

# Review of the available evidence on Thiazides Diuretics in the management of Heart Failure

## FOR THE WHO MODEL LIST OF ESSENTIAL MEDICINES

CeVEAS

NHS Centre for the Evaluation of Effectiveness of Health Care  
Local Health Unit, Modena – Italy

WHO Collaborating Centre for Evidence-Based Research Synthesis  
and Guideline Development in Reproductive Health

Person to contact:

Dr. Nicola Magrini, MD  
CeVEAS  
Viale Muratori 201 41100 Modena.  
Tel +39-059-435200  
Fax +39-059-435222  
Web page <http://www.ceveas.it>  
e-mail: [n.magrini@ausl.mo.it](mailto:n.magrini@ausl.mo.it)

July 2008

***Contributors:***

***CeVEAS, Modena, Italy***

NHS Centre for the Evaluation of the Effectiveness of Health Care

WHO Collaborating Centre for Evidence-Based Research Synthesis and Guideline Development in Reproductive Health

Nicola Magrini

Director, Clinical Pharmacologist

Anna Maria Marata

Clinical Pharmacologist, Cardiologist

Simona Di Mario

Pediatrician, Epidemiologist

Lisa Daya

Pharmacologist

Luca Vignatelli

Neurologist, Epidemiologist

## 1. Summary statement of the proposal

Based on currently available evidence including several guidelines, direct evidence from a single study (case series design), indirect evidence from one systematic review of randomized controlled trials and one large randomized controlled trial, it is proposed to keep thiazide diuretics in the WHO Model List of Essential Medicines (EML 15, revised March 2007) available at the URL: [http://www.who.int/medicines/publications/08\\_ENGLISH\\_indexFINAL\\_EML15.pdf](http://www.who.int/medicines/publications/08_ENGLISH_indexFINAL_EML15.pdf) (last accessed 09 June 2008) as in the subsection 12.4 Medicines used in heart failure.

The proposal is based on the following evidence and considerations:

1. there is robust evidence that thiazide diuretics may have an important role in the prevention of heart failure (HF) in patient with hypertension (Davies 2006, a large RCT – ALLHAT. For the description of the study see Table 1 at page 7, for the abstract of the study see Annex C, reference 17);
2. there is less robust evidence that thiazide diuretics may have a role in the treatment of HF in the management of outpatients with mild HF (Faris 2006, a Cochrane systematic review. For the description of the study see page 13) and as an adjunctive option to loop diuretics for patients with refractory oedema or not responsive to furosemide alone (Dormans 1996, case series study. For the description of the study see Table 1 at page 7). In particular the study from Dormans showed that thiazides combined with furosemide are effective in reducing the body weight and the oedema in patient with HF not responsive to furosemide alone;
3. all the guidelines available coherently suggest to use all classes of diuretics and thiazides in particular for the prevention of HF and as an ancillary therapy in HF combined with loop diuretics or as single treatment in case of mild HF (see Annex B, 11 guidelines included). Keeping thiazides diuretics for the prevention and treatment of HF (alone or in combination with other diuretics) will also be consistent with most current guidelines in consideration of their prominent role in the treatment of chronic hypertension and thus in the prevention of HF;
4. thiazide diuretics are considered to be cost-effective drugs, with a favourable profile in term of balance between benefits and harms.

## 2. Name of the focal point in WHO submitting or supporting the application

Dr. Suzanne Hill was consulted in the development of this application.

## 3. Name of the organization(s) consulted and/or supporting the application

CEVEAS, NHS Centre for the Evaluation of the Effectiveness of Health Care, World Health Organization Collaborating Centre for Evidence Based Research Synthesis and Guideline Development in Reproductive Health. Modena, Italy.

## 4. International Nonproprietary Name (INN, generic name) of the medicine Thiazide diuretics:

INN were taken from the British National Formulary (BNF) [available upon registration at the URL: <http://www.bnf.org.uk/bnf/index.htm>], and FDA Physicians' Desk Reference Book (PDR) [available upon registration at the URL: <http://www.pdr.net/login/Login.aspx>]:

- chlorothiazide
- hydrochlorothiazide
- bendroflumethiazide

- cyclopentiazide
- methyclothiazide
- trichlormethiazide
- benzthiazide
- hydroflumethiazide
- chlorthalidone
- indapamide
- xipamide

#### **5. Formulation proposed for inclusion; including adult and paediatric (if appropriate)**

Hydrochlorothiazide is taken as the reference drug for the whole class of thiazide diuretics and thiazide-like diuretics. It is proposed to maintain hydrochlorothiazide in the Model List of Essential Medicines, as in the subsection 12.4 Medicines used in heart failure of the current edition (EML 15, revised March 2007) with the following possible formulations:

Hydrochlorothiazide

tablets 25, 50, 100 mg;

capsules 12,5 mg ;

oral suspension 50 mg/5 ml.

Other members of the class may be used as alternatives, depending on quality, price and local availability.

#### **6. International availability - sources, if possible manufacturers (Annex A)**

A comprehensive listing for thiazide diuretics is available in Annex A.

Generic thiazide diuretics are registered in many countries in the developed and developing world. Their choice will depend on their prices and availability at local (national) level.

#### **7. Whether listing is requested as an individual medicine or as an example of a therapeutic group**

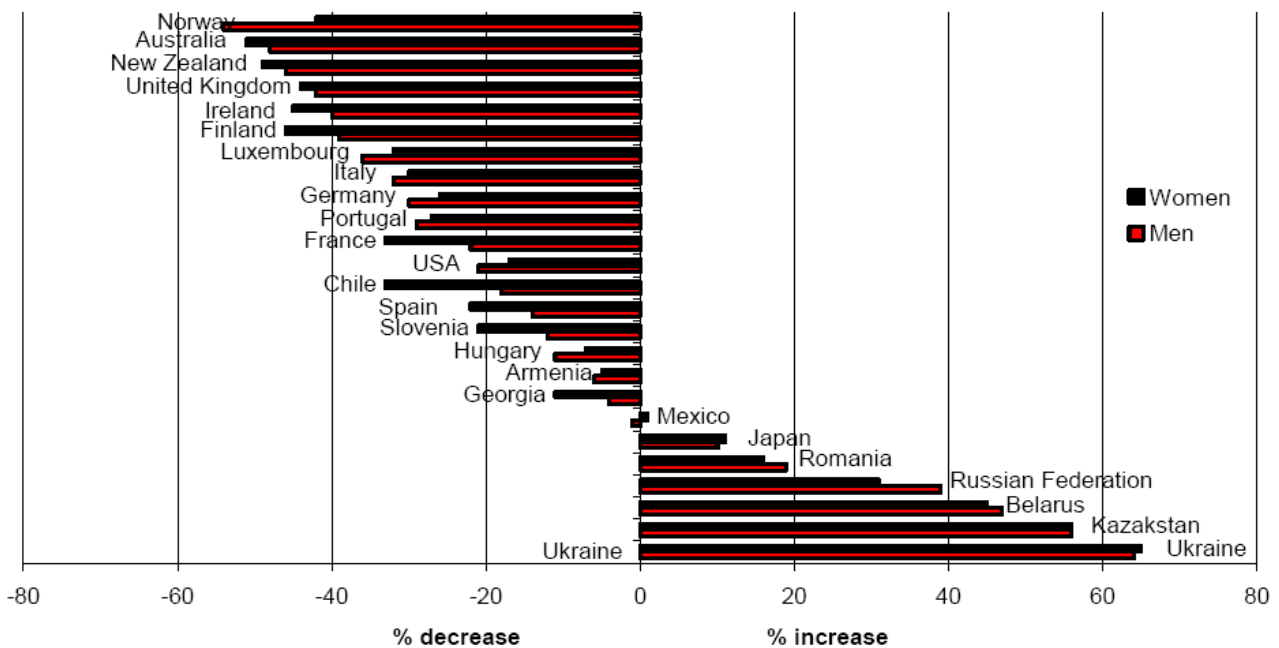
Listing is requested on the Model List of Essential Medicines as a single drug (as already in the subsection 12.4 *Medicines used in heart failure*, of the current EML). Among the whole class of thiazide diuretics hydrochlorothiazide is taken as the drug of reference. Other members of the class may serve as alternatives, depending on quality, price and local availability.

#### **8. Information supporting the public health relevance (epidemiological information on disease burden, assessment on current use, target population)**

As stated in the 2003 World Health Organization (WHO) document on prevention of cardiovascular disease, “non-communicable disease accounts for a large and increasing burden of disease worldwide” (WHO 2003). Cardiovascular disease (CVD) is the most important single cause of non-communicable disease, accounting in 2001 for 29% of all deaths and 10% of the global disease burden. Although the incidence of CVD has been decreasing over the last 20 years in many high-income populations, its incidence in low and middle-income populations has been rising steadily, due to ageing of the population and to better control of communicable disease and

malnutrition, so that approximately three-quarters of global deaths from CVD now occur in those populations (Figure 1). This is especially true in sub-Saharan Africa, India, China and Russia. World-wide, deaths from cardiovascular disease exceed those caused by cancer, infectious disease and trauma, constituting a deadly epidemic. It is predicted that in the next two decades there will be tripling of ischemic heart disease and stroke mortality in Latin America, the Middle East and sub-Saharan Africa (Callow 2006).

*Changes in death rates from coronary heart disease, men and women aged 35 to 74, between 1990 and 2000, selected countries*



**Notes:** ICD codes 410-414 (8th and 9th Revision), I20-I25 (10th revision). Age-standardised using the European standard population. **Sources:** World Health Organization (2004) [www3.who.int/whosis](http://www3.who.int/whosis)

HF is a complication of coronary artery disease, hypertension, valvular disease and acute myocardial infarction. Based on studies conducted in western countries the lifetime risk of developing HF is about 20% for both men and women (Lloyd-Jones 2001). Data on HF prevalence in developed countries range from 2% in USA and Europe (Davies 2001) to more than 6% in Australia (Abhayaratna 2006). Once HF has developed the median survival time is 1.7 years for men and 3.2 years for women. Five year mortality rate is 50% for both sexes. Mortality associated with HF over the past 20 years has declined significantly in men; at the contrary the reduction has been only marginal in women (Roger 2004).

Epidemiological data from developing countries on HF are rare but it is estimated that low and middle income countries contribute about 80% of global CVD-related deaths and 87% of CVD8 related disabilities (Callow 2006). CHF is estimated to have a case-fatality rate of 24% among Nigerian children (Omokhodion 2005).

Risk factors for CVD such as tobacco smoking, high level of blood cholesterol, diabetes, physical inactivity, and obesity, need to be taken into account when defining individual risk of CHD and when planning preventive and therapeutic intervention. There is a worrying increase in the distribution all of these risk factors among people in developing countries. The risk factors for CVD affect in different proportion male and female: smoking seems to be more prevalent among youth boys than girls in developing countries (Global Youth Tobacco Survey Collaborating Group 2003). The same apply also to adult male (50% prevalence of smoking) and adult female (9%

prevalence), the highest prevalence being the one of males in Eastern-Europe (rate over 60%) (Mackay 2002). Obesity is reported to be more prevalent among women in Brazil, Egypt, South Africa and Seychelles (Nishida 2005). Moreover women from developing countries have higher blood pressure than women from developed countries; they also show higher blood pressure than their male counterpart (WHO 2005). Although the prevalence of diabetes is lower in developing countries, it is rapidly increasing. The prevalence is highest in the Eastern Mediterranean and Middle East (7%), South and Central America (5.6%), Western Pacific (3%) and Africa (2.4%). The prevalence is higher among women than among men in Latin America and in the Western Pacific (International Diabetes Federation 2003).

Moreover developing countries display a set of specific risk factor for HF like acute respiratory infections (36% of all HF in children in Nigeria), severe anaemia (28%), and congenital heart disease (25%) (Omokhodion 2005). Among adults rheumatic heart disease remains a major cause of HF in Africa and Asia, especially in the young. Hypertension is an important cause of HF especially in the African and African-American population. Chagas' disease is still a cause of HF in South America. However, as countries go through epidemiological transition and undergo socio-economic development, the epidemiology of HF becomes increasingly similar to that of Western Europe and North America with coronary artery disease being the single most common cause of HF (Mendez 2001).

In addition to changes in life style, whenever a drug therapy is needed thiazide diuretics play a relevant role in the treatment of hypertension and in treatment and prevention of HF, alone or in combination with other drugs. Thiazides can be used either for short or long term treatments according with the underlying conditions.

## 9. Treatment details

Thiazides and related diuretics were introduced in 1957 and became widely accepted as an effective, inexpensive, and generally well-tolerated antihypertensive treatment. Thiazides and related compounds are moderately potent diuretics; they inhibit sodium reabsorption at the beginning of the distal convoluted tubule; they act within 1 to 2 hours of oral administration and most of them have a duration of action of 12 to 24 hours; they are usually administered early in the day so that the diuresis does not interfere with sleep.

They can be classified in: *thiazide diuretics* (chlorothiazide, hydrochlorothiazide, bendroflumethiazide, cyclopenthiiazide methyclothiazide, trichlormethiazide, hydroflumethiazide, benzthiazide), and *sulphonamide diuretics* (chlorthalidone, indapamide, xipamide). Each of them has specific pharmacokinetic characteristics, but all thiazide and thiazide-like diuretics are thought to be comparably effective at comparable dosages.

They should be used as initial therapy for most patients with hypertension either alone or in association with one of the others classes or in presence of oedema due to HF or other causes. They demonstrated to be beneficial in a series of cases in patients with severe congestive HF for reducing fluid retention (Dormans 1996) and to be beneficial in a large randomized clinical trial in hypertensive patients for the prevention of HF (Davies 2006).

## Evidence supporting thiazides in the treatment and prevention of HF

Author/Year	Study type/Objective	Population	Intervention	Outcomes	Results
<b>Dormans 1996</b>	Open study (observational not controlled study)  To assess the effectiveness of thiazides in the <u>treatment</u> of HF	20 patients with severe congestive HF and a proven diuretic resistance to high dose furosemide	Addition of hydrochlorothiazide to the other medications already prescribed.	Body weight reduction  Mean daily urine volume increase  Fractional sodium excretion increase  Side effect: hypokalaemia	<i>Mean±SD (p value)</i>  6.7±3.3 Kg per patient  1166±940 ml (p<0.001)  8±6% (p<0.001)  15/20 patients serum potassium<3.5mmol/l
<b>Davies 2006</b>	Double blind RCT  To assess the effectiveness of thiazides in the <u>prevention</u> of HF	33.357 high risk hypertensive patients aged ≥55 years.	Amlodipine or lisinopril versus chlortalidone	Hospital admission within 1 year Death within 1 year	<i>RR (95% CI)</i> 2.22 (1.69 to 2.91)  2.08 (1.58 to 2.74)

Table 1

### 9.1 Indications for use

The following indications are reported as available from the BNF and the FDA.

#### *Thiazides and related compounds listed in BNF and their indications for use:*

- **Bendroflumethiazide** (bendrofluazide), indicated for oedema and hypertension. It is widely used for mild or moderate HF and for hypertension, alone in the treatment of mild hypertension or with other drugs in more severe hypertension.
- **Chlortalidone** (chlorthalidone), indicated for ascites due to cirrhosis in stable patients (under close supervision), oedema due to nephrotic syndrome, hypertension, mild to moderate chronic HF, diabetes insipidus.

Chlortalidone is a thiazide-related compound, has a longer duration of action than the thiazides and may be given on alternate days to control oedema. It is also useful if acute retention is liable to be precipitated by a more rapid diuresis or if patients dislike the altered pattern of micturition promoted by other diuretics;

- **Cyclopenthiiazide**, indicated for oedema, hypertension, HF;

Other thiazide diuretics (including clopamide, benzthiazide, cyclopenthiiazide, hydrochlorothiazide, and hydroflumethiazide) do not offer any significant advantage over bendroflumethiazide and chlortalidone;

- **Indapamide**, indicated for essential hypertension;
- **Xipamide**, indicated for oedema, hypertension.

Indapamide and xipamide are chemically related to chlortalidone. Indapamide is claimed to lower blood pressure with less metabolic disturbance, particularly less aggravation of diabetes mellitus.

*Thiazides and related compounds listed in the FDA and their indications for use:*

- **Chlorothiazide (date of approval: 1961)** is indicated:
  1. as adjunctive therapy in oedema associated with congestive HF, hepatic cirrhosis and corticosteroid and oestrogen therapy;
  2. has also been found useful in oedema due to various forms of renal dysfunction such as nephrotic syndrome, acute glomerulonephritis and chronic renal failure;
  3. in the management of hypertension either as the sole therapeutic agent or in enhance the effectiveness of other antihypertensive drugs in the more severe forms of hypertension.
- **Chlorothiazide sodium (date of approval: 1958)** is indicated:
  1. as adjunctive therapy in oedema associated with congestive HF, hepatic cirrhosis and corticosteroid and oestrogen therapy;
  2. intra-venous chlorothiazide sodium has also been found useful in oedema due to various forms of renal dysfunction such as nephrotic syndrome, acute glomerulonephritis and chronic renal failure.
- **Hydrochlorothiazide (date of approval: 1959)** is indicated:
  1. in the management of hypertension either as the sole therapeutic agent or in combination with other antihypertensives;
  2. unlike potassium sparing combination diuretic products it may be used in those patients in whom the development of hyperkalemia cannot be risked, including patients taking ACE inhibitors drugs.
- **Methyclothiazide (date of approval: 1960)** is indicated:
  1. in the management of hypertension either as the sole therapeutic agent or to enhance the effectiveness of other antihypertensive drugs in the more severe forms of hypertension;
  2. as adjunctive therapy in oedema associated with congestive HF, hepatic cirrhosis and corticosteroid and oestrogen therapy;
  3. it has also been found useful in oedema due to various forms of renal dysfunction such as nephrotic syndrome, acute glomerulonephritis and chronic renal failure.
- **Chlorthalidone (date of approval: 1960)** is indicated:
  1. in the management of hypertension either as the sole therapeutic agent or in combination with other antihypertensive drugs;
  2. as adjunctive therapy in oedema associated with congestive HF, hepatic cirrhosis and corticosteroid and oestrogen therapy;
  3. it has also been found useful in oedema due to various forms of renal dysfunction such as nephrotic syndrome, acute glomerulonephritis and chronic renal failure.
- **Indapamide (date of approval: 1983)** is indicated:
  1. for the treatment of hypertension, alone or in combination with other antihypertensive drugs;
  2. is also indicated for the treatment of salt and fluid retention associated with congestive HF.

## 9.2 Dosage regimens (*from BNF 54 and MICROMEDEX*®)

- **Chlorothiazide:** oedema, 0.5 to 1 g once or twice a day, orally. Hypertension, initially 0.5 g to 1 g/day as a single or divided dose; adjust dosage according to the blood pressure response.
- **Chlorothiazide sodium:** intravenously in doses similar to those given by mouth.
- **Hydrochlorothiazide:** oedema, initially 25 to 200 mg daily for several days; maintenance 25 to 100 mg daily or intermittently. Hypertension, initially 12.5 to 50 mg daily as a single dose.
- **Methyclothiazide:** oedema (adults), 2.5 mg to 10 mg once daily; maximum effective single dose is 10 mg. Hypertension (adults), 2.5 to 5 mg once daily.
- **Trichlormethiazide:** oedema, 2 to 4 mg once daily. Hypertension, 2 to 4 mg once daily.
- **Bendroflumethiazide:** oedema, initially 5–10 mg daily in the morning *or* on alternate days; maintenance 5–10 mg 1–3 times weekly, Hypertension, 2.5 mg daily in the morning; higher doses rarely necessary.
- **Chlorthalidone:** oedema, up to 50 mg daily, hypertension, 25 mg daily in the morning, increased to 50 mg daily if necessary (but see notes above), HF, 25–50 mg daily in the morning, increased if necessary to 100–200 mg daily (reduce to lowest effective dose for maintenance).
- **Cyclopenthiazide:** HF, 250–500 micrograms daily in the morning increased if necessary to 1 mg daily (reduce to lowest effective dose for maintenance), hypertension, initially 250 micrograms daily in the morning, increased if necessary to 500 micrograms daily (but see notes above), oedema, up to 500 micrograms daily for a short period.
- **Indapamide:** 2.5 mg daily
- **Xipamide:** oedema, initially 40 mg daily by mouth, subsequently reduced to 20 mg daily according to response. Hypertension, 20 mg daily as a single morning dose, either alone or with other antihypertensives.

## 9.3 Duration of therapy

It is necessary to consider different options, according to the baseline condition that need to be tackled.

- Oedema of congestive HF: in the initial phase the drugs are usually given daily for several days, until dry weight is attained. In the maintenance phase therapy can be administered daily or intermittently (on a 3 to 5 day per week schedule).
- Hypertension: in the initial phase daily administration of attack dose are required. If blood pressure control is not satisfactory after 8 to 12 weeks another antihypertensive must be added. In the maintenance phase the lower effective dosage should be kept. In patient with hypertension, thiazides should be used chronically for the prevention of HF.

## 9.4 Reference to existing WHO and other clinical guidelines

*Existing WHO relevant documents* with related web link (6 documents in total) were identified and consulted:

- Revised Global Burden of Disease (GBD) 2002 Estimates. Incidence, prevalence, mortality, YLL, YLD and DALYs by sex, cause and region, estimates for 2002 as reported in the World Health Report 2004 (WHO 2004), available at:  
<http://www.who.int/healthinfo/bodgbd2002revised/en/index.html>  
and also at: <http://www.dcp2.org/pubs/GBD/3/Table/3.10>
- Avoiding heart attacks and strokes. WHO 2005, available at:  
[http://www.who.int/cardiovascular\\_diseases/resources/cvd\\_report.pdf](http://www.who.int/cardiovascular_diseases/resources/cvd_report.pdf)
- The Atlas of Heart Disease and Stroke. WHO, available at:  
[http://www.who.int/cardiovascular\\_diseases/resources/atlas/en/index.html](http://www.who.int/cardiovascular_diseases/resources/atlas/en/index.html)
- Prevention of recurrent heart attacks and strokes in low and middle income populations. Evidence-based recommendations for policy makers and health professionals. WHO, overview available at:  
[http://www.who.int/cardiovascular\\_diseases/resources/pub0402/en/index.html](http://www.who.int/cardiovascular_diseases/resources/pub0402/en/index.html)
- WHO CVD-risk management package for low- and medium-resource settings. WHO 2002, available at:  
[http://www.who.int/cardiovascular\\_diseases/resources/pub0401/en/index.html](http://www.who.int/cardiovascular_diseases/resources/pub0401/en/index.html)

*All available relevant guidelines* for the treatment of HF have been identified (see paragraph 10.1 for the search strategy) and assessed in this document. The following guidelines have been consulted:

1. ACC/AHA 2005 guideline update for the diagnosis and management of chronic HF in the adult. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Update the 2001 Guidelines for the Evaluation and Management of Heart Failure). *American College of Cardiology Foundation*. 2005
2. Heart failure - systolic dysfunction. *University of Michigan Health System* 2006
3. VHA/DoD clinical practice guideline for the diagnosis and management of hypertension in the primary care setting. *Department of Veterans Affairs*. 2004
4. Management of adults with chronic heart failure. *Michigan Quality Improvement Consortium*. 2007
5. The pharmacologic management of chronic heart failure. *Department of Veterans Affairs*. 2003
6. Chronic heart failure. National clinical guideline for diagnosis and management in primary and secondary care. *National Collaborating Centre for Chronic Conditions*. 2003
7. Guidelines for the diagnosis and treatment of chronic heart failure (update 2005). *European Society of Cardiology*. 2005

8. Heart Failure Society of America. Managing patients with hypertension and heart failure: HFSA 2006 comprehensive heart failure practice guideline. *Heart Failure Society of America*. 2006
9. Management of chronic heart failure. A national clinical guideline. *Scottish Intercollegiate Guidelines Network*. SIGN 2007
10. Guidelines for the prevention, detection and management of chronic heart failure in Australia, 2006. *Cardiac Society of Australia and New Zealand National Heart Foundation of Australia*. 2006
11. Postoperative management in adults. A practical guide to postoperative care for clinical staff. *Scottish Intercollegiate Guidelines Network*. SIGN 2004

### **9.5 Need for special diagnostic or treatment facilities and skills**

As thiazide diuretics can cause fluid and electrolyte imbalance, hyperuricemia, hyperglycemia, hypercholesterolemia and hypertriglyceridemia, periodic laboratory testing is needed. Lab tests required are as following:

- serum electrolyte;
- serum BUN (blood urea nitrogen);
- serum uric acid;
- serum glucose;
- serum cholesterol;
- serum triglyceride.

### **10. Summary of comparative effectiveness in a variety of clinical settings**

Based on primary and secondary studies retrieved and according to major recommendations from evidence based guidelines consulted, thiazide diuretics appear to be effective in the treatment of hypertension, and prevention of HF both in terms of reduced morbidity and mortality.

Based on more limited evidence, thiazides appear to play also a role as first treatment of mild HF and as an ancillary therapy, in association with other diuretics and other classes of drugs, for the treatment of moderate or severe HF (see detailed description of relevant studies in the following paragraphs).

Few head to head studies published more than a decade ago, have compared different molecules of thiazide diuretics: no major differences were detected both in term of effectiveness and safety (Bowlus 1964; Channick 1981; Clark 1979; de Leeuw 1997; Flack 1996; Licht 1983).

#### **10.1 Identification of clinical evidence (search strategy, systematic reviews identified, reasons for selection/exclusion of particular data)**

**Guidelines** were searched through the National Guideline Clearinghouse (data last search 30 August 2007). The following search criteria were used:

Keyword: *heart failure* → 443 records retrieved

Disease/condition: *heart failure* → 76 records retrieved  
Guidelines categories: *treatment* → 51 records retrieved  
Publication Dates: *2003 to 2007* (five years) → 44 records retrieved

Twenty out of 44 records were excluded based on title assessment (not pertaining to HF). Eight additional records were excluded based on the following previously defined criteria:

- composition of group that authored the guideline not stated;
- methods used to collect/select evidence not stated;
- methods used to assess the quality and strength of the evidence not stated;
- methods used to formulate the recommendations not stated;
- rating scheme for the strength of the recommendations not stated;
- method of guideline validation not stated;

Five out of the 16 records retrieved referred to different paragraphs of the same guideline (Heart Failure Society of America 2006) and were therefore presented as a unique guideline. In total 11 guidelines were included in the revision. For a detailed analysis of guidelines' recommendations see Annex B

In addition the scientific databases Medline, Embase, and the Cochrane library have been searched for **randomized controlled trials and systematic reviews** (search limits) using the following MeSH and free terms:

1. thiazides
2. diuretic
3. heart failure
4. #1 or #2
5. #3 and #4

Abstract of the references retrieved (89 references) are reported in Annex C

## **10.2 Summary of available estimates of comparative effectiveness (appraisal of quality, outcome measures, summary of results)**

One Cochrane systematic review on *Diuretics for heart failure* (Faris 2006), including 14 trials (525 participants) showed that mortality was lower for participants treated with diuretics than for placebo, odds ratio (OR) for death 0.24, 95% confidence interval (95% CI) 0.07 to 0.83;  $P = 0.02$ . Admission for worsening HF was reduced in those taking diuretics in two trials (169 participants), OR 0.07 (95% CI 0.01 to 0.52;  $P = 0.01$ ). In four trials comparing diuretics to active control (91 participants), diuretics improved exercise capacity in participants with chronic HF (CHF), weighted mean difference (WMD): 0.72, 95% CI: 0.40 to 1.04;  $P < 0.0001$ . The trials included varied in size, characteristics of participant populations, setting, duration, drug dosage, ancillary therapy for CHF. More specifically two trials compared ACE inhibitors versus thiazides diuretics (Sievert 1989, a cross over RCT including 16 patients; Nordrehaug 1992, a cross over RCT including 29 patients), four trials compared placebo versus various diuretics, two trials compared placebo versus potassium sparing diuretics, three trials compared ACE inhibitors versus loop diuretics, and finally two trials compared ACE inhibitors versus association of loop and potassium sparing diuretics. Participants involved were prevalently males, aged comprised between 21 and 82 years. The authors concluded that *"The combined results from small and relatively heterogeneous studies provide strong evidence that diuretics relieve symptoms, reduce episodes of decompensation and increase exercise capacity, but weak evidence for an effect on mortality in patients with chronic heart failure. This evidence is not sufficient by current standards to justify widespread use of diuretics to influence clinical outcomes in chronic heart failure since diuretics were introduced without the backing of large RCTs that would now be considered essential. On the other hand, clinical experience with diuretics in heart failure*

*following the seminal work of Slater and Nabarro in 1958 (Slater 1958), provides clinicians with the evidence of experience for continuing to use diuretics as first-line treatment of patients with chronic heart failure. Taking all the evidence together, the current use of diuretics in the management of heart failure is justifiable."*

Another Cochrane systematic review on *Beta-blockers for hypertension* (Wiysonge 2007) including 13 RCTs assessing effectiveness of beta-blockers on more than 91 thousand patients, found that in patients with hypertension beta-blocker drugs, compared with thiazide diuretics (4 RCTs assessing over 18 thousand hypertensive patients) do not reduce total mortality (RR: 1.04; 95% CI: 0.91 to 1.19), coronary heart disease (RR: 1.12; 95% CI: 0.82 to 1.54), stroke (RR: 1.17; 95% CI: 0.65 to 2.09), cardiovascular mortality (RR: 1.09; 95% CI: 0.90 to 1.32) and cardiovascular disease (RR: 1.13; 95% CI: 0.99 to 1.28) while increase withdrawal due to adverse effect (RR: 1.86; 95% CI: 1.39 to 2.50). The authors concluded that *"First-line beta-blockers for elevated blood pressure were not as good at decreasing mortality and morbidity as other classes of drugs: thiazides, calcium channel blockers, and renin angiotensin system inhibitors"*.

## **11. Summary of comparative evidence on safety**

Based on primary and secondary studies retrieved, thiazide diuretics appear to be safe in the treatment of HF as they also represent the first choice treatment for hypertension, and to have a good risk/benefits ratio as long as a periodic control of fluid and electrolyte balance can be assured.

More specifically as discussed in the review on *Diuretic-related side effects* (Sica 2004), many of the supposed negative effects of diuretics are less common than was once thought. Much of the change correlates with the understanding that the blood pressure lowering effect of thiazide diuretics does not increase with increasing beyond a daily dose of 25 mg while frequency of side effects clearly increase for high dose (100-200 mg/day). At currently recommended dosage regimen adverse effects of thiazide diuretics are rare and generally easy to correct. The review assess published trials including data on frequency of diuretics related side effects like the Medical Research Council (MRC) trial, the Systolic Hypertension in Elderly Program (SHEP) trial, the Swedish trial in Old Patient with Hypertension (STOP Hypertension) trial, the Multiple Risk Factors Intervention (MRFIT) trial. Based on these trials the review indicate that, using the lowest therapeutic dose of thiazide diuretics, the overall balance between benefits and harms is favourable to thiazides use, since they appear to consistently reduce cardiovascular mortality and morbidity, with little overall increase of uncommon and usually easy to treat side effects.

This is in line with the conclusions of author of the review (Sica 2004 ): *"Diuretic-related side effects occur more commonly with loop and/or K<sup>+</sup> -sparing agents and are less so with thiazide-type diuretics, as they are currently used in the treatment of hypertension ... Many diuretic-related side effects can be avoided or effectively tempered by selection of the lowest dose necessary for effective BP and/or volume control."*

### **11.1 Estimate of total patient exposure to date**

Since their first introduction in the '50s, thiazides have been widely used in several million of people all over the world both for the treatment of hypertension and for the prevention and treatment of symptoms (oedema) during HF.

### **11.2 Description of adverse effects/reactions**

The side effects of the thiazides diuretics are dose dependent. Low doses of thiazides (12.5 – 25 mg of HCTZ) are associated with a lower incidence of side effects than doses greater than 25 mg (see

above). A review of *diuretics side effects* (Sica 2004) including data from the MRC trial, the SHEP trial, the STOP Hypertension trial, the MRFIT trial, indicates that diuretics (and more specifically thiazides) side effects are:

**Hyponatremia** (uncommon but serious complication). Thiazides are more likely than loop diuretics to cause hyponatremia.

**Hypokalemia**. High dose thiazides cause during the first days of therapy an average falls of 0.6 mmol/L (in a dose-dependent manner) in patients not taking K<sup>+</sup> supplements. Long acting diuretics (such as chlorthalidone) cause hypokalemia more frequently than short acting ones.

**Hypomagnesemia**. Thiazides increase urinary Mg<sup>2+</sup> excretion. Prolonged therapy reduces Mg<sup>2+</sup> plasma concentration of 5-10% on average. Moreover the side effect is more frequent among elderly patients.

**Acid-base changes**. Mild metabolic alkalosis is common with thiazides, particularly when used at high dosage. Loop diuretics cause more severe alkalosis.

**Hyperuricemia**: thiazides can increase serum urate concentration by as much as 35%. The effect is dose-dependent. In the MRC trial patients taking high dose thiazides had significantly more withdrawals for gout than placebo treated patients.

**Hyperglycemia**: prolonged thiazide therapy can cause glucose intolerance and can rarely be associated with new onset diabetes mellitus. In a review of all placebo-controlled hypertension trials with diuretics the increase in new-onset diabetes was only of about 1% compared to placebo (Moser 1993); in a subsequent large prospective cohort study it was observed that patients receiving thiazides do not have a higher risk to develop new-onset diabetes compared to placebo patients (Gress 2000).

**Hyperlipidemia**: thiazide diuretic can increase serum cholesterol levels in a dose-dependent way, and can raise triglyceride levels in short-term therapy. Long-term clinical trials show, however, that this effect is not confirmed when diuretics are taken for longer period; patients with baseline cholesterol level above 250 mg/dl have a decrease in total cholesterol while taking diuretics from the second to the fifth year of treatment. The SHEP trial confirm these findings and show that, even in case of increase of cholesterol level, the cardiovascular events are not increased in patients in treatment with diuretics and with cholesterol levels above 280 mg/dl compared with the ones with cholesterol levels lower than 200 mg/dl.

**Impotence**: thiazide and thiazide-like diuretics are associated with decreased libido, erectile dysfunction, and difficult ejaculation. The MRC trial showed that patients receiving thiazide experienced impotence 22 time more frequently than patients receiving placebo or beta blockers.

**Photosensitivity**: hydrochlorothiazide cause photosensitivity more frequently than other thiazide diuretics

**Carcinogenesis**: 12 clinical studies, 3 cohort and 9 case control studies studied the association between use of diuretics and renal cell carcinoma. In all case control studies the association was found to be significant (average OR 1.55), and to be related with the duration of the diuretic therapy. No association was found between diuretic therapy and breast cancer. A large RCT (STOP Hypertension trial 2) conducted in Swedish in the other

hand, do not confirm the association between diuretics therapy and cancer development (Lindholm 2001).

### **11.3 Identification of variation in safety due to health systems and patient factors**

Since safety is strictly linked to the possibility to monitor fluid and electrolyte imbalance, health system capacity to monitor patient, especially when presenting other concomitant disease/condition, is a crucial issue.

#### *Drug-drug interactions.*

Thiazides have a well established profile in terms of drug interactions (see also treatment of hypertension). Many of the interactions of hydrochlorothiazide and other thiazides are due to their effects on fluid and electrolyte balance.

Diuretic-induced hypokaliemia may enhance the toxicity of digitalis glycosides and may also increase the risk of arrhythmias with drugs that prolong the QT interval, such as astemizole, terfenadine, halofantrine, pimozone and sotalol.

Thiazides may enhance the neuromuscular blocking action of competitive neuromuscular blockers, such as atracurium, probably by their hypokalaemic effect. The potassium depleting effect of diuretics may be enhanced by corticosteroids, corticotropin, beta2- agonists such as salbutamol, carbenoxolone, amphotericin B.

Thiazides may also enhance the effect of other antihypertensives, particularly the first dose hypotension that occur with alpha blockers or ACE inhibitors. Orthostatic hypotensions associated with diuretics may be enhanced by alcohol, barbiturates or opioids.

Thiazides should not usually be used with lithium since that association may lead to toxic blood concentrations of lithium. However some diuretics, like chlorothiazide, can increase lithium clearance thus leading to a reduced lithium plasmatic concentration.

Other drugs for which increased toxicity has been reported when given with thiazides include allopurinol and tetracycline.

Thiazides may alter the requirements for hypoglycaemics in diabetic patients.

### **11.4 Summary of comparative safety against comparators**

The whole class of thiazides and thiazide-like diuretic is proposed as it is in the EML. Safety appears to be linked to the correct dosage of thiazide diuretics used. In general, as appear from the side effect review (Sica 2004) thiazides appear to be safer than loop diuretics with respect to alkalosis, while they result to cause more frequently than other diuretics hyponatremia and impotence.

## **12. Summary of available data on comparative costs and cost-effectiveness**

The cost of these very old drugs, available in most cases also as generic formulations, is not an issue in term of access and availability. We did not retrieve any cost-effectiveness analysis of diuretics for treatment or prevention of HF but we did find two economic studies that assessed

the cost-effectiveness of thiazides for treatment of hypertension in a variety of clinical settings (Adigun 2003; Johannesson 1993).

The first study was conducted in Western Nigeria (Adigun 2003): 150 hypertensive patients with or without diabetes admitted to the hypertension clinic of a university teaching hospital were assessed for antihypertensive drugs' prescription and blood pressure reduction to evaluate the efficacy, safety, rationality and pharmaco-economics of old and newer antihypertensive drugs. Thiazides diuretics were the drugs most frequently prescribed (56% of the total), followed by calcium channel blockers (51%) and ACE inhibitors (24%). Overall, 56% of all patient attained normotension with thiazides, and 71% with calcium channel blockers. The cost-effectiveness analysis (expressed as a percentage of treated patients achieving normal blood pressure, per monthly drug expenditure in US dollars \$) indicates that at the same monthly expenditure, thiazides will normalize blood pressures in five-fold more patients, compared to calcium channel blockers.

The second study was conducted in Sweden (Johannesson 1993) on middle-aged men with mild to moderate uncomplicated hypertension randomly treated with metoprolol or thiazides (MAPHY trial). The study showed that metoprolol was cost-saving compared with thiazide diuretics when both direct and indirect costs of morbidity were included. When only direct costs were included, the cost per life-year gained was \$US2400. As happen for other studies, but even more in case of cost-effectiveness studies, external validity of the conclusions of the above cited studies can be low; extrapolation of the results to other settings should be done with caution. Cost-effectiveness in fact depends not only on relative risk but also on absolute risk level, which varies with the patient's condition, presence of other risk factors, age, sex etc.

### **12.1 Range of cost of the proposed medicine**

The thiazides are already comprised in the WHO EML as antihypertensive drugs and are among the most cost-effective drugs.

We used the *International Drug Price Indicator Guide*, published by Management Sciences for Health (MSH), to obtain present prices of thiazides. The MSH Drug Price Indicator Guide catalogues the prices of medicines achieved through tender agreements between selected national governments and generic firms. MSH cautions, however, that these tender agreements may not represent an "international" price (personal communication, Jim Rankin, MSH, October 2006). We present these prices as examples of how inexpensive thiazides are, but not as final price.

Costs are reported as lowest and highest buyer price for a single tablet for oral use:

- Bendroflumethiazide (strength 2.5 mg): from 0.0047 to 0.0083 US\$/Tab-cap.
- Bendroflumethiazide (strength 5 mg): from 0.0064 to 0.00119 US\$/Tab-cap.
- Chlorthalidone (strength 50 mg): from a single source 0.0418 US\$/Tab-cap.
- Hydrochlorothiazide (strength 50 mg): from 0.0028 to 0.1230 US\$/Tab-cap.
- Hydrochlorothiazide (strength 25 mg): from 0.0026 to 0.0057 US\$/Tab-cap.
- Hydrochlorothiazide+Triamterene (strength 25+50 mg): from 0.0120 to 0.0184 US\$/Tab-cap.

### **12.2 Comparative cost-effectiveness presented as range of cost per routine outcome**

The thiazides are already comprised in the WHO EML as antihypertensive drugs.

**13. Summary of regulatory status of the medicine (in country of origin, and preferably in other countries as well)**

Thiazides diuretics have been approved for use in USA since the end of the 1950s (first Chlorothiazide sodium date of approval: 1958; last Indapamide, date of approval: 1983).

**14. Availability of pharmacopoeial standards (British Pharmacopoeia, International Pharmacopoeia, United States Pharmacopoeia)**

**Chlorothiazide**

European Pharmacopoeia: Yes (Version 5.5)

United States Pharmacopoeia: Yes (Version 27)

**Chlorothiazide sodium**

United States Pharmacopoeia: Yes (Version 27)

**Hydrochlorothiazide**

European Pharmacopoeia: Yes (Version 5.5)

United States Pharmacopoeia: Yes (Version 27)

International Pharmacopoeia: Yes (2003, Volume 5)

Chinese Pharmacopoeia: Yes (2000)

The Pharmacopoeia of Japan: Yes (2001, 14th ed.)

Polish Pharmacopoeia: Yes (2002, 6th ed.)

Vietnamese Pharmacopoeia: Yes (2002, 3th ed)

**Bendroflumethiazide**

British Pharmacopoeia: Yes (British National Formulary 54)

European Pharmacopoeia: Yes (Version 5.5)

United States Pharmacopoeia: Yes (Version 27)

**Cyclopenthiiazide**

British Pharmacopoeia: Yes (British National Formulary 54)

**Methyclothiazide**

United States Pharmacopoeia: Yes (Version 27)

**Trichlormethiazide**

United States Pharmacopoeia: Yes (Version 27)

The Pharmacopoeia of Japan: Yes (2001, 14th ed.)

**Chlorthalidone**

British Pharmacopoeia: Yes (British National Formulary 54)

European Pharmacopoeia: Yes (Version 5.5)

United States Pharmacopoeia: Yes (Version 27)

International Pharmacopoeia: Yes (2003, volume 5)

Chinese Pharmacopoeia: Yes (2000)

**Indapamide**

British Pharmacopoeia: Yes (British National Formulary 54)

European Pharmacopoeia: Yes (Version 5.5)

United States Pharmacopoeia: Yes (Version 27)

Chinese Pharmacopoeia: Yes (2000)

### **Xipamide**

British Pharmacopoeia: Yes (British National Formulary 54)

## **15. Proposed (new/adapted) text for the WHO Model Formulary**

### Description:

As an example, *hydrochlorothiazide* will be quoted as representative of a generic thiazides and related diuretics available (considering its projected availability and price).

Hydrochlorothiazide is a thiazide diuretic, a class of diuretics derived from benzothiadiazine. Thiazide diuretic act inhibiting Na<sup>+</sup>/Cl<sup>-</sup> reabsorption in the cortical thick ascending limb of the loop of Henle and the distal convoluted tubules in the kidneys by blocking the thiazide-sensitive Na<sup>+</sup>/Cl<sup>-</sup> symporter: the urinary excretion of sodium and chloride is increased in approximately equivalent amounts. The chemical structure of the original thiazide diuretics contains a thiazide ring system; thiazide-like diuretics, such as chlortalidone and metolazone, do not contain the thiazide ring but have the same effect of thiazide diuretics on the Na<sup>+</sup>/Cl<sup>-</sup> symporter.

### How Supplied:

- tablets 25mg, 50 mg, 100 mg
- capsules 12.5 mg
- oral suspension 50 mg/5 ml

### Use:

Hydrochlorothiazide and the other thiazide diuretics are used in the treatment of hypertension, either alone or with other antihypertensives; they are also used to treat oedema associated with HF and with renal and hepatic disorders.

The following information are summarized from *MICROMEDEX*®

### Contraindications:

Anuria; renal decompensation; Addison's disease; hypersensitivity to thiazides or related diuretics or sulfonamides-derived drugs.

### Adverse Effects:

The side effects are, generally, dose dependent: hydrochlorothiazide and the other thiazide diuretics may cause a number of metabolic disturbances, especially at high doses.

The main adverse effects are hypokalaemia, hypomagnesaemia, hyponatraemia, hypercalcaemia, hypochloraemic alkalosis, hyperuricaemia, gout, hyperglycaemia, altered plasma lipid concentration. The effects are uncommon at low doses; higher doses can cause more marked metabolic changes.

Other adverse effects are postural hypotension, mild gastro-intestinal effects (nausea, gastric irritation, constipation or diarrhoea), impotence and yellow vision.

Less commonly thiazide diuretics can produce: rashes, photosensitivity; blood disorders (including neutropenia and thrombocytopenia). Pancreatitis, intrahepatic cholestasis, and hypersensitivity reactions (including pneumonia, pulmonary oedema, severe skin reactions, allergic myocarditis) are also reported.

#### Warnings:

- *Patients with lupus erythematosus:*

Lupus erythematosus exacerbation or activation has occurred.

- *Patients with renal function impairment:*

Use with caution in severe renal disease since these agents may worsen azotemia. Avoid if creatinine clearance less than 30 mL/minute. It is advised to monitor renal function periodically.

- *Hypersensitivity reactions:*

Hypersensitivity reactions may occur in patients with or without a history of allergy or bronchial asthma; cross-sensitivity with sulfonamide may also occur.

- *Patients with hepatic functions impairment:*

Use with caution since minor alterations of fluid and electrolyte balance may precipitate hepatic coma. Avoid in severe liver disease; increased risk of hypomagnesaemia in alcoholic cirrhosis.

#### Precautions:

- *Fluid/electrolyte balance:* all thiazides diuretics can produce changes in fluid and electrolyte balance (e.g. hyponatremia, hypochloremic alkalosis, hypokaliemia, hypomagnesemia, changes in serum and urinary calcium). They should be used with caution in patients with existing fluid and electrolyte disturbances or who are at risk from changes in fluid and electrolyte balance, such as elderly.
- *Glucose tolerance:* the thiazides diuretics may cause hyperglycemia and aggravate or unmask diabetes mellitus; blood-glucose concentrations should be monitored in patients taking antidiabetics, since requirements may change.
- *Porphyria:* hydrochlorothiazide has been associated with acute attacks of porphyria and is considered unsafe in porphyric patients.
- *Photosensitivity:* photosensitivity may occur; therefore, caution patients to take protective measures (i.e. sunscreens) against exposure to ultraviolet light and/or sunlight until tolerance is determined;
- *Pregnancy (see above)*
- *Lactation:* amount too small to be harmful; large doses may suppress lactation.

#### Drug Interactions:

Many of the interactions of hydrochlorothiazide and other thiazides are due to their effects on fluid and electrolyte balance. In fact diuretic-induced hypokaliemia may enhance the toxicity of digitalis glycosides and may also increase the risk of arrhythmias with drugs that prolong the QT interval, such as astemizole, terfenadine, halofantrine, pimozide and sotalol.

Thiazides may enhance the neuromuscular blocking action of competitive neuromuscular blockers, such as atracurium, probably by their hypokalaemic effect. The potassium depleting effect of diuretics may be enhanced by corticosteroids, corticotropin, beta<sub>2</sub>- agonists such as salbutamol, carbenoxolone, amphotericin B.

Thiazides may enhance the effect of other antihypertensives, particularly the first dose hypotension that occur with alpha blockers or ACE inhibitors. Orthostatic hypotensions associated with diuretics may be enhanced by alcohol, barbiturates or opioids.

Thiazides should not usually be used with lithium since that association may lead to toxic blood concentrations of lithium. However some diuretics, like chlorothiazide, can increase lithium clearance thus leading to a reduced lithium plasmatic concentration.

Other drugs for which increased toxicity has been reported when given with thiazides include allopurinol and tetracycline.

Thiazides may alter the requirements for hypoglycaemics in diabetic patients.

Paediatric Use:

Safety and efficacy of hydrochlorothiazide and the other thiazides diuretics have not been studied in paediatric patients.

Pregnancy Use:

Routine use during normal pregnancy is inappropriate; diuretics decrease plasma volume and can decrease placental perfusion. Thiazides are indicated in pregnancy when oedema is due to pathologic causes, just as they are in the absence of pregnancy.

Thiazides cross the placental barrier and appear in cord blood. In general hydrochlorothiazide and the other thiazides diuretics should be used during pregnancy only when clearly needed and when potential benefits outweigh the potential risk to the foetus. These risks include foetal or neonatal jaundice, thrombocytopenia, haemolytic anaemia, electrolyte imbalances and hypoglycaemia.

Dosage and Administration:

Oedema:

- initial 25 to 200 mg daily for several days or until dry weight is attained;
- maintenance 25 to 100 mg daily or intermittently; refractory patients may require up to 200 mg daily.

Hypertension:

- initial 12.5 to 50 mg daily as a single dose; doses > 50 mg are often associated with marked reductions in serum potassium. Patients usually do not require doses > 50 mg daily when combined with other antihypertensives.

**References (arranged alphabetically)**

AAVV. A better diuretic for patients with heart failure. Better control of potassium loss.

MMW.Fortschr.Med. 2002;144:56

AAVV. Diuretics in heart failure. Fewer electrolyte disorders-better prognosis. MMW.Fortschr.Med.

2003;145:55

AAVV. Favorable prognostic effect of heart failure therapy. Diuretic makes heart muscle more elastic.

MMW.Fortschr.Med. 2003;145:60

AAVV. Reducing hospital stay and costs in heart failure. The proper diuretic makes the difference.

MMW.Fortschr.Med. 2003;145:58

AAVV. Which diuretic in heart failure? For the prognosis, they are not all equal. MMW.Fortschr.Med.

2002;144:52

AAVV. Which loop diuretic for heart failure? For prognosis the choices are not all the same. *MMW.Fortschr.Med.* 2002;144:50

Abhayaratna WP, Smith WT, Becker NG, et al. Prevalence of heart failure and systolic ventricular dysfunction in older Australians: the Canberra Heart Study. *Med J Aust.* 2006;184:151-4

ACC/AHA 2005 guideline update for the diagnosis and management of chronic heart failure in the adult. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Update the 2001 Guidelines for the Evaluation and Management of Heart Failure). American College of Cardiology Foundation. 2005

Adigun AQ, Ishola DA, Akintomide AO, Ajayi AA. Shifting trends in the pharmacologic treatment of hypertension in a Nigerian tertiary hospital: a real-world evaluation of the efficacy, safety, rationality and pharmaco-economics of old and newer antihypertensive drugs. *J Hum Hypertens.* 2003;17:277-85

Ahmed A, Husain A, Love TE, et al. Heart failure, chronic diuretic use, and increase in mortality and hospitalization: an observational study using propensity score methods. *Eur.Heart J.* 2006;27:1431-9

Ben Dov IZ, Bursztyn M. Letter by Ben-Dov and Bursztyn regarding article, "Role of diuretics in the prevention of heart failure: the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial". *Circulation* 2007;115:e18

Bischoff A. Essential basics in therapy of heart failure. Without diuretics the prognosis is poor. *MMW.Fortschr.Med.* 2002;144:6-8

Boni E, Bezzi M, Carminati L, et al. Expiratory flow limitation is associated with orthopnea and reversed by vasodilators and diuretics in left heart failure. *Chest* 2005;128:1050-7

Bouvy ML, Heerdink ER, Urquhart J, et al. Effect of a pharmacist-led intervention on diuretic compliance in heart failure patients: a randomized controlled study. *J.Card Fail.* 2003;9:404-11

Bowlus WE, Langford HG. A comparison of the antihypertensive effect of chlorthalidone and hydrochlorothiazide. *Clin Pharmacol Ther.* 1964;5:708-11

Braunschweig F, Linde C, Eriksson MJ, et al. Continuous haemodynamic monitoring during withdrawal of diuretics in patients with congestive heart failure. *Eur.Heart J.* 2002;23:59-69

British National Formulary, 55, 2008. BMJ Group and RPS Publishing. Access on subscription at <http://www.bnf.org/bnf/> (last accessed 07.07.2008)

Callow AD. Cardiovascular disease 2005-the global picture. *Vascul Pharmacol* 2006;45:302-7

Cardiac Society of Australia and New Zealand National Heart Foundation of Australia. Guidelines for the prevention, detection and management of chronic heart failure in Australia, 2006. Cardiac Society of Australia and New Zealand National Heart Foundation of Australia. 2006

Cataliotti A, Boerrigter G, Chen HH, et al. Differential actions of vasopeptidase inhibition versus angiotensin-converting enzyme inhibition on diuretic therapy in experimental congestive heart failure. *Circulation* 2002;105:639-44

Cayley WE. Diuretics for treatment of patients with heart failure? *Am.Fam.Physician.* 2006;74:411-3

Channick BJ, Kessler WB, Marks AD, Adlin EV. A comparison of chlorthalidone-reserpine and hydrochlorothiazide-methyldopa as step 2 therapy for hypertension. *Clin Ther.* 1981;4:175-83

- Chapman PJ. A case report of acute heart failure caused by a patient delaying taking his diuretic medication. *Aust.Dent.J.* 2002;47:66-7
- Chen HH, Redfield MM, Nordstrom LJ, et al. Angiotensin II AT1 receptor antagonism prevents detrimental renal actions of acute diuretic therapy in human heart failure. *Am.J.Physiol Renal Physiol* 2003;284:F1115-F1119
- Cheng TO. Beta blockers versus diuretics for congestive heart failure in African-American patients. *Am.J.Cardiol.* 2006;98:568
- Christ M, Ludwig N, Maisch B. Value of aldosterone receptor blockade in diuretic therapy of patients with chronic heart failure. *Herz* 2002;27:135-49
- Chuen MJ, MacFadyen RJ. Dose-dependent association between use of loop diuretics and mortality in advanced systolic heart failure. *Am.J.Cardiol.* 2006;98:1416-7
- Chui MA, Deer M, Bennett SJ, et al. Association between adherence to diuretic therapy and health care utilization in patients with heart failure. *Pharmacotherapy* 2003;23:326-32
- Clark EC, Podolsky S, Thompson EJ. Double-blind comparison of hydrochlorothiazide plus triameterene therapy versus chlorthalidone therapy in hypertension. *South Med J.* 1979;72:798-802
- Costanzo MR, Guglin ME, Saltzberg MT, et al. Ultrafiltration versus intravenous diuretics for patients hospitalized for acute decompensated heart failure. *J.Am.Coll.Cardiol.* 2007;49:675-83
- Costanzo MR, Johannes RS, Pine M, et al. The safety of intravenous diuretics alone versus diuretics plus parenteral vasoactive therapies in hospitalized patients with acutely decompensated heart failure: a propensity score and instrumental variable analysis using the Acutely Decompensated Heart Failure National Registry (ADHERE) database. *Am.Heart J.* 2007;154:267-77
- Costanzo MR, Saltzberg M, O'Sullivan J, et al. Early ultrafiltration in patients with decompensated heart failure and diuretic resistance. *J.Am.Coll.Cardiol.* 2005;46:2047-51
- Davies M, Hobbs F, Davis R, et al. Prevalence of left-ventricular systolic dysfunction and heart failure in the Echocardiographic Heart of England Screening study: a population based study. *Lancet.* 2001;358:439-44
- Davis BR, Piller LB, Cutler JA, et al. Role of diuretics in the prevention of heart failure: the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial. *Circulation* 2006;113:2201-10
- Davis BR, Piller LB, Cutler JA, et al for the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial Collaborative Research Group. Role of diuretics in the prevention of heart failure: the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial. *Circulation.* 2006;113:2201-10
- De Bruyne LK. Mechanisms and management of diuretic resistance in congestive heart failure. *Postgrad.Med.J.* 2003;79:268-71
- Department of Veterans Affairs. The pharmacologic management of chronic heart failure. Department of Veterans Affairs. 2003
- de Leeuw PW, Notter T, Zilles P. Comparison of different fixed antihypertensive combination drugs: a double-blind, placebo-controlled parallel group study. *J Hypertens.* 1997;15:87-91
- De Pasquale CG, Dunne JS, Minson RB, et al. Hypotension is associated with diuretic resistance in severe chronic heart failure, independent of renal function. *Eur.J.Heart Fail.* 2005;7:888-91

- Di Pasquale P, Sarullo FM, Paterna S. Novel strategies: challenge loop diuretics and sodium management in heart failure--part II. *Congest.Heart Fail.* 2007;13:170-6
- Domanski M, Norman J, Pitt B, et al. Diuretic use, progressive heart failure, and death in patients in the Studies Of Left Ventricular Dysfunction (SOLVD). *J.Am.Coll.Cardiol.* 2003;42:705-8
- Domanski M, Tian X, Haigney M, et al. Diuretic use, progressive heart failure, and death in patients in the DIG study. *J.Card Fail.* 2006;12:327-32
- Dormans TP, Gerlag PG. Combination of high-dose furosemide and hydrochlorothiazide in the treatment of refractory congestive heart failure. *Eur Heart J.* 1996;17:1867-74
- Earl G, Davenport J, Narula J. Furosemide challenge in patients with heart failure and adverse reactions to sulfa-containing diuretics. *Ann.Intern.Med.* 2003;138:358-9
- Erdmann E. The value of diuretics in chronic heart failure demonstrated by an implanted haemodynamic monitor. *Eur.Heart J.* 2002;23:7-9
- Eshaghian S, Horwich TB, Fonarow GC. Relation of loop diuretic dose to mortality in advanced heart failure. *Am.J.Cardiol.* 2006;97:1759-64
- European Society of Cardiology. Guidelines for the diagnosis and treatment of chronic heart failure (update 2005). European Society of Cardiology. 2005
- Evaluation and management of patients with acute decompensated heart failure: HFSA 2006 comprehensive heart failure practice guideline. Heart Failure Society of America. 2006
- Evaluation and management of patients with heart failure and preserved left ventricular ejection fraction: HFSA 2006 comprehensive heart failure practice guideline. Heart Failure Society of America. 2006
- Evaluation and therapy for heart failure in the setting of ischemic heart disease: HFSA 2006 comprehensive heart failure practice guideline. Heart Failure Society of America. 2006
- Evidence-based recommendations for policy makers and health professionals. WHO available at: [http://www.who.int/cardiovascular\\_diseases/resources/pub0402/en/index.html](http://www.who.int/cardiovascular_diseases/resources/pub0402/en/index.html) (last accessed 29 August 2007)
- Faggiano P, Opasich C, Tavazzi L, et al. Prescription patterns of diuretics in chronic heart failure: a contemporary background as a clue to their role in treatment. *J.Card Fail.* 2003;9:210-8
- Faris R, Flather M, Purcell H, et al. Current evidence supporting the role of diuretics in heart failure: a meta analysis of randomised controlled trials. *Int.J.Cardiol.* 2002;82:149-58
- Faris R, Flather MD, Purcell H, et al. Diuretics for heart failure. *Cochrane.Database.Syst.Rev.* 2006;CD003838
- Flack JM, Cushman WC. Evidence for the efficacy of low-dose diuretic monotherapy. *Am J Med.* 1996;101:53S-60S
- Futterman LG, Lemberg L. Diuretics, the most critical therapy in heart failure, yet often neglected in the literature. *Am.J.Crit Care* 2003;12:376-80
- Galve E, Mallol A, Catalan R, et al. Clinical and neurohumoral consequences of diuretic withdrawal in patients with chronic, stabilized heart failure and systolic dysfunction. *Eur.J.Heart Fail.* 2005;7:892-8

- Ghali JK. Diuretic use, progressive heart failure, and death in patients in SOLVD. *J.Am.Coll.Cardiol.* 2004;43:1723
- Global Youth Tobacco Survey Collaborating Group. Differences in worldwide tobacco use by gender: findings from the Global Youth Tobacco Survey. *J Sch Health.* 2003;73:207-15
- Gress TW, Nieto FJ, Shahar E, Wofford MR, Brancati FL. Hypertension and antihypertensive therapy as risk factors for type 2 diabetes mellitus. *Atherosclerosis Risk in Communities Study. N Engl J Med.* 2000;342:905-12
- Gullestad L, Madsen S. Diuretics not the first-choice-drug in chronic heart failure. *Tidsskr.Nor Laegeforen.* 2007;127:621
- Guntheroth WG. Decompensated heart failure and diuretic resistance. *J.Am.Coll.Cardiol.* 2006;48:1059-60
- Gupta S, Neyses L. Current thinking regarding the use of diuretics in heart failure. *Heart Fail.Monit.* 2006;5:50-3
- Gupta S, Neyses L. Diuretic usage in heart failure: a continuing conundrum in 2005. *Eur.Heart J.* 2005;26:644-9
- Heart Failure Society of America. Heart failure in patients with left ventricular systolic dysfunction: HFSA 2006 comprehensive heart failure practice guideline. Heart Failure Society of America. 2006
- Heart Failure Society of America. Management of heart failure in special populations: HFSA 2006 comprehensive heart failure practice guideline. Heart Failure Society of America. 2006
- Heart Failure Society of America. Managing patients with hypertension and heart failure: HFSA 2006 comprehensive heart failure practice guideline. Heart Failure Society of America. 2006
- Howard PA, Dunn MI. Effectiveness of continuous infusions of loop diuretics for severe heart failure. *J.Cardiovasc.Med.(Hagerstown.)* 2006;7:5-10
- Howard PA, Dunn MI. Severe heart failure in the elderly: potential benefits of high-dose and continuous infusion diuretics. *Drugs Aging* 2002;19:249-56
- International Diabetes Federation. Estimated prevalence of diabetes and numbers of people with diabetes, 2003 and 2025, selected countries, the world. Brussels: International Diabetes Federation; 2003. [Web site of the British Heart Foundation]. Available: [www.heartstats.org/temp/TABsp12.8spweb06.xls](http://www.heartstats.org/temp/TABsp12.8spweb06.xls) (last accessed 29 August 2007)
- Iyengar S, Abraham WT. Diuretic resistance in heart failure. *Curr Heart Fail Rep.* 2006;3:41-5
- Iyengar S, Abraham WT. Diuretics for the treatment of acute decompensated heart failure. *Heart Fail Rev.* 2007;12:125-30
- Johannesson M, Wikstrand J, Jönsson B, Berglund G, Tuomilehto J. Cost-effectiveness of antihypertensive treatment: metoprolol versus thiazide diuretics. *Pharmacoeconomics.* 1993;3:36-44
- Johnson W, Omland T, Hall C, et al. Neurohormonal activation rapidly decreases after intravenous therapy with diuretics and vasodilators for class IV heart failure. *J Am Coll Cardiol.* 2002;39:1623-9
- Jolobe OM. Diuretic usage in heart failure: a continuing conundrum in 2005. *Eur Heart J.* 2006;27:886-7

- Kensley K. How should diuretic-refractory, volume-overloaded heart failure patients be managed? *J Invasive Cardiol.* 2003;15:A17
- Krum H, Cameron P. Diuretics in the treatment of heart failure: mainstay of therapy or potential hazard? *J Card Fail.* 2006;12:333-5
- Lepor NE. Diuretic therapy, natriuretic peptides, and heart failure. *Rev Cardiovasc Med.* 2005;6:184-6
- Liang KV, Hiniker AR, Williams AW, et al. Use of a novel ultrafiltration device as a treatment strategy for diuretic resistant, refractory heart failure: initial clinical experience in a single center. *J Card Fail.* 2006;12:707-14
- Libetta C, Sepe V, Zucchi M, et al. Standard hemodiafiltration improves diuretic responsiveness in advanced congestive heart failure. *Cardiology* 2006;105:122-3
- Licht JH, Haley RJ, Pugh B, Lewis SB. Diuretic regimens in essential hypertension. A comparison of hypokalemic effects, BP control, and cost. *Arch Intern Med.* 1983;143:1694-9
- Lindholm LH, Anderson H, Ekblom T, Hansson L, Lanke J, Dahlöf B, de Faire U, Forsén K, Hedner T, Linjer E, Scherstén B, Wester P, Möller T. Relation between drug treatment and cancer in hypertensives in the Swedish Trial in Old Patients with Hypertension 2: a 5-year, prospective, randomised, controlled trial. *Lancet.* 2001;358:539-44
- Liu C, Chen H, Zhou C, et al. Potent potentiating diuretic effects of prednisone in congestive heart failure. *J Cardiovasc Pharmacol.* 2006;48:173-6
- Lloyd-Jones DM. The risk of congestive heart failure: sobering lessons from the Framingham Heart Study. *Curr Cardiol Rep* 2001;13:184-90
- Lopez B, Querejeta R, Gonzalez A, et al. Effects of loop diuretics on myocardial fibrosis and collagen type I turnover in chronic heart failure. *J Am Coll Cardiol.* 2004;43:2028-35
- Mackay J, Eriksen M. The tobacco atlas. Geneva: World Health Organization; 2002. Available at: [www.who.int/tobacco/statistics/tobacco\\_atlas/en/](http://www.who.int/tobacco/statistics/tobacco_atlas/en/) (last accessed 29 August 2007)
- Mendez GF, Cowie MR. The epidemiological features of heart failure in developing countries: a review of the literature. *Int J Cardiol.* 2001;80:213-9
- Michigan University. Management of adults with chronic heart failure. Michigan Quality Improvement Consortium. 2007
- Micromedex. Thomson Reuters. Available under subscription at: <http://www.micromedex.com/> (last accessed 07.07.2008)
- Moser M, Ross H. The treatment of hypertension in diabetic patients. *Diabetes Care.* 1993;16:542-7
- Mueller TM, Vuckovic KM, Knox DA, Williams RE. Telemanagement of heart failure: a diuretic treatment algorithm for advanced practice nurses. *Heart Lung* 2002;31:340-7
- National Collaborating Centre for Chronic Conditions. Chronic heart failure. National clinical guideline for diagnosis and management in primary and secondary care. National Collaborating Centre for Chronic Conditions. 2003
- Neuberg GW, Miller AB, O'Connor CM, et al. Diuretic resistance predicts mortality in patients with advanced heart failure. *Am.Heart J.* 2002;144:31-8

- Nishida C, Mucavele P. Monitoring the rapidly emerging public health problem of overweight and obesity: the WHO Global Database on Body Mass Index. *SCN News* 2005;5-12
- Nordrehaug JE, Omsj  IH, Vollset SE. A 3-month double-blind cross-over study of the effect of benazepril and hydrochlorothiazide on functional class in symptomatic mild heart failure. *J Intern Med.* 1992 Jun;231(6):589-94
- Omokhodion SI, Lagunju IA. Prognostic indices in childhood heart failure. *West Afr J Med* 2005;24:325-8
- Pasquale PD, Sarullo FM, Paterna S. Novel strategies: challenge loop diuretics and sodium management in heart failure--Part I. *Congest.Heart Fail.* 2007;13:93-8
- Paul RV. Rational diuretic management in congestive heart failure: a case-based review. *Crit Care Nurs.Clin.North Am.* 2003;15:453-60
- Paul S. Balancing diuretic therapy in heart failure: Loop diuretics, thiazides, and aldosterone antagonists. *Congestive Heart Fail.* 2002;8:307-12
- Prasun MA, Kocheril AG, Klass PH, et al. The effects of a sliding scale diuretic titration protocol in patients with heart failure. *J.Cardiovasc.Nurs.* 2005;20:62-70
- Prevention of recurrent heart attacks and strokes in low and middle income populations 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). *Circ J.* 2007;71:1137-40
- Ravnan SL, Ravnan MC, Deedwania PC. Pharmacotherapy in congestive heart failure: diuretic resistance and strategies to overcome resistance in patients with congestive heart failure. *Congest Heart Fail.* 2002;8:80-5
- Ravnan SL, Deedwania PC. The rational use of diuretics in heart failure. *Curr Cardiol Rep.* 2003;5:237-42
- Reyes AJ. Diuretics in the treatment of patients who present congestive heart failure and hypertension. *J Hum Hypertens.* 2002;16 Suppl 1:S104-S113
- Reyes AJ. Heart failure, dementia, and diuretics: is uric acid involved? *Arch.Intern.Med.* 2006;166:2286
- Reyes AJ. The increase in serum uric acid concentration caused by diuretics might be beneficial in heart failure. *Eur.J.Heart Fail.* 2005;7:461-7
- Roger VL, Weston SA, Redfield MM, et al. Trends in heart failure incidence and survival in a community-based population. *JAMA.* 2004;292:344-50
- Rosenberg J, Gustafsson F, Galatius S, et al. Combination therapy with metolazone and loop diuretics in outpatients with refractory heart failure: an observational study and review of the literature. *Cardiovasc.Drugs Ther.* 2005;19:301-6
- Rudd P. Diuretics were superior to calcium channel blockers and short term ACE inhibitors for reducing heart failure in hypertension. *Evid Based Med.* 2007;12:17
- Rudd P. Diuretics were superior to calcium-channel blockers and short-term ACE inhibitors for reducing heart failure in hypertension. *ACP J Club.* 2007;146:16
- Sackner-Bernstein JD, Obeleniene R. How should diuretic-refractory, volume-overloaded heart failure patients be managed? *J Invasive Cardiol.* 2003;15:585-90

Sackner-Bernstein JD. Management of diuretic-refractory, volume-overloaded patients with acutely decompensated heart failure. *Curr Cardiol Rep.* 2005;7:204-10

Salvador DR, Rey NR, Ramos GC, et al. Continuous infusion versus bolus injection of loop diuretics in congestive heart failure. *Cochrane Database Syst Rev.* 2005;CD003178

Seeland U, Kouchi I, Zolk O, et al. Effects of diuretic treatment on cardiac and circulating RAS in chronic heart failure post-myocardial infarction in rats. *Eur J Heart Fail.* 2003;5:241-6

Shah SU, Anjum S, Littler WA. Use of diuretics in cardiovascular diseases: (1) heart failure. *Postgrad Med J.* 2004;80:201-5

Sica DA. Pharmacotherapy in congestive heart failure: drug absorption in the management of congestive heart failure: loop diuretics. *Congest Heart Fail.* 2003;9:287-92

Sica Da. Diuretic-related side effects: development and treatment. *J Clin Hypertens.* 2004;6:532-40

Sica DA. Sodium and water retention in heart failure and diuretic therapy: basic mechanisms. *Cleve Clin J Med.* 2006;73 Suppl 2:S2-S7

Sica DA, Gehr TW, Frishman WH. Use of diuretics in the treatment of heart failure in the elderly. *Clin Geriatr Med.* 2007;23:107-21

Sidorenko BA, Preobrazhenskii DV, Batyraliev TA, et al. The place of diuretics in the treatment of chronic heart failure. Part I. *Kardiologiia* 2005;45:76-83

Sidorenko BA, Preobrazhenskii DV, Bataraliev TA, et al. Changing views on the place of loop and thiazide diuretics in the treatment of chronic heart failure. Part II. Influence on outcomes and clinical application. *Kardiologiia* 2005;45:99-104

Sievert H, Offermann T, Hopf R, Kaltenbach M, Bussmann WD. [Basic therapy of chronic heart failure with digitalis or diuretics?] [Article in German] *Dtsch Med Wochenschr.* 1989 Mar 10;114(10):363-7

Scottish Intercollegiate Guidelines Network. Management of chronic heart failure. A national clinical guideline. Scottish Intercollegiate Guidelines Network. SIGN 2007

Scottish Intercollegiate Guidelines Network. Postoperative management in adults. A practical guide to postoperative care for clinical staff. Scottish Intercollegiate Guidelines Network. SIGN 2004

Slater JDH, Nabarro JDN. Clinical experience with chlorothiazide. *Lancet* 1958;1:124-26

Spannheimer A, Muller K, Falkenstein P, et al. Long-term diuretic treatment in heart failure: are there differences between furosemide and torasemide?. *Schweiz Rundsch Med Prax.* 2002;91:1467-75  
Splendiani G, Condo S. Diuretic therapy in heart failure. *G Ital Nefrol.* 2006;23 Suppl 34:S74-S76

Stiefelhagen P. Chronic arthritic patient develops diuretic refractory ankle oedema. What lies behind apparent heart failure?. *MMW Fortschr Med.* 2003;145:16

Sun WY, Reiser IW, Chou SY. Risk factors for acute renal insufficiency induced by diuretics in patients with congestive heart failure. *Am J Kidney Dis.* 2006;47:798-808

Taniguchi I, Kawai M. The clinical usefulness of diuretics for chronic heart failure in ALLHAT. *Nippon Rinsho* 2007;65 Suppl 4:547-52

Timio M, Saronio P, Venanzi S, et al. Use of diuretics in congestive heart failure: renal effects. *G Ital Nefrol.* 2006;23 Suppl 34:S44-S46

Tuma P, Hrdy P. Diuretics in therapy of "diuretic resistance" by patients with congestive heart failure. *Vnitr Lek.* 2006;52:782-9

University of Michigan Health System. Heart failure - systolic dysfunction. University of Michigan Health System 2006

VHA/DoD clinical practice guideline for the diagnosis and management of hypertension in the primary care setting. Department of Veterans Affairs. 2004

Wiysonge CS, Bradley H, Mayosi BM, Maroney R, Mbewu A, Opie LH, Volmink J. Beta-blockers for hypertension. *Cochrane Database of Systematic Reviews* 2007, Issue 1. Art. No.: CD002003

World Health Organization. Prevention of Recurrent Heart Attacks and strokes in Low and Middle Income Populations. Evidence-based Recommendations for Policy Makers and Health Professionals Nonserial Publication. Geneva: World Health Organization; 2003

World Health Organization. The Atlas of Heart Disease and Stroke. WHO available at: [http://www.who.int/cardiovascular\\_diseases/resources/atlas/en/index.html](http://www.who.int/cardiovascular_diseases/resources/atlas/en/index.html) (last accessed 29 August 2007)

World Health Organization. Avoiding heart attacks and strokes. WHO 2005 available at: [http://www.who.int/cardiovascular\\_diseases/resources/cvd\\_report.pdf](http://www.who.int/cardiovascular_diseases/resources/cvd_report.pdf) (last accessed 29 August 2007)

World Health Organization. WHO CVD-risk management package for low- and medium-resource settings. WHO 2002 available at: [http://www.who.int/cardiovascular\\_diseases/resources/pub0401/en/index.html](http://www.who.int/cardiovascular_diseases/resources/pub0401/en/index.html) (last accessed 29 August 2007)

World Health Organization. Revised Global Burden of Disease (GBD) 2002 Estimates. Incidence, prevalence, mortality, YLL, YLD and DALYs by sex, cause and region, estimates for 2002 as reported in the World Health Report 2004. Available at: <http://www.who.int/healthinfo/bodgbd2002revised/en/index.html> and at: <http://www.dcp2.org/pubs/GBD/3/Table/3.10> (last accessed 29 August 2007)

World Health Organization. The SURF report 2: surveillance of chronic disease risk factors. Country-level data and comparable estimates. Geneva: World Health Organization; 2005, available at: [www.who.int/ncd\\_surveillance/infobase/web/surf2/start.html](http://www.who.int/ncd_surveillance/infobase/web/surf2/start.html) (last accessed 29 August 2007)

Yoshida J, Yamamoto K, Mano T, et al. Different effects of long and short-acting loop diuretics on survival rate in Dahl high-salt heart failure model rats. *Cardiovasc Res.* 2005;68:118-27

## Annex A

### Global manufacturers of thiazide diuretics – January 2008

#### **CYCLOPENTHAZIDE:**

ATC: C03AA07 Diuretic, benzothiadiazide

L: CYCLOPENTHAZIDUM  
D: CYCLOPENTHAZID  
F: CYCLOPENTHAZIDE  
S: CICLOPENTIAZIDA

#### **Trades name (manufacturer, country)**

Navidrex (Goldshield: GB)  
Navidrex (Novartis: AG, AN, AW, BB, BM, BS, GD, GY, HT, JM, KY, LC, NZ, TT, VC)  
Prothiazide (Pacific: NZ)

#### **CHLOROTHIAZIDE:**

ATC: C03AA04 Diuretic, benzothiadiazide

L: CHLOROTHIAZIDUM  
I: CLOROTIAZIDE  
D: CHLOROTHIAZID  
F: CHLOROTHIAZIDE  
S: CLOROTIAZIDA

#### **Trades name (manufacturer, country)**

AZIDE (FAWNS & MCALLAN: AU)  
CHLOROSAL (TEVA: IL)  
CHLOTRIDE (AMRAD: AU)  
CHLOTRIDE (MERCK SHARP & DOHME: DK, NL)  
CHLOTRIDE (TSUN TSUN: HK)  
DIUBRAM (BRAMBLE: AU)  
DIURET (PROTEA: AU)  
DIURIGEN (GOLDLINE: US)  
DIURIL (FROSST: CA)  
DIURIL (MERCK: US)  
DIURILIX (THERAPLIX: FR)  
DIURONE (KNOLL: AU)  
DIUROSULFONA (MEDIX: ES)  
FENURIL (PHARMACIA: SE)  
NIAGAR (SINTESA: BE)  
SALISAN (FERROSAN: DK)  
SALURETIL (WELLCONE: ES)  
SALURIC (CAHILL MAY ROBERTS: IE)  
SALURIC (MERCK SHARP & DOHME: UK)  
SALUTRID (LEIRAS: FI)  
URINEX (ORION: FI)

Chlorothiazide SODIUM SALT:  
OS: Chlorothiazide Sodium USAN

#### **Trades name (manufacturer, country)**

DIURIL [INJ.] (MERCK: US)

#### **METHYLCLOTHIAZIDE**

ATC: C03AA08 Diuretic, benzothiadiazide

L: METHYLCLOTHIAZIDUM  
I: METICLOTIAZIDE  
D: METHYLCLOTHIAZID

F: METHYCLOTHIAZIDE

S: METICLOTIAZIDA

**Trades name (manufacturer, country)**

Aquatensen (Wallace: US)

Enduron (Abbott: HK, US)

Methyclothiazide (Mylan: US)

**TRICHLORMETHIAZIDE**

ATC: C03AA06 Diuretic, benzothiadiazide

L: TRICHLORMETHIAZIDUM

I: TRICLORMETIAZIDE

D: TRICHLORMETHIAZID

F: TRICHLORMETHIAZIDE

S: TRICLORMETIAZIDA

**Trades name (manufacturer, country)**

Anatran (Tobishi: JP)

Anistadin (Maruko: JP)

Aponorin (Kodama: JP)

Aquazide (Jones: US)

Carvacron (Taiyo: JP)

Chlopolidine (Tsuruhara: JP)

Cretonin (Hokuriku: JP)

Diurese (American Urologicals: US)

Flutoria (Towa Yakuhin: JP)

Naqua (Key: US)

Nydor (Taro: IL)

Polynease (Sawai: JP)

Sanamiron (Zensei: JP)

Schebitran (Nichiiko: JP)

Trametol (Green Cross: JP)

Trichlormethiazide (Camall: US)

**CHLORTALIDONE**

ATC: C03BA04 Diuretic

L: CHLORTALIDONUM

I: CLORTALIDONE

D: CHLORTALIDON

F: CHLORTALIDONE

S: CLORTALIDONA

**Trades name (manufacturer, country)**

Akuadon (Yurtoglu: TR)

Apo-Chlorthalidone (Apotex: CA)

Aquadon (Teva: IL)

Chlortalidone EG (Eurogenerics: BE)

Chlortalidone (Eurogenerics: LU)

Clortalil (EMS: BR)

Euretico (Casasco: AR)

Higrotona (Novartis: ES)

Higroton (Novartis: BR, MX)

Higroton (Rhone-Poulenc Rorer: US)

Huma-Thalidone (Humanpharma: HU)

Hygroton (Alliance: GB)

Hygroton (Biochemie: HU)

Hygroton (Ciba-Geigy: LU)

Hygroton (Mason: HK)

Hygroton (Novartis: AG, AN, AR, AU, AW, BB, BE, BN, BS, CH, DE, ET, GD, GH, GY, HT, ID, JM, KE, KY, LC, LY, MT, NG, NL, NZ, PL, PT, SD, TT, TZ, VC, ZW)

Hygroton (Novartis Pharma: AT)  
Hygroton (Pliva: HR)  
Hygroton (Rhone-Poulenc Rorer: US)  
Hythaltion (Sarabhai: IN)  
Hythaltion (SG: IN)  
Igroton (Novartis: IT)  
Saluretin (Balkanpharma: BG)  
Thalitone (Monarch: US)  
Urandil (Leciva: CZ, PL)

## **HYDROCHLOROTHIAZIDE**

ATC: C03AA03 Diuretic, benzothiadiazide

L: HYDROCHLOROTHIAZIDUM  
I: IDROCLOROTIAZIDE  
D: HYDROCHLOROTHIAZID  
F: HYDROCHLOROTHIAZIDE  
S: HIDROCLOROTIAZIDA

### **Trades name (manufacturer, country)**

Apo-Hydro (Apotex: CA, SG)  
Aquazide-25 (Western Research: US)  
Aquazide-H (Western Research: US)  
Aquazide (Sun: IN)  
Chlorzide (Foy: US)  
Chlothia (Iwaki: JP)  
Clorana (Sanofi Synthelabo: BR)  
Dehydratin (Balkanpharma: BG)  
Di-Ertride (Malaysia Chemist: SG)  
Dichlorosal (Teva: IL)  
Dichlotride (B.L.H.: TH)  
Dichlotride (Merck Sharp e Dohme: AU, BE, DK, LU)  
Dichlotride (Tsun Tsun: HK)  
Diclotride (Merck Sharp e Dohme: MX)  
Didralin (medochemie: SG)  
Disalunil (Berlin-Chemie: DE, PL)  
Disothiazid (Dexxon: IL)  
Diu-Melusin (Schwarz: DE)  
Diunorm (Slaviamed: YU)  
Diural (Austral: AR)  
Diurex (Bago: AR)  
Diurisel (vet.) (Selecta: DE)  
Drenol (Pharmacia Brasil: BR)  
Esidrex (Ciba-Geigy: LU)  
Esidrex (Geminis: ES)  
Esidrex (Novartis: AG, AN, AW, BB, BM, BS, CH, ET, FR, GD, GH, GY, HT, IT, JM, KE, KY, LC, LY, MT, NG, NL, NO, SD, SE, TT, TZ, VC, ZW)  
Esidrex (Novartis Pharma: AT)  
Esidrix (Novartis: DE, US)  
Ezide (Econo Med: US)  
H.C.T. (Kimia: ID)  
HCT 1A Pharma (1A: DE)  
HCT Biochemie (BC: DE)  
HCT gamma (Worwag: DE)  
HCT Hexal (Hexal: DE)  
HCT Muti (Intermuti: DE)  
HCT von ct (ct-Arzneimittel: DE)  
HCT-beta (betapharm: DE)  
HCT-Isis (Alpharma: DE)  
Hexazide (Hexal: ZA)  
Hidro-Niagarin (Zambon: BR)  
Hidroclorotiazida L.CH. (Chile: CL)  
Hidroclorotiazida (Infabra: BR)

Hidroclorotiazida (Lab. Neo. Quim.: BR)  
 Hidroclorotiazida (Magistra: RO)  
 Hidroclorozil (IMA: BR)  
 Hidronol (Labomed: CL)  
 Hidrosaluretil (Alcala: ES)  
 Hydrex (Orion: FI)  
 Hydro-Chlor (Vortech: US)  
 Hydrochlorothiazid Leciva (Leciva: CZ)  
 Hydrochlorothiazide Solution (Roxane: US)  
 Hydrochlorothiazide (Ivax: US)  
 Hydrochlorothiazide (Mylan: US)  
 Hydrochlorothiazide (Remedica: CY)  
 Hydrochlorothiazidum (Polpharma: PL)  
 HydroDIURIL (Merck: US)  
 Hydromal (Roberts: US)  
 Hydrozide (Atlantic: HK, SG, TH)  
 Hypothiazid (Chinoin: RU)  
 Hypothiazid (Sanofi-Synthelabo: HU)  
 Maschitt (Showa Yakuhin Kako: JP)  
 Microzide (Watson: US)  
 Modrex (United Pharmaceutical: AE, BH, DZ, IQ, LY, OM, QA, SA, SD, YE)  
 Nefrix (Sicomed: RO)  
 Newtolide (Towa Yakuhin: JP)  
 Oretic (Abbott: US)  
 Pantemon (Tatsumi Kagaku: JP)  
 Pluvius (Hexa: AR)  
 Ridaq (Pharmacare: ZA)  
 Tandiur (Raymos: AR)  
 Thiadril (Vangard: US)  
 Vetidrex (vet.) (Novartis: FR)

### **INDAPAMIDE**

ATC: C03BA11 Antihypertensive agent - Diuretic, benzothiadiazide

L: INDAPAMIDUM  
 I: INDAPAMIDE  
 D: INDAPAMID  
 F: INDAPAMIDE  
 S: INDAPAMIDA

### **Trades name (manufacturer, country)**

Amoron (Jaka-80: HR)  
 Amoron (Salus: SI)  
 Angelan (Universal Pharm.: HK)  
 Apo-Indapamide (Apotex: CA, SG)  
 Arifon (Anpharm: PL)  
 Arifon (Zorka: YU)  
 Bajaten (Merck: AR)  
 Buturetic (Duncan: AR)  
 Docindapa (Docpharma: BE)  
 Extur (Normon: ES)  
 Flubest (Yurtoglu: TR)  
 Fludex SR (Servier: CH, TR)  
 Fludex (Eutherapie: FR)  
 Fludex (Les Laboratoires: AT)  
 Fludex (Servier: NL, PT, TR)  
 Fludin (Saba: TR)  
 Fluidema (Baldacci: PT)  
 Flupamid (Sanovel: TR)  
 Flutans (Drogsan: TR)  
 Frumeron (Remedica: CY)  
 Inda-Puren (Alpharma: DE)  
 Indacar (Pharmacodande: DK)

Indaflex (Lampugnani: IT)  
 Indalix (Triomed: ZA)  
 Indamid (Ilsan: TR)  
 Indamol (Aventis Pharma: IT)  
 Indapamid HF (Hemofarm: CZ)  
 Indapamid-Cophar (Cophar: CH)  
 Indapamid-Mepha (Mepha: CH)  
 Indapamida Chobet (Soubeiran Chobet: AR)  
 Indapamida Merck (Merck: ES)  
 Indapamida Normon (Normon: ES)  
 Indapamide Edmond (Edmond: IT)  
 Indapamide EG (Eurogenerics: BE)  
 Indapamide GNR (GNR: IT)  
 Indapamide Merck (Merck Generics: IT)  
 Indapamide-Eurogenerics (Eurogenerics: LU)  
 Indapamide (Alpharma (Vet): GB)  
 Indapamide (APS: GB)  
 Indapamide (Hillcross: GB)  
 Indapamide (Ivax: GB)  
 Indapamide (Merck: BE)  
 Indapamide (Sterwin: GB)  
 Indapamid (Hemofarm: RU)  
 Indapamid (Ilsan: TR)  
 Indapamid (Panfarma: YU)  
 Indapamid (Remevita: YU)  
 Indapen (Orva: TR)  
 Indapress (Labomed: CL)  
 Indapsan (Sanofi Synthelabo: RO, RU)  
 Indicontin Continus (Modi-Mundipharma: IN)  
 Indolin (Benedetti: IT)  
 Indurin (Terra: TR)  
 Lescoprid (Zdravlje: YU)  
 Lozol (Aventis Behring: US)  
 Merck-Indapamide (Merck: BE)  
 Millibar (Lisapharma: SG)  
 Napamide (Hind Wing: HK)  
 Napsival (Promeco: AR)  
 Natrilix SR (Serdia: IN)  
 Natrilix SR (Servier: BR, CR, GB, GT, HN, ID, IE, NI, PA, SG, SV, TH)  
 Natrilix (Grupo Farma: CO)  
 Natrilix (Servier: AR, AU, DE, FI, GB, NO, ZA)  
 Natrilix (Servier-F: IT)  
 Nindaxa (Ashbourne: GB)  
 Noranat (Labinca: AR)  
 Novo-Indapamide (Novopharm: CA)  
 Nu-Indapamide (Nu-Pharm: CA)  
 PMS-Indapamide (Pharmascience: CA)  
 Pretanix (Servier: HU)  
 Rinalix (Xepa-Soul Pattinson: SG)  
 Tandix (Azevedos: PT)  
 Tendap (Asetris: CH)  
 Tertensif (J.D.C.: SI)  
 Tertensif (Servier: CZ, ES, HR, RO, YU)  
 Veroxil (Baldacci: IT)

Indapamide HEMIHYDRATE:

IS: Indapamid hemihydrat

**Trades name (manufacturer, country)**

Arifon (Servier: RU)  
 Clonilix (Clonmel: IE)  
 Dapa-Tabs (Alphapharm: AU, SG)  
 Fludapamid (Spirig: CH)  
 Fludex (Servier: AT, BE, DK, LU)

Frumeron (Pharmadica: TH)  
 Gen-Indapamide (Genpharm: CA)  
 Inamide (Gerard: IE)  
 Indahexal (Hexal: AU)  
 indapamid von ct (ct-Arzneimittel: DE)  
 Indapamide "NM" (Gerard: DK)  
 Indapamide-Chinoïn (Sanofi-Synthelabo: HU)  
 Indapamide-Generics (Generics: LU)  
 Indap (Pro.Med: CZ, RU)  
 Insig (Sigma: AU)  
 Ipamix (Gentili: IT)  
 Lozide (Servier: CA)  
 Millibar (Lisapharma: IT)  
 Napamide (Douglas: AU, NZ, SG)  
 Napamide (TTN: TH)  
 Naplin (Pacific: NZ)  
 Natrilix SR (Servier: AN, AW, BB, BM, BS, BZ, GD, GY, JM, KY, LC, TT, VC)  
 Natrilix (Grupo Farma: CO)  
 Natrilix (Servier: AR, AU, DE, FI, GB, NO, ZA)  
 Natrilix (Servier-F: IT)  
 Nindaxa (Ashbourne: GB)  
 Noranat (Labinca: AR)  
 Novo-Indapamide (Novopharm: CA)  
 Nu-Indapamide (Nu-Pharm: CA)  
 PMS-Indapamide (Pharmascience: CA)  
 Pretanix (Servier: HU)  
 Rinalix (Xepa-Soul Pattinson: SG)  
 Tandix (Azevedos: PT)  
 Tendap (Asetris: CH)  
 Tertensif (J.D.C.: SI)  
 Tertensif (Servier: CZ, ES, HR, RO, YU)  
 Veroxil (Baldacci: IT)

### **BENDROFLUMETIAZIDE**

ATC: C03AA01 Diuretic, benzothiadiazide

L: BENDROFLUMETHIAZIDUM

I: BENDROFLUMETIAZIDE

D: BENDROFLUMETHIAZID

F: BENDROFLUMETHIAZIDE

S: BENDROFLUMETIAZIDA

#### **Trades name (manufacturer, country)**

Aprinox (Abbott: EG, OM)

Aprinox (Hillcross: GB)

Aprinox (Ivax: GB)

Aprinox (Knoll: AU)

Aprinox (Sovereign: GB)

Aprinox (Swire Loxley: HK)

Bendroflumethiazide (Alpharma (Vet): GB)

Bendroflumethiazide (APS: GB)

Bendroflumethiazide (Generics: GB)

Bendroflumethiazide (Hillcross: GB)

Bendroflumethiazide (Ivax: GB)

Bezide (Carlisle: AG, AN, AW, BB, BS, BZ, GD, GY, JM, LC, SR, TT, VC)

Centyl (Leo: DK, IE, NO)

Naturetin (Princeton: US)

Neo-Naclex (Glaxo Vellcome: NZ)

Neo-NaClex (Goldshield: GB)

Salures (Pharmacia: SE)

Urizid (Rekah: IL)

## **XIPAMIDE**

ATC: C03BA10 Diuretic

L: XIPAMIDUM

I: XIPAMIDE

D: XIPAMID

F: XIPAMIDE

S: XIPAMIDA

### **Trades name (manufacturer, country)**

Aquafor (Viatris: IT)

Aquaphoril (ASTA Medica: DE)

Aquaphoril (Viatris Pharma: AT)

Aquaphor (Eli Lilly: RO)

Aquaphor (Lilly: DE, RU, SI)

Demiax (Merck: ES)

Diurexan (ASTA Medica: BE, GB, IE, LU)

Diurexan (Dyechem: HK)

Diurex (Lacer: ES)

Lumitens (Solvay: FR)

### **Abbreviations:**

L = latin name

I = italian name

F = french name

D = german name

S = spanish name

AD = Andorra	ER = Eritrea	LC = Saint Lucia
AE = United Arab Emirates	ES = Spain	LI = Liechtenstein
AF = Afghanistan	ET = Ethiopia	LK = Sri Lanka
AG = Antigua and Barbuda	FI = Finland	LR = Liberia
AI = Anguilla	FJ = Fiji	LS = Lesotho
AL = Albania	FK = Falkland Islands (Malvinas)	LT = Lithuania
AM = Armenia	FM = Micronesia	LU = Luxembourg
AN = Netherlands Antilles	FO = Faroe Islands	LV = Latvia
AO = Angola	FR = France	LY = Libya
AQ = Antarctica	FX = France, Metropolitan	MA = Morocco
AR = Argentina	GA = Gabon	MC = Monaco
AS = American Samoa	GB = United Kingdom	MD = Moldova
AT = Austria	GD = Grenada	MG = Madagascar
AU = Australia	GE = Georgia	MH = Marshall Islands
AW = Aruba	GF = French Guiana	MK = Macedonia
AZ = Azerbaijan	GH = Ghana	ML = Mali
BA = Bosnia and Herzegovina	GI = Gibraltar	MM = Myanmar
BB = Barbados	GL = Greenland	MN = Mongolia
BD = Bangladesh	GM = Gambia	MO = Macau
BE = Belgium	GN = Guinea	MP = Northern Mariana Islands
BF = Burkina Faso	GP = Guadeloupe	MQ = Martinique
BG = Bulgaria	GQ = Equatorial Guinea	MR = Mauritania
BH = Baharain	GR = Greece	MS = Montserrat
BI = Burundi	GS = S. Georgia and S. Sandwich Is	MT = Malta
BJ = Benin	GT = Guatemala	MU = Mauritius
BM = Bermuda	GU = Guam	MV = Maldives
BN = Brunei Darussalam	GW = Guinea-Bissau	MW = Malawi
BO = Bolivia	GY = Guyana	MX = Mexico
BR = Brazil	HK = Hong Kong	MY = Malaysia
BS = Bahamas	HM = Heard and MacDonal Islands	MZ = Mozambique
BT = Bhutan	HN = Honduras	NA = Namibia
BV = Bouvet Island	HR = Croatia (Hrvatska)	NC = New Caledonia
BW = Botswana	HT = Haiti	NE = Niger
BY = Belarus	HU = Hungary	NF = Norfolk Island
BZ = Belize	ID = Indonesia	NG = Nigeria
CA = Canada	IE = Ireland	NI = Nicaragua
CC = Cocos (Keeling) Islands	IL = Israel	NL = Netherland
CF = Central African Republic	IN = India	NO = Norway
CG = Congo	IO = British Indian Ocean Territor	NP = Nepal
CH = Switzerland	IQ = Iraq	NR = Nauru
CI = Cote D'Ivoire (Ivory Coast)	IR = Iran	NT = Neutral Zone
CK = Cook Islands	IS = Iceland	NU = Niue
CL = Chile	IT = Italy	NZ = New Zealand (Aotearoa)
CM = Cameroon	JM = Jamaica	OM = Oman
CN = China	JO = Jordan	PA = Panama
CO = Colombia	JP = Japan	PE = Peru
CR = Costa Rica	KE = Kenya	PF = French Polynesia
CU = Cuba	KG = Kyrgyzstan	PG = Papua New Guinea
CV = Cape Verde	KH = Cambogia	PH = Philippines
CX = Christmas Island	KI = Kiribati	PK = Pakistan
CY = Cyprus	KM = Comoros	PL = Poland
CZ = Czech Republic	KN = Saint Kitts and Nevis	PM = St. Pierre and Miquelon
DE = Germany	KP = Korea (North)	PN = Pitcairn
DJ = Djibouti	KR = Korea (South)	PR = Puerto Rico
DK = Denmark	KW = Kuwait	PT = Portugal
DM = Dominica	KY = Cayman Islands	PW = Palau
DO = Dominican Republic	KZ = Kazakhstan	PY = Paraguay
DZ = Algeria	LA = Laos	QA = Qatar
EC = Ecuador	LB = Lebanon	RE = Reunion
EE = Estonia		RO = Romania
EG = Egypt		RU = Russian Federation
EH = Western Sahara		RW = Rwanda

SA = Saudi Arabia  
SC = Seychelles  
SD = Sudan  
SE = Sweden  
SG = Singapore  
SH = St. Helena  
SI = Slovenia  
SJ = Svalbard and Jan Mayen  
Island  
SK = Slovak Republic  
SL = Sierra Leone  
SM = San Marino  
SN = Senegal  
SO = Somalia  
SR = Suriname  
ST = Sao Tome and Principe  
SV = El Salvador  
SY = Syria  
SZ = Swaziland  
Sb = Solomon Island

TC = Turks and Caicos Island  
TD = Chad  
TF = French Southern Territories  
TG = Togo  
TH = Thailand  
TJ = Tajikistan  
TK = Tokelau  
TM = Turkmenistan  
TN = Tunisia  
TO = Tonga  
TP = East Timor  
TR = Turkey  
TT = Trinidad and Tobago  
TV = Tuvalu  
TW = Taiwan  
TZ = Tanzania  
UA = Ukraine  
UG = Uganda  
UM = US Minor Outlying Islands  
US = United States

UY = Uruguay  
UZ = Uzbekistan  
VA = Vatican City State (Holy  
See)  
VC = Saint Vincent and the  
Grenadi  
VE = Venezuela  
VG = Virgin Islands (British)  
VI = Virgin Islands (U.S.)  
VN = Viet Nam  
VU = Vanuatu  
WF = Wallis and Futuna Islands  
WS = Samoa  
YE = Yemen  
YT = Mayotte  
YU = Yugoslavia  
ZA = South Africa  
ZM = Zambia  
ZR = Zaire  
ZW = Zimbabwe

## Annex B

### Evidence Tables – Guidelines on Heart Failure treatment and prevention and Thiazides Diuretics – January 2008

In this Annex, a summary of the recommendations included in the guidelines identified is presented.

Recommendations are reported as they are presented along with the grading system used in the guideline. Different grading system can be used in different guidelines. At the end of Annex B a comparative table explaining the meaning of the different grading systems is available for consultation.

#### References:

- Document 1: ACC/AHA 2005 guideline update for the diagnosis and management of chronic heart failure in the adult. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Update the 2001 Guidelines for the Evaluation and Management of Heart Failure). American College of Cardiology Foundation. 2005;
- Document 2: Heart failure - systolic dysfunction. University of Michigan Health System 2006;
- Document 3: VHA/DoD clinical practice guideline for the diagnosis and management of hypertension in the primary care setting. Department of Veterans Affairs. 2004;
- Document 4: Management of adults with chronic heart failure. Michigan Quality Improvement Consortium. 2007; (based on the ACC/AHA 2005 guideline update for the diagnosis and management of chronic heart failure in the adult)
- Document 5: The pharmacologic management of chronic heart failure. Department of Veterans Affairs. 2003; (based on the ACC/AHA guidelines for the evaluation and management of chronic heart failure in the adult: a report of the American College of Cardiology/American Heart Association Task Force on Practice guidelines 2001)
- Document 6: Chronic heart failure. National clinical guideline for diagnosis and management in primary and secondary care. National Collaborating Centre for Chronic Conditions. NICE 2003;
- Document 7: Guidelines for the diagnosis and treatment of chronic heart failure (update 2005). European Society of Cardiology. 2005;
- Document 8: Heart Failure Society of America. HFSA 2006 comprehensive heart failure practice guideline. Heart Failure Society of America. 2006;
- Document 9: Management of chronic heart failure. A national clinical guideline. Scottish Intercollegiate Guidelines Network. SIGN 2007;
- Document 10: Guidelines for the prevention, detection and management of chronic heart failure in Australia, 2006. Cardiac Society of Australia and New Zealand National Heart Foundation of Australia. 2006;
- Document 11: Postoperative management in adults. A practical guide to postoperative care for clinical staff. Scottish Intercollegiate Guidelines Network. SIGN 2004.

Heart Failure			
Ref	Argument	Agency - Year	Recommendations
1	Diagnosis and management of chronic heart failure in the adult	ACC/AHA - 2005	<p><u>Recommendation 1.</u> In patients at high risk for developing HF, systolic and diastolic hypertension should be controlled in accordance with contemporary guidelines. (<i>Level of Evidence A; Recommendation Class I</i>).</p> <p>Additional comments from the GL:</p> <p><b>Diuretic-based antihypertensive therapy</b> has repeatedly been shown to prevent HF in a wide range of target populations. In particular <b>thiazide diuretics</b> may be preferred in hypertensive HF patients with mild fluid retention because they confer more persistent antihypertensive effects.</p> <p><u>Recommendation 2.</u> <b>Diuretics</b> and salt restriction are indicated in patients with current or prior symptoms of HF and reduced LVEF who have evidence of fluid retention. (<i>Level of Evidence C; Recommendation Class I</i>)</p> <p>Additional comments from the GL:</p> <p>In table 4 of the guideline loop diuretics, <b>thiazide diuretics</b>, potassium sparing diuretics and sequential nephron blockade are cited as suitable diuretics (see table 4 below*).</p> <p><u>Recommendation 3.</u> Physicians should use <b>diuretics</b> to control pulmonary congestion and peripheral edema in patients with HF and normal LVEF. (<i>Level of Evidence C; Recommendation Class I</i>)</p> <p><u>Recommendation 4.</u> Physicians should <b>control systolic and diastolic hypertension</b> and diabetes mellitus in patients with HF in accordance with recommended guidelines. (<i>Level of Evidence C; Recommendation Class I</i>)</p> <p>Additional comments from the GL:</p> <p>Approximately two thirds of patients with HF have a past or current history of hypertension, and approximately one third have diabetes mellitus. Both disorders can contribute to the development of systolic or diastolic dysfunction, either directly or by contributing (together with hyperlipidemia) to the development of coronary artery disease. Long-term treatment of both hypertension and hyperlipidemia decrease the risk of developing HF. In 2 large-scale multicenter studies, the treatment of hypertension reduced both the risk of death and the risk of HF; this was true regardless of whether the elevation of blood pressure was primarily systolic or diastolic. The benefits of lowering blood pressure may be particularly marked in patients with diabetes mellitus.</p>
2	Management of heart failure with systolic dysfunction.	University of Michigan Health System 2006	<p><u>Recommendation 1.</u> In symptomatic patients with systolic dysfunction (EF &lt; 40%) who have no contraindications diuretics should be used to maintain appropriate fluid balance. (<i>Recommendation C</i>).</p> <p>Additional comments from the GL:</p> <p>Combining a loop diuretic with a <b>thiazide diuretic</b> increases diuretic potency by minimizing distal tubular compensation.</p> <p>Epidemiologic data have identified hypertension as a risk factor for heart failure through two potential mechanisms. (1) Hypertension may lead to left ventricular hypertrophy and subsequent diastolic dysfunction. (2)</p>

Heart Failure			
Ref	Argument	Agency - Year	Recommendations
			Hypertension is a recognized risk factor for coronary artery disease, which is the most common etiology of left ventricular systolic dysfunction. Treating hypertension may prevent the development of clinical heart failure. In the SHEP trial (Systolic Hypertension in the Elderly Program), 4736 patients with systolic hypertension were treated with <b>chlorthalidone versus placebo</b> . The treatment group had a relative risk of fatal or nonfatal heart failure of 0.51 (p<0.001). The study did not distinguish between diastolic or systolic dysfunction as the etiology of failure. Meta-analyses have corroborated this finding.
3	Diagnosis and management of hypertension in the primary care setting.	Department of Veterans Affairs. 2004	<p><u>Recommendation 1.</u> In patient with uncomplicated hypertension <b>thiazide-type diuretics</b> are recommended as first line therapy either as monotherapy or in combination with other agents (<i>Recommendation A</i>)</p> <p><u>Recommendation 2.</u> In hypertensive patient with comorbidity such as diabetes mellitus, chronic kidney disease, post stroke <b>thiazide-type diuretics</b> are recommended as first line therapy (<i>Recommendation A</i>)</p> <p><u>Recommendation 3.</u> If a <b>thiazide-type diuretic</b> is not chosen as the initial drug, it should be used as the second agent, unless contraindicated or not tolerated, because it frequently enhances the effects of the initial agent and has the best cardiovascular outcome data. (<i>Recommendation A</i>)</p> <p><u>Recommendation 4.</u> In hypertensive patient living in high ambient temperatures or in other extreme conditions that increase dehydration risk <b>thiazide-type diuretics</b> are not recommended as first line therapy. If thiazide diuretics are used, low doses are recommended. If possible, the patient should be monitored for signs and symptoms of dehydration and adequate blood pressure control for the first 7-10 days of deployment while they are becoming acclimatized. (<i>Recommendation based on consensus opinion that considers the available literature, experience in the field, and physiology</i>).</p>
4	Management of adults with chronic heart failure.	Michigan Quality Improvement Consortium. 2007	<p><u>Recommendation 1.</u> In adult patients with diagnosis of left ventricular systolic dysfunction, including heart failure, <b>diuretics</b> and sodium restriction are recommended for evidence of fluid retention (<i>Recommendation A</i>).</p> <p>Additional comments from the GL: It is based on the ACC/AHA 2005 Guideline Update for the Diagnosis and Management of Chronic Heart Failure in the Adult (ref 1 in Annex B)</p>
5	Management of chronic heart failure.	Department of Veterans Affairs. 2003	<p><u>Recommendation 1.</u> Patients with HF in Stage C with signs of fluid overload should receive a <b>diuretic</b> (<i>Fair Overall Quality of Evidence; Recommendation A</i>). Use <b>combination of loop diuretic</b> and either <b>thiazide</b> or metolazone in patients refractory to loop diuretics (<i>Recommendation B</i>).</p> <p><u>Recommendation 2.</u> In patients with HF due to diastolic dysfunction with symptoms of volume overload judicious use of <b>diuretics</b> is recommended (<i>Level of evidence C; Recommendation I</i>)</p> <p>Additional comments from the GL: Warning:</p> <ul style="list-style-type: none"> <li>- Thiazides lose effectiveness in patients with CrCl &lt; 30 mL/min</li> <li>- Monitor serum K<sup>+</sup> at 1 to 2 weeks after initiating therapy or changing dose, then every few months; more frequently if patient is also on digoxin or has demonstrated hypokalemia</li> <li>- Add potassium supplement or low dose potassium-sparing diuretic if the patient becomes hypokalemic (serum K<sup>+</sup> &lt; 4.0)</li> </ul>

Heart Failure			
Ref	Argument	Agency - Year	Recommendations
			<p>mEq/L)</p> <ul style="list-style-type: none"> <li>- Use cautiously in poorly controlled DM, symptomatic benign prostatic hyperplasia, or in patients with increased risk of volume depletion</li> <li>- Reserve indapamide for patients with CrCl &lt; 25 mL/min</li> <li>- Reserve metolazone for intermittent use as an adjunct to loop diuretics for diuresis in patients with HF or in patients with CrCl &lt; 25 mL/min; thiazide/loop combinations are also effective and are less expensive</li> </ul> <p>It is based on the ACC/AHA 2001 Guideline Update for the Diagnosis and Management of Chronic Heart Failure in the Adult.</p>
6	Diagnosis and management in primary and secondary care of chronic heart failure in adult.	NICE. 2003	<p><u>Recommendation 1.</u> <b>Diuretics</b> should be routinely used for the relief of congestive symptoms and fluid retention in patients with heart failure, and titrated (up and down) according to need following the initiation of subsequent heart failure therapies. (<i>Recommendation C</i>)</p> <p>Additional comments from the GL:</p> <p>Diuretics remain a key element in the treatment of heart failure. Diuretics preceded the advent of randomised control trials, and there are no large or long-term placebo controlled trials of their use. A systematic review of a number of small randomised trials indicated a possible benefit from diuretics in terms of mortality, compared to placebo.</p> <p><b>Thiazides</b> may be effective when added to loop diuretics when fluid retention is resistant, but can promote dramatic diuresis and disturbance in fluid balance and electrolytes. Patients must be closely monitored and specialist advice is required.</p>
7	Diagnosis and treatment of chronic heart failure.	European Society of Cardiology. 2005	<p><u>Recommendation 1.</u> <b>Diuretics</b> are essential for symptomatic treatment when fluid overload is present and manifest as pulmonary congestion or peripheral oedema. The use of diuretics results in rapid improvement of dyspnoea and increased exercise tolerance (<i>Recommendation I, Level of evidence A</i>)</p> <p><u>Recommendation 1.</u> There are no controlled randomized trials that have assessed the effect on symptoms or survival of these agents. <b>Diuretics</b> should always be administered <b>in combination with ACE inhibitors and beta-blockers</b> if tolerated. (<i>Recommendation I, Level of evidence C</i>).</p>
8	Diagnosis and treatment of heart failure	Heart Failure Society of America. 2006	<p><u>Recommendation 1.</u> In patient with HF and clinical evidence of volume overload and preserved left ventricular ejection fraction diuretic treatment is recommended. Treatment may begin with either <b>thiazide</b> or loop diuretic. In more severe volume overload or if response to a thiazide is inadequate, treatment with a loop diuretic should be implemented. Excessive diuresis, which may lead to orthostatic changes in blood pressure and worsening renal function, should be avoided. (<i>Strength of evidence C</i>).</p> <p><u>Recommendation 2.</u> in patient with HF, clinical evidence of fluid load and left ventricular systolic dysfunction diuretic therapy is recommended to restore and maintain normal status (<i>Strength of evidence A</i>). In these patients <b>loop diuretics</b> rather than thiazide type diuretics are generally necessary to restore normal volume status in patient with HF (<i>Strength of evidence B</i>).</p>
9	Management of chronic heart failure.	Scottish Intercollegiate Guidelines Network. SIGN 2007	<p><u>Recommendation 1.</u> In HF patient with dyspnoea or oedema <b>diuretic therapy</b> should be considered (<i>Recommendation B; Level of evidence 1+</i>). A metaanalysis has demonstrated a 75% reduction in mortality (OR 0.25; 95%CI 0.07-0.84) and a 63% improvement in exercise capacity (OR 0.37; 95%CI .1-0.64). In most cases the agent of choice will be a loop diuretic although <b>thiazide</b> might suffice when fluid retention is very mild.</p>
10	Prevention,	Cardiac	<p><u>Recommendation 1.</u> <b>Diuretics</b> should be used in fluid overloaded patients to increase urine output and weight reduction of 0.5-1.0</p>

Heart Failure			
Ref	Argument	Agency - Year	Recommendations
	detection and management of chronic heart failure.	Society of Australia and New Zealand National Heart Foundation of Australia. 2006	kg/die. Usually loop diuretics are used, or a combination of loop and thiazide diuretics ( <i>Recommendation D</i> ).
11	Postoperative management in adults.	Scottish Intercollegiate Guidelines Network. SIGN 2004.	<u>Recommendation 1</u> . Diuretics should be used to treat fluid overload.

From: ACC/AHA 2005 guideline update for the diagnosis and management of chronic heart failure in the adult. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Update the 2001 Guidelines for the Evaluation and Management of Heart Failure). American College of Cardiology Foundation. 2005

**Table 4. Oral Diuretics Recommended for Use in the Treatment of Fluid Retention in Chronic Heart Failure**

Drug	Initial Daily Dose(s)	Maximum Total Daily Dose	Duration of Action
<b>Loop diuretics</b>			
Bumetanide	0.5 to 1.0 mg once or twice	10 mg	4 to 6 hours
Furosemide	20 to 40 mg once or twice	600 mg	6 to 8 hours
Torsemide	10 to 20 mg once	200 mg	12 to 16 hours
<b>Thiazide diuretics</b>			
Chlorothiazide	250 to 500 mg once or twice	1000 mg	6 to 12 hours
Chlorthalidone	12.5 to 25 mg once	100 mg	24 to 72 hours
Hydrochlorothiazide	25 mg once or twice	200 mg	6 to 12 hours
Indapamide	2.5 once	5 mg	36 hours
Metolazone	2.5 mg once	20 mg	12 to 24 hours
<b>Potassium-sparing diuretics†</b>			
Amiloride	5 mg once	20 mg	24 hours
Spironolactone	12.5 to 25 mg once	50 mg*	2 to 3 days
Triamterene	50 to 75 mg twice	200 mg	7 to 9 hours
<b>Sequential nephron blockade</b>			
Metolazone	2.5 to 10 mg once plus loop diuretic		
Hydrochlorothiazide	25 to 100 mg once or twice plus loop diuretic		
Chlorothiazide (IV)	500 to 1000 mg once plus loop diuretic		

mg indicates milligrams; IV, intravenous.

\*Higher doses may occasionally be used with close monitoring.

†Eplerenone, although also a diuretic, is primarily used in chronic heart failure as a suppressor of the renin-angiotensin-aldosterone system.

Comparative table with the different grading systems adopted in the guidelines analysed.

Agency	Level of evidence	Strength of recommendation
American College of Cardiology/American Heart Association ACC/AHA, USA	A = data derived from multiple randomized clinical trials or meta-analyses; B = data derived from a single randomized trial, or nonrandomized studies; C = only consensus opinion of experts, case studies, or standard-of-care.	I = conditions for which there is evidence and/or general agreement that a given procedure or treatment is beneficial, useful, and effective; II = conditions for which there is conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of a procedure or treatment; IIa = weight of evidence/opinion is in favor of usefulness/efficacy; IIb = usefulness/efficacy is less well established by evidence/opinion; III = conditions for which there is evidence and/or general agreement that a procedure/treatment is not useful/effective and in some cases may be harmful.
University of Michigan Health System, USA	A = randomized controlled trials; B=controlled trials, no randomization; C = observational trials; D = opinion of expert panel	Intensity of shading (white, light grey, dark grey) reflects strength of recommendation.
Department of Veterans Affairs VHA/DoD, USA	I = evidence obtained from at least one properly randomized controlled trial; II-1 = evidence obtained from well-designed controlled trials without randomisation; II-2 = evidence obtained from well-designed cohort or case-control analytic studies; II-3 = evidence obtained from multiple time series studies; dramatic results in uncontrolled experiments; III = opinions of respected authorities; descriptive studies and case reports; reports of expert committees.	A = a strong recommendation based on randomized controlled trials that the intervention is always indicated and acceptable; B = a recommendation that the intervention may be useful/effective; C = a recommendation that the intervention be considered; D = a recommendation that an intervention may be considered not useful/effective, or may be harmful; I = insufficient evidence to recommend for or against; clinical judgment should be used;  It is also reported the overall quality of evidence (good, fair, poor) and the net effect of the intervention (substantial, moderate, small, zero or negative)
Michigan Quality Improvement Consortium, USA	A = randomized controlled trials; B = controlled trials, no randomization; C = observational studies; D = opinion of expert panel.	
National Institute for Clinical Excellence NICE, UK	Ia = evidence obtained from systematic review of metaanalysis of randomized controlled trias; Ib = evidence obtained from at least one randomised controlled trial;	A = at least one randomised controlled trial as part of a body of literature of overall good quality and consistency addressing the specific recommendation (evidence levels Ia and Ib);

Agency	Level of evidence	Strength of recommendation
	<p>IIa = evidence obtained from at least one well-designed controlled study without randomisation;</p> <p>IIb = evidence obtained from at least one other type of well-designed quasi-experimental study;</p> <p>III = evidence obtained from well-designed non-experimental; descriptive studies, such as comparative studies, correlation studies and case studies;</p> <p>IV = evidence obtained from expert committee reports or opinions and/or clinical experience of respected authorities;</p> <p>DS = evidence from diagnostic studies;</p> <p>NICE = evidence from NICE guidelines or health technology appraisal programme.</p>	<p>B = well-conducted clinical studies but no randomised clinical trials on the topic of recommendation (evidence levels IIa, IIb, III);</p> <p>C = expert committee reports or opinions and/or clinical experience of respected authorities. This grading indicates that directly applicable clinical studies or good quality are absent (evidence level IV);</p> <p>GPP = recommended good practice based on the clinical experience of the Guideline Development Group;</p> <p>DS = evidence from diagnostic studies;</p> <p>NICE = evidence from NICE guidelines or health technology appraisal programme.</p>
European Society of Cardiology	<p>A = data derived from multiple randomized clinical trials or meta-analyses;</p> <p>B = data derived from a single randomized clinical trial or large non-randomized studies;</p> <p>C = consensus of opinion of the experts and/or small studies; retrospective studies and registries.</p>	<p>I = evidence and/or general agreement that a given diagnostic procedure/treatment is beneficial, useful, and effective;</p> <p>II = conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of the treatment;</p> <p>IIa = weight of evidence/opinion is in favour of usefulness/efficacy;</p> <p>IIb = usefulness/efficacy is less well established by evidence/opinion;</p> <p>III* = evidence or general agreement that the treatment is not useful/effective and in some cases may be harmful.</p> <p>*Use of Class III is discouraged by the European Society of Cardiology</p>
Heart Failure Society of America., USA	<p>A = randomized, controlled, clinical trials may be assigned based on results of a single trials;</p> <p>B = cohort and case-control studies post hoc prospective observational studies or registries, subgroup analysis, and meta-analysis;</p> <p>C = expert opinion observational studies-epidemiologic findings safety reporting from large-scale use in practice.</p>	<p>Is recommended = part of routine care, exceptions to therapy should be minimized;</p> <p>Should be considered = majority of patients should receive the intervention, some discretion in application to individual patients should be allowed;</p> <p>May be considered = individualization of therapy is indicated;</p> <p>Is not recommended = therapeutic intervention should not be used.</p>
Scottish Intercollegiate Guidelines Network, SIGN, Scotland	<p>1++ = high quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias;</p> <p>1+ = well-conducted meta-analyses, systematic reviews, or RCTs with a low risk of bias;</p> <p>1- = meta-analyses, systematic reviews, or RCTs with a high risk</p>	<p>A = at least one meta-analysis, systematic review, or RCT rated as 1++, and directly applicable to the target population; or a body of evidence consisting principally of studies rated as 1+, directly applicable to the target population, and demonstrating overall consistency of results;</p> <p>B = a body of evidence including studies rated as 2++, directly applicable to the target population, and demonstrating overall consistency of results;</p>

Agency	Level of evidence	Strength of recommendation
	<p>of bias;</p> <p>2++ = high quality systematic reviews of case control or cohort or studies, high quality case control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal;</p> <p>2+ = well-conducted case control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal;</p> <p>2- = case control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal;</p> <p>3 = non-analytic studies, e.g. case reports, case series;</p> <p>4 = expert opinion.</p>	<p>or extrapolated evidence from studies rated as 1++ or 1+;</p> <p>C = a body of evidence including studies rated as 2+, directly applicable to the target population and demonstrating overall consistency of results; or extrapolated evidence from studies rated as 2++;</p> <p>D = evidence level 3 or 4; or extrapolated evidence from studies rated as 2+ good practice points;</p> <p>√ = recommended best practice based on the clinical experience of the guideline development group.</p>
<p>Cardiac Society of Australia and New Zealand National Heart Foundation of Australia, Australia New Zealand</p>	<p>I = Evidence obtained from a systematic review of all relevant RCTs;</p> <p>II = Evidence obtained from at least one properly designed RCT;</p> <p>III-1 = Evidence obtained from well designed pseudo-RCTs (alternate allocation or some other method);</p> <p>III-2 = Evidence obtained from comparative studies with concurrent controls and allocation not randomised (cohort studies), case-control studies, or interrupted time series with a control group;</p> <p>III-3 = Evidence obtained from comparative studies with historical control, two or more single-arm studies, or interrupted time series without a parallel control group;</p> <p>IV = Evidence obtained from case series, either post-test or pre-test and post-test.</p>	<p>A = rich body of high-quality RCT data;</p> <p>B = limited body of RCT data or high-quality non-RCT data;</p> <p>C = limited evidence;</p> <p>D = no evidence available — panel consensus judgement.</p>

## Annex C

### Search strategy and results of primary and secondary studies, Thiazides Diuretics – January 2008

The following electronic bibliographic databases were searched: *Medline, Embase, Cochrane library*.

The following search terms were used to locate the relevant studies:

- 1 thiazides
- 2 diuretic
- 3 heart failure
- 4 #1 or #2
- 5 #4 and #3

The following limits were settled:

- study type: RCT, SR
- time limits: from January 2002 to August 2007

**Records selected** based on abstract assessment: 89

The most relevant records are highlighted in green.

1. 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). *Circ.J.* 2007;**71**:1137-40.

Abstract: 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

2. Ben Dov IZ, Bursztyn M. Letter by Ben-Dov and Bursztyn regarding article, "Role of diuretics in the prevention of heart failure: the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial". *Circulation* 2007;**115**:e18.
3. Costanzo MR, Guglin ME, Saltzberg MT, Jessup ML, Bart BA, Teerlink JR *et al*. Ultrafiltration versus intravenous diuretics for patients hospitalized for acute decompensated heart failure. *J.Am.Coll.Cardiol.* 2007;**49**:675-83.

Abstract: OBJECTIVES: This study was designed to compare the safety and efficacy of venovenous ultrafiltration and standard intravenous diuretic therapy for hypervolemic heart failure (HF) patients. BACKGROUND: Early ultrafiltration may be an alternative to intravenous diuretics in patients with decompensated HF and volume overload. METHODS: Patients hospitalized for HF with  $>$  or  $=2$  signs of hypervolemia were randomized to ultrafiltration or intravenous diuretics. Primary end points were weight loss and dyspnea assessment at 48 h after randomization. Secondary end points included net fluid loss at 48 h, functional capacity, HF rehospitalizations, and unscheduled visits in 90 days. Safety end points included changes in renal function, electrolytes, and blood pressure. RESULTS: Two hundred patients (63  $\pm$  15 years, 69% men, 71% ejection fraction  $<$  or  $=40\%$ ) were randomized to ultrafiltration or intravenous diuretics. At 48 h, weight (5.0  $\pm$  3.1 kg vs. 3.1  $\pm$  3.5 kg;  $p = 0.001$ ) and net fluid loss (4.6 vs. 3.3 l;  $p = 0.001$ ) were greater in the ultrafiltration group. Dyspnea scores were similar. At 90 days, the ultrafiltration group had fewer patients rehospitalized for HF (16 of 89 [18%] vs. 28 of 87 [32%];  $p = 0.037$ ), HF rehospitalizations (0.22  $\pm$  0.54 vs. 0.46  $\pm$  0.76;  $p = 0.022$ ), rehospitalization days (1.4  $\pm$  4.2 vs. 3.8  $\pm$  8.5;  $p = 0.022$ ) per patient, and unscheduled visits (14 of 65 [21%] vs. 29 of 66 [44%];  $p = 0.009$ ). No serum creatinine differences occurred between groups. Nine deaths occurred in the ultrafiltration group and 11 in the diuretics group. CONCLUSIONS: In decompensated HF, ultrafiltration safely produces greater weight and fluid loss than intravenous diuretics, reduces 90-day resource utilization for HF, and is an effective alternative therapy. (The UNLOAD trial; <http://clinicaltrials.gov/ct/show/NCT00124137?order=1>; NCT00124137)

4. Costanzo MR, Johannes RS, Pine M, Gupta V, Saltzberg M, Hay J *et al.* The safety of intravenous diuretics alone versus diuretics plus parenteral vasoactive therapies in hospitalized patients with acutely decompensated heart failure: a propensity score and instrumental variable analysis using the Acutely Decompensated Heart Failure National Registry (ADHERE) database. *Am.Heart J.* 2007;**154**:267-77. Abstract: BACKGROUND: The treatment of acute decompensated heart failure remains problematic and most often requires parenteral therapies. Significant concerns have been expressed regarding risks and benefits of individual therapies, especially nesiritide (NES), but few studies have compared the relative safety of varied intravenous therapies on clinical outcomes. METHODS: We compared the safety of intravenous diuretics (DIUR), inotropes (INO), and vasodilators (nitroglycerin [NTG]) on mortality rates and worsening renal function in 99,963 inpatients with acutely decompensated heart failure (ADHF). Patients with a diagnosis of ADHF within 48 hours were grouped by intended primary treatment (intravenous agents administered during the first 2 hours of intravenous therapy). Treatments studied were (a) intended monotherapy (DIUR), (b) intended combination therapy (DIUR + NES, NTG, or INO), and (c) sequential therapy (intended DIUR monotherapy followed by a second agent administered  $>2$  hours later). Propensity-matched cohorts and instrumental analysis were used to adjust for differences among patients in treatment groups. RESULTS: Intended DIUR monotherapy yielded an unadjusted inpatient mortality rate of 3.2%. After intended DIUR monotherapy, inpatient mortality was not higher for sequential use of NES than for sequential use of NTG (3.4% vs 6.2%,  $P = .0028$ ). In all regimens, INOs were associated with higher inpatient mortality than were diuretics or vasodilators used alone. The rate of

worsening renal function was higher with combination of diuretic-based regimens with NES (risk ratio 1.44,  $P < .0001$ ) or NTG (RR 1.2,  $P = .012$ ) compared with diuretics alone. CONCLUSIONS: Compared with alternative intravenous regimens, administration of vasodilators, including NES, was not associated with increased inpatient mortality. A large randomized controlled clinical trial is being planned to prospectively address the question of risks and benefits of NES for ADHF

5. Di Pasquale P, Sarullo FM, Paterna S. Novel strategies: challenge loop diuretics and sodium management in heart failure--part II. *Congest.Heart Fail.* 2007;13:170-6. Abstract: The conflicting results of diuretic treatments in heart failure (HF) and the importance of Na management in the context of the cardiorenal syndrome and neurohormonal activation in HF have suggested novel and counterintuitive strategies, focused primarily on the use of vasopressin antagonists and hypertonic saline solution with high doses of loop diuretics and their neurohormonal interference. The emerging novel therapies involving direct inhibition of vasopressin receptors appear to show promising results. The use of hypertonic saline solution mixed with a high dose of loop diuretics produces, probably by indirect mechanisms, a reduction or inhibition of the activated neurohormonal systems in HF patients. This treatment opens a new window on the role of sodium management in these patients and on the relation between sodium and the kidney's role and function in heart failure. The authors review the current evidence for these therapies and suggest hypothetical bases for their efficacy
6. Gullestad L, Madsen S. [Diuretics not the first-choice-drug in chronic heart failure]. *Tidsskr.Nor Laegeforen.* 2007;127:621.
7. Iyengar S, Abraham WT. Diuretics for the treatment of acute decompensated heart failure. *Heart Fail.Rev.* 2007;12:125-30.

Abstract: Diuretics have been a mainstay for the treatment of acute decompensated heart failure (ADHF) for the past four decades, though their short-term gains have been questioned recently given their potential long-term deleterious systemic effects. The methods of diuretic administration as well as the optimal dosing regimen of these agents are both areas that have been increasingly coming under scrutiny. The lack of rigorous clinical trials examining diuretic use in ADHF, however, has led to a general adoption of non-evidence based treatment algorithms for this patient population. Though the use of intravenous vasodilators for the treatment of decompensated heart failure has grown tremendously over the last few years, the fact remains that diuretics are still indispensable for alleviating congestive symptoms. Given this reality and until further information is available about the most ideal utilization of these medications, diuretics will continue to represent a double-edged sword for physicians treating this disease process

8. Pasquale PD, Sarullo FM, Paterna S. Novel strategies: challenge loop diuretics and sodium management in heart failure--Part I. *Congest.Heart Fail.* 2007;13:93-8. Abstract: This is the first of a 2-part series. This article reviews the relationships among diuretics, neurohormonal activation, renal function, fluid and Na management, the cardiorenal syndrome, and heart failure. Part II will describe novel therapies based on these relationships,

focusing particularly on vasopressin antagonists and treatment using hypertonic saline solution with high-dose loop diuretics. Heart failure (HF) is a complex hemodynamic disorder characterized by chronic and progressive pump failure and fluid accumulation. Diuretics are a vital component of symptomatic management, and enhancing diuretic response in the setting of diuretic resistance is therefore pivotal. In HF patients treated with diuretics, compensatory pathophysiologic mechanisms to maintain vascular resistance, such as nonosmotic stimulation of vasopressin secretion and activation of the renin-angiotensin-aldosterone system and sympathetic nervous system, promote renal Na and water reabsorption. Thus, there remains a need to develop novel therapies for HF patients who are refractory to conventional medical treatment. The conflicting results of diuretic treatments in HF and the importance of Na management in the context of the cardiorenal syndrome and neurohormonal activation have suggested novel and counterintuitive strategies, focusing primarily on the use of vasopressin antagonists and hypertonic saline solution with high doses of loop diuretics and neurohormonal interference. The authors review the current evidence for these therapies and suggest hypothetical bases for their efficacy

9. Rudd P. Diuretics were superior to calcium channel blockers and short term ACE inhibitors for reducing heart failure in hypertension. *Evid.Based.Med.* 2007;**12**:17.
10. Rudd P. Diuretics were superior to calcium-channel blockers and short-term ACE inhibitors for reducing heart failure in hypertension. *ACP J.Club.* 2007;**146**:16.
11. Sica DA, Gehr TW, Frishman WH. Use of diuretics in the treatment of heart failure in the elderly. *Clin.Geriatr.Med.* 2007;**23**:107-21.  
Abstract: Diuretics are tools of considerable therapeutic importance. First, they effectively reduce blood pressure, while at the same time decreasing the morbidity and mortality associated with hypertension. Diuretics are currently recommended as first-line therapy for the treatment of hypertension. In addition, they remain an important component of heart failure therapy, in that they improve the symptoms of congestion, which typify the more advanced stages of heart failure. This article reviews the mode of action of the various diuretic classes and the physiologic adaptations that follow; sets up the basis for their use in the treatment of volume-retaining states, particularly as applies to the elderly; and reviews diuretic-related side effects that are normally encountered
12. Taniguchi I, Kawai M. [The clinical usefulness of diuretics for chronic heart failure in ALLHAT]. *Nippon Rinsho* 2007;**65 Suppl 4**:547-52.
13. Ahmed A, Husain A, Love TE, Gambassi G, Dell'Italia LJ, Francis GS *et al.* Heart failure, chronic diuretic use, and increase in mortality and hospitalization: an observational study using propensity score methods. *Eur.Heart J.* 2006;**27**:1431-9.  
Abstract: AIMS: Non-potassium-sparing diuretics are commonly used in heart failure (HF). They activate the neurohormonal system, and are potentially harmful. Yet, the long-term effects of chronic diuretic use in HF are largely unknown. We retrospectively analysed the Digitalis Investigation Group (DIG) data to determine the effects of diuretics on HF outcomes. METHODS AND RESULTS: Propensity scores for diuretic use were calculated for each of the

7788 DIG participants using a non-parsimonious multivariable logistic regression model, and were used to match 1391 (81%) no-diuretic patients with 1391 diuretic patients. Effects of diuretics on mortality and hospitalization at 40 months of median follow-up were assessed using matched Cox regression models. All-cause mortality was 21% for no-diuretic patients and 29% for diuretic patients [hazard ratio (HR) 1.31; 95% confidence interval (CI) 1.11-1.55; P = 0.002]. HF hospitalizations occurred in 18% of no-diuretic patients and 23% of diuretic patients (HR 1.37; 95% CI 1.13-1.65; P = 0.001). CONCLUSION: Chronic diuretic use was associated with increased long-term mortality and hospitalizations in a wide spectrum of ambulatory chronic systolic and diastolic HF patients. The findings of the current study challenge the wisdom of routine chronic use of diuretics in HF patients who are asymptomatic or minimally symptomatic without fluid retention, and are on complete neurohormonal blockade. These findings, based on a non-randomized design, need to be further studied in randomized trials

14. Cayley WE. Diuretics for treatment of patients with heart failure? *Am.Fam.Physician* 2006;74:411-3.
15. Cheng TO. Beta blockers versus diuretics for congestive heart failure in African-American patients. *Am.J.Cardiol.* 2006;98:568.
16. Chuen MJ, MacFadyen RJ. Dose-dependent association between use of loop diuretics and mortality in advanced systolic heart failure. *Am.J.Cardiol.* 2006;98:1416-7.
17. Davis BR, Piller LB, Cutler JA, Furberg C, Dunn K, Franklin S *et al.* Role of diuretics in the prevention of heart failure: the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial. *Circulation* 2006;113:2201-10.  
Abstract: BACKGROUND: Hypertension is a major cause of heart failure (HF) and is antecedent in 91% of cases. The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) stipulated assessment of the relative effect of chlorthalidone, lisinopril, and amlodipine in preventing HF. METHODS AND RESULTS: ALLHAT was a double-blind, randomized, clinical trial in 33,357 high-risk hypertensive patients aged > or =55 years. Hospitalized/fatal HF outcomes were examined with proportional-hazards models. Relative risks (95% confidence intervals; P values) of amlodipine or lisinopril versus chlorthalidone were 1.35 (1.21 to 1.50; <0.001) and 1.11 (0.99 to 1.24; 0.09). The proportional hazards assumption of constant relative risk over time was not valid. A more appropriate model showed relative risks of amlodipine or lisinopril versus chlorthalidone during year 1 were 2.22 (1.69 to 2.91; <0.001) and 2.08 (1.58 to 2.74; <0.001), and after year 1, 1.22 (1.08 to 1.38; P=0.001) and 0.96 (0.85 to 1.10; 0.58). There was no significant interaction between prior medication use and treatment. Baseline blood pressures were equivalent (146/84 mm Hg) and at year 1 were 137/79, 139/79, and 140/80 mm Hg in those given chlorthalidone, amlodipine, and lisinopril. At 1 year, use of added open-label atenolol, diuretics, angiotensin-converting enzyme inhibitors, and calcium channel blockers in the treatment groups was similar. CONCLUSIONS: HF risk decreased with chlorthalidone versus amlodipine or lisinopril use during year 1. Subsequently, risk for those individuals taking chlorthalidone versus amlodipine remained decreased but less so, whereas it was equivalent to those given lisinopril.

Prior medication use, follow-up blood pressures, and concomitant medications are unlikely to explain most of the HF differences. Diuretics are superior to calcium channel blockers and, at least in the short term, angiotensin-converting enzyme inhibitors in preventing HF in hypertensive individuals

18. Domanski M, Tian X, Haigney M, Pitt B. Diuretic use, progressive heart failure, and death in patients in the DIG study. *J.Card Fail.* 2006;12:327-32. Abstract: BACKGROUND: Nonpotassium-sparing diuretics (NPSDs), have been associated with increased sudden cardiac death (SCD) and progressive heart failure (HF) death in HF patients. METHODS AND RESULTS: In 6797 Digitalis Investigation Group study patients, risk ratios were calculated for death, cardiovascular death (CVD), death from worsening HF, SCD, and HF hospitalization among those taking a potassium-sparing (PSD), NPSD, or no diuretic. Compared with not taking diuretic, risk of death (relative risk [RR] 1.36, 95% confidence interval [CI] 1.17-1.59,  $P < .0001$ ), CVD (RR = 1.38, 95% CI 1.17-1.63,  $P = .0001$ ), progressive HF death (RR = 1.41, 95% CI 1.06-1.89,  $P = .02$ ), SCD (RR = 1.67, 95% CI 1.23-2.27,  $P = .001$ ), and HF hospitalization (RR = 1.68, 95% CI 1.41-1.99,  $P < .0001$ ) were increased with NPSD. There was no significant difference in any end point for patients taking only PSD compared to no diuretic. PSD only subjects were less likely than NPSD subjects to be hospitalized for HF (RR = 0.71, 95% CI 0.52-0.96,  $P = .02$ ). CONCLUSION: NPSDs are associated with increased risk of death, CVD, progressive HF death, SCD, and HF hospitalization. A randomized trial is needed to assess the role of NPSDs versus PSDs in HF patients
  
19. Eshaghian S, Horwich TB, Fonarow GC. Relation of loop diuretic dose to mortality in advanced heart failure. *Am.J.Cardiol.* 2006;97:1759-64. Abstract: Although loop diuretics are widely used in heart failure (HF), their effect on outcomes has not been evaluated in large clinical trials. This study sought to determine the dose-dependent relation between loop diuretic use and HF prognosis. A cohort of 1,354 patients with advanced systolic HF referred to a single center was studied. Patients were divided into quartiles of equivalent total daily loop diuretic dose: 0 to 40, 41 to 80, 81 to 160, and >160 mg. The cohort was 76% male, with a mean age of 53+/-13 years and a mean ejection fraction of 24+/-7%. The mean diuretic dose equivalence was 107+/-87 mg. The diuretic quartile groups were similar in terms of gender, body mass index, ischemic cause of HF, history of hypertension, and spironolactone use, but the highest quartile was associated with a smaller ejection fraction and lower serum sodium and hemoglobin levels but higher serum blood urea nitrogen and creatinine levels. There was a decrease in survival with increasing diuretic dose (83%, 81%, 68%, and 53% for quartiles 1, 2, 3, and 4, respectively). Even after extensive covariate adjustment (age, gender, ischemic cause of HF, the ejection fraction, body mass index, pulmonary capillary wedge pressure, peak oxygen consumption, beta-blocker use, angiotensin-converting enzyme inhibitor or angiotensin receptor blocker use, digoxin use, statin use, serum sodium, blood urea nitrogen, creatinine, hemoglobin, cholesterol, systolic blood pressure, and smoking history), diuretic quartile remained an independent predictor of mortality (quartile 4 vs quartile 1 hazard ratio 4.0, 95% confidence interval 1.9 to 8.4). In conclusion, in this cohort of patients with advanced HF, there was an independent, dose-dependent association between loop diuretic use and impaired survival. Higher loop diuretic dosages identify patients with HF at particularly high risk for mortality

20. Faris R, Flather MD, Purcell H, Poole-Wilson PA, Coats AJ. Diuretics for heart failure. *Cochrane.Database.Syst.Rev.* 2006;CD003838.

Abstract: BACKGROUND: Chronic heart failure is a major cause of morbidity and mortality world-wide. Diuretics are regarded as the first-line treatment for patients with congestive heart failure since they provide symptomatic relief. The effects of diuretics on disease progression and survival remain unclear. OBJECTIVES: To assess the harms and benefits of diuretics for chronic heart failure SEARCH STRATEGY: We searched the Cochrane Central Register of Controlled Trials (Issue 2 2004), MEDLINE 1966-2004, EMBASE 1980-2004 and HERDIN database. We hand searched pertinent journals and reference lists of papers were inspected. We also contacted manufacturers and researchers in the field. SELECTION CRITERIA: Only double-blinded randomised controlled trials of diuretic therapy comparing one diuretic with placebo, or one diuretic with another active agent (e.g. ACE inhibitors, digoxin) in patients with chronic heart failure were eligible for inclusion. DATA COLLECTION AND ANALYSIS: Two reviewers independently abstracted the data and assessed the eligibility and methodological quality of each trial. Extracted data were entered into the Review Manager 4.2 computer software, and analysed by determining the odds ratio for dichotomous data, and difference in means for continuous data, of the treated group compared with controls. The likelihood of heterogeneity of the study population was assessed by the Chi-square test. If there was no evidence of statistical heterogeneity and pooling of results was clinically appropriate, a combined estimate was obtained using the fixed-effects model. MAIN RESULTS: We included 14 trials (525 participants), 7 were placebo-controlled, and 7 compared diuretics against other agents such as ACE inhibitors or digoxin. We analysed the data for mortality and for worsening heart failure. Mortality data were available in 3 of the placebo-controlled trials (202 participants). Mortality was lower for participants treated with diuretics than for placebo, odds ratio (OR) for death 0.24, 95% confidence interval (CI) 0.07 to 0.83; P = 0.02. Admission for worsening heart failure was reduced in those taking diuretics in two trials (169 participants), OR 0.07 (95% CI 0.01 to 0.52; P = 0.01). In four trials comparing diuretics to active control (91 participants), diuretics improved exercise capacity in participants with CHF, difference in means WMD 0.72 , 95% CI 0.40 to 1.04; P < 0.0001. AUTHORS' CONCLUSIONS: The available data from several small trials show that in patients with chronic heart failure, conventional diuretics appear to reduce the risk of death and worsening heart failure compared to placebo. Compared to active control, diuretics appear to improve exercise capacity

21. Guntheroth WG. Decompensated heart failure and diuretic resistance. *J.Am.Coll.Cardiol.* 2006;48:1059-60.

22. Gupta S, Neyses L. Current thinking regarding the use of diuretics in heart failure. *Heart Fail.Monit.* 2006;5:50-3.

Abstract: The majority of therapies used in the contemporary management of chronic heart failure (CHF) have been rigorously evaluated by means of large-scale clinical trials to assess their beneficial effects on quality of life and prognosis. Such therapies include angiotensin-converting enzyme (ACE) inhibitors, beta-blockers, and cardiac resynchronization therapy (CRT). Diuretics are the most commonly prescribed class of drugs in CHF patients and in the

short term they remain the most efficacious treatment for relief from fluid congestion. There is, however, scant evidence to suggest that they confer any long term benefit in terms of disease progression or prognosis to the CHF sufferer. Injudicious use of diuretics has been demonstrated to be potentially harmful and consideration should be paid to avoiding dietary salt indiscretion as well as the pharmacokinetic properties of individual diuretics to achieve optimal diuretic response. In this article, we explore the current insight into the use of diuretics in CHF

23. Howard PA, Dunn MI. Effectiveness of continuous infusions of loop diuretics for severe heart failure. *J.Cardiovasc.Med.(Hagerstown.)* 2006;7:5-10.

Abstract: Heart failure is a growing worldwide epidemic resulting in frequent hospitalizations and increased resource utilization. A major cause of hospitalization is congestive symptoms and impaired functional capacity due to sodium and water retention. Diuretic resistance, which is common among patients with severe heart failure, may inhibit diuresis, thus prolonging hospitalizations. The current evidence suggests that continuous infusions are a potentially effective method for delivering high daily doses of diuretics and rapidly removing large amounts of excess sodium and water. In our experience, continuous intravenous infusions of furosemide are well tolerated and may shorten hospitalizations, which in turn reduces overall costs. Although the current evidence is largely limited to observational reports and small uncontrolled studies, the consistent findings of efficacy and safety warrant the further investigation of this treatment strategy in randomized controlled trials

24. Iyengar S, Abraham WT. Diuretic resistance in heart failure. *Curr.Heart Fail.Rep.* 2006;3:41-5. Abstract: The use of diuretics for the treatment of heart failure (HF) is ubiquitous in any basic HF medical regimen. Although initially these drugs clearly show benefit by relieving symptomatic episodes of decompensated HF, long-term use of these drugs can lead to a "diuretic-resistant" state and is associated with an increased risk of morbidity and mortality. A number of factors may be responsible for this, including dietary noncompliance, inadequate diuretic dosing or methods of administration, and concomitant use of certain medications. Diuretics themselves may set in motion an iatrogenic cardiorenal syndrome leading to worsening renal function and diuretic resistance. The methods for overcoming this resistance are varied and require a focused approach with emphasis on relieving the congestive symptoms related to HF while attempting to preserve renal function and minimize any untoward systemic effects
25. Jolobe OM. Diuretic usage in heart failure: a continuing conundrum in 2005. *Eur.Heart J.* 2006;27:886-7.
26. Krum H, Cameron P. Diuretics in the treatment of heart failure: mainstay of therapy or potential hazard? *J.Card Fail.* 2006;12:333-5.
27. Liang KV, Hiniker AR, Williams AW, Karon BL, Greene EL, Redfield MM. Use of a novel ultrafiltration device as a treatment strategy for diuretic resistant, refractory heart failure: initial clinical experience in a single center. *J.Card Fail.* 2006;12:707-14.

Abstract: BACKGROUND: The System 100 UF device allows ultrafiltration (UF) via peripheral access and is approved for use in heart failure (HF), although clinical trials defining optimal target population and clinical utility are lacking. We report our initial experience with clinical use of this system in very advanced, diuretic resistant HF patients. METHODS AND RESULTS: Eleven HF patients (mean age 70 years) underwent 1 to 5 UF treatments each (total 32 UF). The goal was to remove 4 liters of fluid per 8-hour UF. Baseline creatinine averaged 2.2 mg/dL (range .9-3.2) while estimated glomerular filtration rates (GFRs) averaged 38 mL/min (range 20-87). Nine patients (82%) had moderate (GFR 30-59; n = 3) or severe (GFR <30; n = 6) renal dysfunction. Nine patients (82%) had documented right ventricular dysfunction, 6 with severe tricuspid regurgitation. Average daily intravenous furosemide dose prior to UF was 258 mg (range 80-480). Patients had received nesiritide (n = 4), dopamine (n = 4), and zaroxylyn (n = 7) prior to UF. Of the 32 UF treatments, 13 (41%) removed >3500 mL, 11 (34%) removed 2500-3500 mL, and 8 (25%) removed <2500 mL. Only one UF treatment (3%) was aborted due to hypotension. There were no significant complications related to UF. Five patients (45%) experienced an increase in creatinine of >.3 mg/dl. Five patients required dialysis for persistent diuretic resistant volume overload or uremic symptoms. Six-month mortality was 55%. CONCLUSIONS: Peripheral UF safely but variably removed fluid. In this very high-risk, advanced HF population, 45% of patients developed worsening renal function during UF therapy. Controlled studies are needed to determine the impact of UF on renal function and outcomes in high-risk populations such as this

28. Libetta C, Sepe V, Zucchi M, Campana C, Dal Canton A. Standard hemodiafiltration improves diuretic responsiveness in advanced congestive heart failure. *Cardiology* 2006;**105**:122-3.
29. Liu C, Chen H, Zhou C, Ji Z, Liu G, Gao Y *et al.* Potent potentiating diuretic effects of prednisone in congestive heart failure. *J.Cardiovasc.Pharmacol.* 2006;**48**:173-6. Abstract: Animal studies showed glucocorticoids could specifically dilate renal vasculature, regulate synthesis and release of atrial natriuretic peptide (ANP), upregulate ANP receptors on vascular endothelial cells, and thus have potent potentiating diuresis and natriuresis effects in animal studies; however, their diuretic efficacy in humans is yet to be known. Therefore, we designed this randomized, double-blind, placebo-controlled, clinical study to determine the diuretic efficacy of prednisone, a glucocorticoid, in patients with congestive heart failure (CHF). METHODS: Twenty clinically stable patients with CHF without overt fluid retention were randomized to a prednisone group or placebo group. Prednisone (1 mg/kg/day with a maximum dose of 60 mg/day) was added to standard care for 7 days, leaving other medications unchanged. Variables included urine volume and electrolytes, serum electrolytes, and change from baseline in serum creatinine. RESULTS: Adding prednisone resulted in striking diuresis and natriuresis with time. As compared with the placebo group, the maximum of mean daily urine volume was 810.5 mL larger than those in the placebo group (95% confidence intervals [CI] 276.25 to 1344.86, P < 0.05). The maximum mean daily sodium excretion was 123.8 mmol higher than those patients given placebo (95% CI 11.4 to 236.2, P < 0.05). The placebo-corrected effect on change from baseline in serum creatinine was -19.5  $\mu$ mol/L (95% CI -7.4 to -31.6, P < 0.01), favoring prednisone. CONCLUSIONS: This pilot study showed that prednisone had potent potentiating diuretic effects in patients with heart failure and might improve renal function in the same time. Further prospective randomized

clinical studies are warranted to determine the preferable dose and its efficacy in decompensated congestive heart failure

30. Reyes AJ. Heart failure, dementia, and diuretics: is uric acid involved? *Arch.Intern.Med.* 2006;**166**:2286.
31. Sica DA. Sodium and water retention in heart failure and diuretic therapy: basic mechanisms. *Cleve.Clin.J.Med.* 2006;**73 Suppl 2**:S2-S7.

Abstract: The pathophysiology of sodium and water retention in heart failure is characterized by a complex interplay of hemodynamic and neurohumoral factors. Relative arterial underfilling is an important signal that triggers heart failure-related sodium and water retention. The response to perceived arterial underfilling is modulated by the level of neurohormonal activation, the degree of renal vasoconstriction, and the extent to which renal perfusion pressure is reduced. Sodium retention can also be exceeded by water retention, with the result being dilutional hyponatremia. Sodium and water retention in heart failure also function to dampen the natriuretic response to diuretic therapy. The attenuated response to diuretics in heart failure is both disease-specific and separately influenced by the rate and extent of diuretic absorption, the rapidity of diuretic tubular delivery, and diuretic-related hypertrophic structural changes that surface in the distal tubule

32. Splendiani G., Condo S. [Diuretic therapy in heart failure]. *G.Ital.Nefrol.* 2006;**23 Suppl 34**:S74-S76.

Abstract: Diuretic therapy is a drug therapy that increases urine volume, but not glomerular filtration rate (GFR). The diuretics act predominantly on tubular sites; the drugs that increase GRF are the aminophyllines, the positive inotropy or vasoactive substances that increase afferent arteriolar flux or intraglomerular pressure. We can divide the diuretics into six categories: 1) carbonic anhydrase inhibitors: acetazolamide, dichlorphenamide, methazolamide; 2) osmotic diuretics: glycerol, mannitol, urea; 3) loop diuretics: furosemide, bumetanide, ethacrynic acid, piretanide, torsemide; 4) thiazide and thiazide-like diuretics: chlorothiazide, trichlormethiazide, indapamide, chlorthalidone, metolazone; 5) potassium-sparers: a) kidney epithelial sodium channel inhibitors: amiloride and triamterene; b) aldosterone receptor antagonists: spironolactone, canrenoate potassium, eplerenone; 6) ADH antagonists: lithium salts, demeclocycline and ethanol. Diuretic therapy is useful in treating acute and chronic renal insufficiency, congestive heart failure, cirrhosis, overhydration and hypertension. Diuretic therapy increases urine volume, ion loss (except Na<sup>+</sup>, K<sup>+</sup>), and modifies diffusion (dilute urine) and convection mechanisms (reduced tubular absorption). Therefore, diuretics are very useful non-dangerous drugs

33. Sun WY, Reiser IW, Chou SY. Risk factors for acute renal insufficiency induced by diuretics in patients with congestive heart failure. *Am.J.Kidney Dis.* 2006;**47**:798-808. Abstract: BACKGROUND: In patients with congestive heart failure (CHF), continuous diuretic therapy may result in acute renal insufficiency (ARI). This study examines factors contributing to this complication. METHODS: We analyzed clinical data from 318 consecutive patients who were hospitalized for CHF. All were treated with diuretics and had echocardiography

performed within 4 days of hospitalization. Systolic left ventricular (LV) dysfunction is defined as an ejection fraction less than 50%, and diastolic LV dysfunction, as an ejection fraction of 50% or greater in the presence of LV hypertrophy and a reversed E/A ratio. RESULTS: ARI, defined as a 25% increase in serum creatinine level, occurred in 110 patients (35%) after diuretic therapy. Risk factors for ARI on univariate analyses were older age, higher baseline serum creatinine level, lower baseline serum sodium level, lower mean arterial pressure (MAP) during diuretic therapy, and greater doses and longer duration of diuretic therapy. In multivariate analyses, ARI occurred more frequently in patients with systolic (40%) than diastolic dysfunction (28%). The use of digoxin in patients with systolic LV dysfunction was observed to decrease the risk for ARI by 61%, independent of other agents used for the treatment of patients with CHF. CONCLUSION: Age, baseline renal function and serum sodium concentration, MAP, and intensity of diuretic therapy can identify individuals at risk for ARI while receiving diuretic therapy for CHF. This complication is observed more often in individuals with systolic dysfunction, and its risk may be decreased with the use of digoxin

34. Timio M, Saronio P, Venanzi S, Bellomo G, Timio F. [Use of diuretics in congestive heart failure: renal effects]. *G.Ital.Nefrol.* 2006;23 Suppl 34:S44-S46. Abstract: Diuretics are an integral part of the management of symptomatic heart failure. Although they have been used for several decades, there is still some ambiguity and confusion regarding the outcome and the optimal way of using these common agents. There are no large-scale randomized controlled trials that have evaluated the effect of diuretics on mortality and long-term morbidity in diastolic and systolic dysfunction. Nonetheless, in short-term studies furosemide has demonstrated to reduce symptomatic congestive heart failure and hospitalization, and to improve exercise capacity in the setting of systolic dysfunction. In this review, the classes, sites of action and renal effect of diuretics are reviewed and the various indications, optimal doses and recommendations on effective use and disuse are discussed. Namely, this review addresses the effects of emerging diuretic agents such as eplerenone--a selective mineral corticoid receptor antagonist, nesiritide--a brain natriuretic peptide-recombinant, and conivaptan--a vasopressin antagonist, in attempt to provide an update on current knowledge, even though adequate clinic data are not available for all agents
35. Tuma P, Hrdy P. [Diuretics in therapy of "diuretic resistance" by patients with congestive heart failure]. *Vnitr.Lek.* 2006;52:782-9. Abstract: Loop diuretics are integral part of overall therapy of severe congestive heart failure. Approximately 10-20 % of patients with congestive heart failure (NYHA class III-IV) do not respond satisfactorily to diuretic treatment. Despite its frequency, the term "diuretic resistance" remains inadequately defined. In general, failure to decrease the extracellular fluid volume despite liberal use of diuretics is often termed "diuretic resistance". The combination of diuretics, particularly of loop diuretic with thiazide agents, is recommended for prevention as well as treatment of this complication. Effective management is also continuous infusion of loop diuretic. If it is impossible to achieve adequate response by combination of diuretics, increasing of its dosage or/and frequency or continuous infusion, then dialysis methods may be employed (however it is not intended to discuss this option in this article)

36. Boni E, Bezzi M, Carminati L, Corda L, Grassi V, Tantucci C. Expiratory flow limitation is associated with orthopnea and reversed by vasodilators and diuretics in left heart failure. *Chest* 2005;**128**:1050-7.

Abstract: BACKGROUND: In patients with acute left heart failure (LHF), orthopnea has also been related to the occurrence or worsening of expiratory flow limitation (EFL) in the supine position. We wished to assess whether short-term treatment with vasodilators and diuretics was able to abolish supine EFL and whether this could help to control orthopnea in patients with acute LHF. METHODS: In nine nonobese (ie, mean [ $\pm$  SD] body mass index, 24  $\pm$  5 kg/m<sup>2</sup>), never-smoker patients (two men and seven women; mean age, 77  $\pm$  7 years) with acute LHF (mean ejection fraction, 43  $\pm$  15%), we assessed EFL by the negative expiratory pressure method and dyspnea by the Borg scale, with patients in both the seated and supine positions, before and after short-term treatment with vasodilators and diuretics until hospital discharge. Orthopnea was defined as a positive difference in the Borg score between measurements made with the patient in the supine and seated positions. Postural variations in the end-expiratory lung volume were inferred from changes in inspiratory capacity (IC) that were measured under the same circumstances. RESULTS: Before treatment, with the patient in the seated position the mean dyspnea score was 1.5  $\pm$  0.5, the mean IC was 1.49  $\pm$  0.38 L, seven patients were non-flow-limited, and two patients were flow-limited. During recumbency, the mean dyspnea score was 2.7  $\pm$  0.5 ( $p < 0.01$  vs seated position values), the mean IC was 1.66  $\pm$  0.45 L, and seven patients exhibited EFL. After a mean duration of 17  $\pm$  8 days of treatment (range, 7 to 28 days), EFL was detected in two patients only in the supine position, IC increased both in the seated position (1.65  $\pm$  0.34 L;  $p < 0.01$ ) and the supine position (1.81  $\pm$  0.41 L;  $p = 0.07$ ) position, and, although only two patients denied orthopnea, the mean dyspnea score during recumbency actually decreased to 1.9  $\pm$  1.0 ( $p < 0.05$ ). CONCLUSIONS: Our results indicate that short-term treatment with vasodilators and diuretics is able to control orthopnea and to remove supine EFL in most patients with acute LHF, suggesting a posture-related increase in bronchial obstruction as the main mechanism of EFL, which appears to play a role in the occurrence and severity of orthopnea in these circumstances

37. Costanzo MR, Saltzberg M, O'Sullivan J, Sobotka P. Early ultrafiltration in patients with decompensated heart failure and diuretic resistance. *J.Am.Coll.Cardiol.* 2005;**46**:2047-51. Abstract: OBJECTIVES: We sought to determine if ultrafiltration before intravenous (IV) diuretics in patients with decompensated heart failure and diuretic resistance results in euvolemia and early discharge without hypotension or worsening renal function. BACKGROUND: Heart failure patients with renal insufficiency and diuretic resistance have increased hospital mortality and length of stay. Peripheral veno-venous ultrafiltration may re-establish euvolemia and diuretic responsiveness. METHODS: Ultrafiltration was initiated within 4.7  $\pm$  3.5 h of hospitalization and before IV diuretics in 20 heart failure patients with volume overload and diuretic resistance (age 74.5  $\pm$  8.2 years; 75% ischemic disease; ejection fraction 31  $\pm$  15%) and continued until euvolemia. Re-evaluation was each hospital day, at 30 days, and at 90 days. RESULTS: A total of 8,654  $\pm$  4,205 ml were removed with ultrafiltration. Twelve patients (60%) were discharged in  $\leq$  3 days. One patient was readmitted in 30 days. Weight ( $p = 0.006$ ), Minnesota Living with Heart Failure scores ( $p = 0.003$ ), and Global

Assessment ( $p = 0.00003$ ) improved after ultrafiltration and at 30 and 90 days. Median B-type natriuretic peptide levels decreased after ultrafiltration (from 1,230 pg/ml to 788 pg/ml) and at 30 days (815 pg/ml) ( $p = 0.035$ ). Blood pressure, renal function, and medications were unchanged. CONCLUSIONS: In heart failure patients with volume overload and diuretic resistance, ultrafiltration before IV diuretics effectively and safely decreases length of stay and readmissions. Clinical benefits persist at three months

38. De Pasquale CG, Dunne JS, Minson RB, Arnold LF. Hypotension is associated with diuretic resistance in severe chronic heart failure, independent of renal function. *Eur.J.Heart Fail.* 2005;7:888-91.

Abstract: BACKGROUND: Diuretic resistance and systemic hypotension are common in chronic heart failure (CHF), however, the two have not been associated. AIMS: Since blood pressure (BP) might be an important determinant of sodium excretion, we searched for an association between BP and diuretic dosage in severe CHF. METHODS: Our heart failure database was retrospectively reviewed for patients with severe left ventricular systolic dysfunction. The 54-patient cohort was divided on the basis of furosemide dosage (high-dose  $>$  or  $=$  250 mg daily,  $n=26$ ). RESULTS: Patients taking high-dose furosemide had higher serum creatinine, and lower systolic and diastolic BP. On logistic regression analysis, increased serum creatinine and reduced diastolic BP were independent predictors of the use of high-dose furosemide. Grouping these variables into tertiles, the odds ratio for the use of high-dose furosemide was 4.0 as diastolic BP decreased ( $p<0.01$ ), and 6.8 as serum creatinine increased ( $p<0.001$ ). CONCLUSIONS: We have found an association between hypotension and the use of high-dose furosemide in severe CHF, which is independent of renal function, and which may be an important physiologic mechanism of diuretic resistance in severe CHF

39. Galve E, Mallol A, Catalan R, Palet J, Mendez S, Nieto E *et al.* Clinical and neurohumoral consequences of diuretic withdrawal in patients with chronic, stabilized heart failure and systolic dysfunction. *Eur.J.Heart Fail.* 2005;7:892-8.

Abstract: BACKGROUND: Loop diuretics are beneficial in heart failure in the short term because they eliminate fluid retention, but in the long-term, they could adversely influence prognosis due to activation of neurohumoral mechanisms. AIMS: To explore the changes induced by diuretic withdrawal in chronic nonadvanced heart failure. METHODS: Diuretics were withdrawn in 26 stabilized heart failure patients with systolic dysfunction (ejection fraction [EF] $<45\%$ ). Clinical status was evaluated by physical exam, exercise capacity (corridor test) and New York Heart Association (NYHA) class. Biochemical and neurohumoral determinations were performed at baseline and at 3 months. RESULTS: At 3 months, 17 out of 26 patients (65%) were able to tolerate diuretic interruption without a deterioration in exercise capacity or New York Heart Association functional class. Renal function parameters improved (baseline urea 46.2 $\pm$ 10.8 to 39.2 $\pm$ 10.1 mg/dl at 3 months,  $p=0.014$ ; creatinine 1.1 $\pm$ 0.23 to 0.98 $\pm$ 0.2 mg/dl,  $p=0.013$ ). Glucose metabolism also improved (fasting glucose 151 $\pm$ 91 to 122 $\pm$ 14 mg/dl,  $p=0.035$ ). Heart rate and systolic blood pressure did not significantly change, while diastolic blood pressure increased (from 80 $\pm$ 10 to 87 $\pm$ 13 mm Hg,  $p=0.006$ ). Neurohumoral determinations showed a decrease in plasma renin activity (4.19 $\pm$ 5.96 to 2.88 $\pm$ 4.98 ng/ml,  $p=0.026$ ), with no changes in aldosterone, arginine-vasopressin, endothelin-1 and norepinephrine. In contrast, atrial natriuretic peptide significantly increased (115 $\pm$ 87 to

168±155 pg/ml, p=0.004). CONCLUSION: Diuretic withdrawal in stabilized heart failure with systolic dysfunction is associated with an improvement in renal function parameters, glucose metabolism and some neurohumoral parameters, such as plasma renin activity; however, atrial natriuretic peptide levels increased

40. Gupta S, Neyses L. Diuretic usage in heart failure: a continuing conundrum in 2005. *Eur. Heart J.* 2005;26:644-9.

Abstract: Several large well-designed clinical trials have shown that the use of diuretics is beneficial in patients with hypertension. However, similarly robust data regarding their role in chronic heart failure are lacking. Historically, diuretics were developed for treatment of sodium and water retention in oedematous disorders and clinically, they remain the most potent drugs available to relieve symptoms and eliminate oedema in the congested patient with heart failure. In the non-congested patient, however, diuretics continue to be used on a purely clinical basis without sufficient characterization of benefits, adverse effects, and potential influence on mortality. There are also concerns that chronic diuretic usage can cause adverse vascular effects, unfavourable neuroendocrine activation, electrolyte imbalances, and life-threatening arrhythmias. In this article, we review the limited evidence available regarding the benefits and perils of using diuretics in heart failure

41. Lepor NE. Diuretic therapy, natriuretic peptides, and heart failure. *Rev. Cardiovasc. Med.* 2005;6:184-6.
42. Prasun MA, Kocheril AG, Klass PH, Dunlap SH, Piano MR. The effects of a sliding scale diuretic titration protocol in patients with heart failure. *J. Cardiovasc. Nurs.* 2005;20:62-70. Abstract: Patients with heart failure (HF) are often instructed to temporarily adjust their diuretic dose. This approach has become routine in some HF management programs; however, no study has specifically examined the effects of a patient-directed flexible diuretic protocol. For the purposes of this study, patients were randomized into a usual care (UC) group (n = 31) or a flexible diuretic titration (DT) group (n = 35). The DT group completed a 6-item diuretic titration protocol once a day, for 3 months. The 6-minute walk distance, plasma B-type natriuretic peptide (NT-BNP), plasma norepinephrine (NE), and quality of life (QOL) were measured at baseline and at 3 months. Hospitalizations, emergency department (ED) visits, and mortality rates were measured at 3 months. Compared to baseline, at 3 months, there was a significant increase in the DT group's 6-minute walk distance (646 ± 60 ft vs 761 ± 61 ft, P = .01) and total QOL score (53 ± 5 vs 38 ± 5, P = .001), whereas these parameters remained unchanged within the UC group. There were significantly less ED visits in the DT group compared with those in the UC group (3% vs 23%, P = .015). No differences were found between the groups in HF-related hospitalizations or mortality. Within both groups, no differences were found between baseline and 3-month NE or NT-BNP plasma values. Patients with heart failure who used a sliding scale diuretic titration protocol had significant improvements in their exercise tolerance and QOL, had fewer ED visits, and had no change in plasma NE or NT-BNP levels

43. Reyes AJ. The increase in serum uric acid concentration caused by diuretics might be beneficial in heart failure. *Eur.J.Heart Fail.* 2005;7:461-7. Abstract: Patients with mild-moderate chronic heart failure (CHF) often have raised levels of serum uric acid (UA). This is due, amongst other factors, to reduced UA excretion by the kidneys, which is partly explained by restriction of sodium intake and treatment with diuretics. The decline in renal function that parallels worsening cardiac function also contributes to elevated serum UA in patients with advanced CHF. However, UA production also appears to be augmented in CHF. Because UA scavenges various reactive oxygen species, diuretic-induced elevations in serum UA could be beneficial in patients with CHF. This concept is supported by the superior performance of antihypertensive therapy with diuretics in preventing heart failure. The present hypothesis may be tested by examining the effects of add-on treatment with a thiazide-type diuretic on morbidity and mortality, or surrogate variables, in asymptomatic patients with left ventricular dysfunction but without fluid retention
44. Rosenberg J, Gustafsson F, Galatius S, Hildebrandt PR. Combination therapy with metolazone and loop diuretics in outpatients with refractory heart failure: an observational study and review of the literature. *Cardiovasc.Drugs Ther.* 2005;19:301-6. Abstract: Metolazone is a potent thiazide-like diuretic. It is recommended in severe congestive heart failure (HF). We conducted a review of the existing literature and found that the available information on the use of metolazone in HF is based on studies containing less than 250 patients in total. Nevertheless, metolazone is widely used, often in combination with a loop diuretic. Absorption of metolazone seems to be reduced in HF. Metolazone produces a diuretic response despite a low glomerular filtration rate. A wide dose range of metolazone has been investigated (< or =2.5 to 200 mg), leaving no clear dosing recommendation. However, in most studies a low starting dose (< or =5 mg) was used. We further report an observational study on 21 patients with refractory systolic HF from our specialized outpatient HF clinic. The aim was to evaluate the effects of metolazone in combination with a loop diuretic in contemporary HF patients. RESULTS: We registered 42 episodes of treatment with metolazone. The maximal dose of metolazone was 5 mg. NYHA functional class improved. A significant reduction during treatment in weight, blood pressure, plasma-sodium and -potassium was seen whereas plasma-BUN and -creatinine increased significantly. Clinically important hypokalemia (<2.5 mM) or hyponatremia (<125 mM) were observed during 10% of the treatment episodes. CONCLUSION: The literature review and the observational study support the use of low-dose metolazone (< or =5 mg) on top of oral loop diuretics, as an effective and relatively safe treatment in contemporary outpatients with refractory HF
45. Sackner-Bernstein JD. Management of diuretic-refractory, volume-overloaded patients with acutely decompensated heart failure. *Curr.Cardiol.Rep.* 2005;7:204-10. Abstract: Fluid overload is a common presentation for decompensated heart failure, yet management strategies are poorly defined because of relatively few randomized clinical trials that delineate an optimal strategy. Patients refractory to diuretic therapy may be considered for treatment with inotropes or vasodilators, and others may be considered for venovenous ultrafiltration. The rationale for use of each therapy is reviewed

46. Salvador DR, Rey NR, Ramos GC, Punzalan FE. Continuous infusion versus bolus injection of loop diuretics in congestive heart failure. *Cochrane.Database.Syst.Rev.* 2005;CD003178. Abstract: BACKGROUND: Loop diuretics, when given as intermittent bolus injections in acutely decompensated heart failure, may cause fluctuations in intravascular volume, increased toxicity and development of tolerance. Continuous infusion has been proposed to avoid these complications and result in greater diuresis, hopefully leading to faster symptom resolution, decrease in morbidity and possibly, mortality. OBJECTIVES: To compare the effects and adverse effects of continuous intravenous infusion of loop diuretics with those of bolus intravenous administration among patients with congestive heart failure Class III-IV. SEARCH STRATEGY: We searched the Cochrane Central Register of Controlled Trials (The Cochrane Library Issue 2, 2003), MEDLINE (1966 to 2003), EMBASE (1980 to 2003) and the HERDIN database. We also contacted pharmaceutical companies. SELECTION CRITERIA: Randomized controlled trials comparing the efficacy of continuous intravenous infusion versus bolus intravenous administration of loop diuretics in congestive heart failure were included DATA COLLECTION AND ANALYSIS: Two reviewers independently assessed study eligibility, methodological quality and did data extraction. Included studies were assessed for validity. Authors were contacted when feasible. Adverse effects information was collected from the trials. MAIN RESULTS: Eight trials involving 254 patients were included. In seven studies which reported on urine output, the output (as measured in cc/24 hours) was noted to be greater in patients given continuous infusion with a weighted mean difference (WMD) of 271 cc/24 hour (95%CI 93.1 to 449; p<0.01). Electrolyte disturbances (hypokalemia, hypomagnesemia) were not significantly different in the two treatment groups with a relative risk (RR) of 1.47 (95%CI 0.52 to 4.15; p=0.5). Less adverse effects (tinnitus and hearing loss) were noted when continuous infusion was given, RR 0.06 (95%CI 0.01 to 0.44; p=0.005). Based on a single study, the duration of hospital stay was significantly shortened by 3.1 days with continuous infusion WMD -3.1 (95%CI -4.06 to -2.20; p<0.0001) while cardiac mortality was significantly different in the two treatment groups, RR 0.47 (95% CI 0.33 to 0.69; p<0.0001). Based on two studies, all cause mortality was significantly different in the two treatment groups, RR 0.52 (95%CI 0.38 to 0.71; p<0.0001). AUTHORS' CONCLUSIONS: Currently available data are insufficient to confidently assess the merits of the two methods of giving intravenous diuretics. Based on small and relatively heterogenous studies, this review showed greater diuresis and a better safety profile when loop diuretics were given as continuous infusion. The existing data still does not allow definitive recommendations for clinical practice and larger studies should be done to more adequately settle this issue
47. Sidorenko BA, Preobrazhenskii DV, Batyraliev TA, Pershukov IV, Makhmutkhodzhaev SA. [The place of diuretics in the treatment of chronic heart failure. Part I]. *Kardiologiya* 2005;45:76-83.
- Abstract: In series of papers the authors analyze the literature data concerned with clinical pharmacology of four main classes of diuretics and their use in long-term treatment of congestive chronic heart failure (CHF). Part I is devoted to basic clinical pharmacology of three main classes of diuretics -- loop, thiazide and potassium-sparing. The site of action in nephron, mechanisms and duration of action different loop and thiazide diuretics with emphasis to furosenide, torasemide, hydrochlorothiazide, metolazone and indapamide as well as

contraindications and limitations for their use in the complex treatment of CHF are considered in detail. In long-term comparative studies showed long acting loop diuretic torasemide improved symptomatology and functional class of NYHA in patients with CHF in compared with furosemide. Thiazide-like diuretic indapamide does also act as vasodilator and decreases afterload of left ventricle of heart. But indapamide should be used with special caution because of their capacity to prolong the Q-T interval, which associates with polymorphic ventricular tachycardia, or torsades de pointes

48. Sidorenko BA, Preobrazhenskii DV, Bataraliev TA, Pershukov IV, Makhmutkhodzhaev SA. [Changing views on the place of loop and thiazide diuretics in the treatment of chronic heart failure. Part II. Influence on outcomes and clinical application]. *Kardiologiia* 2005;45:99-104. Abstract: Results of studies of effects of loop and thiazide diuretics on clinical outcomes in patients with chronic heart failure (CHF) are discussed. A number of prospective trials have shown that in patients with CHF not receiving angiotensin converting enzyme inhibitors (ACEI) diuretics lessen considerably probability of decompensation. At the same time retrospective analysis of some large randomized trials revealed elevated mortality among patients with CHF receiving high doses of loop diuretics without potassium sparing diuretics. Especially significant during treatment with high doses of loop diuretics is elevated risk of sudden (or arrhythmic) death which according to data from SOLVD and PRAISE trials increases 30-50%. Current recommendations on the use of loop and thiazide diuretics in complex therapy of patients with CHF are given. An attention is paid to that therapy of CHF should be started with prescription of ACEI and diuretic added in the presence of symptoms and signs of congestion. In moderate and severe CHF as basic therapy it is recommended to use combination of ACEI, b-adrenoblocker and spironolactone, which allow to confine to medium doses of loop diuretics (furosemide not more than 80 mg/day). Mechanisms of diuretic resistance in CHF and methods of its management are also reviewed in detail
49. Yoshida J, Yamamoto K, Mano T, Sakata Y, Nishio M, Ohtani T *et al.* Different effects of long- and short-acting loop diuretics on survival rate in Dahl high-salt heart failure model rats. *Cardiovasc.Res.* 2005;68:118-27.

Abstract: OBJECTIVES: We compared therapeutic effects of furosemide, a short-acting loop diuretic, and azosemide, a long-acting one, in hypertensive heart failure rats to test the hypothesis that long-acting diuretics are superior to short-acting types in heart failure. METHODS: Dahl salt-sensitive rats fed an 8% NaCl diet from age 8 weeks were divided at age 21 weeks (compensated hypertrophic stage) into three groups: rats treated with furosemide (40 mg/kg/day), those treated with azosemide (80 mg/kg/day) and untreated rats. Rats fed a 0.3% NaCl diet served as controls. RESULTS: Both medications prevented left ventricular systolic dysfunction and enlargement at age 31 weeks, and attenuated macrophage infiltration, reactive oxygen species generation, and gelatinolytic activity to the same degree. Azosemide suppressed left ventricular fibrosis to the control level, but furosemide did not. Azosemide ameliorated myocardial catecholamine depletion and improved survival rate. Furosemide increased plasma norepinephrine levels and did not exert such beneficial effects. CONCLUSIONS: Azosemide provided better prognosis in heart failure rats compared with furosemide, partly through attenuation of the reflex increase in cardiac sympathetic neuronal

activity caused by the development of heart failure. The current findings suggest a need for clinical trials examining whether long- and short-acting diuretics provide a different prognosis in patients with heart failure

50. Ghali JK. Diuretic use, progressive heart failure, and death in patients in SOLVD. *J.Am.Coll.Cardiol.* 2004;**43**:1723.
51. Lopez B, Querejeta R, Gonzalez A, Sanchez E, Larman M, Diez J. Effects of loop diuretics on myocardial fibrosis and collagen type I turnover in chronic heart failure. *J.Am.Coll.Cardiol.* 2004;**43**:2028-35.  
Abstract: OBJECTIVES: This individually randomized, open-label, parallel-group pilot study was designed to test the hypothesis that the ability of loop diuretics to interfere with cardiac fibrosis in chronic heart failure (CHF) may be different between compounds. BACKGROUND: The apparent mortality and cardiac benefits seen in studies comparing torasemide with furosemide in CHF suggest that torasemide may have beneficial effects beyond diuresis (e.g., on the process of cardiac fibrosis). METHODS: Patients with New York Heart Association functional class II to IV CHF received diuretic therapy with either 10 to 20 mg/day oral torasemide (n = 19) or 20 to 40 mg/day oral furosemide (n = 17), in addition to their existing standard CHF therapy for eight months. At baseline and after eight months, right septal endomyocardial biopsies were obtained to quantify collagen volume fraction (CVF) with an automated image analysis system. Serum carboxy-terminal peptide of procollagen type I (PIP) and serum carboxy-terminal telopeptide of collagen type I (CITP), indexes of collagen type I synthesis and degradation, respectively, were measured by specific radioimmunoassays. RESULTS: In torasemide-treated patients, CVF decreased from 7.96 +/- 0.54% to 4.48 +/- 0.26% (p < 0.01), and PIP decreased from 143 +/- 7 to 111 +/- 3 microg/l (p < 0.01). Neither CVF nor PIP changed significantly in furosemide-treated patients. In all patients, CVF was directly correlated with PIP (r = 0.88, p < 0.001) before and after treatment. No changes in CITP were observed with treatment in either group. CONCLUSIONS: These findings suggest that loop diuretics possess different abilities to reverse myocardial fibrosis and reduce collagen type I synthesis in patients with CHF
52. Salvador DR, Rey NR, Ramos GC, Punzalan FE. Continuous infusion versus bolus injection of loop diuretics in congestive heart failure. *Cochrane.Database.Syst.Rev.* 2004;CD003178.  
Abstract: BACKGROUND: Loop diuretics, when given as intermittent bolus injections in acutely decompensated heart failure, may cause fluctuations in intravascular volume, increased toxicity and development of tolerance. Continuous infusion has been proposed to avoid these complications and result in greater diuresis, hopefully leading to faster symptom resolution, decrease in morbidity and possibly, mortality. OBJECTIVES: To compare the effects and adverse effects of continuous intravenous infusion of loop diuretics with those of bolus intravenous administration among patients with congestive heart failure Class III-IV. SEARCH STRATEGY: We searched the Cochrane Central Register of Controlled Trials (The Cochrane Library Issue 2, 2003), MEDLINE (1966 to 2003), EMBASE (1980 to 2003) and the HERDIN database. We also contacted pharmaceutical companies. SELECTION CRITERIA: Randomized controlled trials comparing the efficacy of continuous intravenous infusion versus bolus intravenous administration of loop diuretics in congestive heart failure were included DATA

COLLECTION AND ANALYSIS: Two reviewers independently assessed study eligibility, methodological quality and did data extraction. Included studies were assessed for validity. Authors were contacted when feasible. Adverse effects information was collected from the trials. MAIN RESULTS: Eight trials involving 254 patients were included. In seven studies which reported on urine output, the output (as measured in cc/24 hours) was noted to be greater in patients given continuous infusion with a weighted mean difference (WMD) of 271 cc/24 hour (95%CI 93.1 to 449;  $p<0.01$ ). Electrolyte disturbances (hypokalemia, hypomagnesemia) were not significantly different in the two treatment groups with a relative risk (RR) of 1.47 (95%CI 0.52 to 4.15;  $p=0.5$ ). Less adverse effects (tinnitus and hearing loss) were noted when continuous infusion was given, RR 0.06 (95%CI 0.01 to 0.44;  $p=0.005$ ). Based on a single study, the duration of hospital stay was significantly shortened by 3.1 days with continuous infusion WMD -3.1 (95%CI -4.06 to -2.20;  $p<0.0001$ ) while cardiac mortality was not significantly different in the two treatment groups, RR 0.47 (95% CI 0.33 to 0.69;  $p<0.0001$ ). Based on two studies, all cause mortality was not significantly different in the two treatment groups, RR 0.52 (95%CI 0.38 to 0.71;  $p<0.0001$ ). REVIEWER'S CONCLUSIONS: Currently available data are insufficient to confidently assess the merits of the two methods of giving intravenous diuretics. Based on small and relatively heterogenous studies, this review showed greater diuresis and a better safety profile when loop diuretics were given as continuous infusion. The existing data still does not allow definitive recommendations for clinical practice and larger studies should be done to more adequately settle this issue

53. Shah SU, Anjum S, Littler WA. Use of diuretics in cardiovascular diseases: (1) heart failure. *Postgrad.Med.J.* 2004;**80**:201-5.

Abstract: Diuretics are used extensively in hospitals and in community medical practice for the management of cardiovascular diseases. They are used frequently as the first line treatment for mild to moderate hypertension and are an integral part of the management of symptomatic heart failure. Although diuretics have been used for several decades, there is still some ambiguity and confusion regarding the optimal way of using these common drugs. In this paper, the classes and action of diuretics are reviewed, and the various indications, optimal doses, and recommendations on the effective use of these agents are discussed

54. [Diuretics in heart failure. Fewer electrolyte disorders -- better prognosis]. *MMW.Fortschr.Med.* 2003;**145**:55.
55. [Favorable prognostic effect of heart failure therapy. Diuretic makes heart muscle more elastic]. *MMW.Fortschr.Med.* 2003;**145**:60.
56. [Reducing hospital stay and costs in heart failure. The proper diuretic makes the difference]. *MMW.Fortschr.Med.* 2003;**145**:58.
57. Bouvy ML, Heerdink ER, Urquhart J, Grobbee DE, Hoes AW, Leufkens HG. Effect of a pharmacist-led intervention on diuretic compliance in heart failure patients: a randomized controlled study. *J.Card Fail.* 2003;**9**:404-11.

Abstract: BACKGROUND: Noncompliance is a major factor in the morbidity and unnecessary hospital readmissions for patients with heart failure. Several studies have aimed to reduce rehospitalizations in heart failure patients through a comprehensive, multidisciplinary approach. Medication compliance was rarely measured in these studies or, when it was measured, the method employed was seldom valid. We aimed at determining the effect of a pharmacist-led intervention on medication compliance in patients with heart failure. METHODS: We conducted a randomized controlled trial into the effect of a pharmacist-led intervention on medication compliance in patients with heart failure (predominantly New York Heart Association [NYHA] II and III) treated with loop diuretics, presenting to a cardiology outpatient clinic or admitted to hospitals in The Netherlands. Patients in the intervention group received monthly consultations from their community pharmacist during a 6-month period. Patients in the control group received usual care. Primary endpoint was medication compliance, assessed with a medication event monitoring system, an electronic pill bottle that registers time of opening. Secondary endpoints were the number of rehospitalizations, death, and quality of life. RESULTS: A total of 152 patients were randomized: 74 patients to the intervention arm and 78 patients to the usual care arm. Over the 6-month study period, patients in the intervention group had 140/7656 days without use of loop diuretics compared with 337/6196 days in the usual care group (relative risk 0.33 [confidence interval (CI) 95% 0.24-0.38]). Two consecutive days of nondosing occurred on 18/7656 days in the intervention group compared with 46/6196 days in the usual care group (relative risk 0.32 [CI 95% 0.19-0.55]). There were no significant differences in rehospitalizations, mortality, or disease-specific quality of life between groups. CONCLUSIONS: A pharmacy-led intervention can improve medication compliance in patients with moderate to severe heart failure, even in those with relatively high compliance. Future interventions should also focus at less compliant patients

58. Chen HH, Redfield MM, Nordstrom LJ, Cataliotti A, Burnett JC, Jr. Angiotensin II AT1 receptor antagonism prevents detrimental renal actions of acute diuretic therapy in human heart failure. *Am.J.Physiol Renal Physiol* 2003;284:F1115-F1119. Abstract: Although effective in relieving symptoms of edema in congestive heart failure (CHF), diuretic-induced natriuresis may be associated with reductions in glomerular filtration rate (GFR) and effective renal plasma flow (ERPF), which subsequently may reduce the duration of natriuresis. Moreover, recent studies have reported that the preservation of GFR is an important predictor of survival in human CHF. We hypothesized that the acute detrimental renal hemodynamic and tubular responses to furosemide in symptomatic human CHF will be attenuated by AT(1) receptor blockade with losartan. We defined the renal hemodynamic and tubular actions and aldosterone responses to furosemide (40 mg, orally) in the presence of acute AT(1) receptor antagonism (losartan, MSD, 50 mg orally) vs. placebo in 10 subjects with CHF (New York Heart Association II-III) in a double-blind, placebo-controlled crossover study. Furosemide with placebo increased sodium excretion and reduced ERPF and GFR ( $P < 0.05$  vs. baseline). After 4 h, sodium excretion compared with baseline was decreased ( $P < 0.05$ ). In contrast, furosemide with losartan resulted in a greater increase in sodium excretion but without reductions in ERPF and GFR ( $P < 0.05$  vs. placebo). After 4 h, sodium excretion was greater compared with the placebo group. Importantly, plasma aldosterone tended to increase

in the placebo group, whereas it was decreased ( $P < 0.05$  vs. baseline) only in the losartan group. These studies underscore the pathophysiological role of the AT(1) receptor in mediating detrimental renal and adrenal properties of diuretics in human CHF. AT(1) receptor antagonism preserves GFR and renal blood flow and enhances sodium excretion during acute diuretic therapy in addition to inhibiting aldosterone secretion. These findings support the use of AT(1) receptor blockade for human CHF requiring acute diuretics to improve renal hemodynamic and tubular function and to suppress aldosterone

59. Chui MA, Deer M, Bennett SJ, Tu W, Oury S, Brater DC *et al.* Association between adherence to diuretic therapy and health care utilization in patients with heart failure. *Pharmacotherapy* 2003;23:326-32.

Abstract: STUDY OBJECTIVE: To determine the relationship between adherence to diuretic therapy and health care utilization. DESIGN: Prospective, observational study. SETTING: University-affiliated medical center. PATIENTS: Forty-two patients with heart failure. INTERVENTION: Electronic monitoring of adherence to diuretic therapy (percentage of diuretic prescription container openings) and to scheduling (percentage of container openings within a specific time). MEASUREMENTS AND MAIN RESULTS: All patients were prescribed a diuretic, most commonly furosemide (88%). Patients varied widely in adherence to therapy ( $\mu = 72\% \pm 30\%$ ) and to scheduling ( $\mu = 43\% \pm 30\%$ ). Education was a predictor of drug-taking adherence ( $p=0.0062$ ) but not of scheduling adherence. Log-linear models revealed that poor scheduling adherence was associated with increased cardiovascular-related hospitalizations ( $\chi^2 11.63, p=0.0006$ ) and predicted more heart failure-related hospitalizations ( $\chi^2 4.04, p=0.0444$ ). In contrast, neither measure was significantly associated with cardiovascular- or heart failure-related emergency department visits. We found a moderate correlation between scheduling adherence and taking adherence ( $r = 0.6513$ ). CONCLUSION: Patients taking a greater proportion of diuretic agents on schedule may decrease the risk of cardiovascular- and heart failure-related hospitalizations. If these findings are confirmed by a larger study, interventions to improve adherence and patient health outcomes should consider the timing of doses as well as the number of daily doses of a diuretic

60. De Bruyne LK. Mechanisms and management of diuretic resistance in congestive heart failure. *Postgrad.Med.J.* 2003;79:268-71.

Abstract: Diuretic drugs are used almost universally in patients with congestive heart failure, most frequently the potent loop diuretics. Despite their unproven effect on survival, their indisputable efficacy in relieving congestive symptoms makes them first line therapy for most patients. In the treatment of more advanced stages of heart failure diuretics may fail to control salt and water retention despite the use of appropriate doses. Diuretic resistance may be caused by decreased renal function and reduced and delayed peak concentrations of loop diuretics in the tubular fluid, but it can also be observed in the absence of these pharmacokinetic abnormalities. When the effect of a short acting diuretic has worn off, postdiuretic salt retention will occur during the rest of the day. Chronic treatment with a loop diuretic results in compensatory hypertrophy of epithelial cells downstream from the thick ascending limb and consequently its diuretic effect will be blunted. Strategies to overcome

diuretic resistance include restriction of sodium intake, changes in dose, changes in timing, and combination diuretic therapy

61. Domanski M, Norman J, Pitt B, Haigney M, Hanlon S, Peyster E. Diuretic use, progressive heart failure, and death in patients in the Studies Of Left Ventricular Dysfunction (SOLVD). *J.Am.Coll.Cardiol.* 2003;42:705-8.

Abstract: OBJECTIVES: We sought to determine whether non-potassium-sparing diuretics (PSDs) in the absence of a PSD may result in progressive heart failure (HF). BACKGROUND: Angiotensin-converting enzyme (ACE) inhibitors incompletely suppress ACE activity in HF patients. Furthermore, non-PSDs are activators of aldosterone secretion. We reasoned that non-PSDs, in the absence of a PSD, might result in progressive HF. METHODS: In the 6,797 patients in the Studies Of Left Ventricular Dysfunction (SOLVD), we compared the risk of hospitalization for, or death from, HF between those taking a PSD and those who were not, adjusting for known covariates. RESULTS: The risk of hospitalization from worsening HF in those taking a PSD relative to those taking only a non-PSD was 0.74 (95% confidence interval [CI] 0.55 to 0.99;  $p = 0.047$ ). The relative risk for cardiovascular death was 0.74 (95% CI 0.59 to 0.93;  $p = 0.011$ ), for death from all causes 0.73 (95% CI 0.59 to 0.90;  $p = 0.004$ ), and for hospitalization for, or death from, HF 0.75 (95% CI 0.58 to 0.97;  $p = 0.030$ ). Compared with patients not taking any diuretic, the risk of hospitalization or death due to worsening HF in patients taking non-PSDs alone was significantly increased (risk ratio [RR] = 1.31, 95% CI 1.09 to 1.57;  $p = 0.0004$ ); this was not observed in patients taking PSDs with or without a non-PSD (RR = 0.99, 95% CI 0.76 to 1.30;  $p = 0.95$ ). CONCLUSIONS: The use of PSDs in HF patients is associated with a reduced risk of death from, or hospitalization for, progressive HF or all-cause or cardiovascular death, compared with patients taking only a non-PSD

62. Earl G, Davenport J, Narula J. Furosemide challenge in patients with heart failure and adverse reactions to sulfa-containing diuretics. *Ann.Intern.Med.* 2003;138:358-9.
63. Faggiano P, Opasich C, Tavazzi L, Achilli F, Gentile A, De Biase L *et al.* Prescription patterns of diuretics in chronic heart failure: a contemporary background as a clue to their role in treatment. *J.Card Fail.* 2003;9 :210-8.

Abstract: BACKGROUND: Diuretics are the cornerstone of treatment for the congestive symptoms of heart failure (HF). Despite their widespread use, diuretic prescription data in clinical practice are scarce. In this study we evaluated the prescription pattern of diuretics in a large population of HF outpatients, enrolled by a national network of hospital-based cardiologists. METHODS AND RESULTS: Among 11070 HF outpatients (mean age 64 +/- 12 years, 72.9% men, 29.8% New York Heart Association [NYHA] class III-IV, mean left ventricular ejection fraction [LVEF] 35+/-12%), 9247 took a diuretic, the most frequently prescribed therapeutic agent (83.5%). Loop diuretics were prescribed alone (65.5%) or combined with other diuretics in 91.6% of patients. By multivariate analysis, the strongest independent predictors of diuretic use were a previous hospital admission for HF (odds ratio [OR] 2.55, 95% confidence interval [CI] 2.28-2.86), NYHA class III-IV (OR 2.52, 95% CI 2.14-2.96), LVEF < 30% (OR 1.87, 95% CI 1.57-2.24). Aldosterone antagonists were prescribed to 2142

patients (23.1%); independent predictors of their use overlapped with those of diuretics and moreover included treatment with loop diuretics (OR 3.52, 95% CI 2.66-4.66) and digoxin (OR 1.45, 95% CI 1.29-1.64). CONCLUSIONS: In this wide series of stable HF outpatients, cardiologists prescribed diuretics in accordance with published guidelines. Evolving prescription patterns of aldosterone-receptor blockers need to be further evaluated

64. Futterman LG, Lemberg L. Diuretics, the most critical therapy in heart failure, yet often neglected in the literature. *Am.J.Crit Care* 2003;12:376-80.

Abstract: Dietary sodium restriction and diuretics are basic requirements in the treatment of CHF. The reduction in pulmonary venous congestion following the use of diuretics leads to a rapid improvement in dyspnea, promotes natriuresis without direct positive inotropic effects, and does not reflexively activate the neuroendocrine system. The recent literature has been replete with reports on the treatment of HF. However, very little has been said about the importance and the methods of use of diuretics in HF. Treatment of HF cannot succeed without regard for the role of the sodium ion in HF. There are nearly 5 million cases of HF in the United States. More than 500,000 new cases are diagnosed each year. Hospital discharges and deaths due to HF have increased more than 100% in the past 2 decades with a 5-year mortality rate close to 50%. Since the leading cause of HF in Western countries is ischemic heart disease, aggressive therapy to halt progression of coronary atherosclerosis can have a major impact on controlling and often curing HF

65. Kensey K. How should diuretic-refractory, volume-overloaded heart failure patients be managed? *J.Invasive.Cardiol.* 2003;15:A17.

66. Paul RV. Rational diuretic management in congestive heart failure: a case-based review. *Crit Care Nurs.Clin.North Am.* 2003;15:453-60.

Abstract: The pharmacology and pharmacokinetics of diuretics are unique among therapeutic drugs. Knowledge of these principles can be used to great advantage in the management of heart failure, whereas ignoring them can lead to either minor or life-threatening adverse consequences. Two major categories of potential therapeutic problems are diuretic resistance and the development of disturbances in serum potassium and other electrolytes. Inhibition of sodium reabsorption in the loop of Henle or distal convoluted tubule leads to renal potassium wasting, whereas inhibition of sodium reabsorption in the collecting duct (either directly, as with triamterene or amiloride, or through aldosterone antagonism) causes potassium retention. Combining diuretics of different classes, a rational and frequently used strategy to counter diuretic resistance, can be anticipated to balance or magnify these effects, depending on the site of action of the individual drugs

67. Ravnani SL, Deedwania PC. The rational use of diuretics in heart failure. *Curr.Cardiol.Rep.* 2003; 5:237-42.

Abstract: Congestive heart failure is a progressive hemodynamic disorder associated with significant morbidity and mortality. Concomitant renal dysfunction is frequently seen in patients with heart failure, and can compromise fluid regulation, leading to acute decompensation, and increased morbidity and mortality. Diuretic therapy has been the

mainstay for treatment of congestive symptoms, despite documented mortality benefits. Misuse or overuse of diuretics can have negative consequences in heart failure, and optimizing diuretic efficiency may improve outcomes. In addition, new agents targeting elevated neuropeptides may prove to be beneficial in regulating fluid status and optimizing renal function

68. Sackner-Bernstein JD, Obeleniene R. How should diuretic-refractory, volume-overloaded heart failure patients be managed? *J.Invasive.Cardiol.* 2003;15:585-90.

Abstract: Hospitalization is often required for patients with decompensated heart failure, usually with volume overload. Intravenous diuretics are recommended to optimize volume status; however, the management of patients refractory to diuretic therapy is not addressed in American Heart Association/American College of Cardiology, European Society of Cardiology or Heart Failure Society of America guidelines. This review focuses the invasive/interventional cardiologist on the rationale for greater involvement in the care of patients admitted to the hospital with decompensated volume overload, in particular when such patients are diuretic refractory

69. Seeland U, Kouchi I, Zolk O, Jockenhovel F, Itter G, Linz W *et al.* Effects of diuretic treatment on cardiac and circulating RAS in chronic heart failure post-myocardial infarction in rats. *Eur.J.Heart Fail.* 2003;5:241-6.

Abstract: BACKGROUND: Cardiac angiotensin converting enzyme (ACE) is activated by an increase in wall stress and is involved in remodeling processes. Heart failure is often treated with ACE inhibitors and diuretics although diuretic treatment could activate the renin-angiotensin system (RAS). AIMS: To examine the effects of diuretic treatment on cardiac and circulating RAS in post-infarction chronic heart failure. METHODS: Myocardial infarction was produced by coronary artery ligation in spontaneously hypertensive rats. The rats were randomly assigned to receive either ramipril (1 mg/kg/day), furosemide (4 mg/kg/day), or combination therapy for 6 weeks, commencing 2 weeks after infarction. RESULTS: All three treatment protocols equivalently attenuated reactive hypertrophy of the right ventricle and ventricular septum and improved left ventricular systolic function. Both cardiac ACE mRNA and activity were significantly increased in untreated rats. This increase was attenuated by both ramipril and furosemide and further depressed by the combination. The increase in activity was completely inhibited by either agent alone. Plasma renin activity was upregulated by ramipril or ramipril plus furosemide but not influenced by infarction or furosemide alone. CONCLUSIONS: Furosemide and ramipril significantly reduced cardiac ACE and remodeling. Diuretics work favorably and do not interfere with the effects of ACE inhibitors. Possibly, a reduction in wall stress due to decreased volume overload accounts for the effects of diuretics on cardiac ACE in the treatment of post-infarction remodeling in hypertensive hearts. These data suggest a new mechanism for the frequently observed beneficial effect of diuretics in heart failure

70. Sica DA. Pharmacotherapy in congestive heart failure: drug absorption in the management of congestive heart failure: loop diuretics. *Congest.Heart Fail.* 2003;9:287-92. Abstract: Congestive heart failure is a disease state distinguished by the regular presence of

both renal and hepatic abnormalities in drug handling. One such abnormality involves flaws in the process of drug absorption. In most instances, congestive heart failure-related abnormalities in drug absorption are of inconsequential significance. However, this is not the case with loop diuretics. Loop diuretic action ordinarily tracks the rate and extent of absorption if a sufficient amount of diuretic has been given to exceed the threshold for diuretic effect. In congestive heart failure, both the rate and absolute amount of loop diuretic absorbed can be reduced as a function of the heart failure state itself. In this setting, drug dissolution characteristics can assume added significance. Furosemide is the loop diuretic with the widest intra- and interpatient variability of absorption. Alternatively, the loop diuretic torsemide is rapidly and fairly completely absorbed independent of the heart failure state. This pattern of absorption establishes it as the preferred loop diuretic in the otherwise diuretic-resistant heart failure patient. However, the exact role of torsemide in the outpatient management of congestive heart failure remains to be determined

71. Stiefelhagen P. [Chronic arthritic patient develops diuretic refractory ankle edema. What lies behind apparent heart failure?]. *MMW.Fortschr.Med.* 2003;**145**:16.
72. [Which diuretic in heart failure? For the prognosis, they are not all equal]. *MMW.Fortschr.Med.* 2002;**144**:52.
73. [Which loop diuretic for heart failure? For prognosis the choices are not all the same]. *MMW.Fortschr.Med.* 2002;**144**:50.
74. [A better diuretic for patients with heart failure. Better control of potassium loss]. *MMW.Fortschr.Med.* 2002;**144**:56.
75. Bischoff A. [Essential basics in therapy of heart failure. Without diuretics the prognosis is poor]. *MMW.Fortschr.Med.* 2002;**144**:6-8.
76. Braunschweig F, Linde C, Eriksson MJ, Hofman-Bang C, Ryden L. Continuous haemodynamic monitoring during withdrawal of diuretics in patients with congestive heart failure. *Eur.Heart J.* 2002;**23**:59-69.  
Abstract: AIMS: Right heart pressure parameters can be recorded continuously with the help of an implanted haemodynamic monitor. The aim of this study was to investigate the usefulness of the device in adjusting diuretic medication in patients with chronic congestive heart failure, and to evaluate the response of right ventricular pressure to increased volume load induced by diuretic withdrawal. METHODS AND RESULTS: Four patients with stable congestive heart failure were implanted with an implantable haemodynamic monitor. Furosemide, the only diuretic used, was reduced by 50% the first week, withdrawn completely for the second week and then reinstated in the initial dose. Right ventricular systolic and diastolic pressure, pulse pressure, dP/dt, estimated diastolic pulmonary artery pressure and heart rate were sampled continuously. Patients were evaluated by body weight, NYHA class, serum creatinine, serum brain natriuretic peptide, the 6 min walk test, quality of life and echocardiography on days 0, 7, 14 and 21. We observed significant changes in right ventricular pressure parameters in parallel with clinical signs and symptoms of worsening heart failure,

such as increased body weight, a shorter walking distance and impaired quality of life. Moreover elevated levels of brain natriuretic peptide and lower creatinine levels were observed. CONCLUSION: Haemodynamic changes due to increased volume load can be detected with an implantable haemodynamic monitor. Such data provide useful information for tailoring an optimal diuretic dose in patients with congestive heart failure

77. Cataliotti A, Boerrigter G, Chen HH, Jougasaki M, Costello LC, Tsuruda T *et al.* Differential actions of vasopeptidase inhibition versus angiotensin-converting enzyme inhibition on diuretic therapy in experimental congestive heart failure. *Circulation* 2002;**105**:639-44. Abstract: BACKGROUND: Omapatrilat (OMA), a vasopeptidase inhibitor, simultaneously inhibits angiotensin-converting enzyme (ACE) and neutral endopeptidase, which degrades vasodilatory factors (eg, ADM) and natriuretic peptides. Based on the beneficial cardiorenal and humoral properties of the natriuretic peptides, we hypothesized that an acute vasopeptidase inhibitor with or without diuretic would result in more favorable cardiorenal and hormonal actions than ACE inhibition plus diuretic (ACEI+D) in congestive heart failure. METHODS AND RESULTS: We compared the actions of OMA alone and with diuretic (OMA+D) to ACEI+D in a model of pacing-induced congestive heart failure. OMA+D decreased pulmonary arterial and pulmonary capillary wedge pressures to a greater level than OMA alone or ACEI+D. Glomerular filtration rate was lower with ACEI+D than with either OMA group. Plasma renin activity and aldosterone immediately increased with ACEI+D, whereas OMA+D resulted in higher plasma renin activity and a delayed increase in aldosterone. OMA alone did not increase plasma renin activity and aldosterone, but resulted in a sustained increase in plasma adrenomedullin, with higher urinary atrial natriuretic peptide, adrenomedullin, and cGMP excretions than with ACEI+D. CONCLUSIONS: Acute administration of OMA with or without diuretic results in more favorable cardiorenal and humoral responses in experimental congestive heart failure than does ACEI+D. There is no acute activation of renin and aldosterone with OMA alone such as occurs with ACEI+D and OMA+D. Thus, OMA with or without a diuretic possesses beneficial cardiorenal and humoral actions comparable to those observed with ACEI+D that can be explained by potentiation of natriuretic peptides
78. Chapman PJ. A case report of acute heart failure caused by a patient delaying taking his diuretic medication. *Aust.Dent.J.* 2002;**47**:66-7. Abstract: Acute heart failure is a life-threatening medical emergency, most commonly occurring as an immediate or delayed complication of acute myocardial infarction (AMI), or resulting from severe hypertension or valvular defects (stenosis or incompetence). Occasionally it is caused by patients' non-compliance with medication orders. In this case the patient had a history of three previous AMIs, controlled hypertension, and controlled congestive heart failure (CHF) for which he took two 40 mg frusemide tablets (a very potent oral diuretic) each morning. Because he had experienced bladder discomfort during the latter stages of previous appointments he decided to delay taking the diuretic until after his appointment and acute heart failure ensued
79. Christ M, Ludwig N, Maisch B. [Value of aldosterone receptor blockade in diuretic therapy of patients with chronic heart failure]. *Herz* 2002;**27**:135-49.

Abstract: PATHOGENESIS: All forms of chronic heart failure (high-output and low-output failure) are accompanied by an "arterial underfilling" inducing the activation of various neurohumoral systems (renin-angiotensin-aldosterone system, sympathetic nervous system, non-osmotic stimulation of vasopressin). Elevated levels of those neurohormones detrimentally modulate renal function. Subsequently, renal salt and volume retention occurs leading to the main symptoms of heart failure, edema formation and dyspnea. DIURETIC THERAPY: Diuretics, which have been discovered more than 40 years ago, beneficially influence renal salt- and volume retention by their effects on tubular sodium reabsorption. While thiazides are recommended in mild forms, loop diuretics are used in severe stages of congestive heart failure. The clinician has to consider the changed pharmacokinetic and -dynamic properties during the application of diuretics in patients with chronic heart failure. In addition, increased sodium reabsorption occurs immediately after cessation of diuretic action often nullifying the preceding diuresis. Thus, salt- and volume restriction should be guaranteed, and a regular application of loop diuretics during the day should be preferred due to the short-acting nature of currently available loop diuretics. Sometimes, diuresis does not longer occur during the treatment with one substance (diuretic resistance), although the therapeutic goals of water excretion have not been achieved. After ruling out factors reducing the actions of diuretics (non-compliance, hyponatremia, etc.), a sequential nephron blockade should be initiated (combination of loop diuretics and a thiazide or an aldosterone-receptor antagonist) to increase diuresis and to elevate symptoms of volume overload. SIDE EFFECTS: Loop diuretics and thiazides often induce mild hypokalemia, which has been demonstrated to be not as benign as thought before. Chronic treatment with oral potassium supplements has several drawbacks, as urine excretion of potassium is subsequently increased and supplementation is not as effective as believed. Diuretic-induced hypokalemia seems to be aldosterone dependent. As aldosterone levels increase during diuretic therapy even during chronic treatment with an angiotensin-converting enzyme (aldosterone-escape) a combined treatment including an aldosterone-receptor antagonist has been suggested. Beneficial effects of aldosterone-receptor blockade on mortality (RALES trial) appear to be mediated by extrarenal and renal mechanisms. The suggested beneficial renal mechanisms of aldosterone receptor blockade are discussed in detail in the review. CONCLUSION: In conclusion, diuretic therapy of patients with congestive heart failure is effective to relieve symptoms and, presumably, to prolong life. As renal function and pharmacokinetics and -dynamics of diuretics are changed in heart failure, diuretic treatment has to be adapted to provide optimal treatment. Increased levels of aldosterone appear to play an important role in diuretic-induced hypokalemia, and in the progression of heart and renal failure. Thus, aldosterone receptor antagonists should be used in the treatment of heart failure more frequently

80. Erdmann E. The value of diuretics in chronic heart failure demonstrated by an implanted haemodynamic monitor. *Eur.Heart J.* 2002;23:7-9.
81. Faris R, Flather M, Purcell H, Henein M, Poole-Wilson P, Coats A. Current evidence supporting the role of diuretics in heart failure: a meta analysis of randomised controlled trials. *Int.J.Cardiol.* 2002;82:149-58.

Abstract: OBJECTIVE: To summarise the current evidence from randomised controlled trials for diuretics in patients with congestive heart failure (CHF). DATA SOURCES: English-language randomised controlled trials and review papers referenced in Medline, Embase between 1966 and 1999. General literature review of pertinent journals was carried out and reference lists of papers were inspected. REVIEW METHOD: STUDY DESIGN: Meta-analysis of randomised controlled trials of diuretic therapy in patients with CHF. STUDY SELECTION: Studies were included if they were randomised comparisons of loop or thiazide diuretics and control, or one diuretic and another active agent (e.g. ACE inhibitors, ibopamine and digoxin). DATA ABSTRACTION: Using a standardised protocol, two reviewers independently abstracted the data and assessed the methodological quality of each paper. DATA SYNTHESIS: The odds ratio (OR) of treated group compared with control was estimated for each end-point outcome and plotted against each other using the fixed-effects model. THE MAIN OUTCOME MEASURES: The primary outcomes of our analysis were effects of diuretics on mortality and morbidity. RESULTS: Eighteen trials met our criteria and were eligible for analysis, involving 928 patients. Eight trials were placebo-controlled. We analysed the data for mortality and for worsening heart failure. A further ten trials compared diuretics against other agents such as ACE inhibitors, ibopamine, and digoxin. Mortality data were available in three of the placebo-controlled trials (n=221); the mortality rate was lower for patients treated with diuretics than for control [the odds ratio for death, 0.25; 95% confidence intervals (CI), 0.07-0.84; P=0.03]. Admissions for worsening heart failure in the four small trials (n=448) showed an odds ratio of 0.31 (95% CI 0.15-0.62; P=0.001). In six studies of diuretics compared to active control, diuretics significantly improved exercise capacity in patients with CHF [OR: 0.37; CI: 0.10-0.64, P=0.007]. CONCLUSION: Compared to active control, diuretics appear to reduce the risk of worsening disease and improve exercise capacity. The available data from small studies show that in CHF conventional diuretics reduce the risk of death and worsening heart failure compared to placebo

82. Howard PA, Dunn MI. Severe heart failure in the elderly: potential benefits of high-dose and continuous infusion diuretics. *Drugs Aging* 2002;19:249-56.

Abstract: Heart failure (HF) is a growing problem among the elderly that results in significant morbidity and mortality. Congestive symptoms because of sodium and water retention are a major cause of impaired functional capacity and frequent hospitalisations. Patients with severe HF often develop resistance to traditional doses of diuretics. Subtherapeutic diuretic regimens may result in prolonged hospitalisation and thus increased costs. Numerous studies have shown that aggressive high-dose regimens of loop diuretics can be safely and effectively used in elderly patients with severe HF. Continuous intravenous infusions are a particularly effective method for delivering high daily doses of diuretics and rapidly removing large amounts of excess sodium and water. In our experience, continuous intravenous infusions are a well tolerated and effective treatment, which may shorten the duration of hospitalisation and in turn reduce the costs of treating elderly patients with HF

83. Johnson W, Omland T, Hall C, Lucas C, Myking OL, Collins C *et al.* Neurohormonal activation rapidly decreases after intravenous therapy with diuretics and vasodilators for class IV heart failure. *J.Am.Coll.Cardiol.* 2002;39:1623-9.

Abstract: OBJECTIVES: This study was designed to determine whether therapy with

vasodilators and diuretics, designed to normalize loading conditions in decompensated heart failure (HF), reduces neurohormonal activation in the short term. BACKGROUND; Elevated vasoactive neurohormone levels in chronic HF have adverse prognostic impact and may be targeted by specific therapies. METHODS: Endothelin-1, catecholamines, renin, aldosterone, angiotensin and atrial natriuretic peptides (ANP, N-ANP and BNP) were measured in 34 patients with advanced HF before and after hemodynamically guided therapy with vasodilators and diuretics. The therapy was designed to reduce filling pressures and systemic vascular resistance (SVR) without inotropic therapy. Blood was drawn before therapy (A), after initial diuretic and nitroprusside therapy to optimize hemodynamics (B, mean 1.4 days) and after transition to an oral regimen designed to maintain improved hemodynamics (C, mean 3.4 days). RESULTS: Mean pulmonary wedge pressure fell from 31 to 18 mm Hg, right atrial pressure from 15 to 8 mm Hg, and SVR from 1,780 to 1,109 dynes/s/cm(-5). Cardiac index increased from 1.7 to 2.6 l/min/m(2) without intravenous inotropic agents (all  $p < \text{or} = 0.05$ ). Average endothelin levels declined by 30%, from 7.7 to 5.5 pg/ml, and remained low at time point C, 5.2 pg/ml ( $p < 0.01$ ). Norepinephrine was 858 at time A, 817 at time B, and fell by time C to 608 pg/ml ( $p < \text{or} = 0.05$ ). The mean plasma BNP level fell by 26% after only 1.4 days and by 53% at time C ( $p < 0.001$ ). CONCLUSIONS: Neurohormonal activation rapidly decreases after short-term therapy tailored to decrease severely elevated filling pressures and SVR without inotropic agents. Therapy designed to address neurohormonal activation should include therapy to improve severe resting hemodynamic compromise

84. Mueller TM, Vuckovic KM, Knox DA, Williams RE. Telemanagement of heart failure: a diuretic treatment algorithm for advanced practice nurses. *Heart Lung* 2002;**31**:340-7. Abstract: Thirty-three percent of patients with heart failure (HF) are readmitted to the hospital with worsening disease within 90 days of discharge. Acute decompensation accounts for nearly 50% of these admissions because of nonadherence with diet guidelines, medication regimens, or both. One way to promote adherence is through a disease management approach that can prevent HF decompensation by providing aggressive follow-up care. Within such an approach, advanced practice nurses can use a decision algorithm to implement pharmacologic and nonpharmacologic interventions. This article presents a diuretic treatment algorithm for advanced practice nurses as part of a telemanagement program. Preliminary data from the implementation of such an algorithm within an established HF program shows a decrease in hospitalizations rates and cost of care. In addition, the algorithm helps define the scope of advanced practice nursing and promotes consistency across health care sites
85. Neuberg GW, Miller AB, O'Connor CM, Belkin RN, Carson PE, Cropp AB *et al.* Diuretic resistance predicts mortality in patients with advanced heart failure. *Am.Heart J.* 2002;**144**:31-8. Abstract: BACKGROUND: In patients with chronic heart failure (CHF), diuretic requirements increase as the disease progresses. Because diuretic resistance can be overcome with escalating doses, the evaluation of CHF severity and prognosis may be incomplete without considering the intensity of therapy. METHODS: The prognostic importance of diuretic resistance (as evidenced by a high-dose requirement) was retrospectively evaluated in 1153 patients with advanced CHF who were enrolled in the Prospective Randomized Amlodipine Survival Evaluation (PRAISE). The relation of loop diuretic and angiotensin-converting enzyme inhibitor doses (defined by their median values) and other baseline characteristics to total and

cause-specific mortality was determined by proportion hazards regression. RESULTS: High diuretic doses were independently associated with mortality, sudden death, and pump failure death (adjusted hazard ratios [HRs] 1.37 [P =.004], 1.39 [P =.042], and 1.51 [P =.034], respectively). Use of metolazone was an independent predictor of total mortality (adjusted HR = 1.37, P =.016) but not of cause-specific mortality. Low angiotensin-converting enzyme inhibitor dose was an independent predictor of pump failure death (adjusted HR = 2.21, P =.0005). Unadjusted mortality risks of congestion and its treatment were additive and comparable to those of established risk factors. CONCLUSIONS: The independent association of high diuretic doses with mortality suggests that diuretic resistance should be considered an indicator of prognosis in patients with chronic CHF. These retrospective observations do not establish harm or rule out a long-term benefit of diuretics in CHF, because selection bias may entirely explain the relation of prescribed therapy to death

86. Paul S. Balancing diuretic therapy in heart failure: Loop diuretics, thiazides, and aldosterone antagonists. *Congestive Heart Fail.* 2002;8:307-12.

Abstract: In heart failure, sodium is retained by the kidneys despite increases in extracellular volume. There is activation of renin secretion, which culminates in the production of angiotensin II, causing vasoconstriction and aldosterone secretion. These synergistically produce an increase in tubular reabsorption of sodium and water. Diuretics are the mainstay of symptomatic treatment to remove excess extracellular fluid in heart failure. Diuretics that affect the ascending loop of Henle are most commonly used. Thiazide diuretics promote a much greater natriuretic effect when combined with a loop diuretic in patients with refractory edema. Recently, spironolactone, an aldosterone receptor blocking agent, has been recommended to attenuate some of the neurohormonal effects of heart failure. Regardless of the diuretic, patients need to be counseled on the importance of avoiding sodium in their diet. (copyright) 2002 CHF, Inc

87. Ravnani SL, Ravnani MC, Deedwania PC. Pharmacotherapy in congestive heart failure: diuretic resistance and strategies to overcome resistance in patients with congestive heart failure. *Congest.Heart Fail.* 2002;8:80-5.

Abstract: Congestive heart failure is a complex clinical hemodynamic disorder characterized by chronic and progressive pump failure and fluid accumulation. Although the overall impact of diuretic therapy on congestive heart failure mortality remains unknown, diuretics remain a vital component of symptomatic congestive heart failure management. Over time, sodium and water excretion are equalized before adequate fluid elimination occurs. This phenomenon is thought to occur in one out of three patients with congestive heart failure on diuretic therapy and is termed diuretic resistance. In congestive heart failure, both pharmacokinetic and pharmacodynamic alterations are thought to be responsible for diuretic resistance. Due to disease chronicity, symptomatic management is vital to improved quality of life and enhancing diuretic response is therefore pivotal

88. Reyes AJ. Diuretics in the treatment of patients who present congestive heart failure and hypertension. *J.Hum.Hypertens.* 2002;16 Suppl 1:S104-S113.

Abstract: The main operational objective of diuretic therapy in patients who present congestive

heart failure and hypertension is to reduce or to suppress excess bodily fluid. Effective diuretic therapy decreases cardiac size when the heart is dilated, and it reduces lung congestion and excess water. Consequently, external respiratory work diminishes and cardiac output would be redistributed in favour of systemic vascular beds other than that of the respiratory muscles; dyspnoea decreases markedly and there is a slight reduction in fatigue. This clinical improvement and the fall in body weight caused by diuretics entail an increase in effort capacity. Subsequent exercise training ameliorates the abnormal ventilatory response to physical effort and the skeletal muscle myopathy that occur in heart failure, and thereby it attenuates dyspnoea and decreases fatigue further. Loop and/or thiazide-type diuretics may be used to augment natriuresis in patients with congestive heart failure and hypertension. The state of renal function, the existence of certain co-morbid conditions, potential untoward drug actions, and possible interactions of diuretics with nutrients and with other drugs are some of the factors that must be considered at the time of deciding on the diuretic drug(s) and dose(s) to be prescribed. Spironolactone has been found to increase life expectancy and to reduce hospitalisation frequency when added to the conventional therapeutic regimen of patients with advanced congestive heart failure and systolic dysfunction. Therefore, spironolactone should be the drug of choice to oppose the kaliuretic effect of a loop or of a thiazide-type diuretic

89. Spannheimer A, Muller K, Falkenstein P, Reitberger U, Gutzwiller F, Follath F. [Long-term diuretic treatment in heart failure: are there differences between furosemide and torasemide?]. *Schweiz.Rundsch.Med.Prax.* 2002;**91**:1467-75.

Abstract: BACKGROUND: Treatment for congestive heart failure (CHF) is an important factor in rising health care costs especially in patients requiring repeated hospitalisations. Diuretics remain the most frequently utilized drugs in symptomatic patients. In this study the long-term outcome under furosemide and torasemide, two loop diuretics with different pharmacokinetic properties, were evaluated during one year in an ambulatory care setting. AIMS: Comparison of hospitalization rates and estimated costs under long-term treatment with furosemide and torasemide in patients with CHF. METHODS: Retrospective analysis of disease course and resource utilization in 222 ambulatory patients receiving long-term treatment with furosemide (n = 111) or torasemide (n = 111). Data were also compared to those of a similar study including 1000 patients in Germany. RESULTS: Patients receiving long-term treatment with torasemide had a lower hospitalisation rate (3.6%) compared to patients on furosemide (5.4%). Corresponding hospitalization rates in the German study were 1.4% under torasemide and 2% under furosemide. The higher hospitalisation rates in Swiss patients could be explained by a higher average age (75 years vs. 69 years) and a longer duration of symptomatic heart failure (4.1 yrs vs. 0.7 yrs). Cost estimates based on the average number of hospital days (0.54 under torasemide compared to 1.05 under furosemide) indicated that the financial burden could be halved by a long-term torasemide treatment. CONCLUSION: Torasemide with its more complete and less variable bioavailability offers potential clinical and economic advantages over furosemide in the long-term treatment in patients with CHF

## Annex D

### Functional classification of heart failure – January 2008

#### ACC/AHA Guidelines for the Evaluation and Management of HF\*

\* Adapted from Hunt SA, Baker DW, Chin MH, et al. ACC/AHA guidelines for the evaluation and management of chronic heart failure in the adult: a report of the American College of Cardiology/American Heart Association Task Force on Practice guidelines (Committee to Revise the 1995 Guidelines for the Evaluation and Management of Heart Failure). 2001, American College of Cardiology Web-site. Available at: [http://www.acc.org/clinical/guidelines/failure/hf\\_index.htm](http://www.acc.org/clinical/guidelines/failure/hf_index.htm)

DISEASE PROGRESSION
Stage A: patients who are high risk for developing HF, but do not have structural heart disease
Stage B: patients who have structural damage to the heart, but have not developed symptoms
Stage C: patients with past or current HF symptoms and evidence of structural heart damage
Stage D: patients with end-stage disease, requiring special interventions

#### NYHA Functional Classification and Objective Assessment of HF\*\*

\*\* Adapted from the Criteria Committee of the American Heart Association. 1994, revisions to the classification of functional capacity and objective assessment of patients with disease of the heart. Circulation 1994;90:644-5.

FUNCTIONAL CAPACITY
Class I: no limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or angina.
Class II: slight limitation of physical activity. Ordinary physical activity results in fatigue, palpitation, dyspnea, or angina.
Class III: marked limitation of physical activity. Comfortable at rest, but less than ordinary physical activity results in fatigue, palpitation, dyspnea, or angina.
Class IV: unable to carry on any physical activity without discomfort. Symptoms are present at rest. With any physical activity, symptoms increase.