゾセミド群として、アゾセミド錠を一日一回朝食後　30mg～60mg経口投与する。原則的に本試験終了時まで観察追跡を行うこととする。 なお投与量については、アゾセミド錠30mgがフロセミド20mgに相当するものとして用量を設定するが、症例に応じて主治医の判断で決めることが可能。　担当医師は、投与開始後８週間以内に、可能な限り安定投与量に到達しておく。また利尿薬の変更にともない心不全症状が出現した場合は、薬剤の減量が原因と考えられる場合には投与量を増量し、経過を追い、心不全症状の出現をエンドポイントとしてカウントしない。フロセミド・アゾセミド以外のループ利尿薬（サイアザイド系利尿薬やカリウム保持性利尿薬は併用可）のみ併用禁止薬とする。 観察期間は最低2年間とする。 割付前、1年後、2年後、および終了時に以下の項目を調査する。 自覚症状、身体所見、重症度（NYHA心機能分類）、身体活動能力指数（METs）、体重、血圧、脈拍、一般血液検査、血中神経体液性因子（ＢＮＰ、ノルエピネフリン）、心電図、胸部レントゲン等。	After screening for eligibility and obtaining written informed consent, patients will be randomized to 2 groups in a 1:1 ratio. Patients discontinued taking previous loop diuretic(s) and are directly rolled over to one of the two arms. One arm is azosemide group, and patients will take azosemide 30-60 mg/day without a placebo run-in period. Patients are treated with standard therapy including digitalis, mineralocorticoid receptor blockers, ACE inhibitors, ARB, beta-blockers, and calcium channel blockers. The dose of each diuretic will be appropriately adjusted according to symptoms of each patient, and patients will be maintained for the rest of the study. The planned minimum follow-up period for each patient is 2 years, and SAS evaluation, electrocardiography, chest X-ray and blood sample will be conducted at the study entry and every 12 months after the randomization.

介入2 (Interventions/ Control_2)	選択基準をみたす慢性心不全患者３００例を対象とし、２群（１：１の割合）に無作為に割付を行い、そのうちの1群をフロセミド群として、フロセミド錠を一日一回朝食後20mg～40mg経口投与する。原則的に本試験終了時まで観察追跡を行うこととする。 なお投与量については、フロセミド20mgがアゾセミド錠30mgに相当するものとして用量を設定するが、症例に応じて主治医の判断で決めることが可能。　担当医師は、投与開始後８週間以内に、可能な限り安定投与量に到達しておく。 また利尿薬の変更にともない心不全症状が出現した場合は、薬剤の減量が原因と考えられる場合には投与量を増量し、経過を追い、心不全症状の出現をエンドポイントとしてカウントしない。フロセミド・アゾセミド以外のループ利尿薬（サイアザイド系利尿薬やカリウム保持性利尿薬は併用可）のみ併用禁止薬とする 観察期間は最低2年間とする。 割付前、1年後、2年後、および終了時に以下の項目を調査する。 自覚症状、身体所見、重症度（NYHA心機能分類）、身体活動能力指数（METs）、体重、血圧、脈拍、一般血液検査、血中神経体液性因子（ＢＮＰ、ノルエピネフリン）、心電図、胸部レントゲン等。	After screening for eligibility and obtaining written informed consent, patients will be randomized to 2 groups in a 1:1 ratio. Patients discontinued taking previous loop diuretic(s) and are directly rolled over to one of the two arms. One arm is furosemide group, and patients will take furosemide 20-40 mg/day without a placebo run-in period. Patients are treated with standard therapy including digitalis, mineralocorticoid receptor blockers, ACE inhibitors, ARB, beta-blockers, and calcium channel blockers. The dose of each diuretic will be appropriately adjusted according to symptoms of each patient, and patients will be maintained for the rest of the study. The planned minimum follow-up period for each patient is 2 years, and SAS evaluation, electrocardiography, chest X-ray and blood sample will be conducted at the study entry and every 12 months after the randomization.
介入3 (Interventions/ Control_3)		
介入4 (Interventions/ Control_4)		
介入5 (Interventions/ Control_5)		
介入6 (Interventions/ Control_6)		
介入7 (Interventions/ Control_7)		
介入8 (Interventions/ Control_8)		
介入9 (Interventions/ Control_9)		
介入10 (Interventions/ Control_10)		

適格性 (Eligibility)		
項目(Item)	日本語(Japanese)	英語(English)

年齢（下限） (Age-lower limit)	20 歳/years-old 以上/<=	
年齢（上限） (Age-upper limit)	適用なし/Not applicable	
性別 (Gender)	男女両方/Male and Female	
選択基準 (Key inclusion criteria)	1．過去６ヶ月以内にFraminghamの心不全基準を満たす心不全が確認されている ２．現在、NYHA II-III（左室駆出率は問わない） ３．１ヶ月以上投薬内容の変更なく安定している ４．現在、ループ利尿薬が投与されている ５．文書による同意を取得できている	1. Clinical diagnosis of heart failure based on a slight modification of the Framingham criteria within 6 months before the entry 2. NYHA II or III 3. No change in baseline therapy and symptoms of heart failure within a month 4. Loop diuretic(s) is (are) administered currently 5. Written informed consent was obtained.
除外基準 (Key exclusion criteria)	１．コントロール不良の糖尿病（空腹時血糖>200 mg/dl、HbA1c > 9%） ２．有症状の低血圧 ３．コントロール不良の高血圧 ４．腎不全（クレアチニン>2.5mg/dl） ５．重篤な肝機能障害 ６．急性冠症候群 ７．生命を脅かす急性疾患を有する症例（植え込み型除細動器の装着例含む） ８．閉塞性肥大型心筋症 ９．肺疾患（ＣＯＰＤ等） １０．原発性肺高血圧症など左心機能障害によらない肺高血圧 １１．過去３ヶ月以内に心筋梗塞や脳梗塞、脳出血を発症した、あるいは経皮的冠動脈形成術、 開心術を受けた症例 １２．冠動脈バイパス術、経皮的冠動脈形成術が予定されている症例 １３．過去１ヶ月以内に血管拡張薬、心不全治療薬の投与量に変更があった症例 １４．悪性腫瘍の存在が明らかな症例 １５．5年以内に悪性腫瘍の摘出術を受けた症例 １６．介助なしに歩行できない症例 １７．重篤な脳血管障害を有する患者 １８．登録時に、カテコラミンやＰＤＥIII阻害薬の静脈内投与を受けている １９．妊娠中、授乳中、妊娠している可能性のある患者、あるいは試験期間中に妊娠を希望する 患者 ２０．主治医が本試験へのエンロールが不適と認める症例	1. Diabetes mellitus that has not been well controlled (fasting blood glucose > 200 mg/dl, HbA1c > 9%) 2. Current symptomatic hypotension 3. Hypertension that has not been controlled to the satisfaction of the investigator 4. Serum creatinine > 2.5 mg/dl 5. Serious liver disease 6. Acute coronary syndrome 7. Any life-threatening acute disease (including patients with implantable cardiac defibrillator) 8. Hemodynamically significant (in the investigators opinion) LV outflow tract obstruction (due to either aortic stenosis or ventricular hypertrophy) 9. Chronic obstructive pulmonary disease or restrictive lung disease 10. Primary pulmonary hypertension or pulmonary hypertension not due to LV dysfunction 11. Acute myocardial infarction or cerebrovascular accident within the last 3 months 12. Percutaneous coronary intervention or open heart surgery within the last 3 months 13. Any change in cardiovascular drug therapy within a month prior to randomization 14. Malignancy 15. Surgery for resecting malignant tumor within 5 years 16. Patients unable to walk without personal aid 17. Serious cerebrovascular disease 18. Patients who require intravenous inotropes 19. Pregnancy 20. Patients who were judged not to be suitable for entry by physicians
目標参加者数 (Target sample size)	300	

責任研究者 (Research contact person)		
項目(Item)	日本語(Japanese)	英語(English)

責任研究者名 (Name of lead principal investigator)	増山　理	Tohru Masuyama
所属組織 (Organization)	兵庫医科大学	Hyogo College of Medicine
所属部署 (Division name)	内科学　循環器内科	Cardiovascular Division, Department of Internal Medicine
住所 (Address)	兵庫県西宮市武庫川町１－１	1-1 Mukogawa-cho, Nishinomiya, Hyogo, Japan

試験問い合わせ窓口(Public contact)		
項目(Item)	日本語(Japanese)	英語(English)
担当者名 (Name of contact person)	辻野　健	Takeshi Tsujino
組織名 (Organization)	兵庫医科大学	Hyogo College of Medicine
部署名 (Division name)	内科学　循環器内科	Cardiovascular Division, Department of Internal Medicine
住所 (Address)	兵庫県西宮市武庫川町１－１	1-1 Mukogawa-cho, Nishinomiya, Hyogo, Japan
電話 (TEL)	0798-45-6553	
試験のホームページURL (Homepage URL)	http://j-melodic.com/	
E-mail (E-mail)	jmelodic@hyo-med.ac.jp	

実施責任組織 (Sponsor)		
項目(Item)	日本語(Japanese)	英語(English)
実施責任組織 (Name of primary sponsor)	J-MELODIC試験組織	The J-MELODIC Program Committee

研究費提供組織(Funding Source)		
項目(Item)	日本語(Japanese)	英語(English)
研究費提供組織 (Source of funding)	厚生労働省	The ministry of health, labor and welfare, Japan
組織の区分 (Category of Org.)	厚生労働省/Government	
研究費拠出国 (Nation of funding)	日本	Japan

その他の関連組織 (Other related organizations)		
項目(Item)	日本語(Japanese)	英語(English)
共同実施組織 (Name of secondary sponsor(s))		
その他の研究費提供組織 (Name of secondary fun d er(s))		

IRBによる審査・承認		
項目(Item)	日本語(Japanese)	英語(English)
倫理委員会による審査・承認 (Research ethics review)	あり/YES	

他機関から発行された試験ID (Secondary IDs)		
項目(Item)	日本語(Japanese)	英語(English)
他機関から発行された試験ＩＤ (Secondary IDs)	はい/YES	
試験ID1 (Study ID_1)	NCT00355667	
ID発行機関1 (Org. issuing International ID_1)	ClinicalTrials.gov	ClinicalTrials.gov
試験ID2 (Study ID_2)		
ID発行機関2 (Org. issuing International ID_2)		
治験届 (IND to MHLW)		

試験実施施設 (Institutions)		
項目(Item)	日本語(Japanese)	英語(English)
試験実施施設数 (No. of institutions)	7	
セッティング (Setting)	プライマリーケア・専門病院・医院両方/All level	

試験実施都道府県 (Prefectures)	秋田県/Akita-ken 新潟県/Niigata-ken 愛知県/Aichi-ken 大阪府/Oosaka-fu 兵庫県/Hyougo-ken 和歌山県/Wakayama-ken 熊本県/Kumamoto-ken

試験進捗状況 (Progress)		
項目(Item)	日本語(Japanese)	英語(English)
試験進捗状況 (Recruitment status)	参加者募集中/Recruiting	
プロトコル確定日 (Date of protocol fixation)	2006/03/17	
登録・組入れ開始（予定）日 (Anticipated trial start date)	2006/06	
フォロー終了(予定)日 (Last follow-up date)	2010/03	
入力終了(予定)日 (Date of closure to data entry)	/	
データ固定（予定）日 (Date trial data considered complete")	/	
解析終了(予定)日 (Date analysis concluded)	/	

関連情報 (Related information)		
項目(Item)	日本語(Japanese)	英語(English)
プロトコル掲載URL (URL releasing protocol)	http://j-melodic.com/	
試験結果の公開状況 (Publication of results)	未公表/Unpublished	
結果掲載URL (URL releasing results)		
主な結果 (Results)		
その他関連情報 (Other related information)		

管理情報		
項目(Item)	日本語(Japanese)	英語(English)
登録日 (Date of registration)	2006/11/23 15:05:59	
最終情報更新日 (Date of last update)	2007/06/08 15:12:04	

閲覧ページへのリンク	
日本語URL	https://center.umin.ac.jp/cgi-open-bin/ctr/ctr.cgi?function=brows&action=brows&recptno=R000000637&type=summary&language=J
英語URL	https://center.umin.ac.jp/cgi-open-bin/ctr/ctr.cgi?function=brows&action=brows&recptno=R000000637&type=summary&language=E

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※ 特定の医薬品や治療法等については、医療関係者や一般の方に向けて広告することは目的としていません。

お問い合わせは、こちらの問い合わせフォーム から御願いいたします。

UMIN Infrastructure for Academic Activities
University hospital Medical Information Network

研究成果の刊行に関する一覧表

書籍：なし

雑誌

発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
The J-MELODIC Program Committee.	Rationale and Design of a Randomized Trial to Assess the Effects of Diuretics in Heart Failure: Japanese Multicenter Evaluation of LOng- versus short-acting Diuretics In Congestive heart failure (J-MELODIC).	Circulation Journal	71	1137-1140	2007
辻野　健、増山　理	利尿薬－ループ利尿薬は慢性心不全の予後を改善するか？－	循環器科	62	426-432	2007

研究成果の刊行物・別刷

Circ J 2007; **71:** 1137–1140

Rationale and Design of a Randomized Trial to Assess the Effects of Diuretics in Heart Failure

— Japanese Multicenter Evaluation of Long- vs Short-Acting Diuretics in Congestive Heart Failure (J-MELODIC) —

The J-MELODIC Program Committee*

Background Diuretics are the most prescribed medication for heart failure (HF) patients, but clinical evidence of the long-term effects of diuretics are lacking. The present study was designed to compare the therapeutic effects of furosemide, a short-acting loop diuretic, and azosemide, a long-acting one, in patients with HF to test the hypothesis that long-acting diuretics are superior therapy.

Methods and Results The Japanese Multicenter Evaluation of LOng- vs short-acting Diuretics In Congestive heart failure (J-MELODIC) is a multicenter, prospective, randomized trial enrolling a total of 300 patients (150 patients in each group). The primary outcome is a composite of cardiovascular death and unplanned admission to hospital for congestive HF. Other outcomes include all-cause mortality, worsening of the symptoms of HF, or a need for modification of therapy. Serial assessment of echocardiographic and neurohumoral parameters will be conducted over a minimum follow-up period of 2 years.

Conclusions The study results will provide important evidence for the treatment of chronic HF. (*Circ J* 2007; **71:** 1137–1140)

Key Words: Azosemide; Diuretics; Furosemide; Heart failure

Heart failure (HF) continues to be prevalent, particularly in the elderly population[1,2] and mortality and morbidity are still high, despite emerging evidence of the beneficial effects of angiotensin-converting enzyme inhibitors, β-blockers, angiotensin II type 1 receptor blockers and aldosterone-receptor antagonists.

Diuretics are the most prescribed drugs for HF[3] and there is no question of their necessity for attenuating symptoms related to fluid retention, and they are recommended as essential in patients with HF symptoms and/or fluid retention[4,5] However, the effects of long-term administration on morbidity and mortality have not been adequately assessed in a prospective clinical study, and retrospective analysis does not necessarily indicate diuretic-induced improvement of mortality[3]

Loop diuretics are more widely used in the treatment of HF than thiazide diuretics and can be divided into 2 classes: short-acting and long-acting[3] In clinical practice, furosemide, a short-acting loop diuretic, is the most commonly used in the treatment of HF[4] McCurley et al demonstrated adverse effects of furosemide in a tachycardia-induced HF model[6] and Yoshida et al demonstrated that administration of furosemide did not improve mortality rate in a hypertensive HF model, despite a significant reduction in blood pressure[7] Thus, a lack of improvement in the mortality rate of HF patients with prescription of diuretics may be partly explained by the wide-spread use of short-acting loop diuretics.

Yoshida et al also reported that the administration of azosemide, a long-acting loop diuretic, improved mortality rate in their hypertensive HF model[7] If the effects on mortality and/or morbidity of HF patients are different among the classes of diuretics, we should choose a class that provides a better prognosis. Thus, we designed a multicenter prospective study, J-MELODIC (Japanese Multicenter Evaluation of LOng- vs short-acting Diuretics In Congestive HF) to obtain clinical evidence of the effects of diuretics in HF.

Aims

The aim of this trial is to test our hypothesis that long-acting diuretics give a better prognosis for HF patients than short-acting ones, and we will compare the effects of furosemide, a short-acting loop diuretic, and azosemide, a long-acting one.

Study Design

The study uses a multicenter, prospective, randomized, open, blinded endpoint (PROBE) design.

Ethical Issues

The study will be conducted in accordance with the principles stated in the Declaration of Helsinki, 1964, as revised

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**Members are listed in Appendix I.*

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Table 1 Definition of Heart Failure

Major	*Minor*
Paroxysmal nocturnal dyspnea	*Edema*
Orthopnea	*Night cough*
Abnormal jugular venous distention	*Dyspnea on exertion*
Pulmonary rales	*Hepatomegaly*
Cardiomegaly	*Pleural effusion*
Pulmonary edema	*Tachycardia (>120 beats/min)*
Presence of a third heart sound	*Weight loss of ≥4.5 kg in 5 days (considered a major criterion if it occurs during therapeutic interventions for heart failure)*
Central venous pressure >16 cmH_2O	
Hepatojugular reflux	

A patient is considered to have heart failure if 2 major criteria are present or if 1 major and 2 minor criteria are present concurrently.

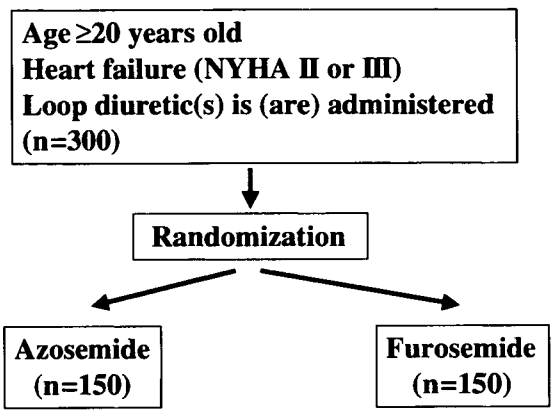

Fig 1. J-MELODIC study design.

in South Africa in 1996. The Ethical Committee in Hyogo College of Medicine approved this study on October 18, 2005 (No. 298). The study protocol was also submitted to the ethics committee of each participating hospital. Written informed consent will be given by all patients before entry to the study.

Outcome Measures

The primary outcome is a composite of cardiovascular death and unplanned admission to hospital for congestive HF. The secondary outcomes are: all-cause mortality; worsening of symptoms (defined by either a decrease by ≥1 Mets in the SAS questionnaire score or an increase by ≥I class in the New York Heart Association (NYHA) functional class for at least 3 months as compared with the baseline); an increase in brain natriuretic peptide (BNP) by ≥30% of the value at randomization in patients with BNP ≥200 pg/ml at randomization; unplanned admission to hospital for congestive HF, or a need for modification of the treatment for HF (changes in oral medicine for at least 1 month or addition of intravenous drug(s) for at least 4 h). Outcomes will be assessed by the endpoint committee where the allocated group is blinded to all the committee members.

Eligibility

Inclusion Criteria (1) 20 years or older; clinical diagnosis of HF based on a slight modification of the Framingham criteria[8] as previously described[9] within 6 months before the entry (Table 1); current status of HF is NYHA II or III.

(2) Currently, loop diuretic(s) is (are) administered.

(3) No change in baseline therapy or symptoms of HF within past month.

(4) Clinical diagnosis of HF confirmed on hospital records or physician practice data.

Exclusion Criteria (1) Diabetes mellitus that has not been well controlled (fasting blood glucose >200 mg/dl, hemoglobin A_{1c} >9%).

(2) Current symptomatic hypotension.

(3) Hypertension that has not been controlled to the satisfaction of the investigator.

(4) Serum creatinine >2.5 mg/dl.

(5) Serious liver disease; acute coronary syndrome; any life-threatening acute disease.

(6) Other diseases likely to cause death or serious disability during the period of the study.

(7) Patients with implantable cardiac defibrillator.

(8) Hemodynamically significant (in the investigators opinion) left ventricular (LV) outflow tract obstruction (caused by either aortic stenosis or ventricular hypertrophy).

(9) History of serious chronic obstructive pulmonary disease or restrictive lung disease.

(10) Primary pulmonary hypertension or pulmonary hypertension not caused by LV dysfunction.

(11) Acute myocardial infarction, cerebrovascular accident, percutaneous coronary intervention or open heart surgery within the last 3 months.

(12) On a waiting list for percutaneous coronary intervention or open heart surgery.

(13) Any change in cardiovascular drug therapy within the month prior to randomization.

(14) Malignancy; surgery to resect malignant tumor within past 5 years.

(15) Patients unable to walk without personal aid.

(16) Serious cerebrovascular disease.

(17) Patients who require intravenous inotropes.

(18) Pregnancy.

(19) Patients who were judged not to be suitable for entry by physicians.

Randomization and Maintenance Phase

After screening for eligibility and obtaining written informed consent, patients will be randomized to either azosemide or furosemide treatment in a 1:1 ratio (Fig 1). In any arm, patients will be treated with standard therapy including digitalis, mineralocorticoid receptor blockers, thiazide diuretics, angiotensin-converting enzyme inhibitors, angiotensin II type 1 receptor blockers, β-blockers, and calcium-channel blockers.