ADVOR INVESTIGATOR MEETING

1 October 2018

Agenda

13:30	• Introduction KCE & ZOL AV
13:45	• Study and protocol presentation
15:15	• Data management
15:45	• Coffee break
16:00	• Study practicalities
16:25	• EDGE
16:40	• Q&A

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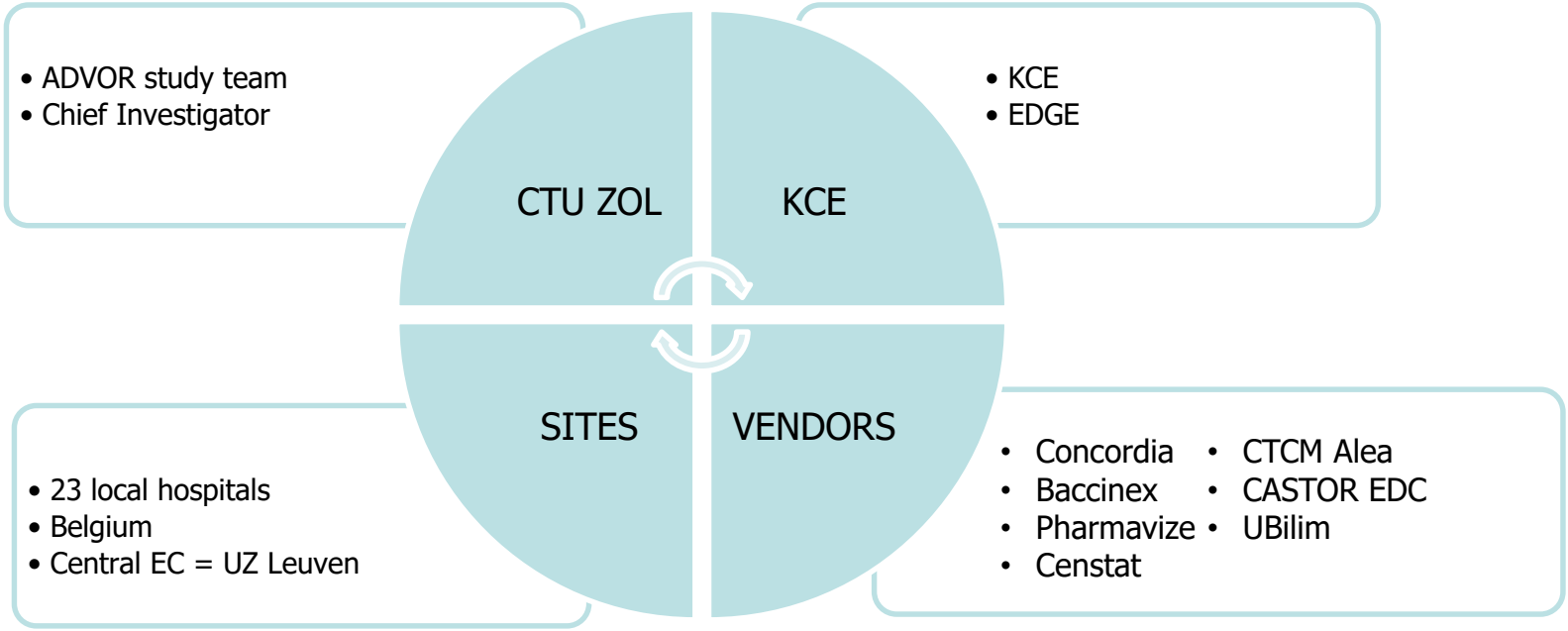
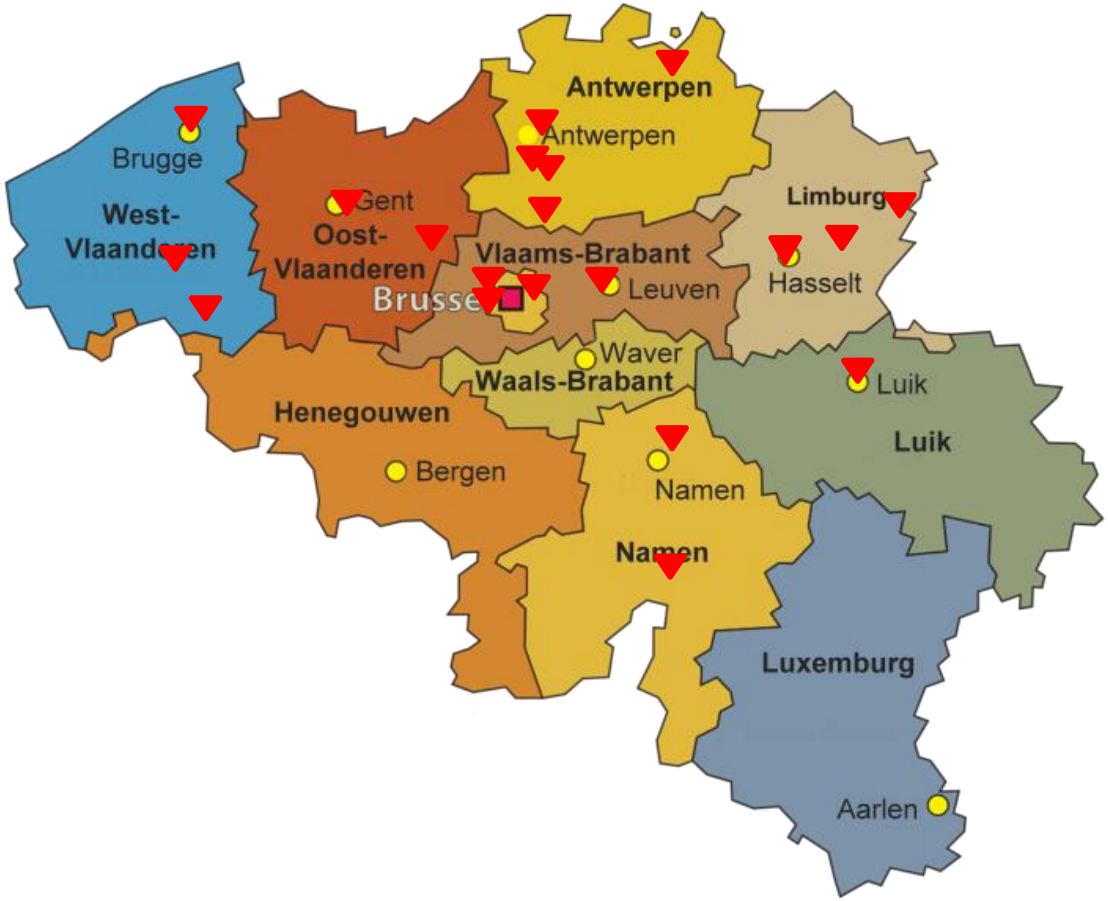
Introduction ADVOR study

- Non-commercial
- Multi-center
- Study sponsor = Ziekenhuis Oost Limburg (ZOL) AV
- Funder = Federaal Kenniscentrum voor de Gezondheidszorg (KCE)



Geographic distribution of the participating sites



ADVOR team

Chief Investigator

* Prof Dr Wilfried Mullens

Scientific team

* Dr Matthias Dupont
* Dr Pieter Martens
* Dr Jeroen Dauw
* Dr Jozine Ter Maaten

Study team

* Evi Theunissen
* Katrien Tartaglia
* Liesbet Van Brussel
* Elly Vandermeulen
* Marlies Dictus
* Ward Eertmans

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Trial Steering Committee (TSC)

TSC members:	
Chief Investigator	Wilfried Mullens MD, PhD
Representative of Sponsor	Griet Vander Velpen MD
Representative of funder (KCE)	Jilly Harrison
Representatives of participating centers	Matthias Dupont MD Walter Droogné MD Pierre Troisfontaines MD
Independent experts	Alexandre Mebazaa MD PhD Frank Ruschitzka MD PhD Johan Lassus MD PhD Kevin Damman MD PhD Gerasimos Filippatos MD PhD Frederik Verbrugge MD PhD Pieter Martens MD
Statistician	Liesbeth Bruckers
Trial Coordinator	Katrien Tartaglia

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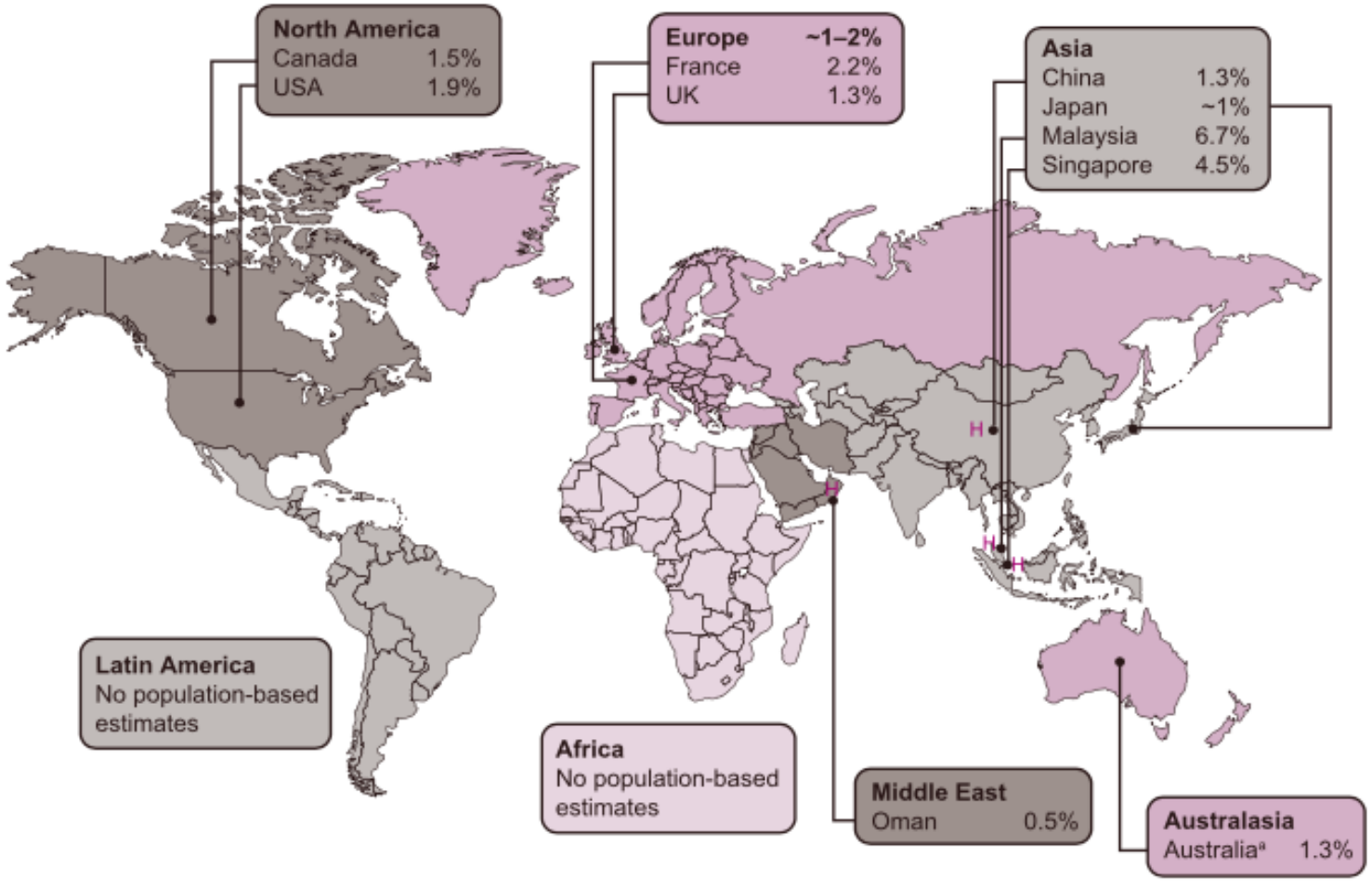
Study rationale and set-up

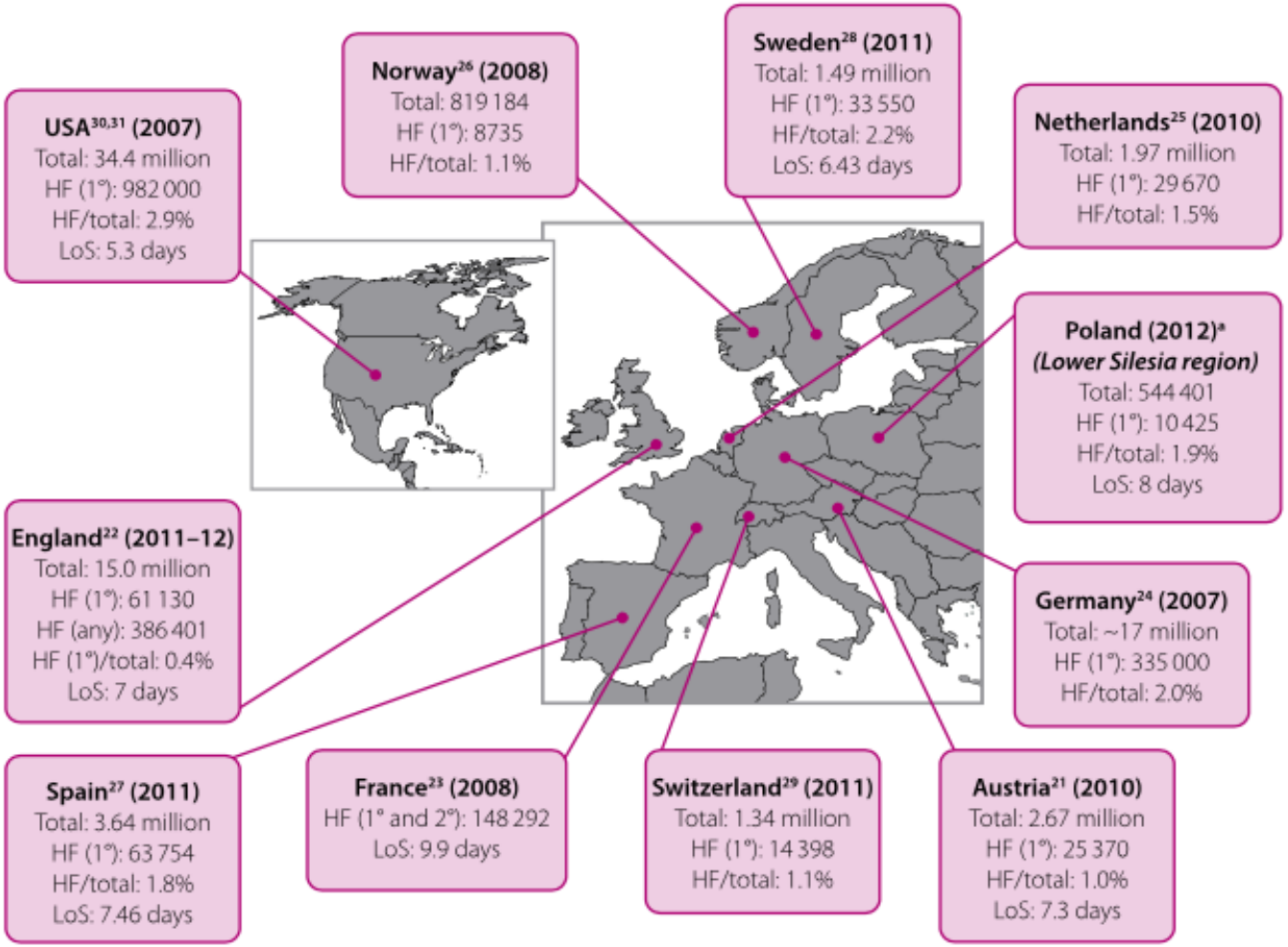
Presenter: Prof. Dr. Wilfried Mullens

HF prevalence



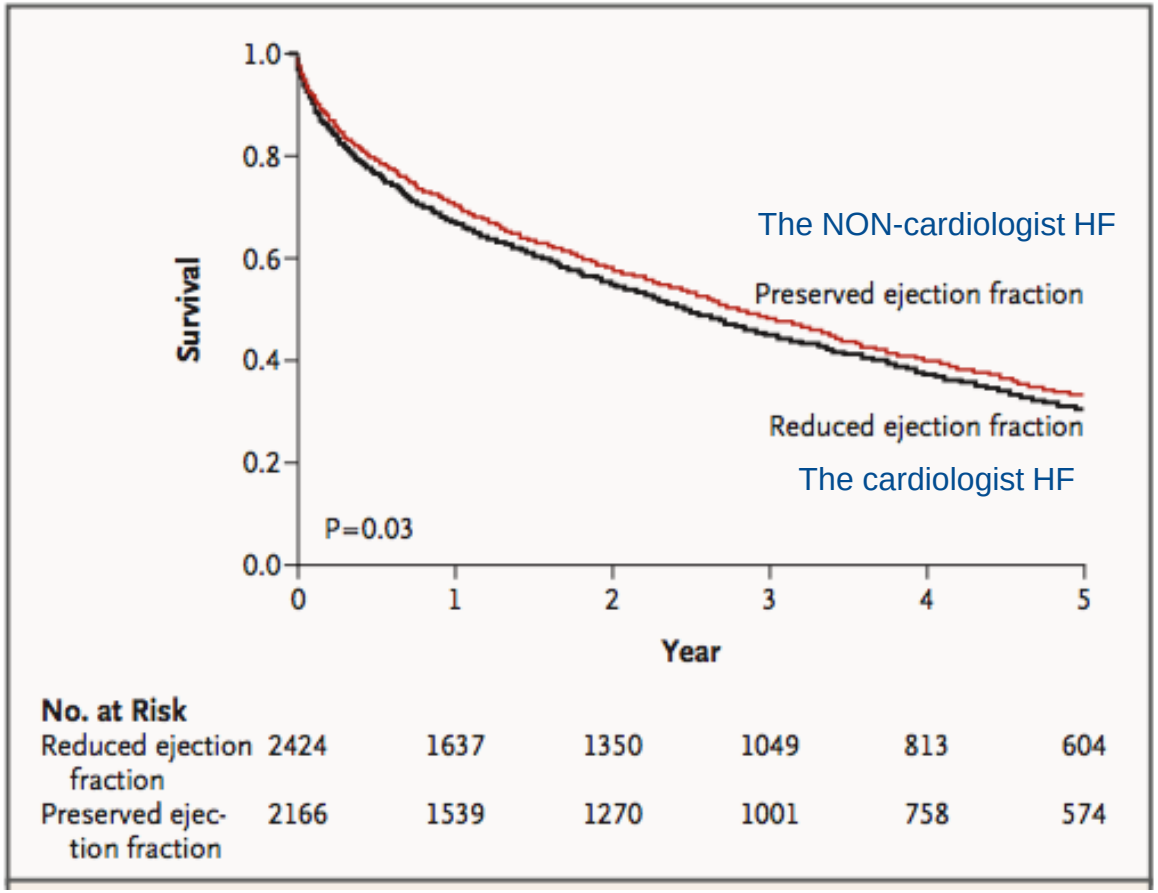
Ponikowski P et al. ESC Heart Fail 2014;1:4-25.

Hospitalization for HF US 3% > EU 1,5%



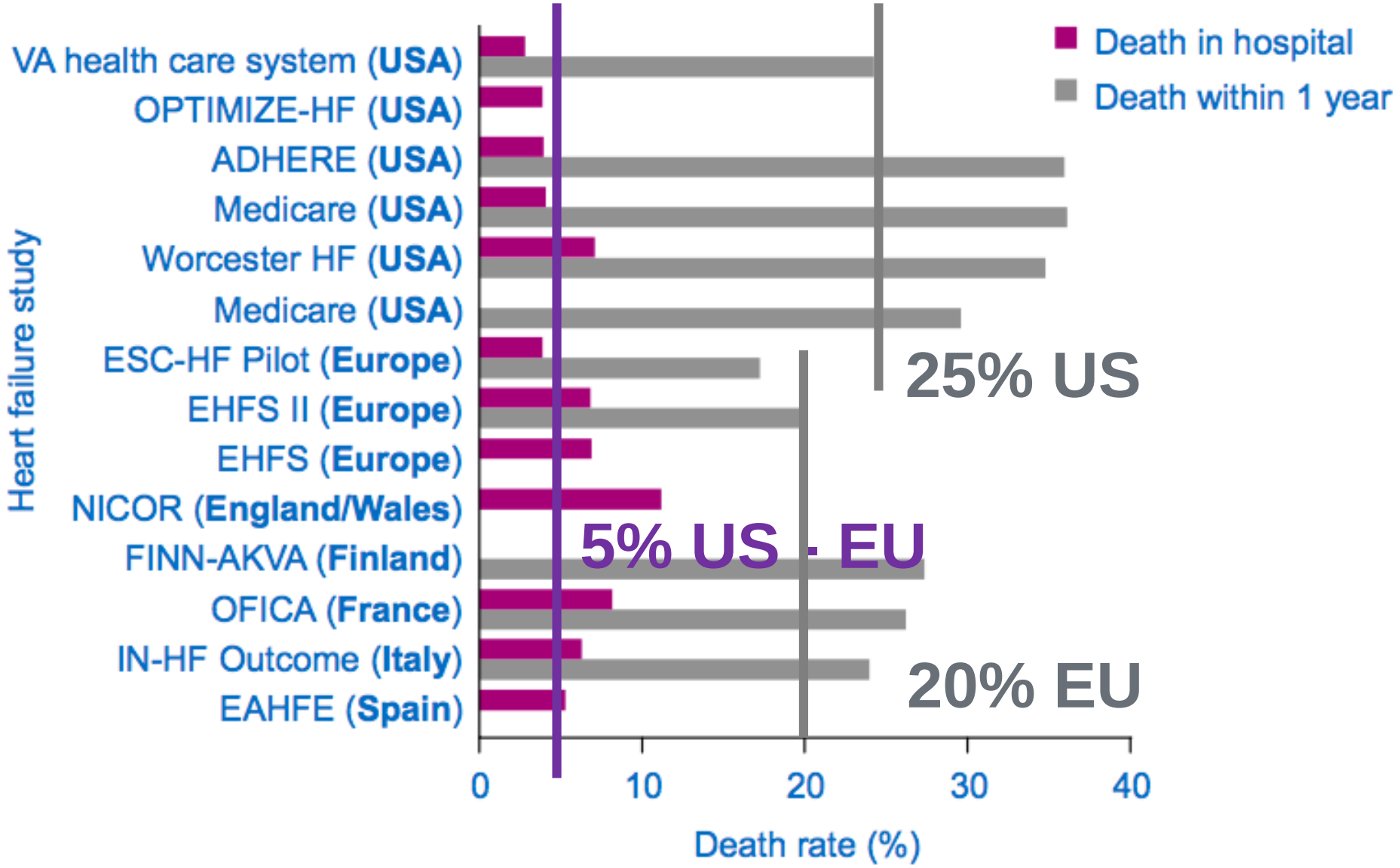
Cowie M et al. ESC Heart Fail 2014;1:110-45..

Different Types of Heart Failure, prognosis

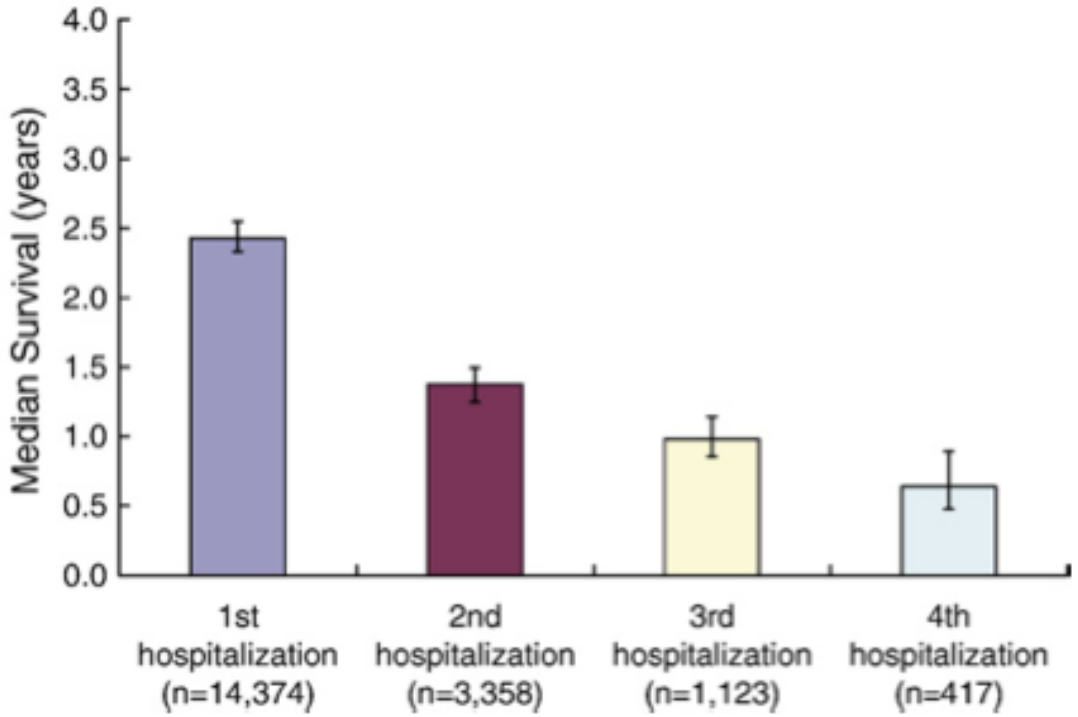


Bhatia et al. NEJM 2006;355:251-9

HF hospitalization associated with mortality



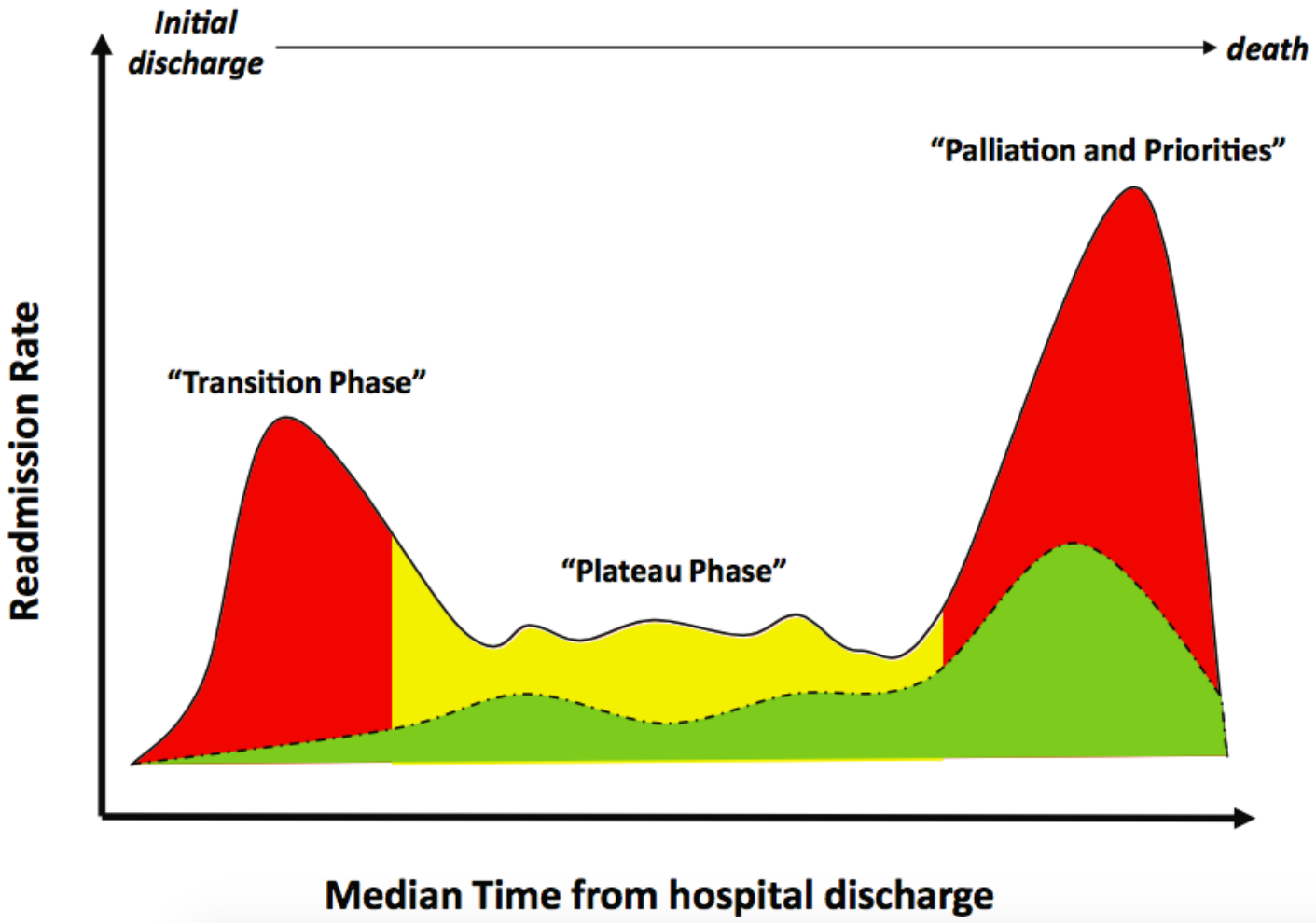
Number of HF hospitalisations related to mortality



Median survival (50% mortality) and 95% confidence limits in patients with HF after each HF hospitalization.

Setoguchi S, Stevenson L. Am Heart J 2007;154:260-6.

Risk for HF hospitalisation



Desai A, Stevenson L , Circ 2012;126:501-506

Re-Hospitalization for HF US > EU

Study	Country/region	Rehospitalization rate (%)	
Medicare[49]	USA	30-day	24.8
Medicare[51]	USA	30-day	26.9
VA health care system[52]	USA	30-day	22.5
ADHERE[8]	USA	30-day	22.1
		1-year	65.8
Medicare[50]	USA	30-day	22.7
		1-year	67.0
Medicare[38]	USA	6–9-month	60
EHFS I[10]	Europe	12-week	24.2
ESC-HF Pilot[4]	Europe	1-year[a]	43.9
EAHFE[48]	Spain	1-year	27.2
CCU[47]	Italy	6-month	38.1
IN-HF Outcome[46]	Italy	1-year	30.7

ADHERE, Acute Decompensated Heart Failure National Registry; CCU, cardiac care unit; EAHFE, Epidemiology Acute Heart Failure Emergency; EHFS, EuroHeart Failure Surveys; ESC-HF, European Society of Cardiology–Heart Failure; IN-HF, Italian Registry on Heart Failure; VA, Veterans Affairs.

EU: 15% @ 30 day – 45% @ 1 year
US: 25% @ 30 day – 65% @ 1 year

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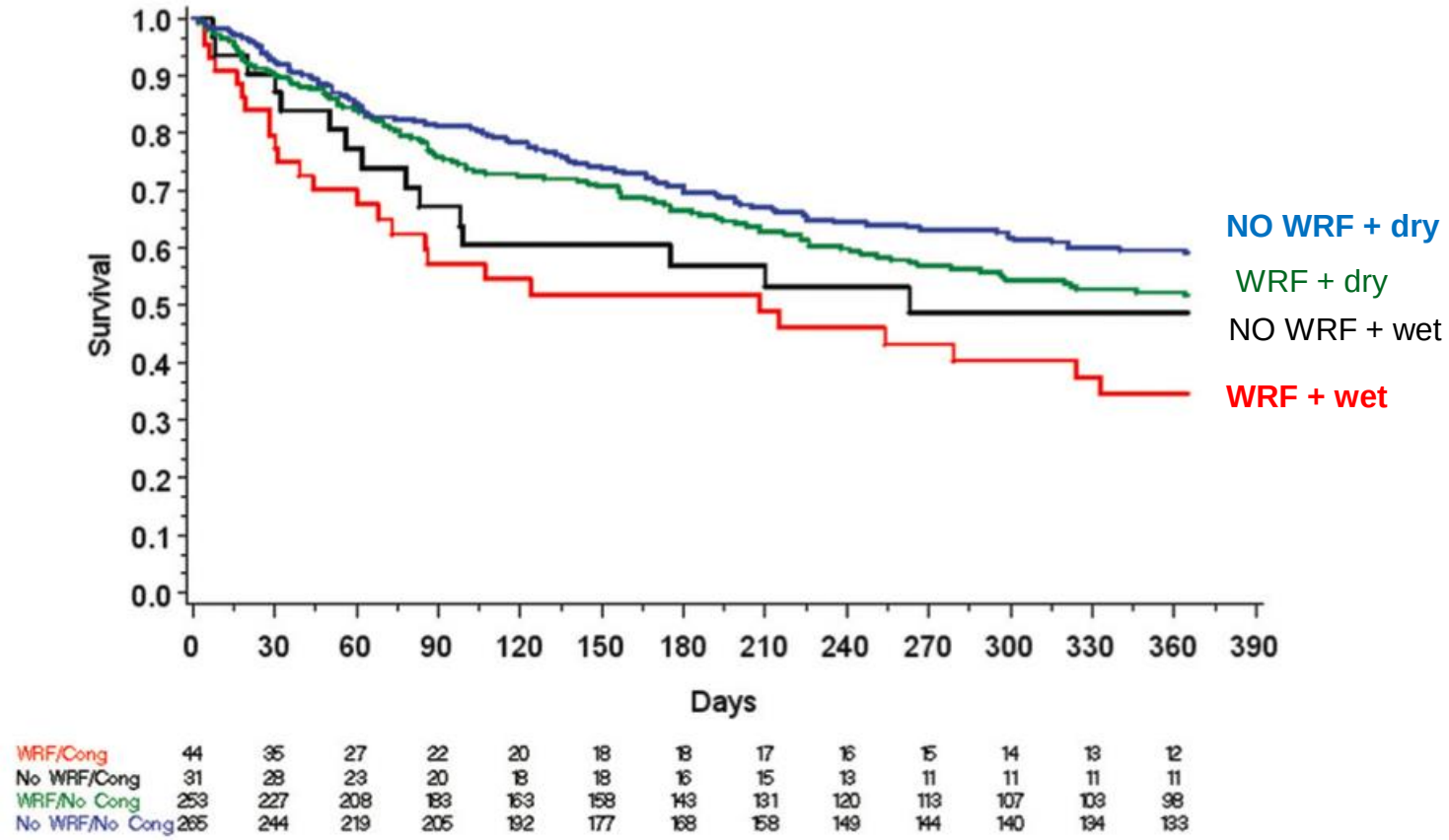
Cowie M et al. ESC Heart Fail 2014;1:110-45..

Recently Hospitalized: 60% risk at 1 year when ongoing congestion



Metra M et al. Circ Heart Fail. 2012;5:54-62

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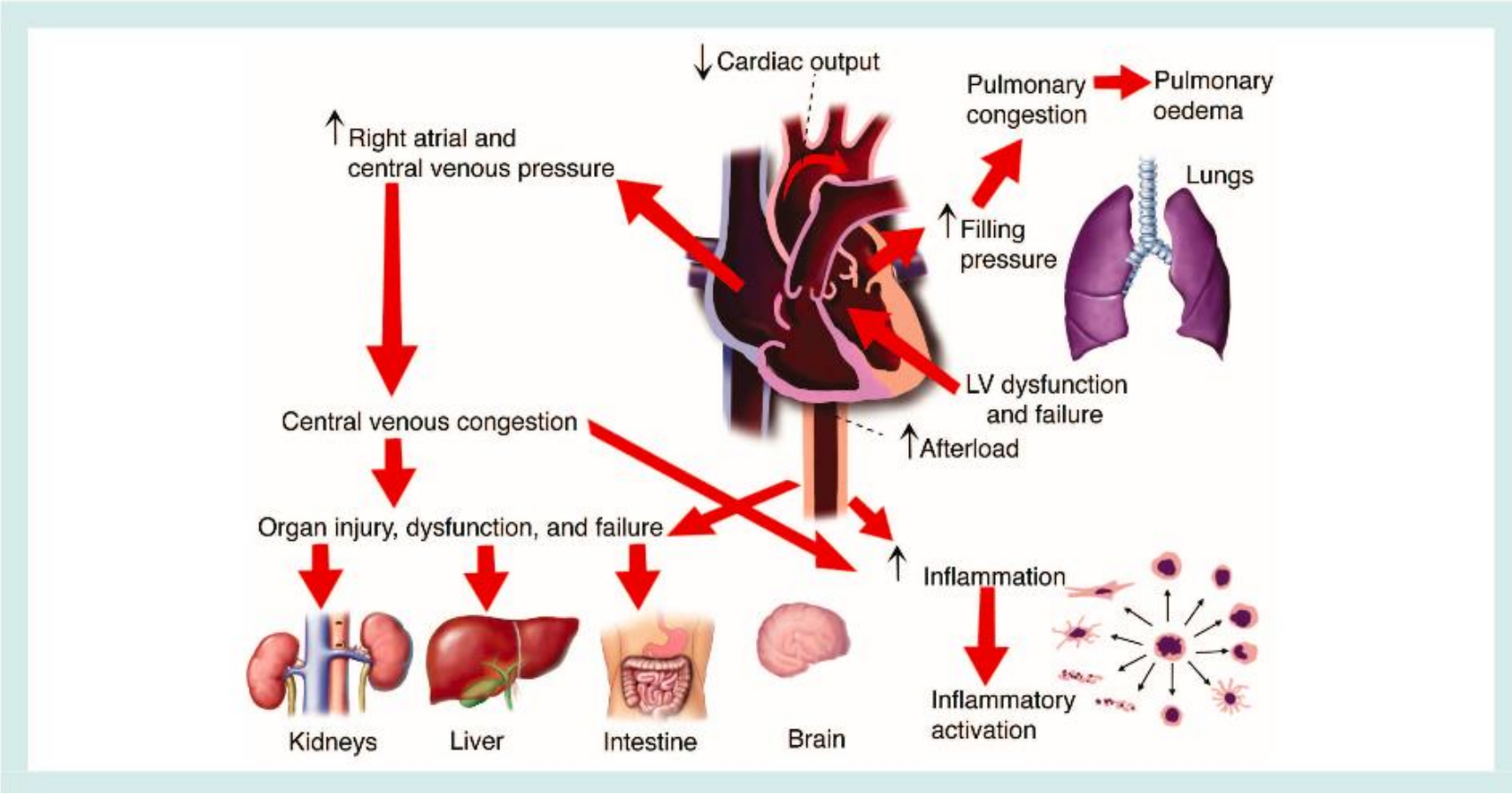
Assessing and grading congestion in acute heart failure: a scientific statement from the Acute Heart Failure Committee of the Heart Failure Association of the European Society of Cardiology and endorsed by the European Society of Intensive Care Medicine

Patients with acute heart failure (AHF) require urgent in-hospital treatment for relief of symptoms. The main reason for hospitalization is congestion, rather than low cardiac output. Although congestion is associated with a poor prognosis, many patients are discharged with persistent signs and symptoms of congestion and/or a high left ventricular filling pressure. Available data suggest that a pre-discharge clinical assessment of congestion is often not performed, and even when it is performed, it is not done systematically because no method to assess congestion prior to discharge has been validated. Grading congestion would be helpful for initiating and following response to therapy. We have reviewed a variety of strategies to assess congestion which should be considered in the care of patients admitted with HF. We propose a combination of available measurements of congestion. Key elements in the measurement of congestion include bedside assessment, laboratory analysis, and dynamic manoeuvres. These strategies expand by suggesting a routine assessment of congestion and a pre-discharge scoring system. A point system is used to quantify the degree of congestion. This score offers a new instrument to direct both current and investigational therapies designed to optimize volume status during and after hospitalization. In conclusion, this document reviews the available methods of evaluating congestion, provides suggestions on how to properly perform these measurements, and proposes a method to quantify the amount of congestion present.

Gheorghiade M, Mebazaa A, et al. Eur J Heart F 2010

Congestion and end-organ dysfunction



Reduction in congestion more than improvement in output should be the goal

Harjola VP, Mullens W, et al. Eur J Heart Fail 2017;19:821-836.

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The core of the problem = our unnatural craving for salt

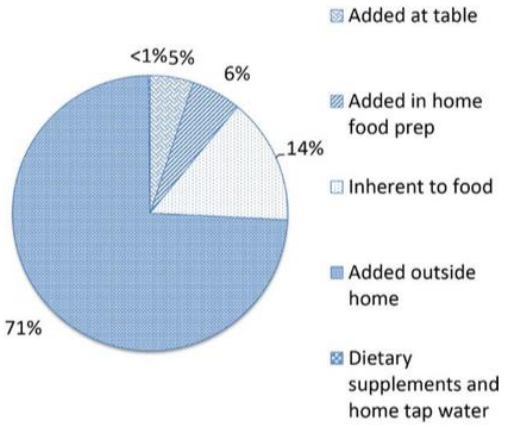
1.2 g

0.3 g/cookie

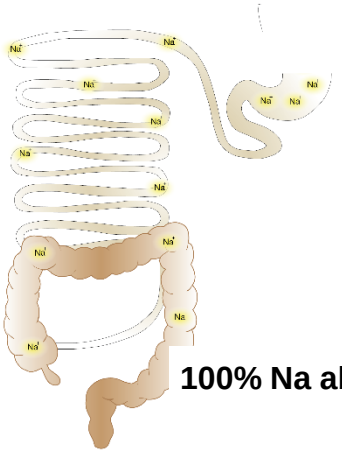
0.5 g/slice

2.5 g

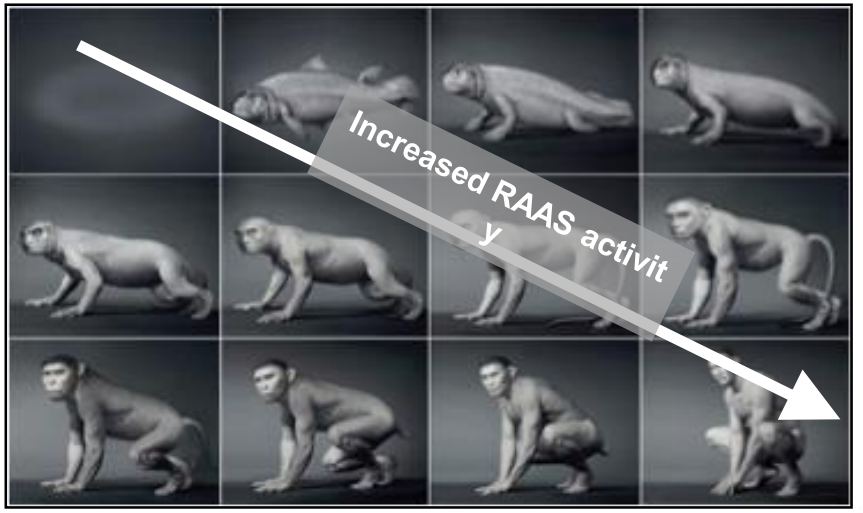
De Souza. Appetite 2012



Harnack L. Circulation 2017;135:1775-1783



100% Na absorption



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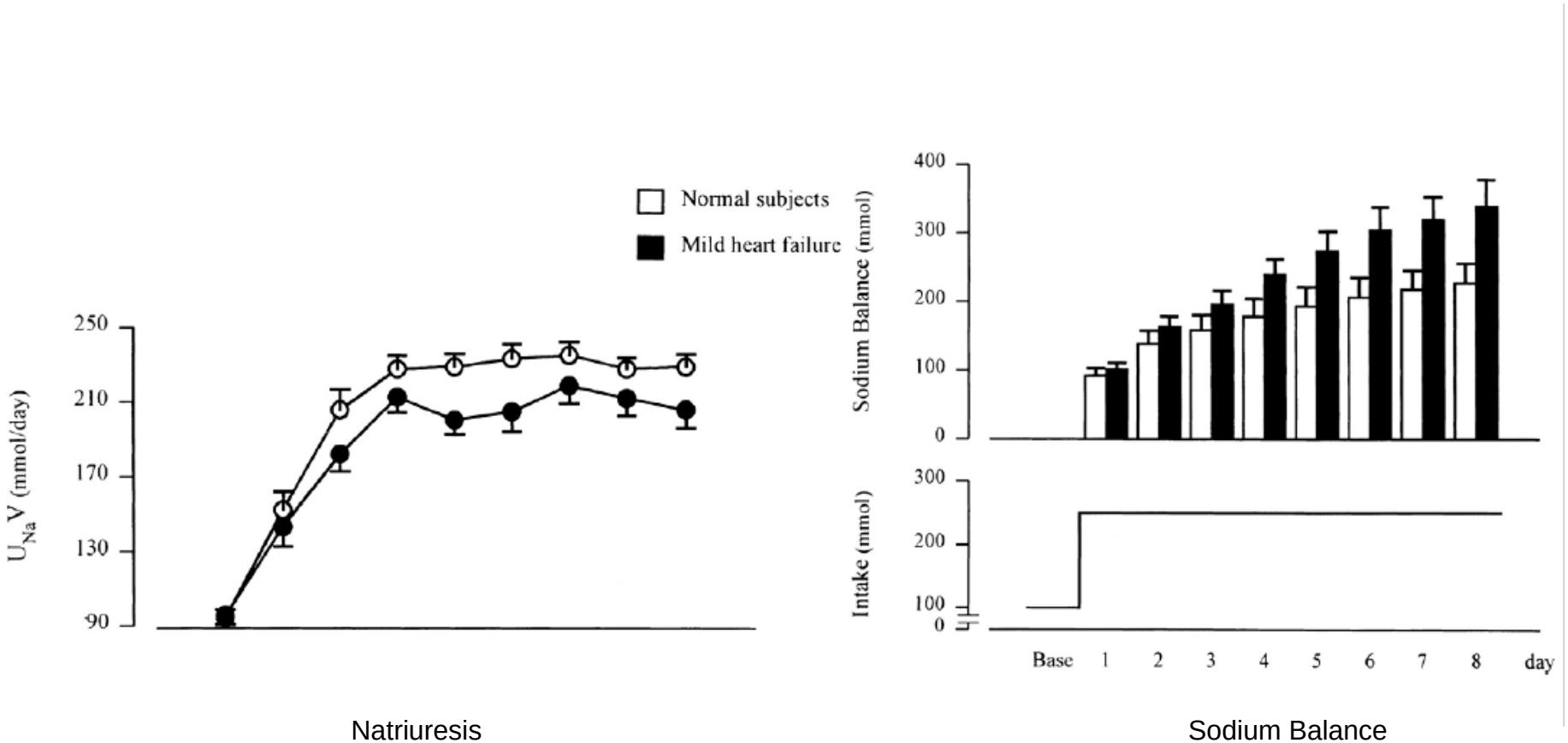
Positive sodium balance - very fast



Natriuresis

Sodium Balance

Volpe M et al. Hypertension 1997

Loss of appropriate natriuresis can be restored with exogenous BNP in preclinical HF

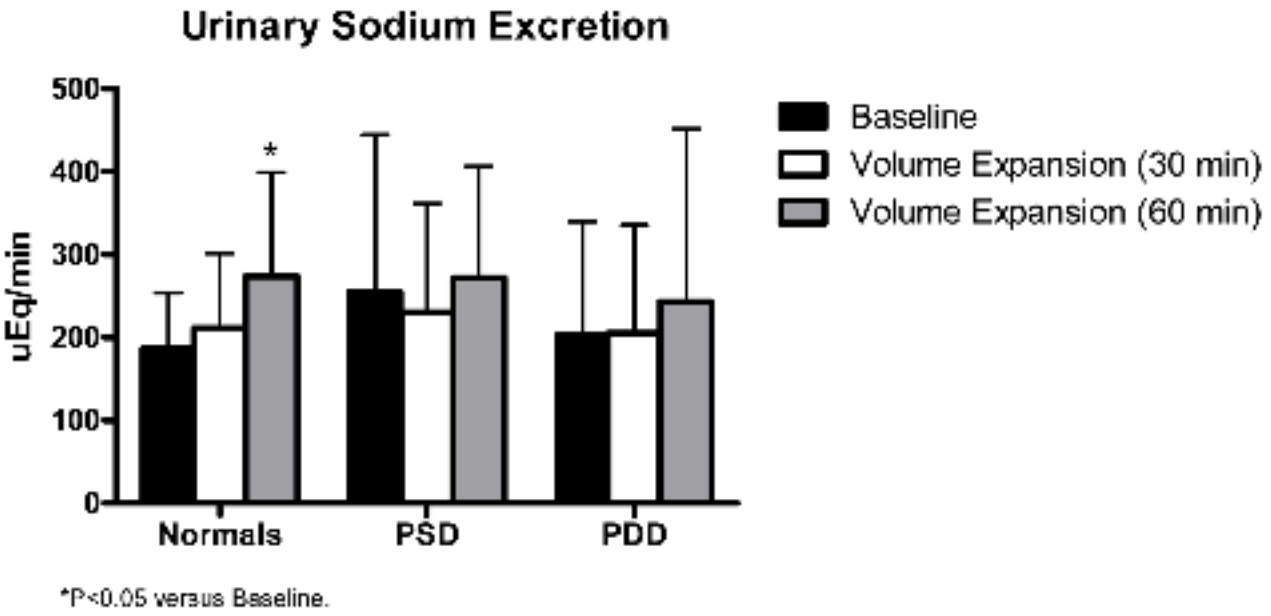
Journal of the American College of Cardiology

Published by Elsevier Inc.

EDITORIAL COMMENT

The Early Intertwining of the Heart and the Kidney Through an Impaired Natriuretic Response to Acute Volume Expansion*

Wilfried Mullens, MD, PHD,†‡
W. H. Wilson Tang, MD§
Genk and Hasselt, Belgium; and Cleveland, Ohio



McKie P et al / Mullens W et al J Am Coll Card 2011.

It doesn't only end but it also starts with the kidney

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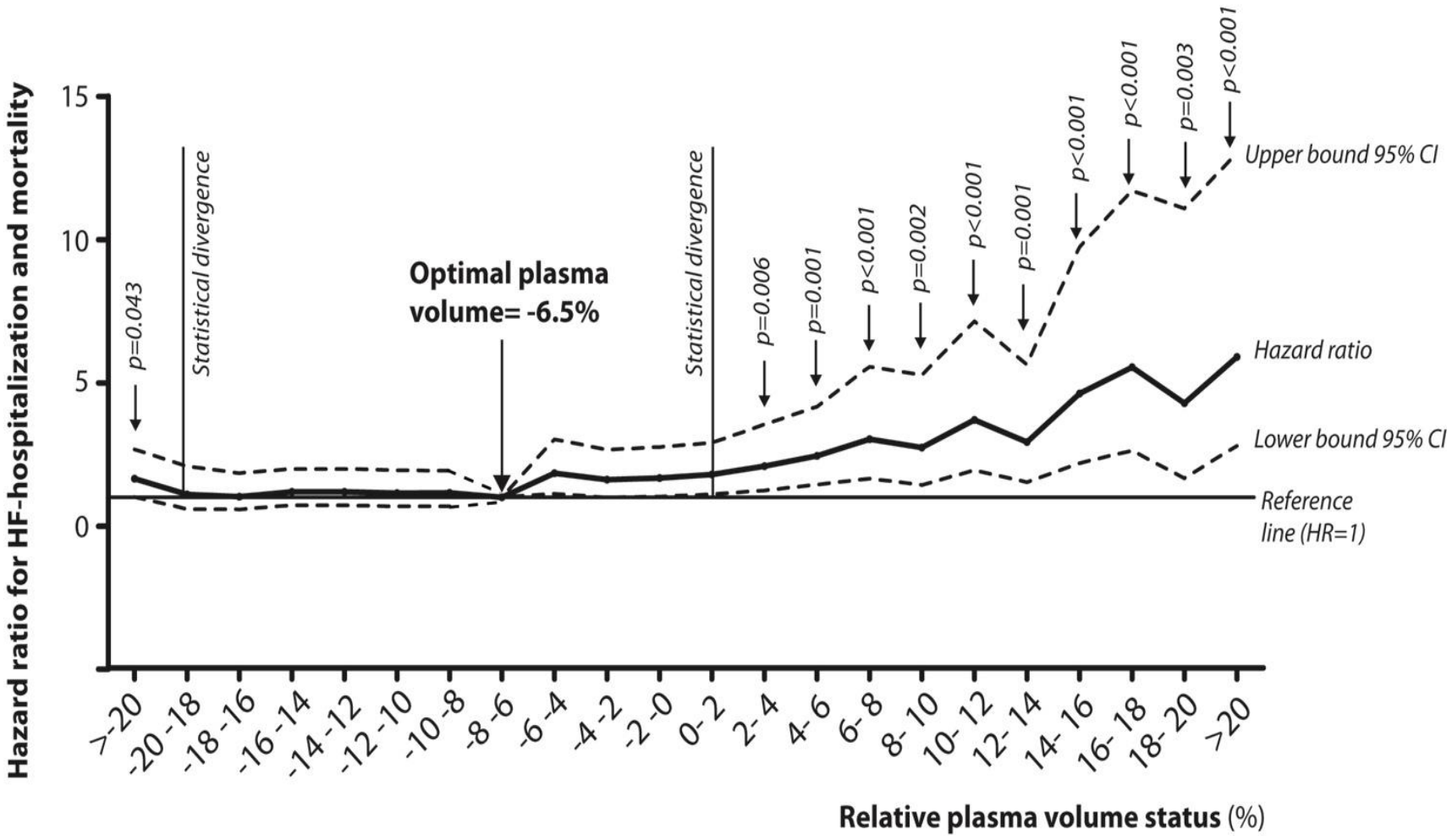
Role of Na in Congestion

1) Increase in plasma volume

2) Increase in interstitial sodium content

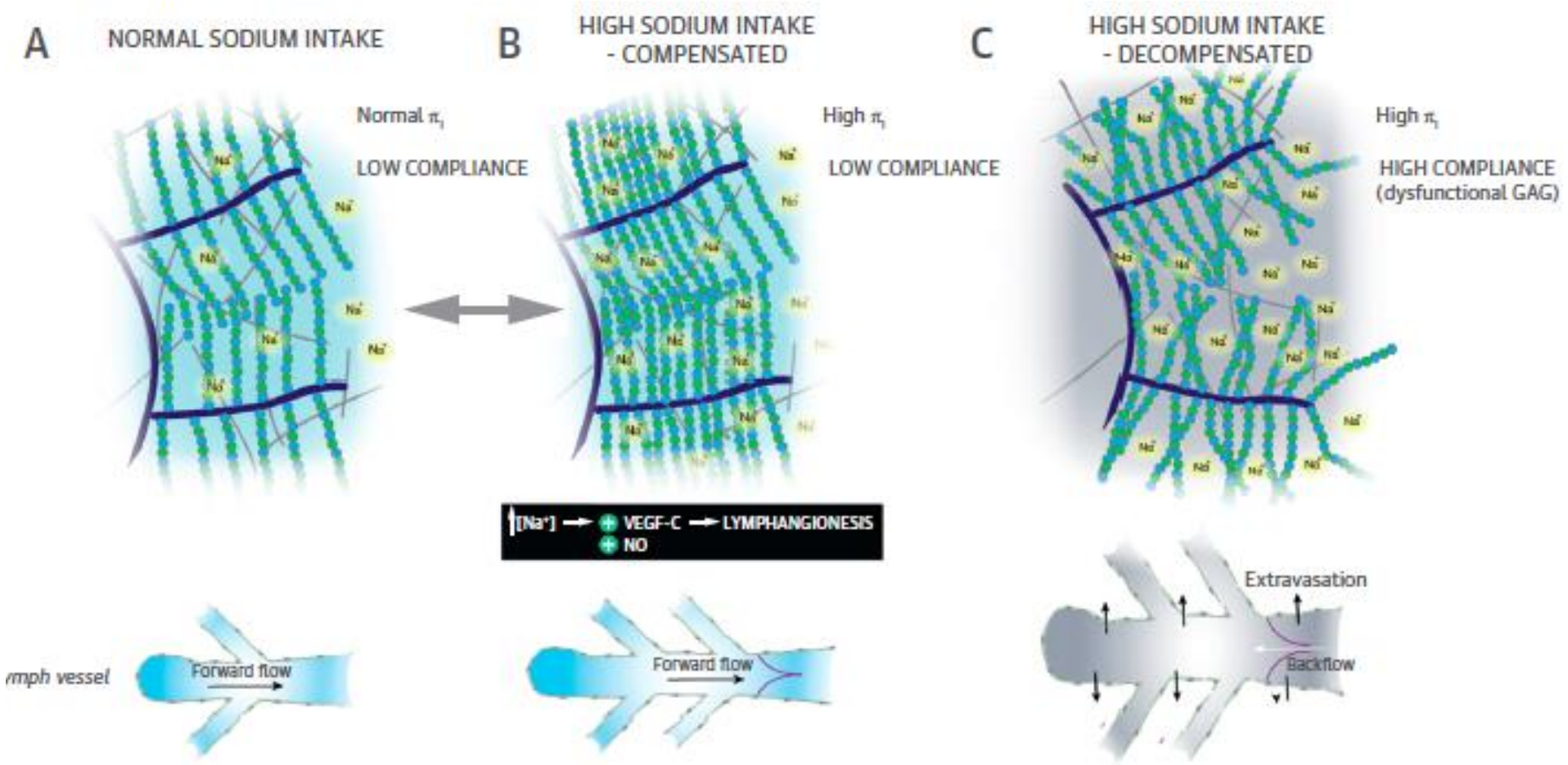
3) Increase in vasoreactivity

Optimal plasma volume in relation to outcome



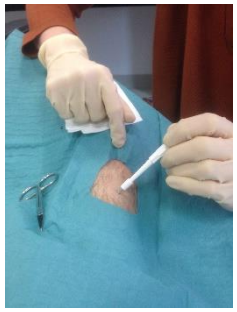
Martens P, Mullens W et al. J Card Fail, in review.

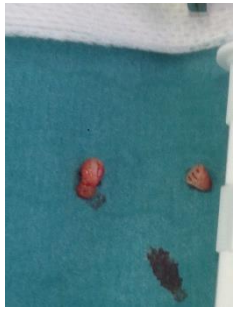
Buffering of sodium in Interstitium: 'not all are equal'

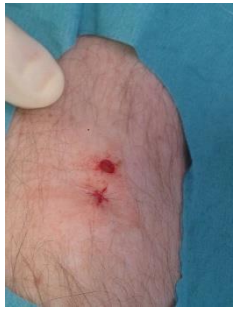


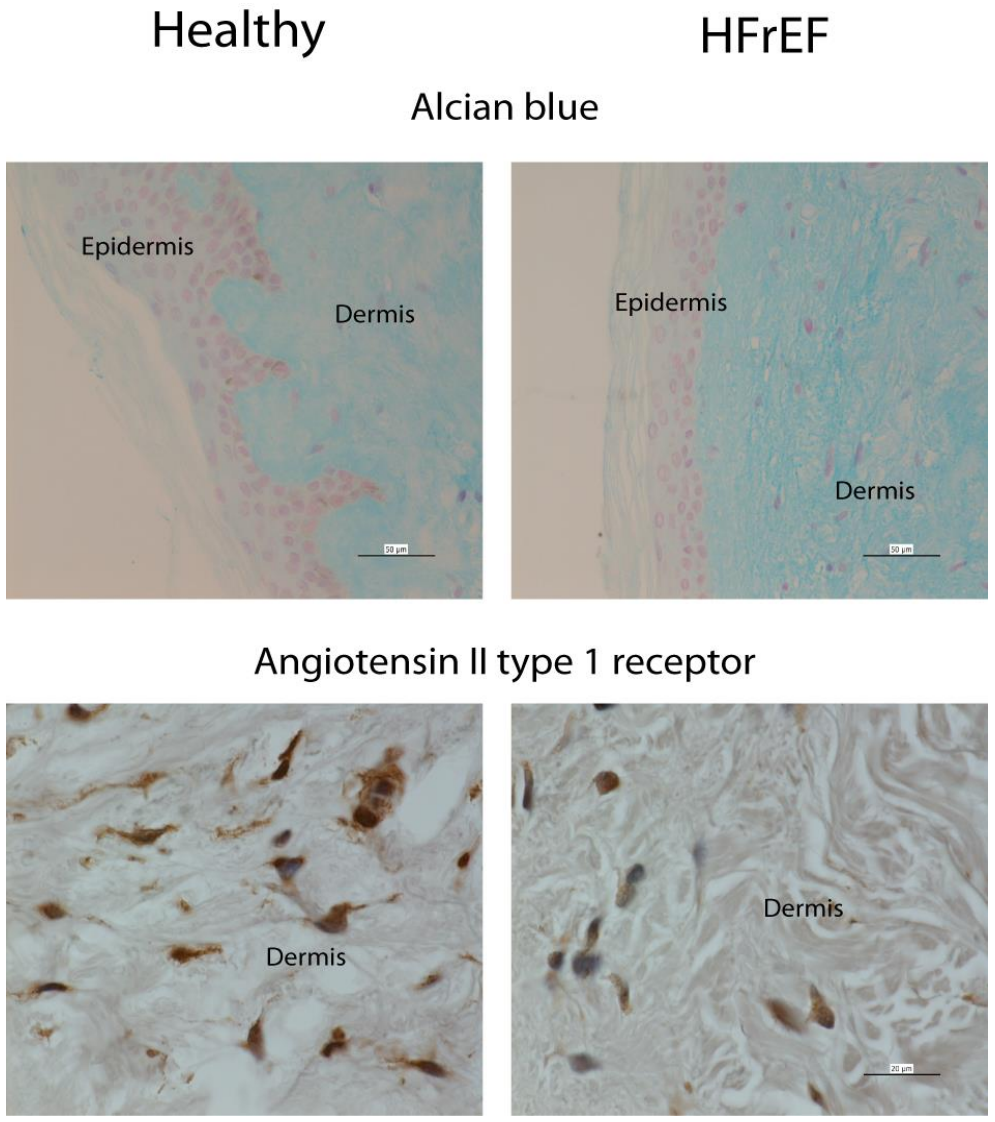
Nijst P, Mullens W et al. J Am Coll Card 2015;65:378-88

GAGs in skin and link with RAAS







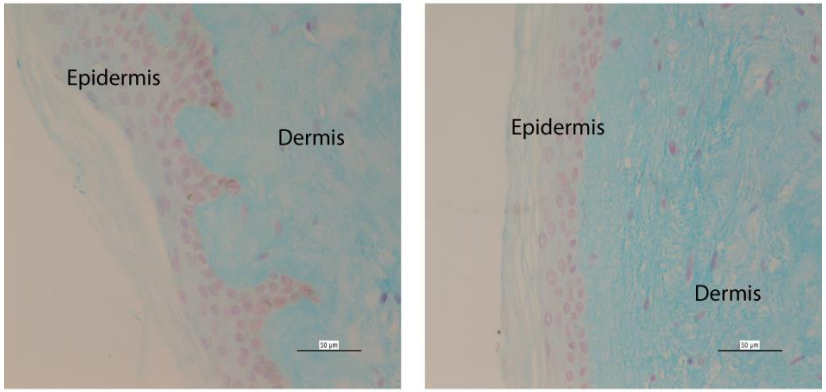


Nijst P, Mullens W. et al. Circ Heart Fail 2018.

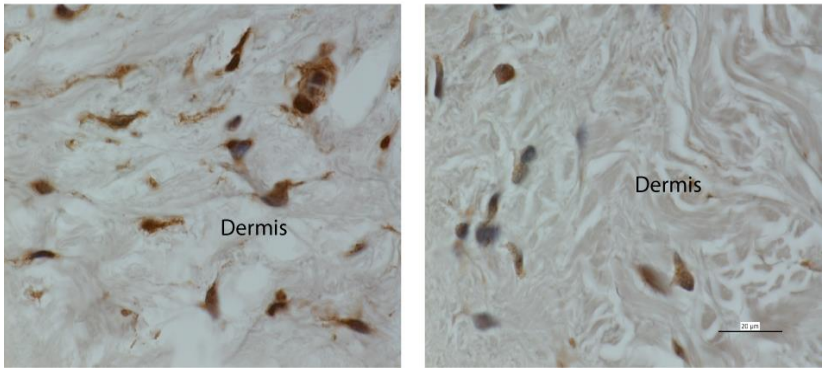
GAGs in skin and link with RAAS

Healthy HFrEF

Alcian blue

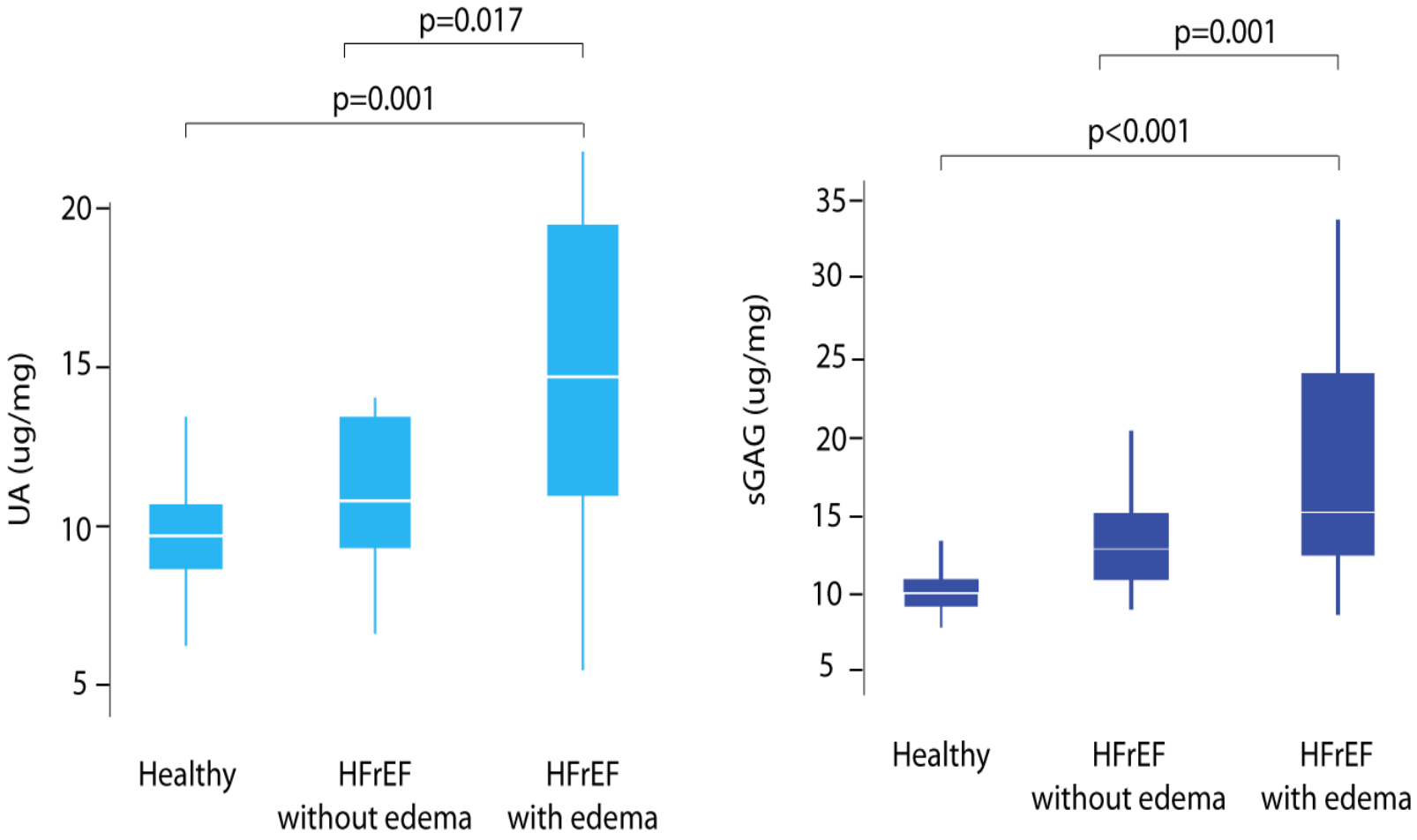


Angiotensin II type 1 receptor



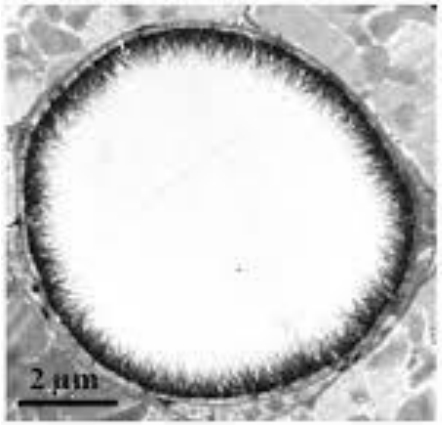
Nijst P, Mullens W. et al. Circ Heart Fail 2018.

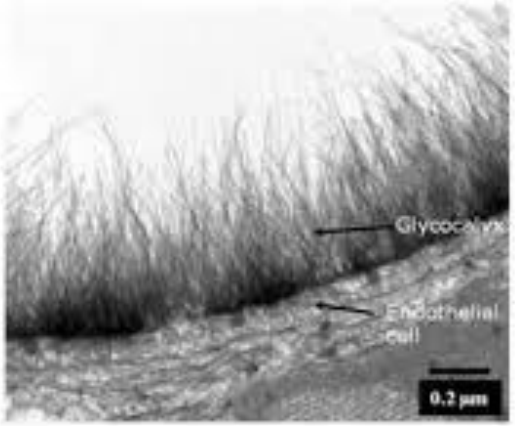
More GAGs in HF / edema

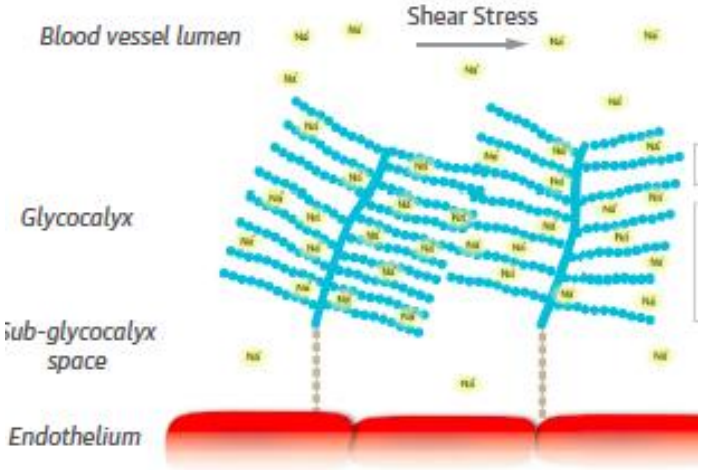


Nijst P, Mullens W. et al. Circ Heart Fail 2018.

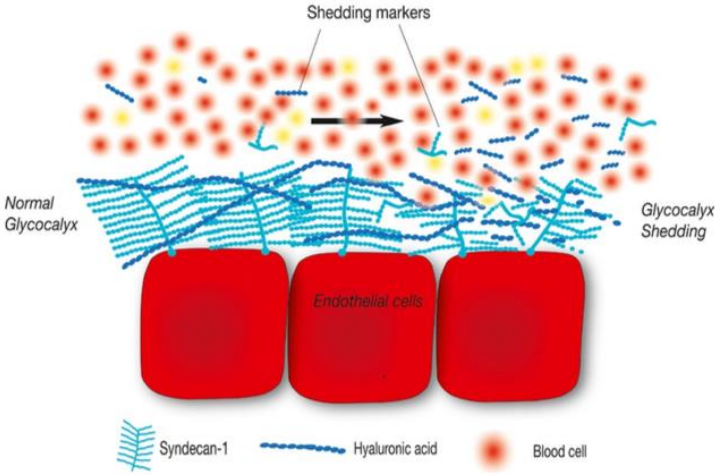
Sodium Handling by Endothelium is determined by Glycocalix







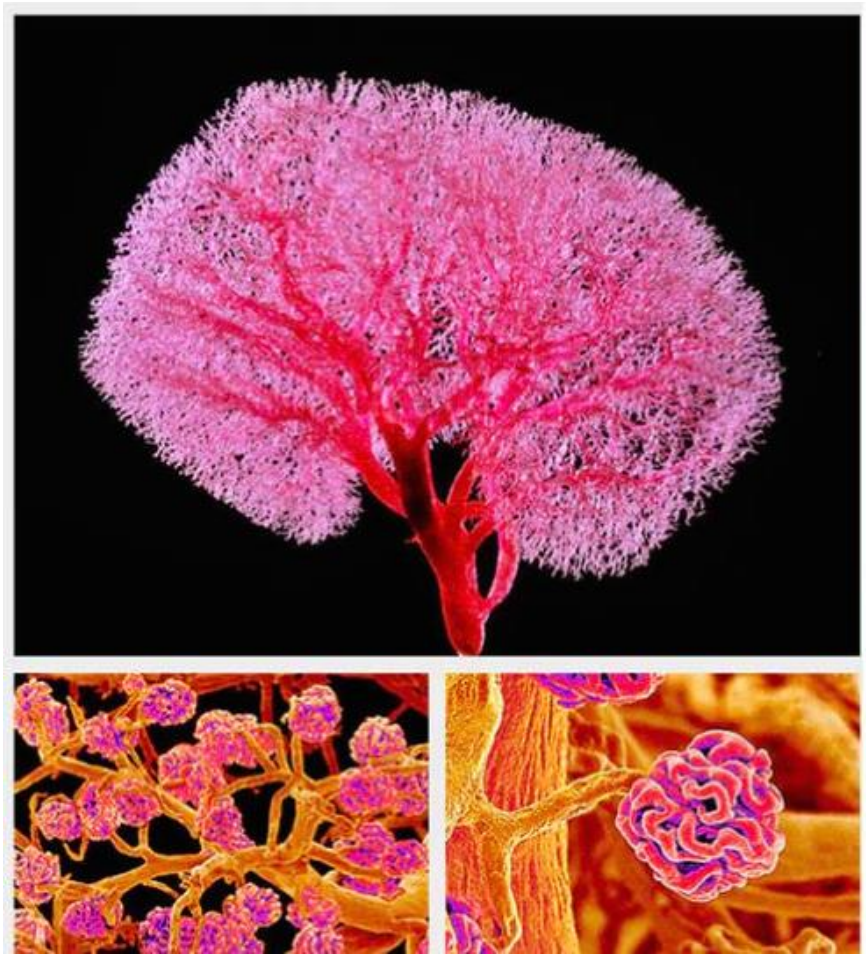
Heart Failure

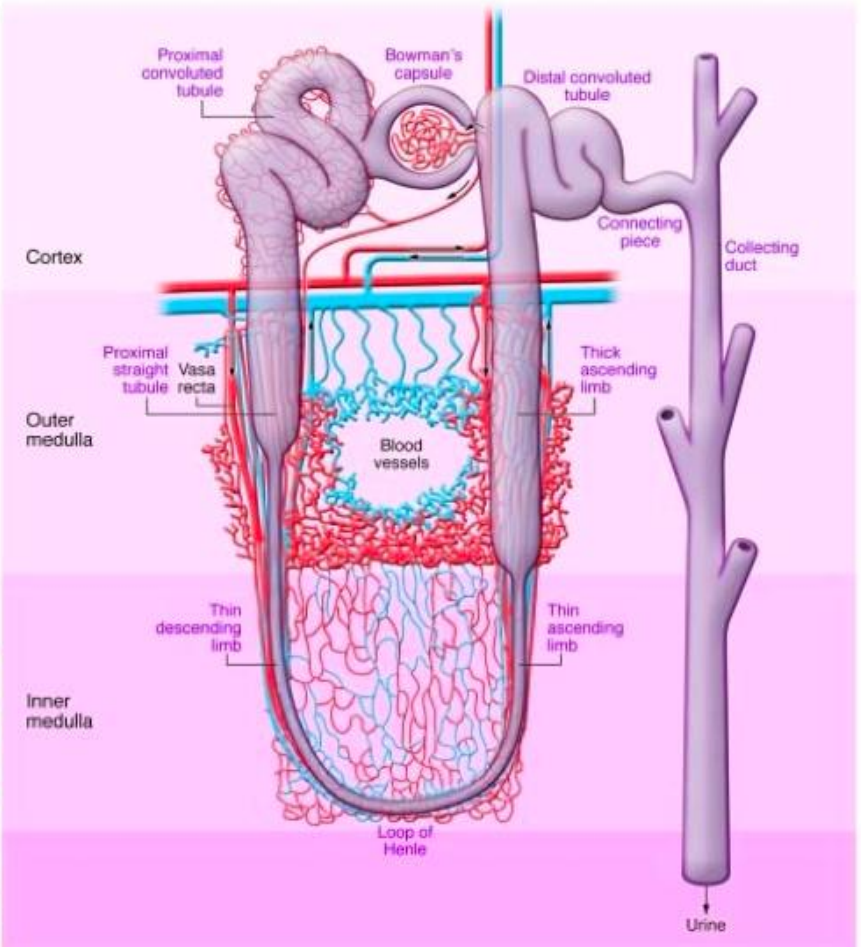


Nijst P, Mullens W et al. J Am Coll Card 2015;65:378-88
Nijst P, Mullens W et al. Microrcirculation 2018;25.

What organ do we need to get rid of Na?

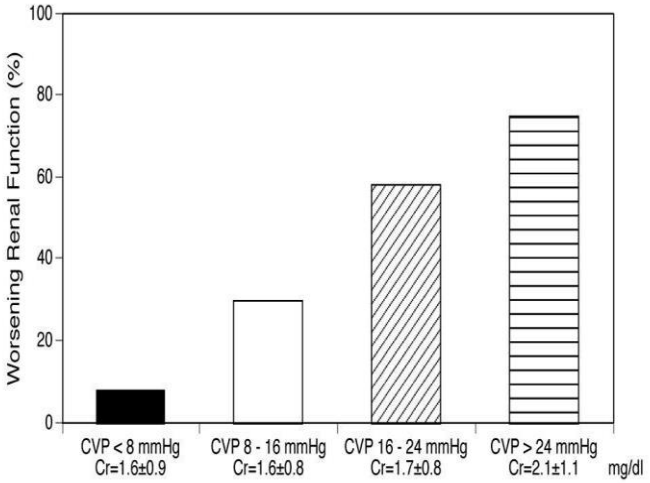
Kidney: a remarkable vascular organ

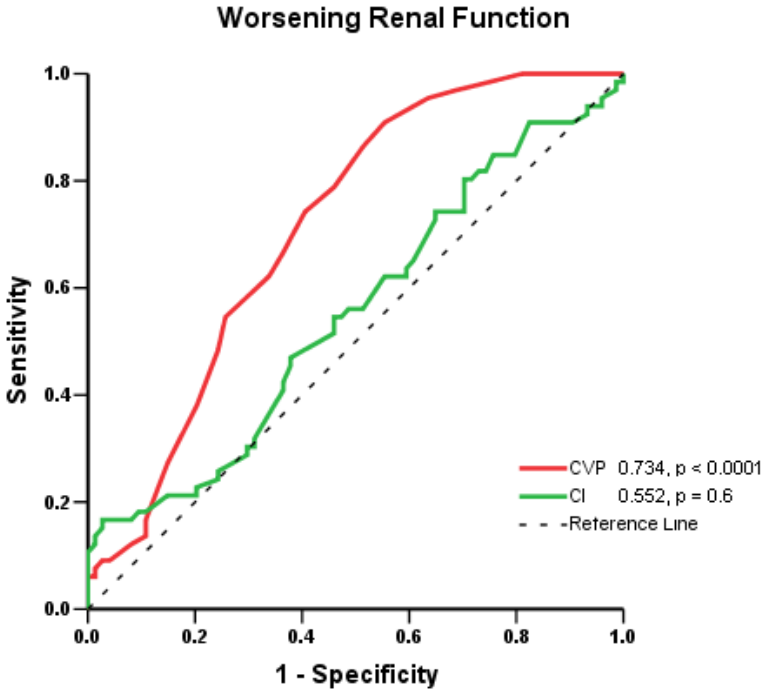




Bonventre LI. J Clin Invest 2011

Cardiac Output or Central Venous Pressure





Increased CVP contributes to WRF in patients admitted with low-ouput HF

Mullens W et al. J Am Coll Card 2009;53:589-96.

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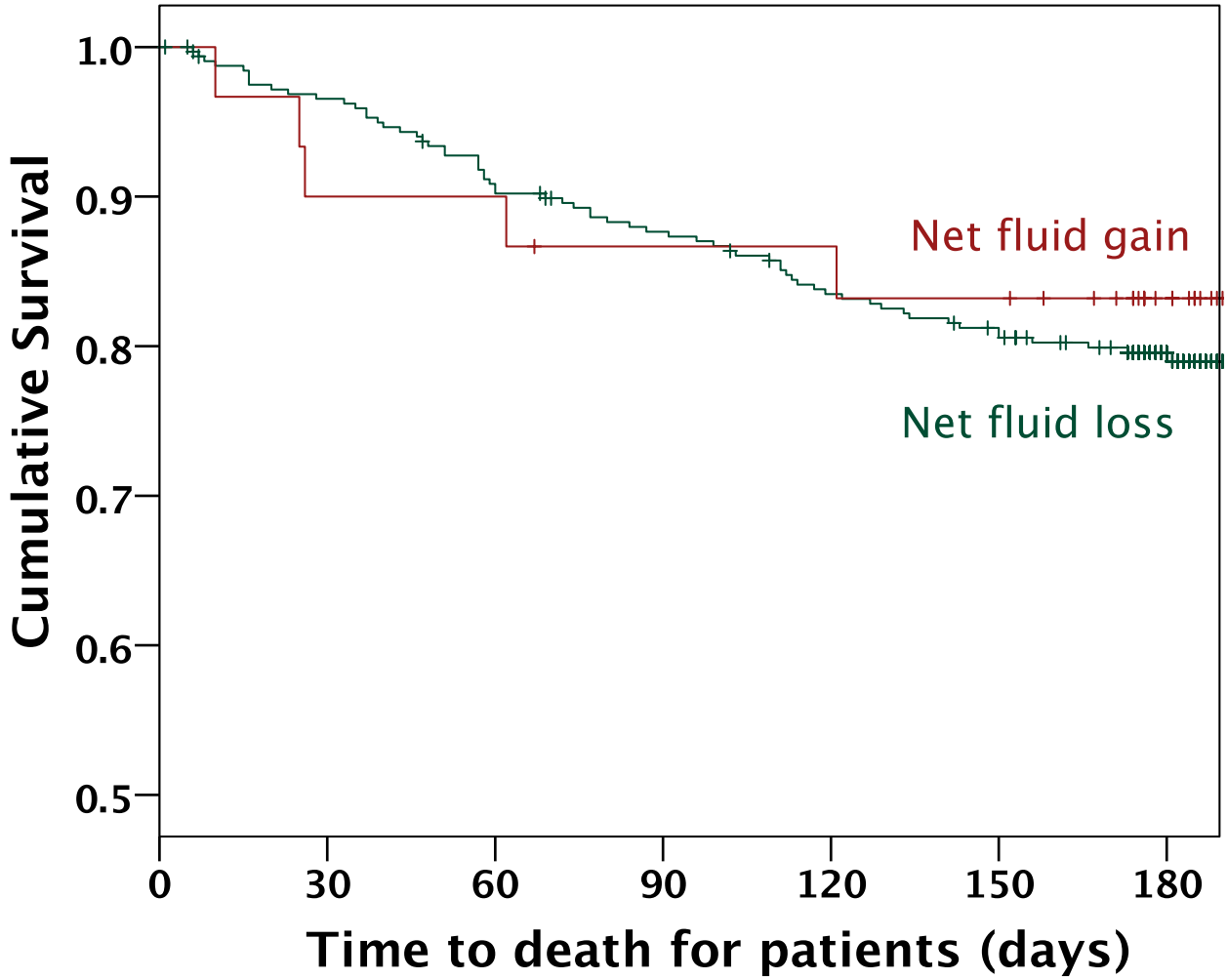
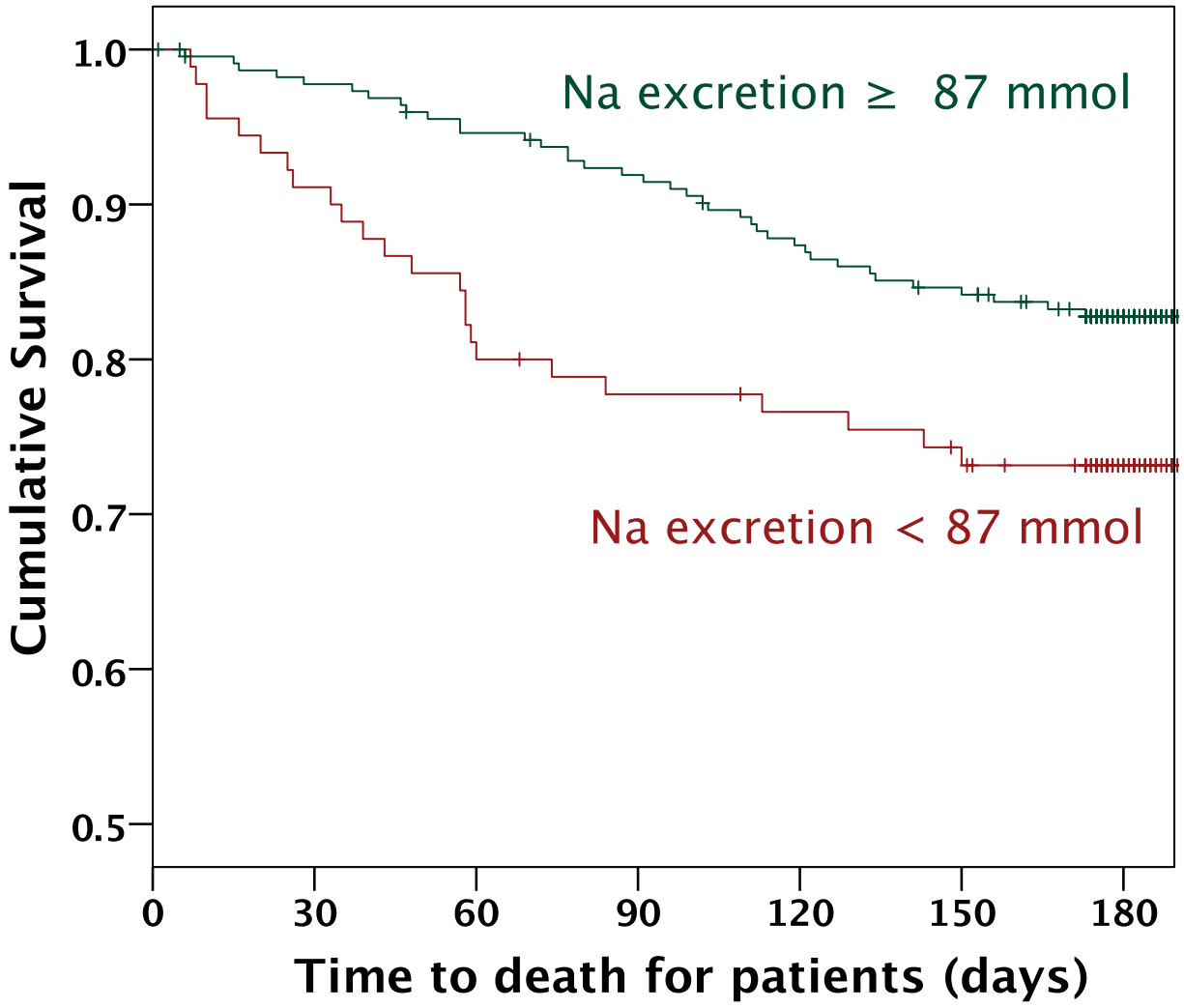
What matters most….Na or H20 excretion?

CaNet fluid loss doesn't predict survival (ROSE-HF)



Hodson, HFSA 2017

However, sodium excretion is significantly associated with survival (ROSE-HF)

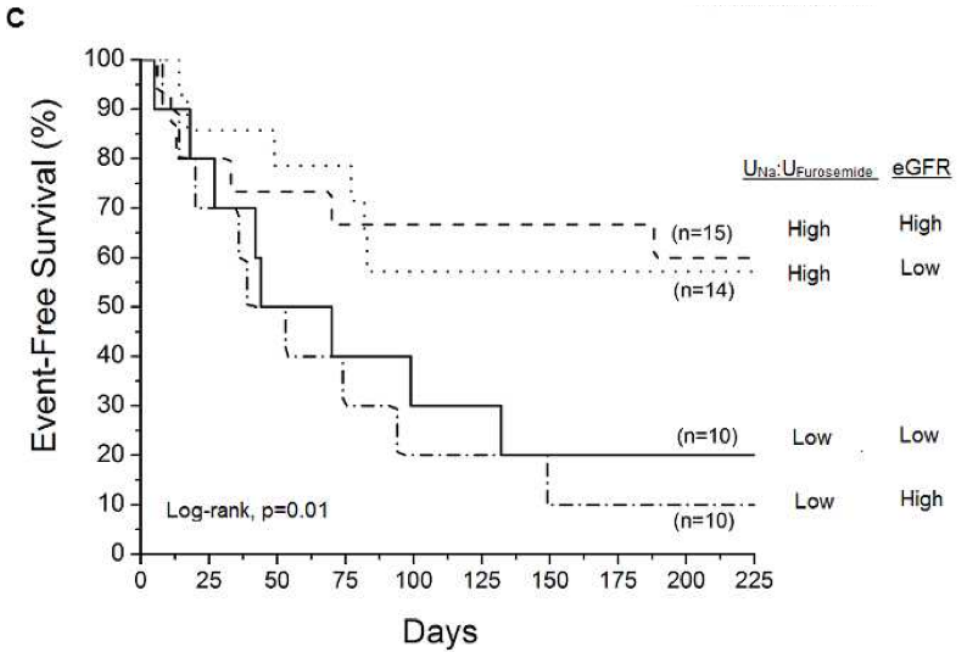


Hodson, HFSA 2017

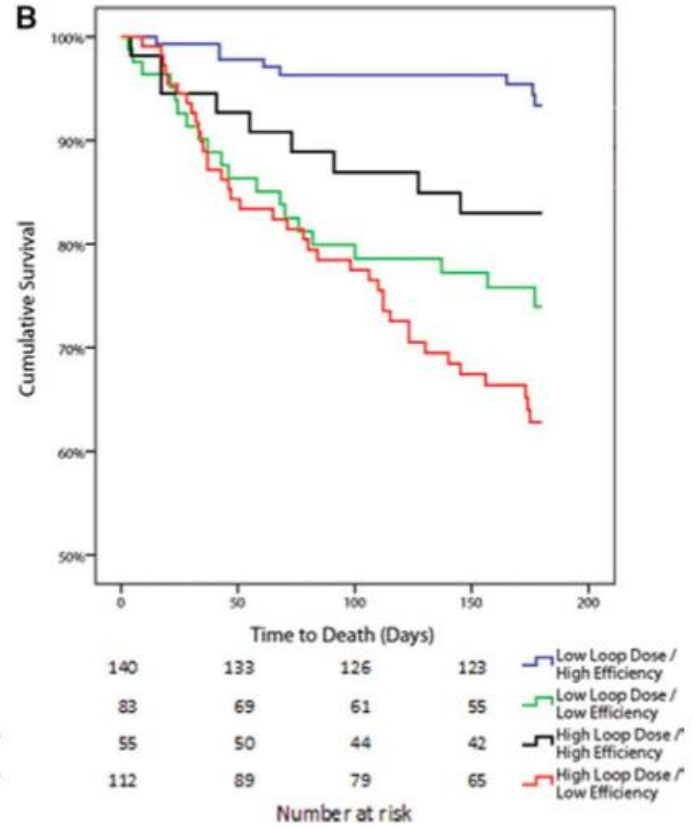
Post-Diuretic spot Urinary Sodium to guide diuretic therapy?

Hospitalized HF - Urinary Na < 50, poor prognosis

Loop diuretic responsiveness = ‘natriuresis/mg loop’
≈ outcome



Singh D, Mullens W, et al. J Card Fail 2014, 20:392-9.



Testani J et al. Circ Heart Fail 2014; 7:261-70.

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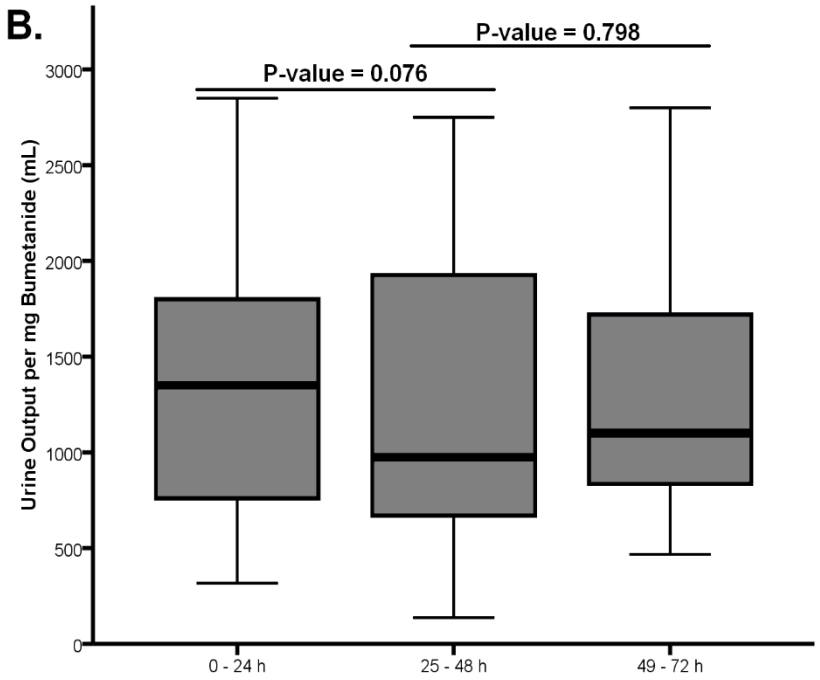
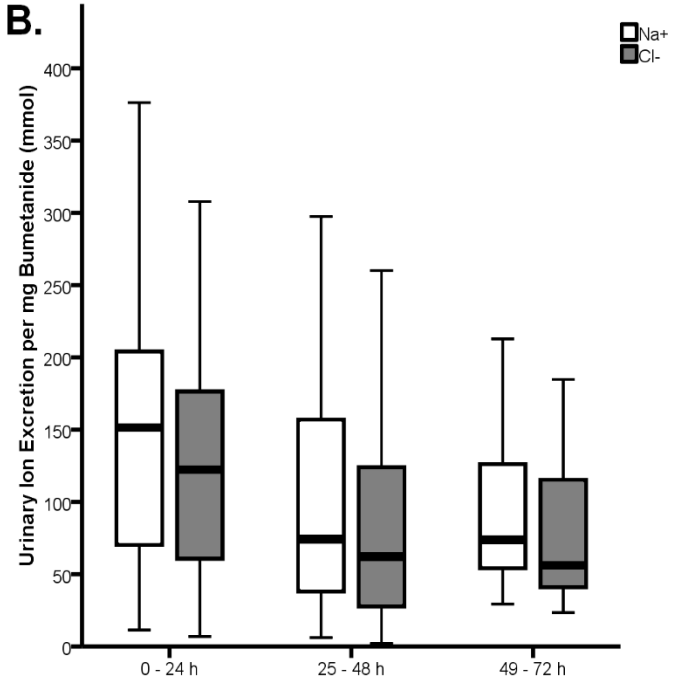
Urinary Composition during Decongestion with Loop Diuretic Therapy





Progressive decrease in Urinary Na and Cl but NOT in urine output when only loop diuretics are used
(even after correction for diuretic dose)

Verbrugge F, Mullens W, et al. Circ Heart Fail 2014.

How to increase renal Na excretion?

Diuretics; the guideline-recommended therapy

Recommendations	Class [a]	Level [b]
Diuretics		
Intravenous loop diuretics are recommended for all patients with AHF admitted with signs/symptoms of fluid overload to improve symptoms. It is recommended to regularly monitor symptoms, urine output, renal function and electrolytes during use of i.v. diuretics.	I	C
In patients with new-onset AHF or those with chronic, decompensated HF not receiving oral diuretics the initial recommended dose should be 20–40 mg i.v. furosemide (or equivalent); for those on chronic diuretic therapy, initial i.v. dose should be at least equivalent to oral dose.	I	B
It is recommended to give diuretics either as intermittent boluses or as a continuous infusion, and the dose and duration should be adjusted according to patients' symptoms and clinical status.	I	B
Combination of loop diuretic with either thiazide-type diuretic or spironolactone may be considered in patients with resistant oedema or insufficient symptomatic response.	IIb	C

Ponikowski P, Eur J Heart Fail 2016.

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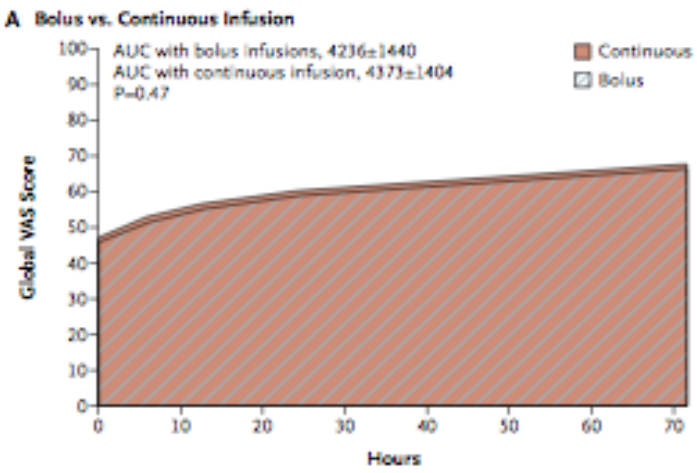
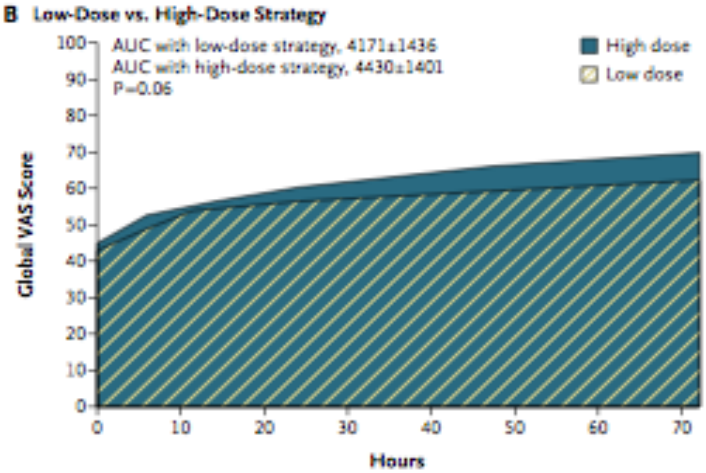
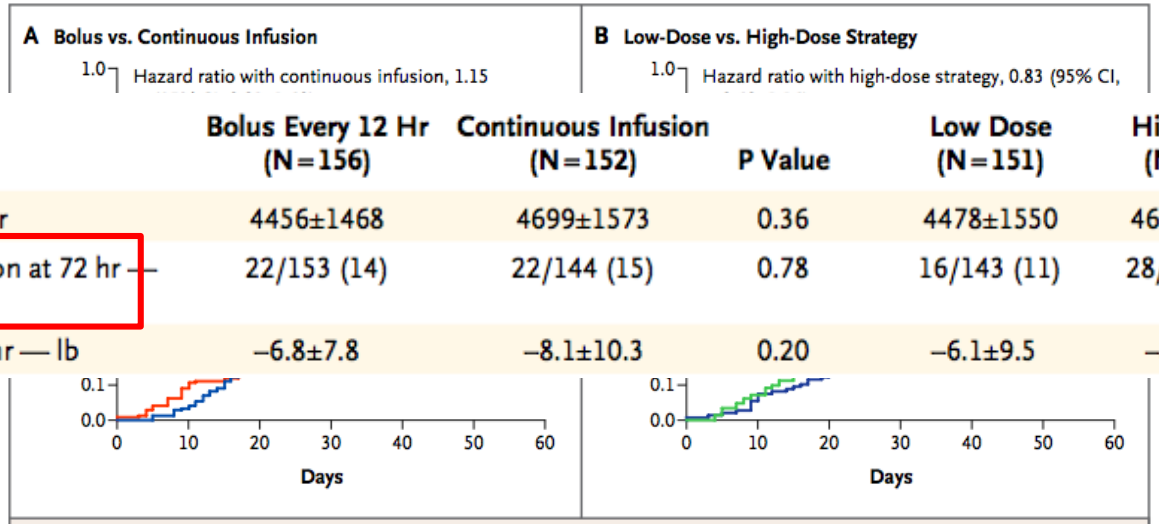
The Diuretic Optimization Strategies Evaluation Study (DOSE)



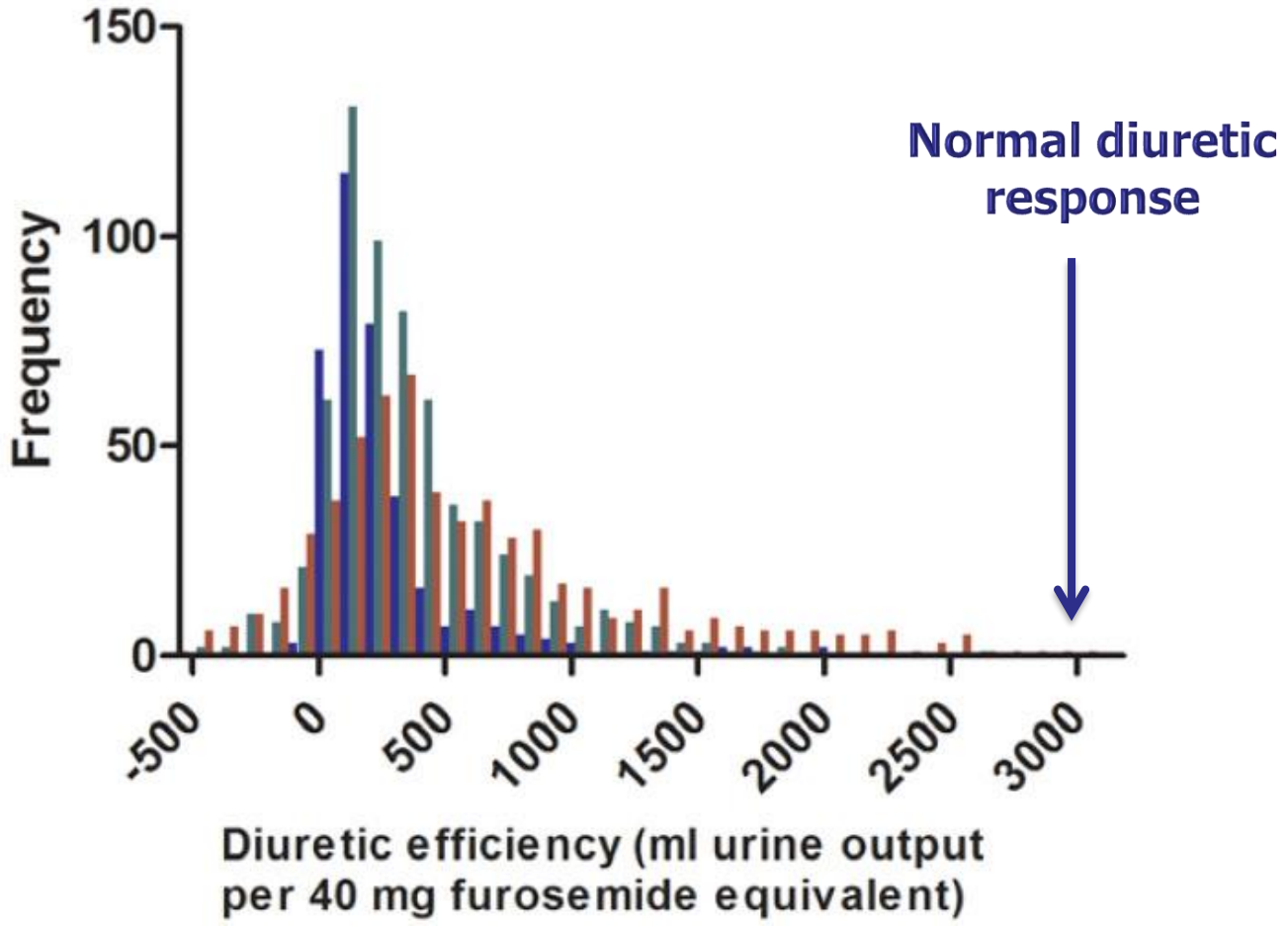




End Point	Bolus Every 12 Hr (N=156)	Continuous Infusion (N=152)	P Value	Low Dose (N=151)	High Dose (N=157)	P Value
AUC for dyspnea at 72 hr	4456±1468	4699±1573	0.36	4478±1550	4668±1496	0.04
Freedom from congestion at 72 hr — no./total no. (%)	22/153 (14)	22/144 (15)	0.78	16/143 (11)	28/154 (18)	0.09
Change in weight at 72 hr — lb	−6.8±7.8	−8.1±10.3	0.20	−6.1±9.5	−8.7±8.5	0.01

Felker M et al. NEJM 2011; 364:797-805

Relative diuretic resistance is omnipresent in HF patients



Testani J et al . Circ Heart Fail 2014.

Decompensated HF in 2018….
Is this what we should accept?

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Pathophysiology-based approach?

Extracellular Volume = Na

Normal kidneys filter a tremendous amount of salt

GFR = 125 mL/min = 180 L/day

Plasma Na^+ = 142 mmol/L

25,560 mmol Na^+ filtered each day ~ > 1 kg sodium

Courtesy of F.Verbrugge

Extracellular Volume = Na

Bad kidneys still filters a lot of salt

GFR = 12,5 mL/min = 20 L/day

Plasma Na^+ = 142 mmol/L

3500 mmol Na^+ filtered each day ~ > 150 g sodium

Courtesy of F.Verbrugge

Problem is not that the kidney filters too little sodium.....

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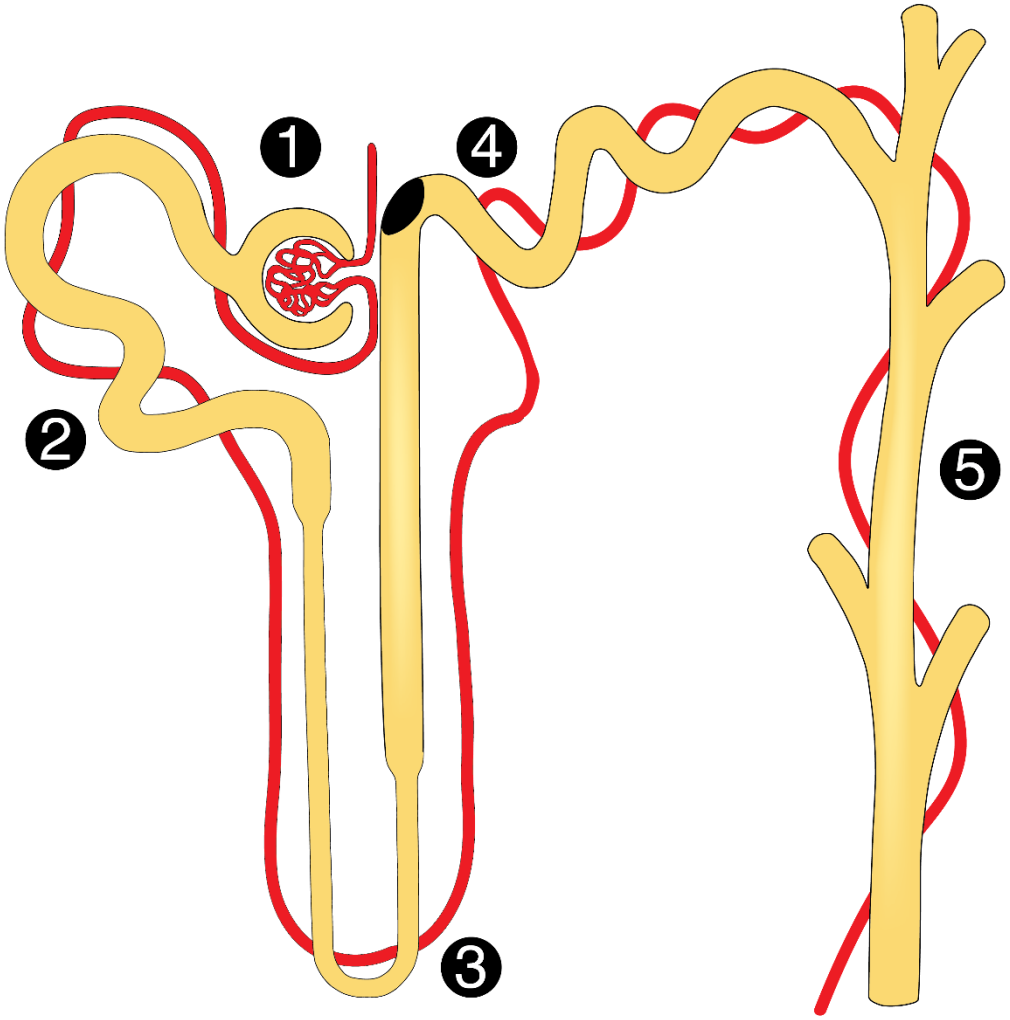
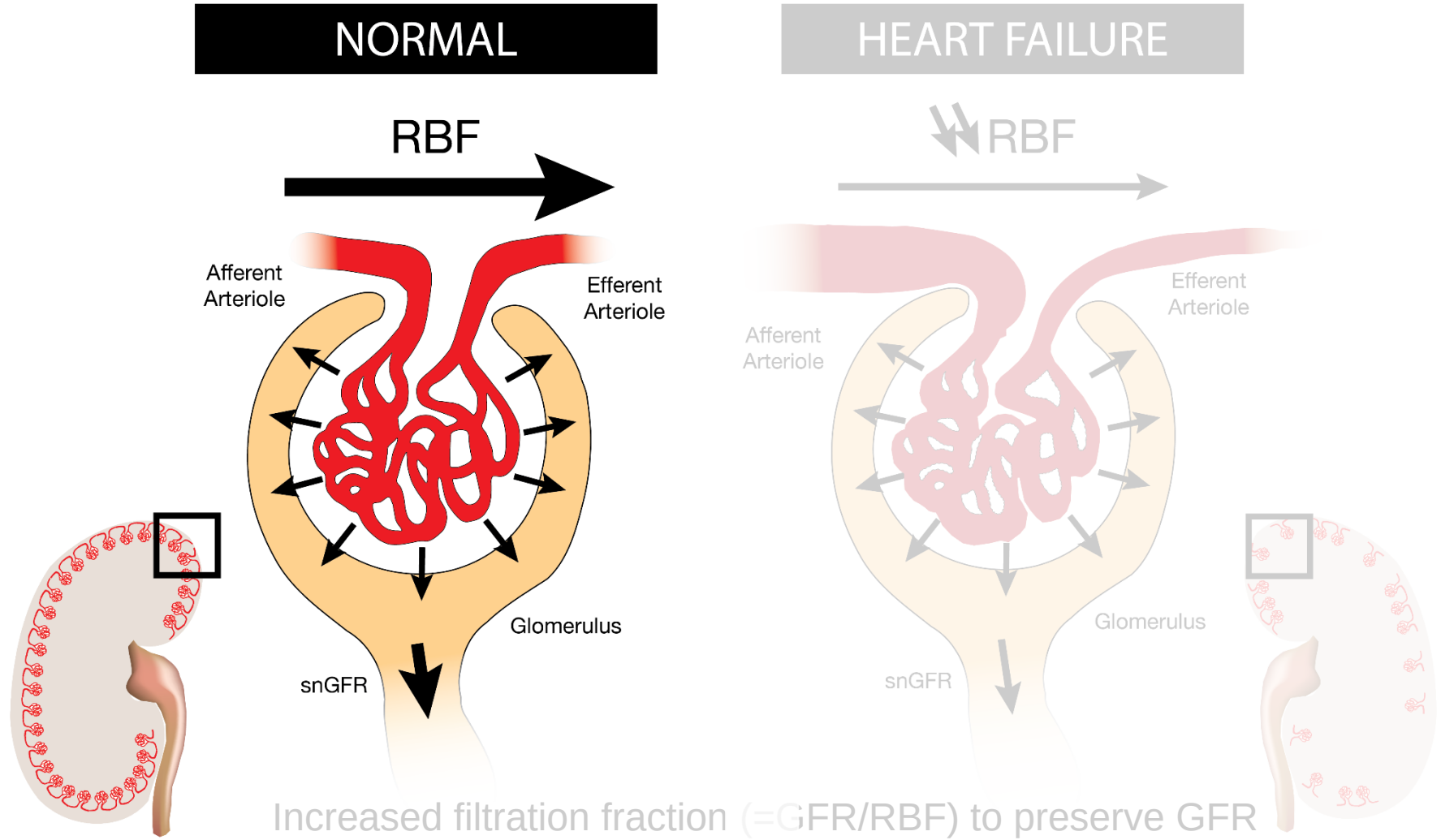
The Kidney



Mullens W et al. Eur Heart J, 2017;38:1872-1882

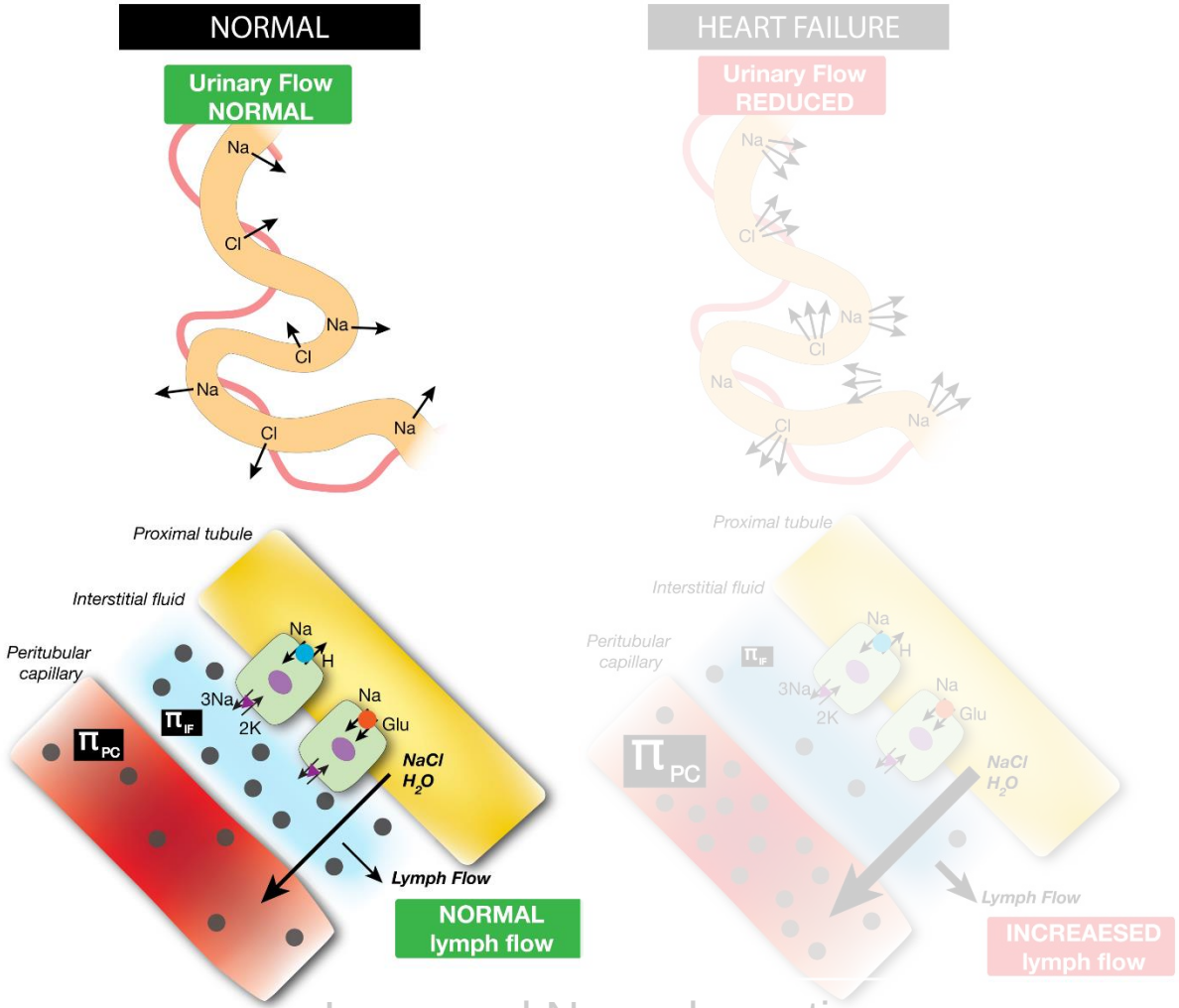
I: Glomerulus



Mullens W et al. Eur Heart J, 2017;38:1872-1882

II: Proximal Tubulus

1) Glomerulotubular Feedback

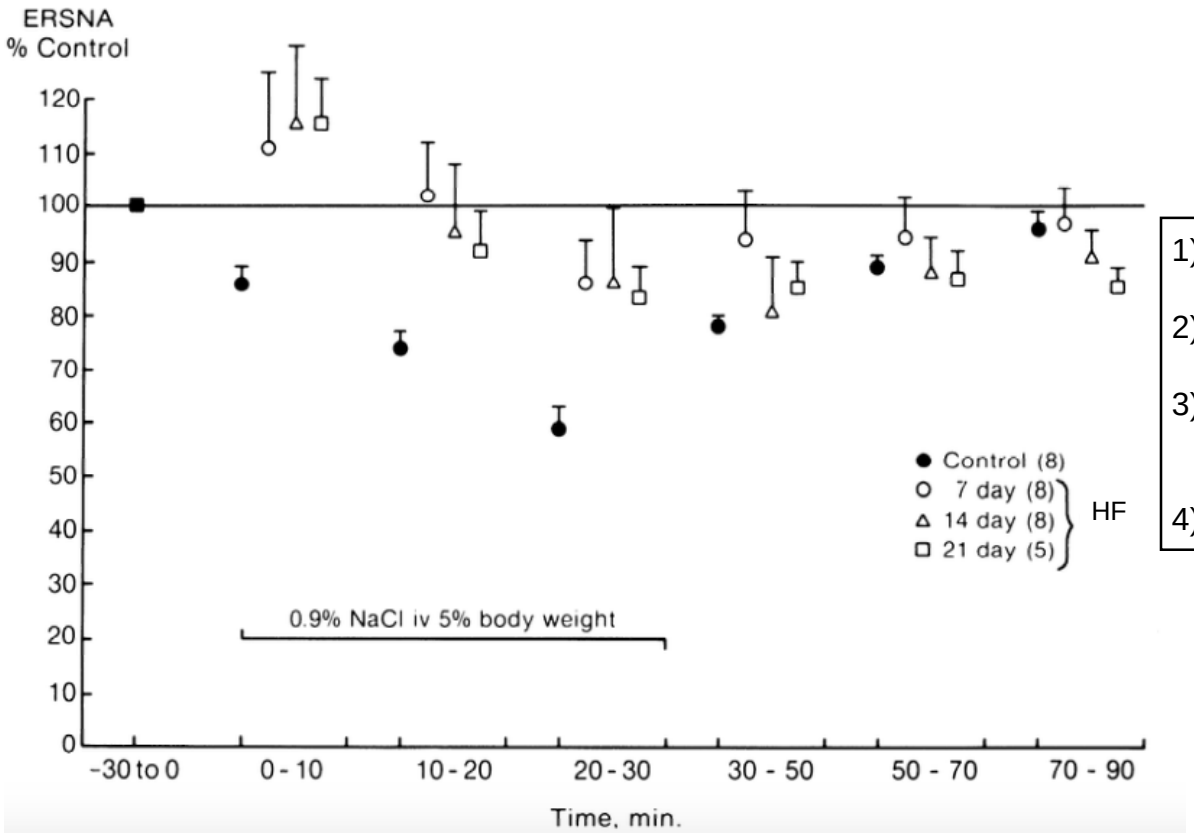


Increased Na reabsorption

Mullens W et al. Eur Heart J, 2017;38:1872-1882

II: Proximal Tubulus

2) Increased Efferent Renal Sympathetic Activation



↑ ERNSA

1) ↑ Renin secretion (beta 1)

2) ↑ Na reabsorption (alpha)

3) ↑ vasoconstriction efferent arteriole (alpha)
(↓↓ RBF, ≈ GFR)

4) ↑ BUN reabsorption (↑ BUN/sCreat)

ACE-i
BB

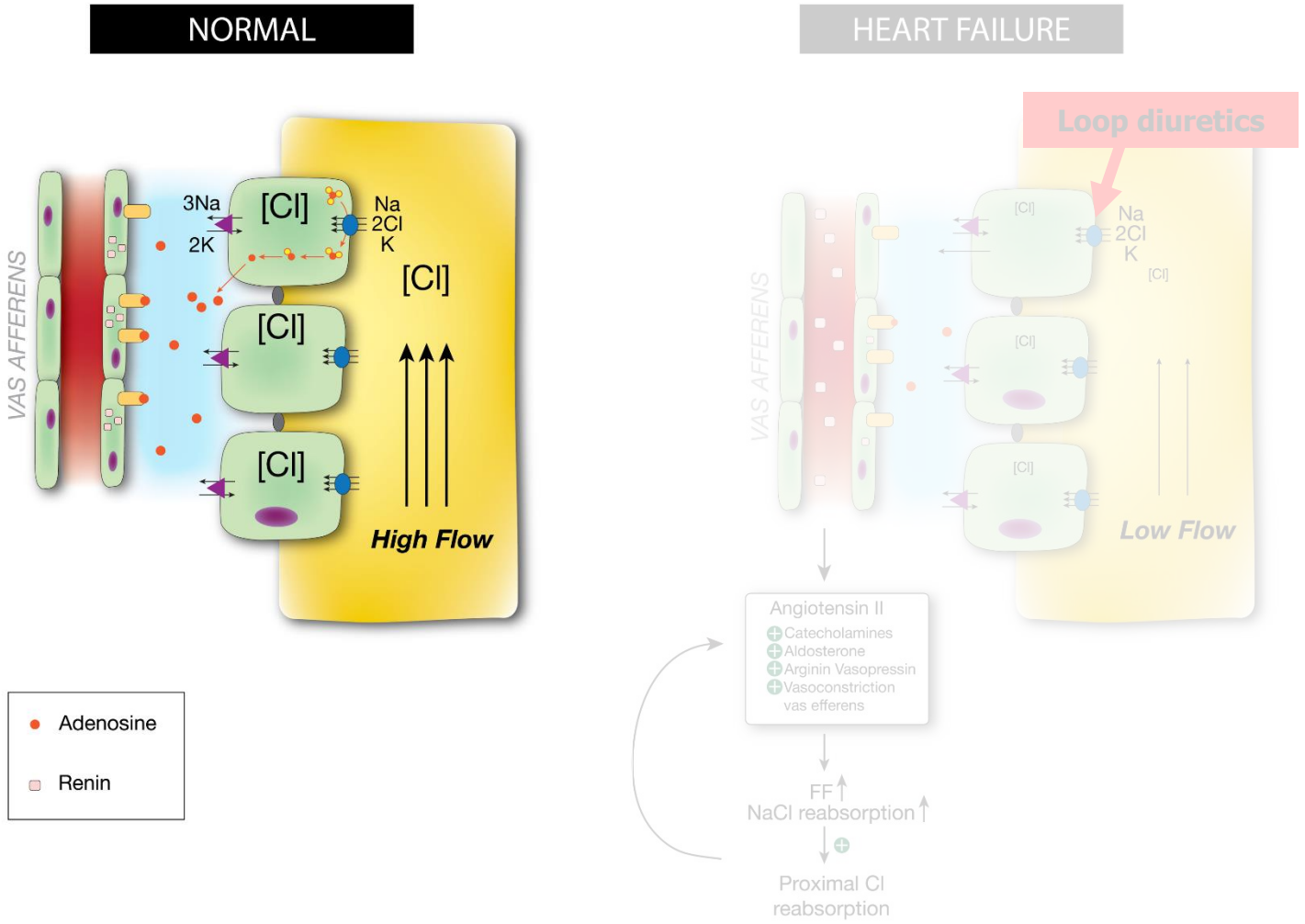
Mainly effect on Renin
↓ GFR

Blunted response to volume expansion

DiBona G et al. Am J Physiol. 1988;11:326-33

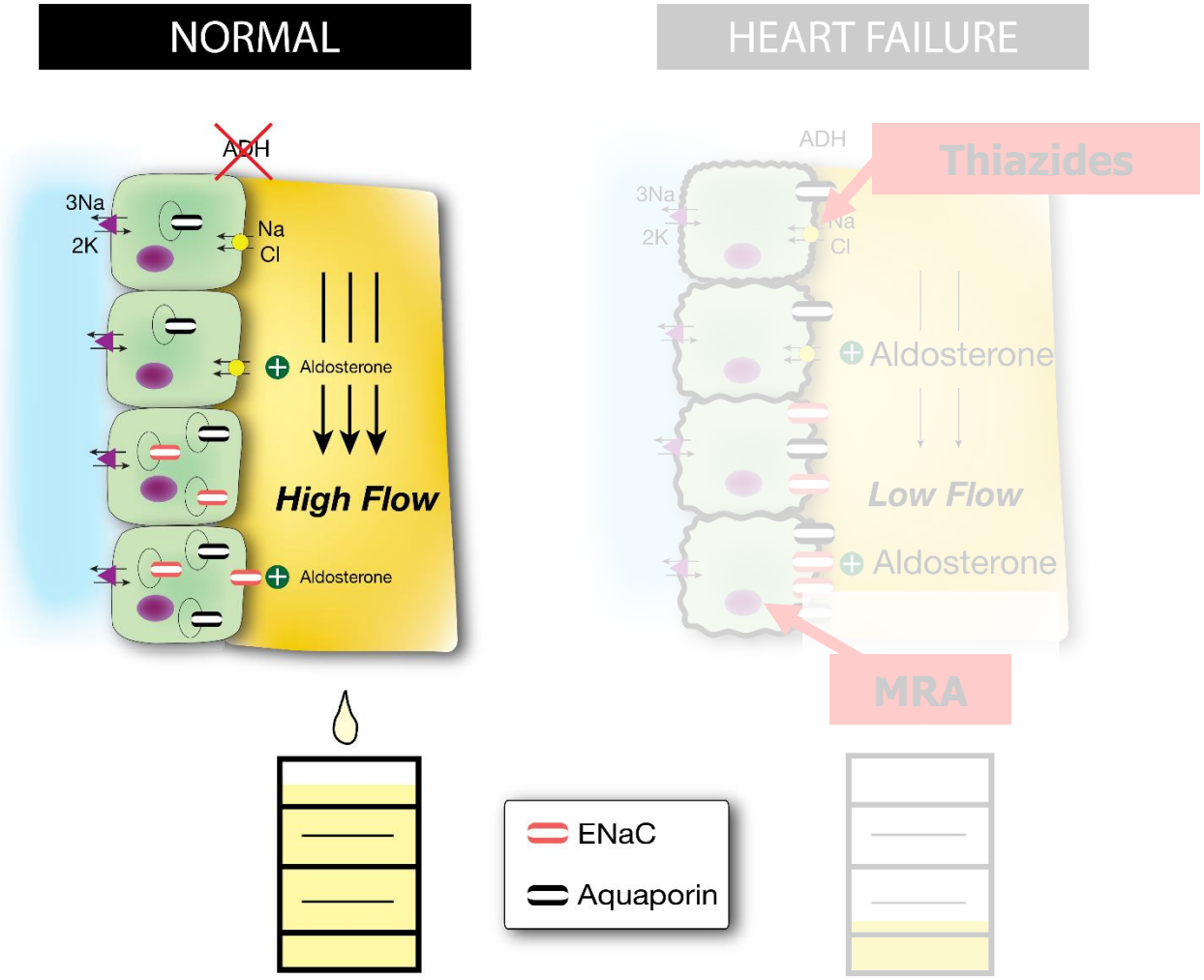
III: Loop of Henle - Macula Densa

Tubuloglomerular Feedback



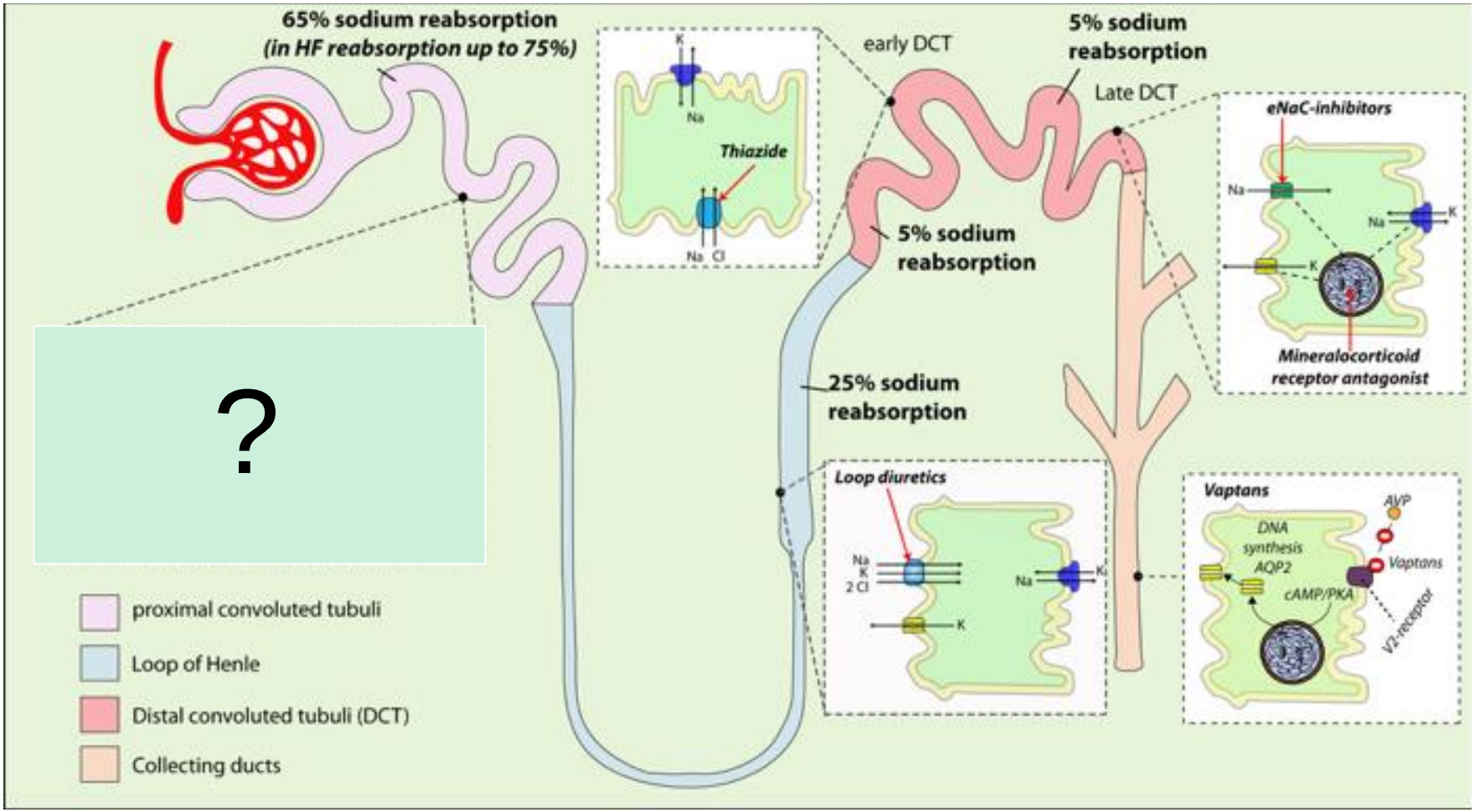
Mullens W et al. Eur Heart J, 2017;38:1872-1882

IV: Distal Nephron



Mullens W et al. Eur Heart J, 2017;38:1872-1882

Future acute HF drug treatment for decongestion?



Courtesy of P.Martens

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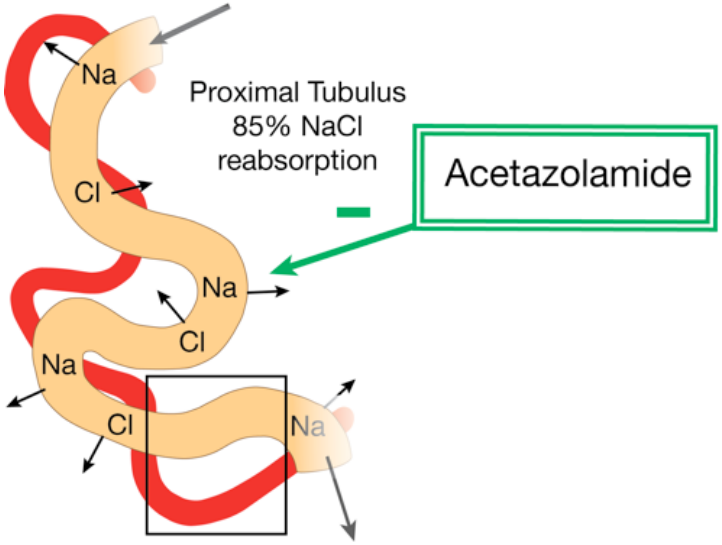
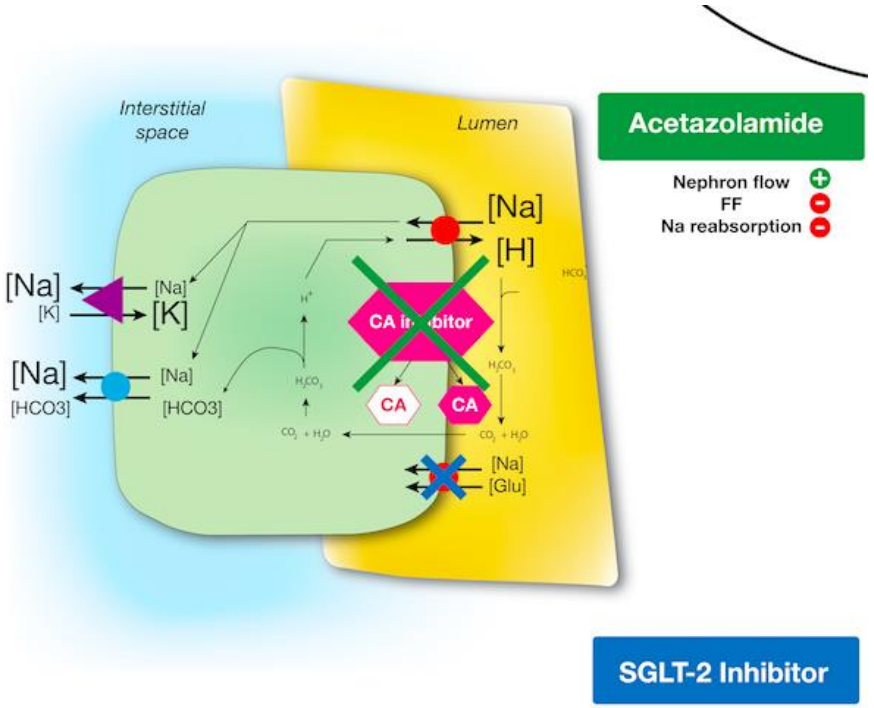
Renal Preservation: Acetazolamide

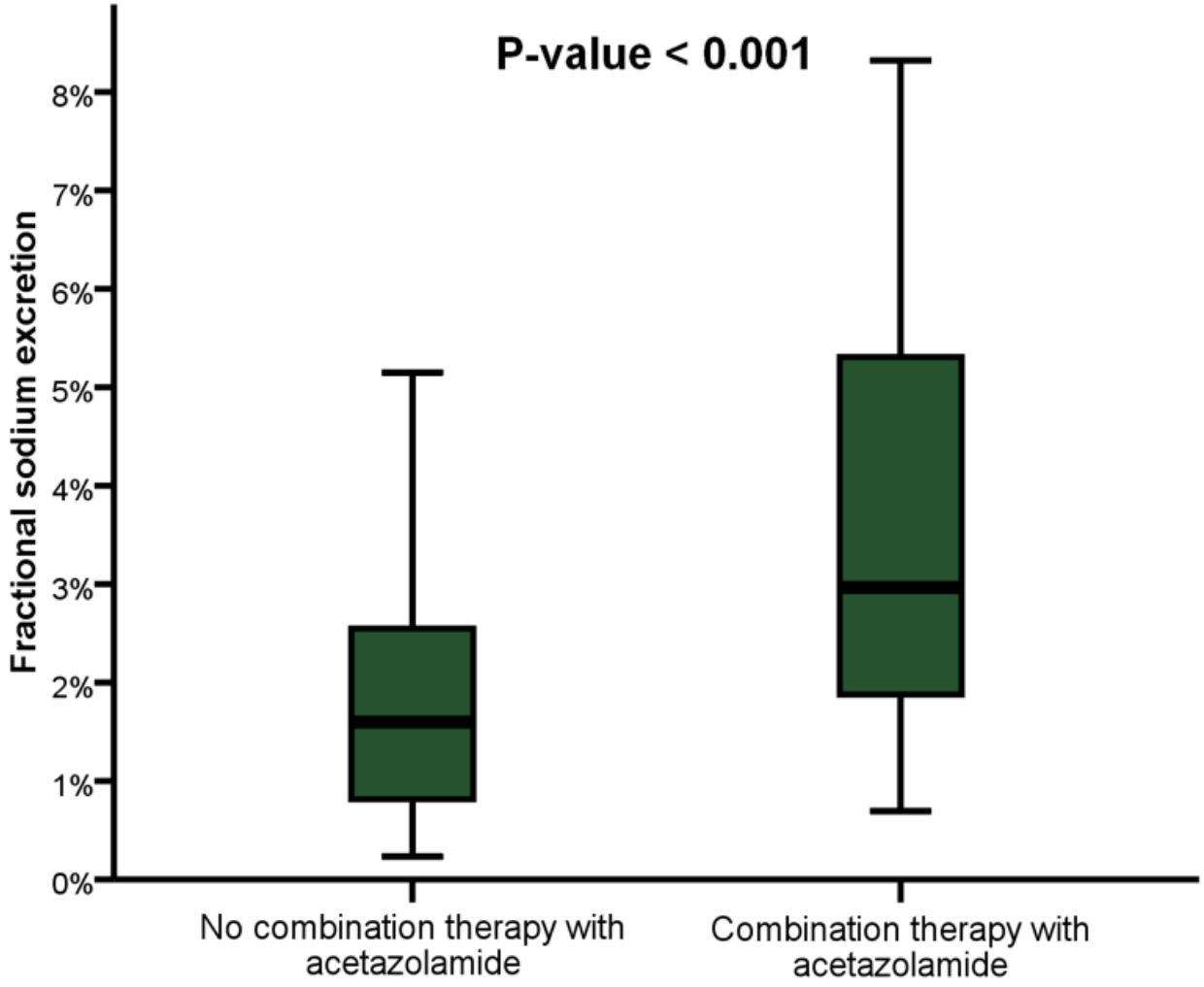




Inhibition Na reabsorption Proximal Tubule (Acetazolamide)

Mullens W et al. Eur Heart J, 2017;38:1872-1882

Decongestion of ADHF @ ZOL



Verbrugge F, Mullens W. Acta Cardiol 2015

Acetazolamide in **D**ecompensated heart failure with **V**olume **O**ve**R**load (ADVOR)

ADVOR

Mullens W. Eur J Heart Fail, In Press

Ziekenhuis Oost-Limburg

SCREENING: patients admitted with ADHF + volume overload

Inclusion

- At least 1 sign of volume overload (oedema, ascitis, pleural effusion)
- ≥ 1 month maintenance dose of loop diuretics (≥ 1 mg bumetanide, ≥ 40 mg furosemide, ≥ 20 mg torsemide)
- BNP > 250 pg/ml or NT-proBNP > 1000 pg/ml
- Assessed LVEF by any imaging techniques within 12 months of inclusion

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Exclusion

- At admission / screening
  - Treatment with acetazolamide and/or IV loop diuretics > 2 mg prior to randomization
  - Estimated glomerular filtration rate <20 mL/min/1.73m²
  - Systolic blood pressure <90mm Hg or MAP <65mm Hg
  - Pregnant/breastfeeding subjects
  - Diagnosis of acute coronary syndrome
  - Current or expected use of "forbidden" agents (e.g. SGLT-2 inhibitors, IV inotropes, vasopressors or nitroprusside)

- At any time before study inclusion
  - History of congenital heart disease or cardiac transplantation and/or ventricular assist device
  - Use of renal replacement therapy or ultrafiltration

- Use of any non-protocol defined diuretic agent should be stopped upon study inclusion

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Background therapy during active study treatment adminstration

- 24h oral intake of fluid and sodium will be restricted to 1500 mL and 1.5 g
- Maintenance infusion with 500 mL glucose 5% and 3g MgSO4 administered over 24h
- Continue neuorhumoral blockers without dose increase with the exception of mineralocorticoid receptor antagonists in case of hypokalaemia despite intravenous potassium supplement.
- Starting an SGLT2 inhibitor and a switch from renin-angiotensin system blockers to saccubutril/valsartan is not allowed
- If K <4 mmol/L, 40 mmol of KCI is added to the maintenance infusion.
- If HCO3- l<20 mmol/L, addition of intravenously 100 ml of NaHCO3 8.4%.
- After decongestion, it is strongly recommended to up-titrate doses of neurohumoral blockers according to the guidelines in the HFrEF patients.

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RANDOMISATION

start urine collection

Group 1: IV therapy with high-dose bumetanide* with placebo

Group 2: IV therapy with high-dose bumetanide* with azetazolamide

DAY 1

TREATMENT PHASE

STUDY START DOSE

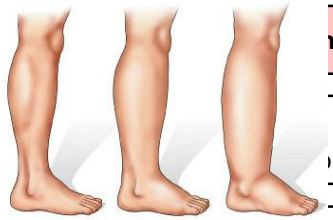
Bolus of IV bumetanide* (2x orally home dose) + 500 mg IV bolus of placebo or azetazolamide

DAY 2

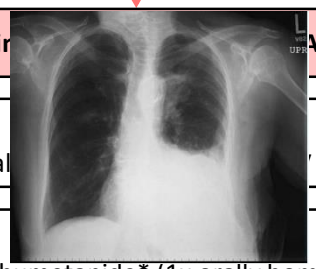
Morning: Volume assessment (oedema, pleural effusion or ascites)

Does the patient have more than trace oedema? NO → Does the patient have pleural effusion? NO → Does the patient have ascites? NO → Successfull decongestion (score ≤1): **Stop IV diuretic treatment AND continue urine collection**

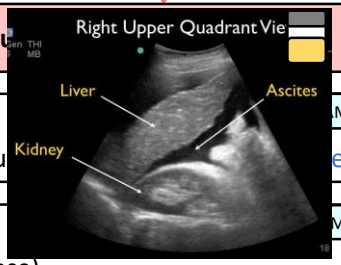
YES



YES



YES



Wait 6 hours

IV bumetanide* (1x orally home dose)

*bumetanide is preferred loop diuretic agent; Conversion factor is 1 mg bumetanide = 20mg torsemide = 40 mg furosemide (IV and oral); Bolus of bumetanide is limited to 5 mg bumetanide

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TREATMENT PHASE

DAY 3

Morning: Volume assessment (oedema, pleural effusion or ascites)

Does the patient have more than trace oedema? → NO → Does the patient have pleural effusion? → NO → Does the patient have ascites? → NO → Successfull decongestion (score ≤1):
Stop IV diuretic treatment AND stop urine collection

YES / YES / YES

Score >1: Continue IV diuretic treatment AND stop urine collection

STUDY DOSE — 8-12 AM
Bolus IV bumetanide (1 x orally home dose) + 500 mg IV bolus of placebo or azetazolamide

STUDY DOSE — 2-6 PM
IV bumetanide (1x orally home dose)

Quantify urine output:

*IF **TOTAL** urinary output < 3.5l:*
→ ESCALATION THERAPY MANDATORY!
- *Doubling IV loop diuretics dose*
- *Add oral chlorthalidone 50 mg daily*
- *Ultrafiltration or renal replacement therapy*

*IF **TOTAL** urinary output ≥ 3.5l:*
→ FOLLOW PROTOCOL

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TREATMENT PHASE

DAY 4

Morning: Volume assessment (oedema, pleural effusion or ascites)

Does the patient have more than trace oedema? → NO → Does the patient have pleural effusion? → NO → Does the patient have ascites? → NO → Successfull decongestion (score ≤1): **Stop IV diuretic treatment**

YES (Does the patient have more than trace oedema?)

YES (Does the patient have pleural effusion?)

YES (Does the patient have ascites?)

Further IV diuretic therapy at the discretion of the treating physician

Primary Endpoint Analysis !

FOLLOW-UP PHASE

DISCHARGE HOSPITAL

FU VISIT @ 3 MONTHS AFTER STUDY START DOSE

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PRIMARY ENDPOINT

Treatment success (decongestion achieved) on the morning of day 4 without the need for escalating diuretic strategy (doubling loop diuretic dose, addition of chlorthalidone, or ultrafiltration)

SECONDARY ENDPOINTS

1) Combined end-point of all-cause mortality and heart failure readmission during 3 months of follow-up

2) Length of index hospital admission

3) Longitudinal changes in EuroQoL five dimensions questionnaire (baseline, day 4, any HF readmission, and 3 months)

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Stop Study Treatment

- The treating physician is **allowed t**o stop the study treatment, which counts as treatment failure in case of persistent volume-overload in following cases:

1. symptomatic hypotension with a systolic blood pressure <100 mmHg
2. asymptomatic hypotension with a systolic blood pressure <90 mmHg
3. an increase of serum Cr levels x 1.5 of the serum Cr level compared to admission value.
4. occurrence of metabolic acidosis (ph < 7.2)

- If any of these events occur when the patient is judged to be euvolemic, the study treatment is stopped and stopping is not considered a treatment failure.

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Table of trial procedures

	Screening phase	Treatment phase				Follow up phase		
		Study Day 1	Morning of Study Day 2	Morning of Study Day 3	Morning of Study Day 4	Discharge	Re-admission	3 Months after study start dose
Informed consent	X							
In- and exclusion criteria	X							
Randomization	X							
Demographics[1]	X							
Medical history	X							
Vitals[2]	X		X	X	X			X
Weight[12]	X		X	X	X	X		X
EQ5D	X				X		X[11]	X
Volume assessment	X		X	X	X	X		X
Study treatment		X[3]	X[4]	X[4]				
Urinary collection[5]		X	X					
Local lab	X[6]		X[7]	X[7]	X[7]			X[7]
Laboratory sub-study[13] blood	X				X[14]			X
Laboratory sub-study[13] Urine		X	X					
Plasma BNP or NT-proBNP[8]	X				X			X
Urine pregnancy testing[9]	X							
Dose of neurohumoral blockers	X				X	X		X
Dose of diuretics	X					X		X
Concomitant medication	X	X	X	X	X			
Adverse Events[10]	X	X	X	X	X	X	X	X

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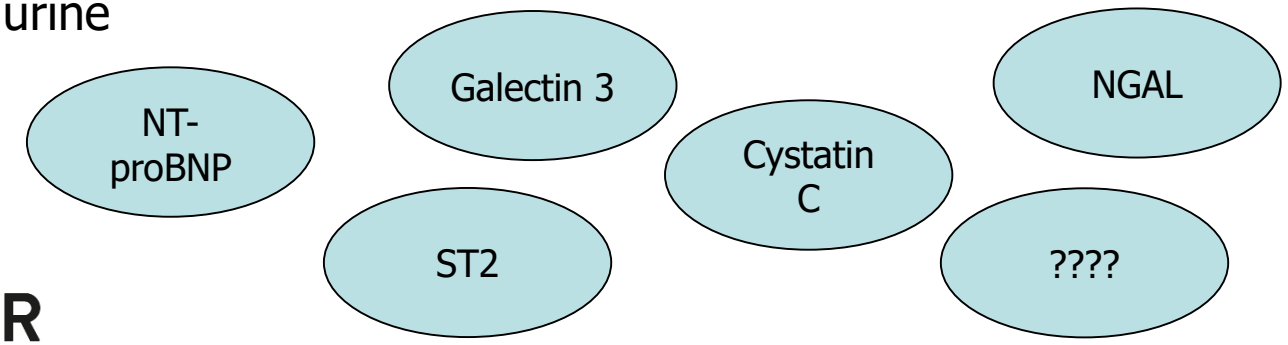
Laboratory substudy

- Investigate the mechanistic and potential favourable effect of acetazolamide and loop diuretics

- New insights into the pathophysiology of decompensated HF
  → identify high risk patient population?

IMPROVED AND PATIENT TAILORED TREATMENT STRATEGIES?

- Biomarkers related to cardiac and renal function/injury obtained from blood and urine



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Substudy set-up

- Optional for the hospital
- Patient needs to sign separate IC for substudy and be eligible for main study
- Kits for blood and urine will be provided by the ADVOR study team
- Samples processed at local hospital and temporary stored in freezer at min -20°
- Shipment to and storage at University Biobank of Limburg (UBiLim)

Collection	Timepoint	Collection material	Storage material
BLOOD – Plasma	▪ Screening ▪ Morning day 4 ▪ Follow-up month 3	10mL EDTA tube	10 x 0,5mL tubes
BLOOD – Serum	▪ Screening ▪ Morning day 4 ▪ Follow-up month 3	5mL SST tube	5 x 0,5mL tubes
URINE	▪ Morning day 2 (Collection period 1) ▪ Morning day 3 (Collection period 2)	11mL urine tube	5 x 1mL tubes

More details can be found in the substudy lab manual

IMP handling

Presenter: Katrien Tartaglia

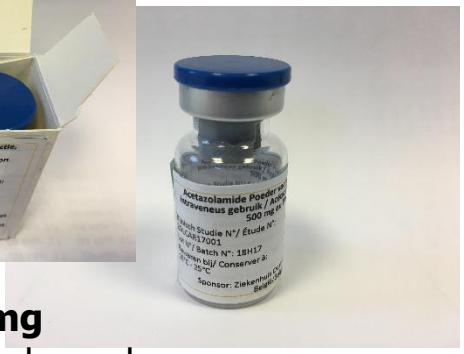
IMP

CONCORDIA INTERNATIONAL CORP

Acetazolamide 500 mg (Diamox ®)
Form: white to white-off lyophilized powder
Route: IV (Glucose 5% 50 ml solution)

BACCINEX SA

Placebo 500 mg
Form: white to white-off lyophilized powder
Route: IV (Glucose 5% 50 ml solution)



Pharmavize

Study medication:
Acetazolamide/placebo 500 mg
Form: white to white-off lyophilized powder
Route: IV (Glucose 5% 50 ml solution)

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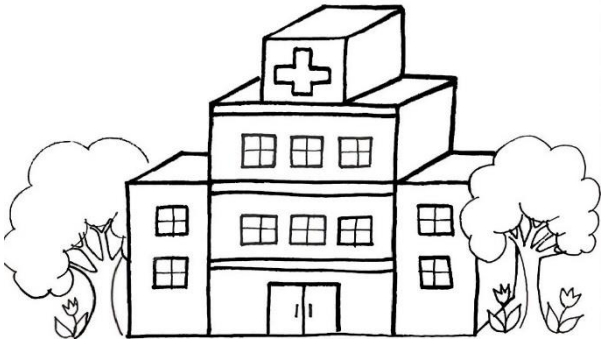
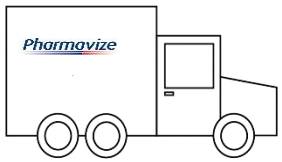
IMP handling



Storage: below 25° C



ADVOR TEAM

ctcm clinical trial center maastricht

ALEA Tools for Clinical Trials

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Safety reporting

Presenter: Katrien Tartaglia

Safety reporting – Definitions according to ICH GCP E6 (R2)

1.2 Adverse Event (AE)

1.50 Serious Adverse Event (SAE) or Serious Adverse Drug Reaction (Serious ADR)

Any untoward medical occurrence that at any dose:

- results in death,
- is life-threatening,
- requires inpatient hospitalization or prolongation of existing hospitalization,
- results in persistent or significant disability/incapacity,

or

- is a congenital anomaly/birth defect

(see the ICH Guideline for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting).

SUSAR is defined as an untoward and unintended response to the study drug, which is not listed in the applicable product information and meets one of the SAE criteria.

Notification to CA (FAGG) within 8 calendar days (death) or 15 calendar days (other SUSAR)

The clinical company

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Safety reporting

WHEN?

From the moment a patient signs the informed consent until the end of the 3 month FU visit.

WHAT?

Any new or worsened event following the safety reporting flow of the ADVOR trial.

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Safety reporting – safety flow (protocol v 1.0, fig4)

Is it a serious adverse event?

No → Is it a non-serious event qualifying as:
- **Related to the IMP**
- **Cardiovascular event**
- **Imbalanced serum electrolytes (K^+, Na^+ and HCO_3)**

No → No Action

Yes → **Is the event a response to the IMP?**

No → Complete AE page in eCRF

Yes → **Is it a SUSAR?**

No → Complete AE page in eCRF

Yes → Complete AE CRF page **within 24h of awareness**

If the SAE is also an endpoint:

- Rehospitalisation for heart failure or any cardiac reason
- All-cause mortality
- Need for renal replacement therapy

Check off endpoint on AE page in eCRF
Submit endpoint package within 1 month

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Monitoring

Presenter: Katrien Tartaglia

Monitoring – Risk based model

ICF

vitals

EQ5D

patient safety

IMP

concomitant medication

patient eligibility

ethnicity

volume assessment

Investigator site file

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Monitoring - Plan

- ✓ Site Initiation Visit (1)
- ✓ Site Monitoring Visits (at least 1/year)
- ✓ Site Closure Visit (1)

Agenda

13:30	• Introduction KCE & ZOL AV
13:45	• Study and protocol presentation
15:15	• Data management
15:45	• Coffee break
16:00	• Study practicalities
16:25	• EDGE
16:40	• Q&A

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Data management

- Data handling
- Data management systems

Data handling

Presenter: Liesbet Van Brussel

Clinical Data Management

= *Multidisciplinary* effort that consists of *all activities* involving the handling of data outlined in the protocol that will be collected/analyzed.

Multidisciplinary:	Study coordinators, investigators, CTU data managers, biostatistician, …
All activities:	Data collection, data coding, data analysis, …

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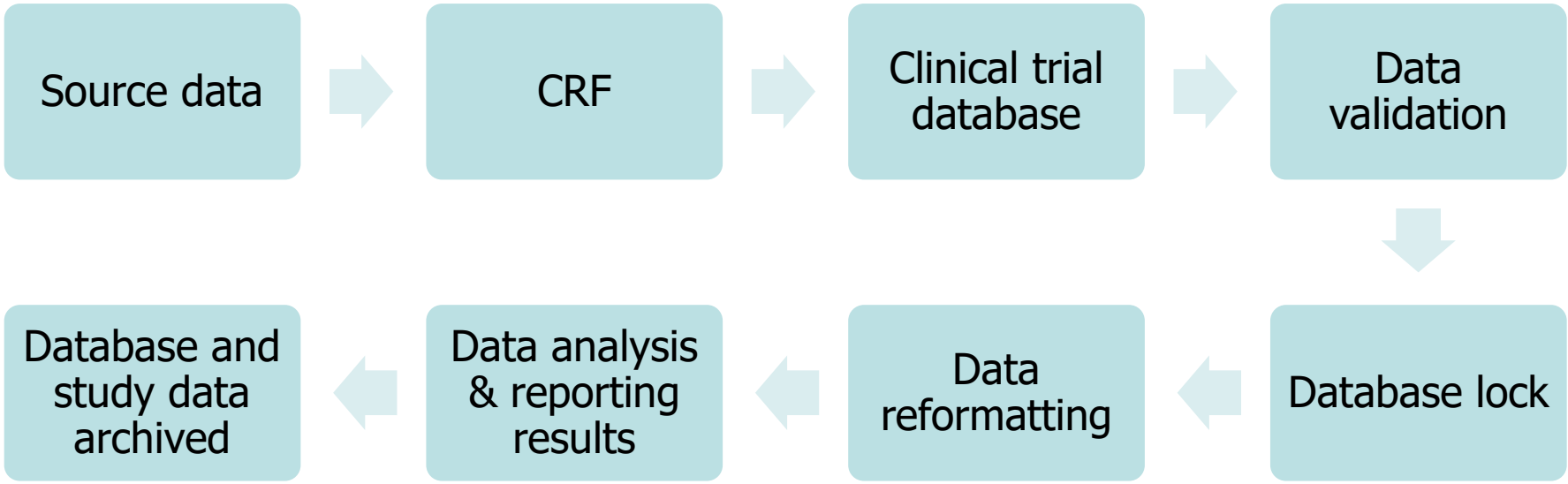
Process of Clinical Data Management



Guidelines and regulations

- Good Clinical Practice (GCP)
  - GCP 2.10 All clinical trial information should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation and verification.
- Good Documentation Practice (GDP)
  - "What is not documented is not done!"
  - Fundamental elements of data quality and data integrity "ALCOA"

ALCOA = 5 key attributes for good documentation

Attributable	• Clearly indicates who recorded the data or performed the activity • Signed/dated, passwords, userid,
Legible	• Possible to read or interpret the data after it is recorded • Permanent • Properly corrected if necessary
Contemporaneous	• Data must be recorded in the correct time frame along with the flow of events
Original	• Or certified copy • Data must be preserved in its unaltered state
Accurate	• Data must correctly reflect the action/observation made • Observations explained if not self-evident

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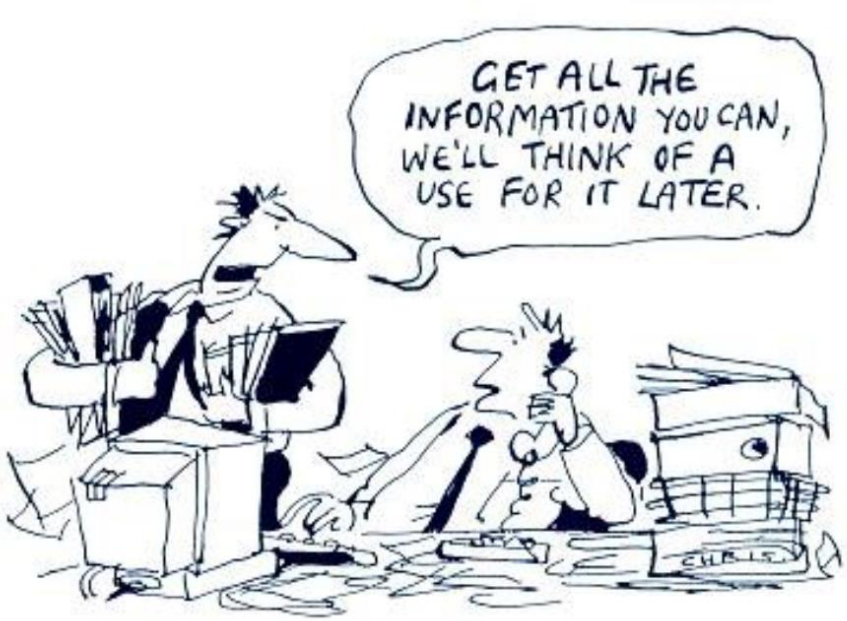
Source documents

"Source documentation is the beginning of a clean, verifiable audit trail."

Good Clinical Practice: A Question & Answer Reference Guide, May 2010



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Source documents

= original documents, data and records or certified copies of clinical findings and observations

- Records on which clinical observations are first recorded
- Roots of Good Documentation Principles
- Legally valid
- Contain source data
- Support the study's findings
- Signed and dated by person completing

Examples:

- Signed Informed Consent forms
- (electronic) patient medical records
- ADVOR worksheets
- EQ-5D questionnaires

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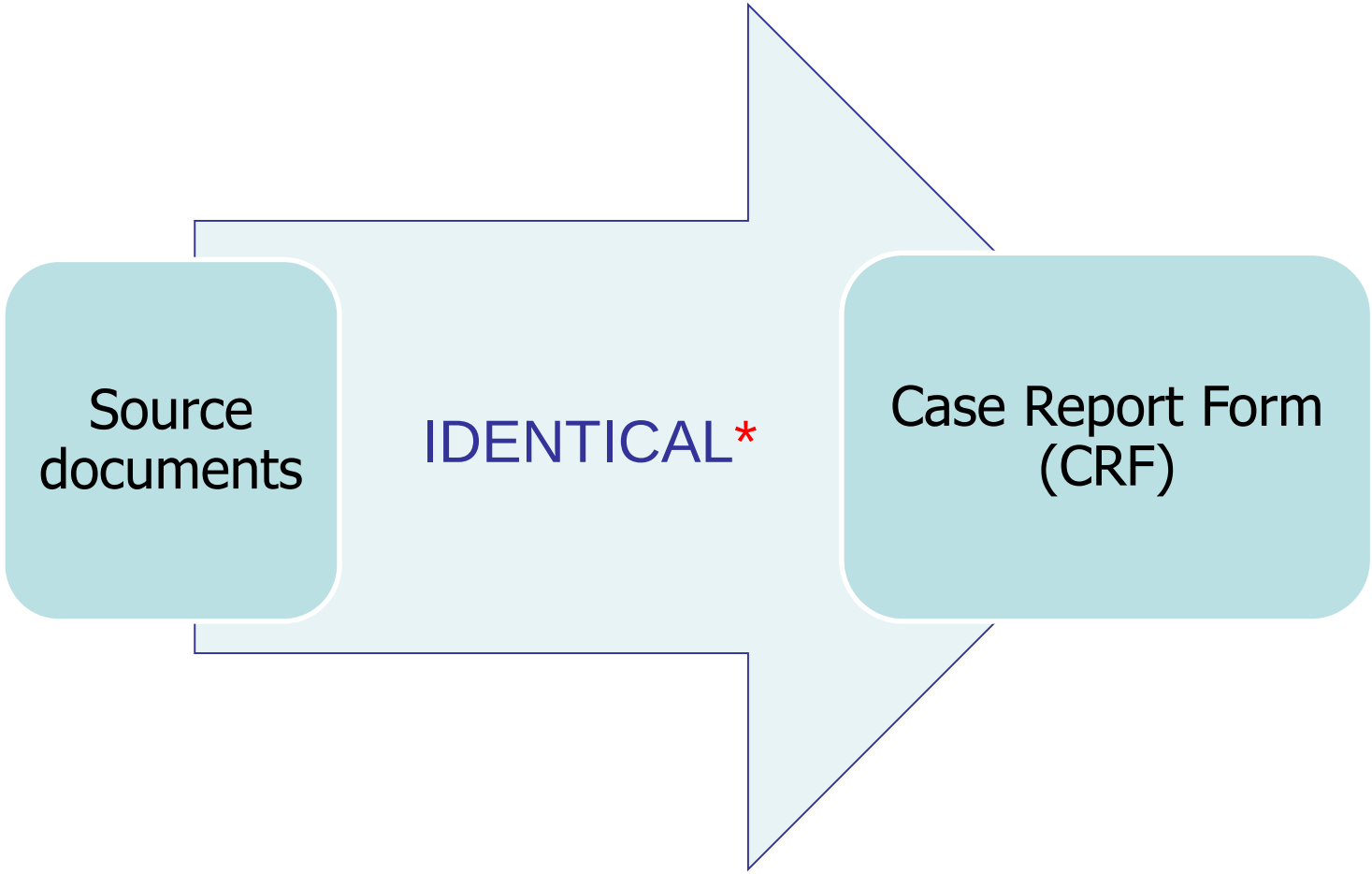
Source documents to CRF



* • Patient's personal data will be treated in compliance with all applicable laws and regulations
  • Data collected will be anonymized

Case Report Form (CRF)

= Paper or electronic document used in a clinical study
to record all protocol-required information of a subject

- Collects study data in a standardized format
  - **ONLY** data required by the protocol
  - Build according to protocol visit schedule
  - Allowing for efficient analysis
- In ADVOR: electronic/web interface (Castor EDC) - eCRF

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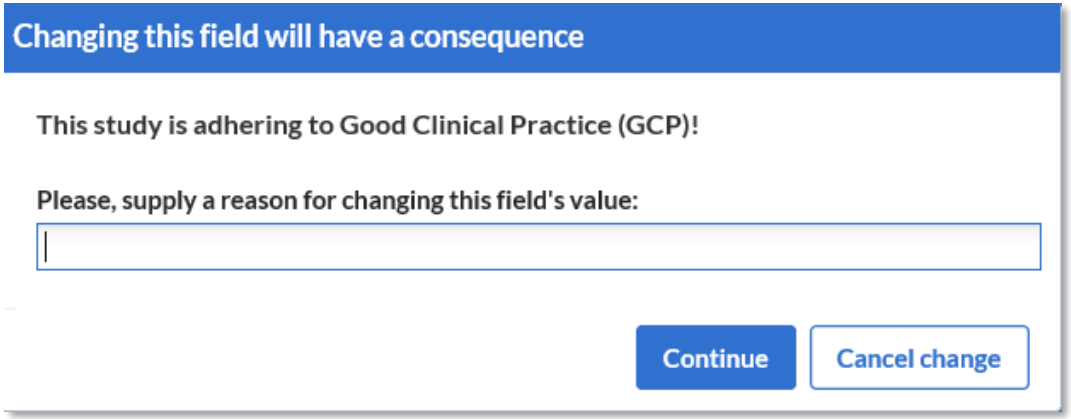
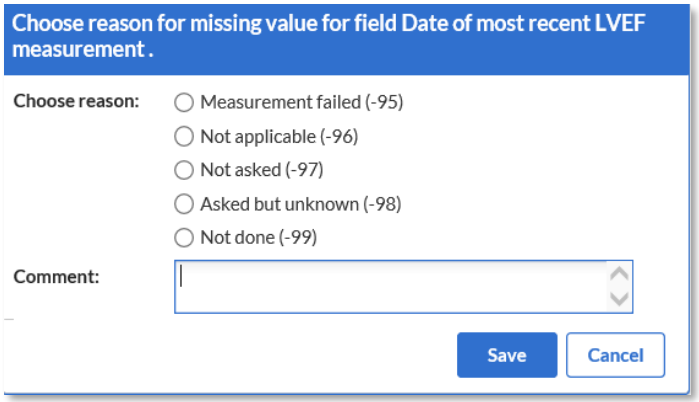
General CRF Completion Guidelines

- ALCOA-attributes
  - Timely (within 5 working days)
  - Data should be entered consistently
    - With the source documents
    - Across data fields
- Text entries in English
- Corrections should be properly made and explained



General CRF Completion Guidelines

- Unknown information should be indicated



- All missing and ambiguous data will be queried
  - Automated queries
  - Manual queries

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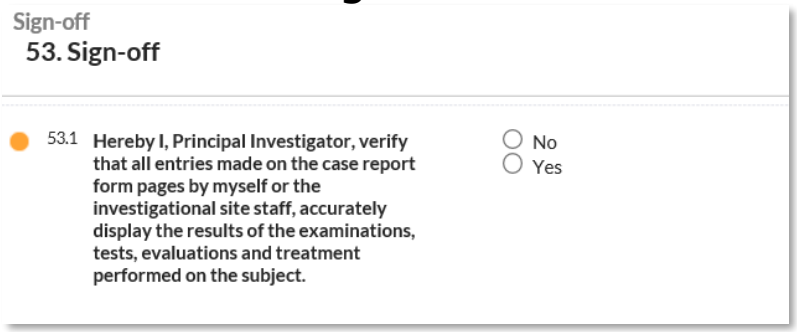
General CRF Completion Guidelines

- Only Investigators and/or designated qualified staff members can enter data
  - Different roles: PI and Study Coordinator

- Sign-off
  - PI
  - On request of the ADVOR team
  - After all CRF pages of the subject are complete and reviewed by the monitor and CTU data manager



Data management systems

Presenter: Liesbet Van Brussel

ONLINE RANDOMISATION

ADVOR

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Background

- ALEA Data Management system
- Build/Maintenance by CTCM
- Used for online randomisation
- Web-based application
- Works on any operating system.

https://prod.tenalea.net/ctcm/dm/

System access

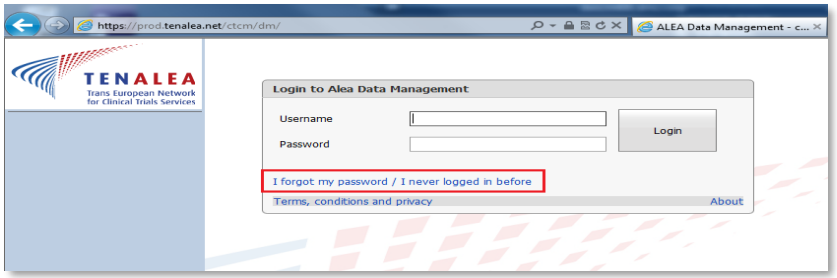
Site delegation and responsibility log

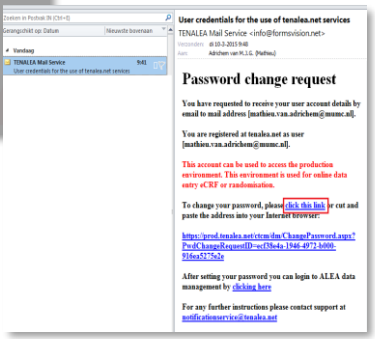
Study training fulfilled (initiation visit)

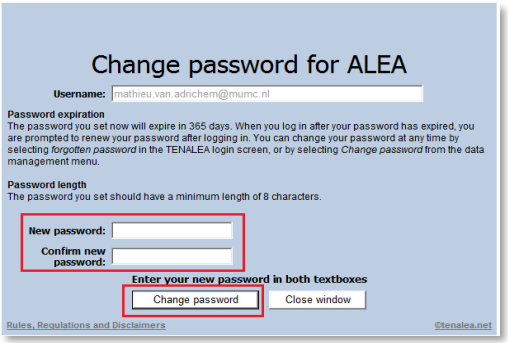
Invitation email link + manual sent by CTCM team

Enter your email address – Email from TENALEA "password change request"

Set and confirm password

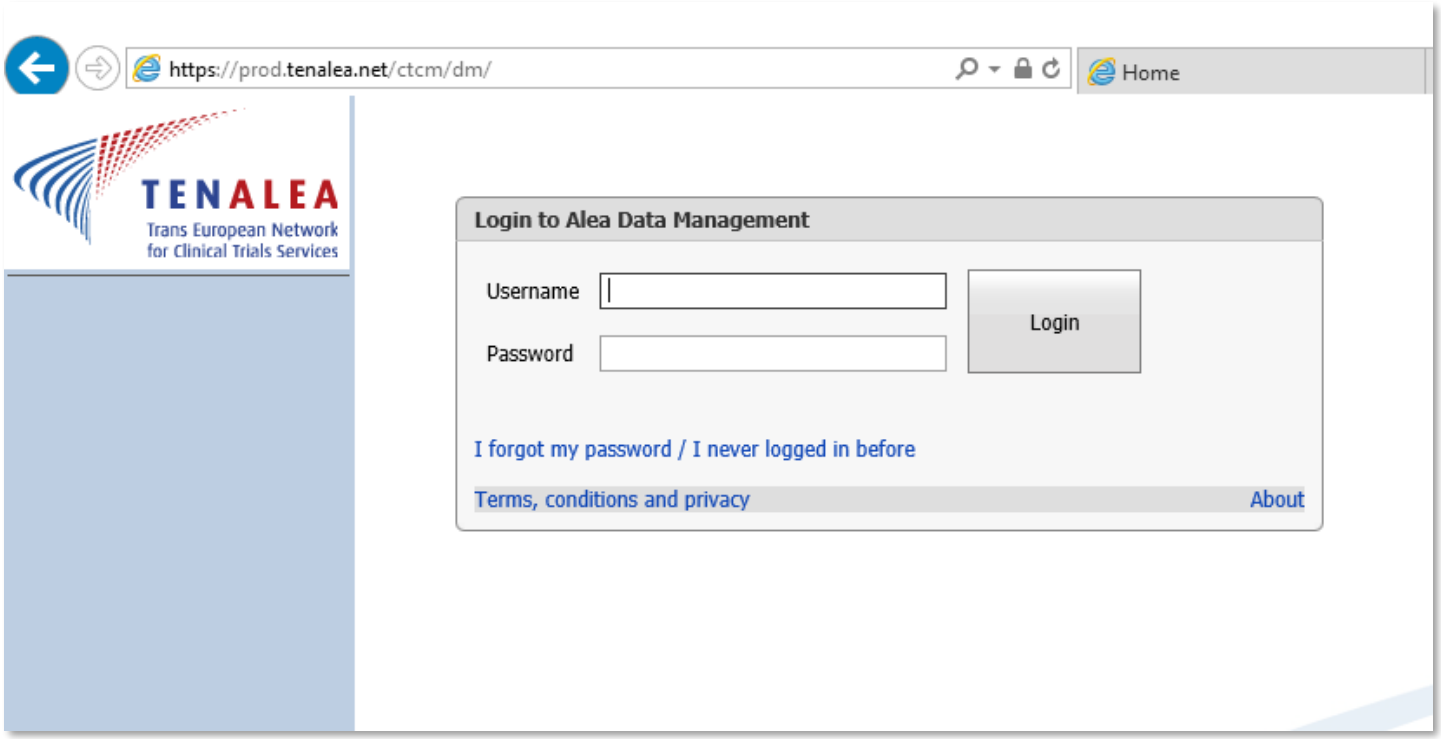




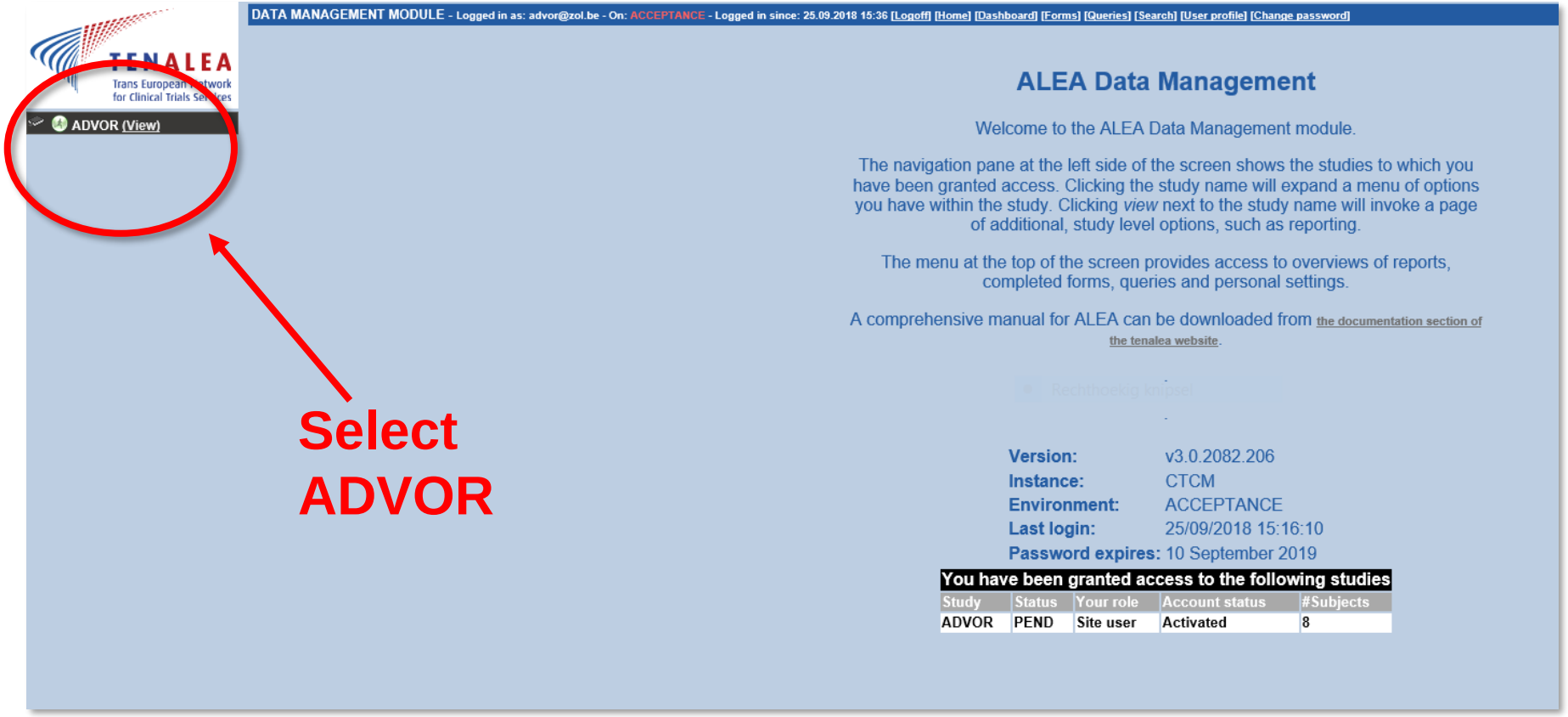


Log-in

- Server (data storage location) = CTCM
- Email address
- Password



Randomisation process



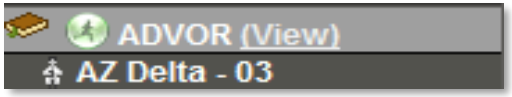
Randomisation process

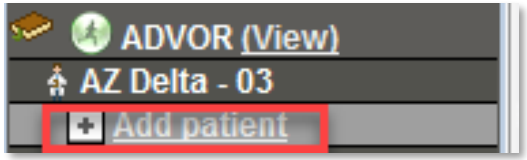
Select ADVOR

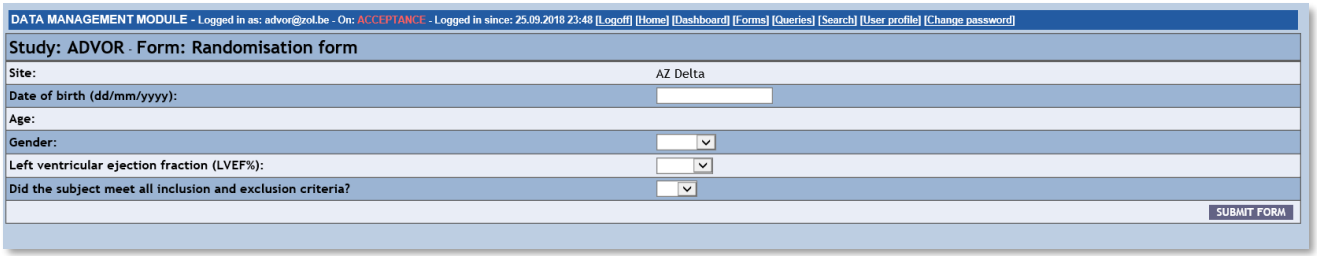
Your site becomes visible

"Add patient"

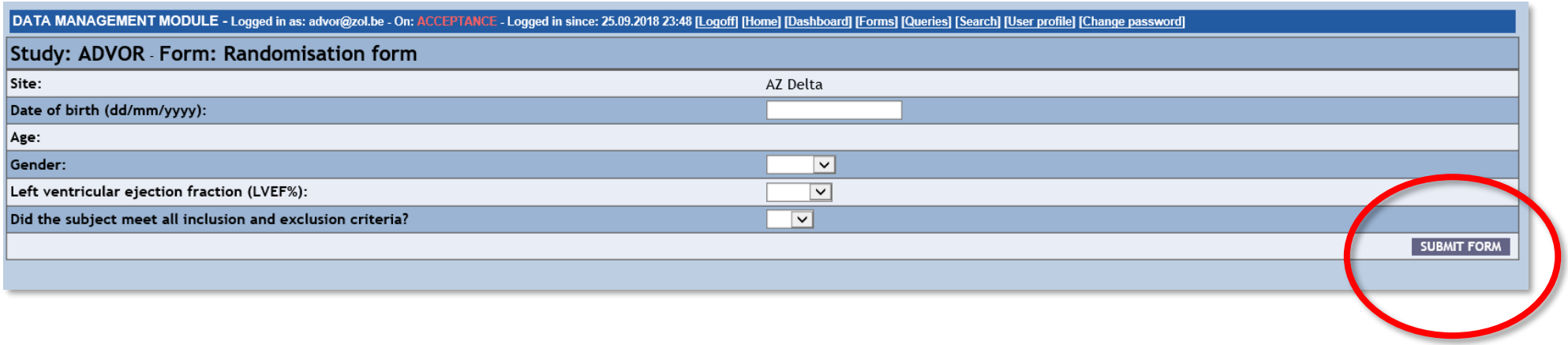
Randomisation form







Randomisation form



- Site: completed automatically
- Date of birth
- Age
- Gender
- LVEF%: =< 40% or >40%
- Inclusion/exclusion criteria?

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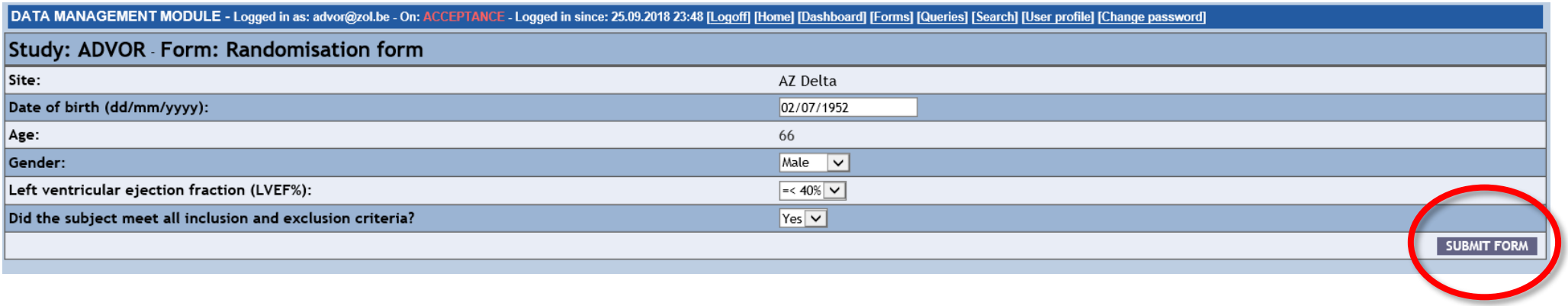
Randomisation form


DATA MANAGEMENT MODULE - Logged in as: advor@zol.be - On: ACCEPTANCE - Logged in since: 25.09.2018 23:48 [Logoff] [Home] [Dashboard] [Forms] [Queries] [Search] [User profile] [Change password]

Study: ADVOR - Form: Randomisation form

Site:	AZ Delta
Date of birth (dd/mm/yyyy):	02/07/1952
Age:	66
Gender:	Male
Left ventricular ejection fraction (LVEF%):	=< 40%
Did the subject meet all inclusion and exclusion criteria?	Yes

SUBMIT FORM

Randomisation form

DATA MANAGEMENT MODULE - Logged in as: advor@zol.be - On: ACCEPTANCE - Logged in since: 25.09.2018 23:48 [Logoff] [Home] [Dashboard] [Forms] [Queries] [Search] [User profile] [Change password]

Form Randomisation form has been submitted.

The patient has been assigned subject number 03RAND003

Questions	Answers
Site:	AZ Delta
Date of birth (dd/mm/yyyy):	02/07/1952
Age:	66
Gender:	Male
Left ventricular ejection fraction (LVEF%):	=< 40%
Did the subject meet all inclusion and exclusion criteria?	Yes
Randomisation: Kit number	The patient has been allocated patient kit: 0060

Subject number in IXRS = format xxRANDyyy

= RANDOMISATION NUMBER in eCRF

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Randomisation notification

- Randomisation e-mail notification to advor-team + to all users of that site.

Notification randomisation ADVOR blinded

Form completed : Randomisation form
Form completed by : Test Account
Form completion date: 26-9-2018 at 0:22:1

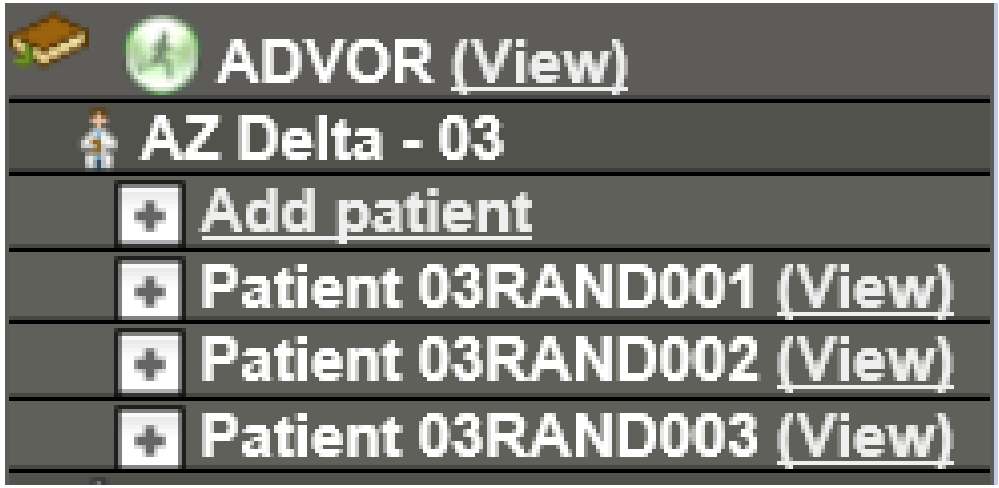
1	Site:	AZ Delta
2	Date of birth:	02/07/1952
3	Age:	66
4	Gender:	Male
5	Left ventricular ejection fraction (LVEF%):	=< 40%
6	Did the subject meet all inclusion and exclusion criteria?	Yes

Patient has been assigned patient number: 03RAND003

Allocated patient pack: 0060

Randomisation overview

- Overview of all randomisated patients for your site



Randomisation error

- In case an error has been made when randomising a subject, please contact CTCM during office hours:
  - By email: datamanagement.ctcm@mumc.nl
  - By phone: +31 (0) 43-387 20 40

CASTOR EDC

ADVOR

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Background

- CASTOR Electronic Data Capture (EDC) system
- Web-based application
- Capture high quality data with audit trail
- Electronic query management
- Electronic data monitoring
- Works with the three latest versions of Google Chrome, Mozilla Firefox, Safari and Internet Explorer
- Works on any operating system.

! Will not be used for randomization ! → ALEA IWRS system

https://data.castoredc.com/

System access

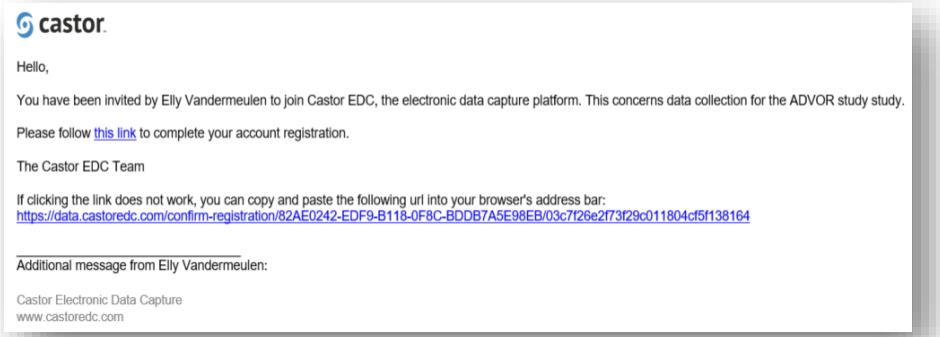
Site delegation and responsibility log

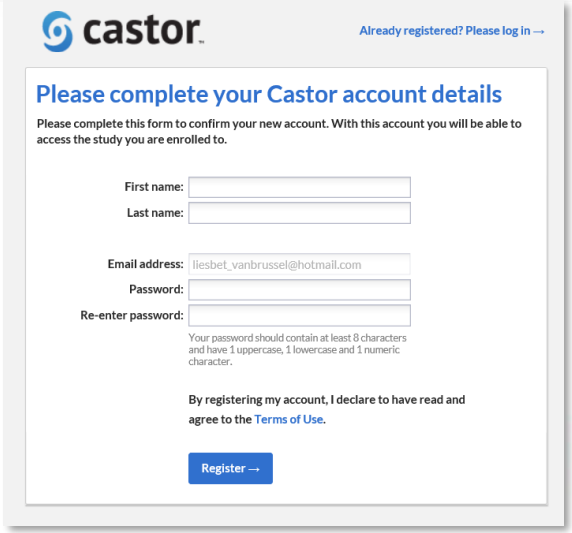
Study training fulfilled (initiation visit)

Invitation link sent by ADVOR study team

Register your Castor account

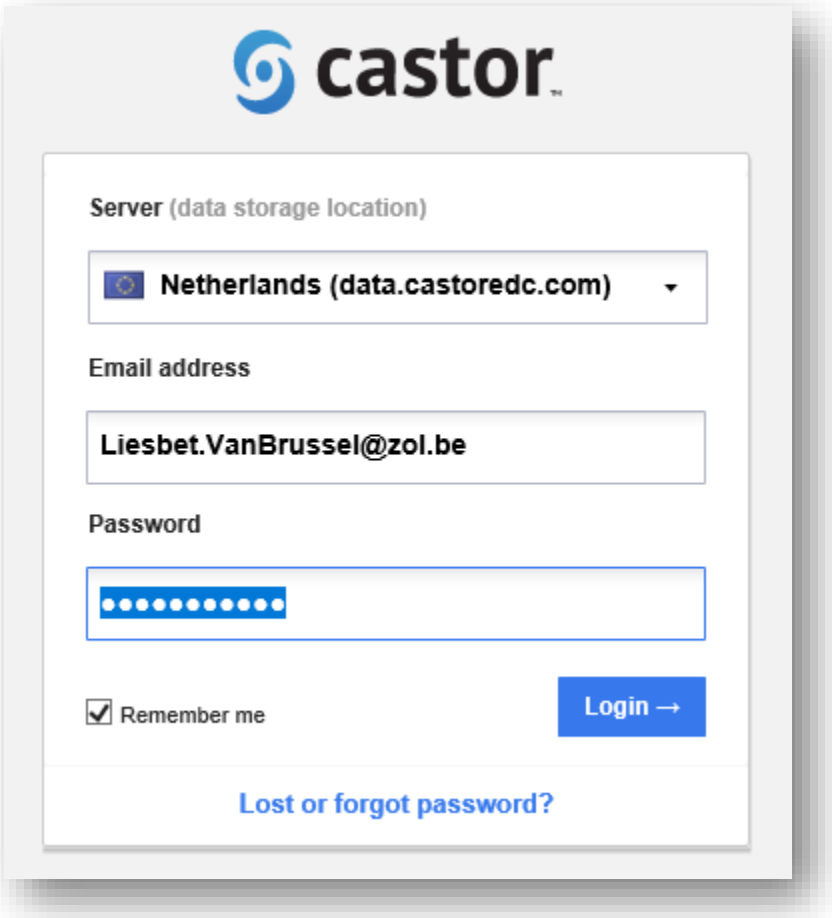
Confirm your registration



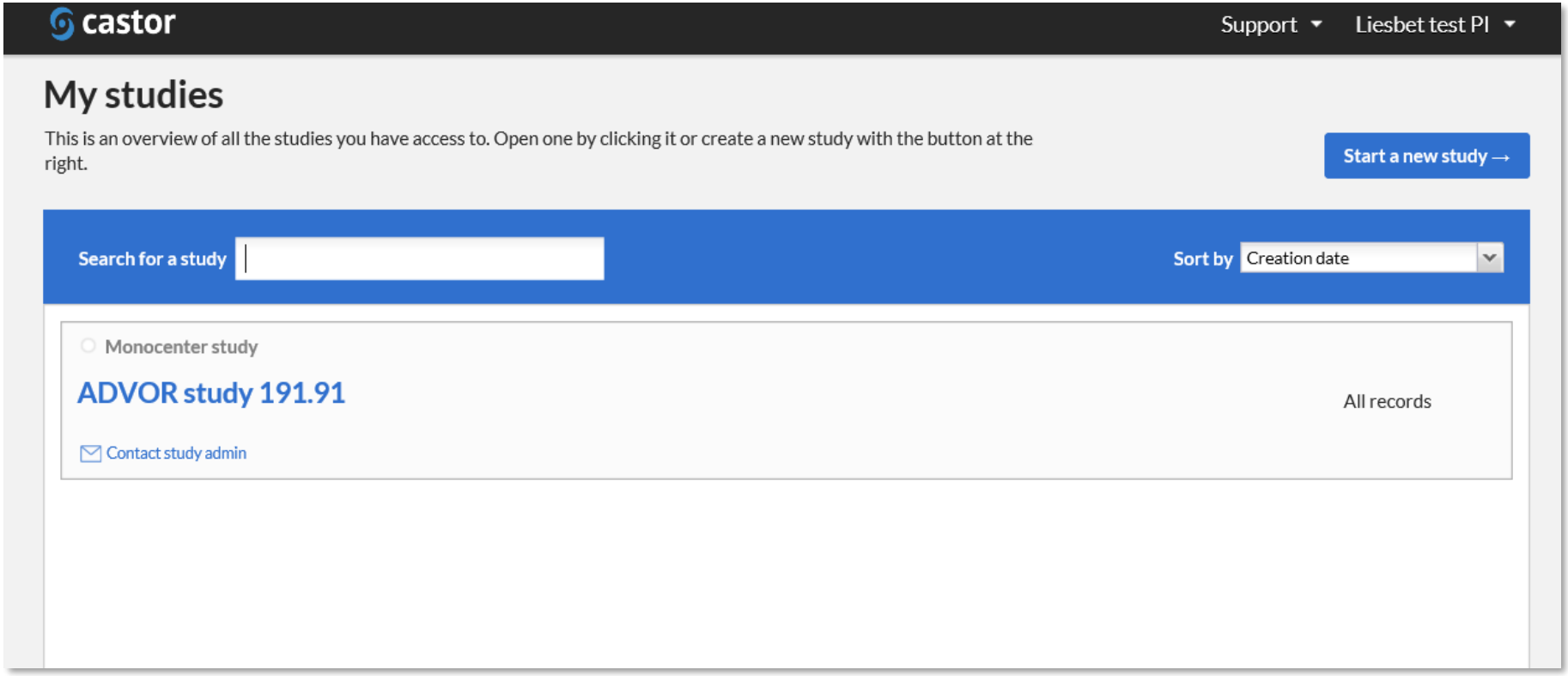


Log-in

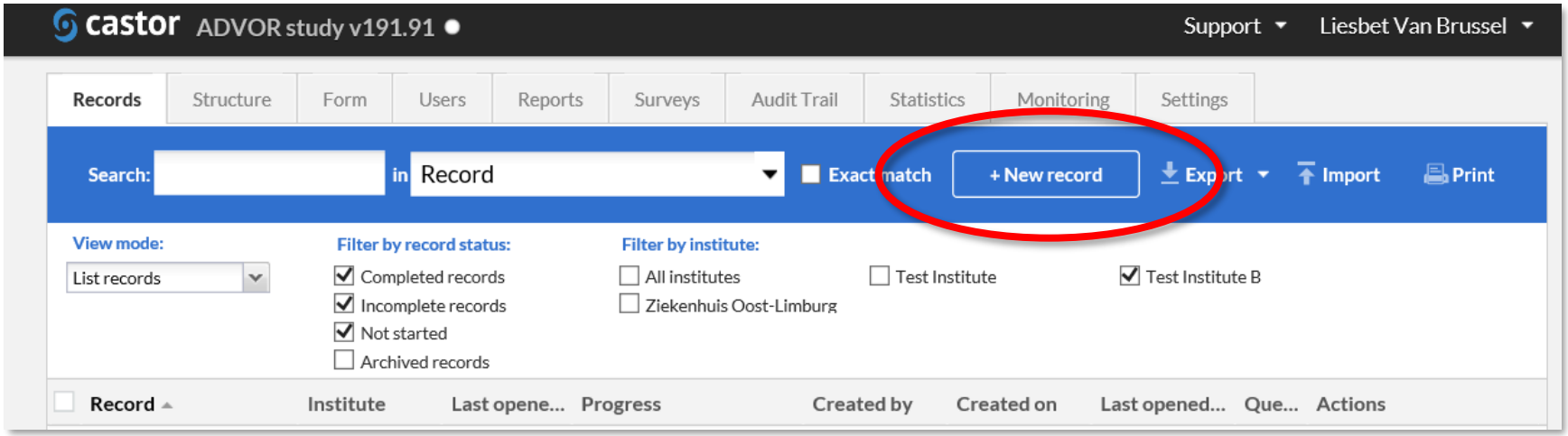
- Server (data storage location) = Netherlands
- Email address
- Password



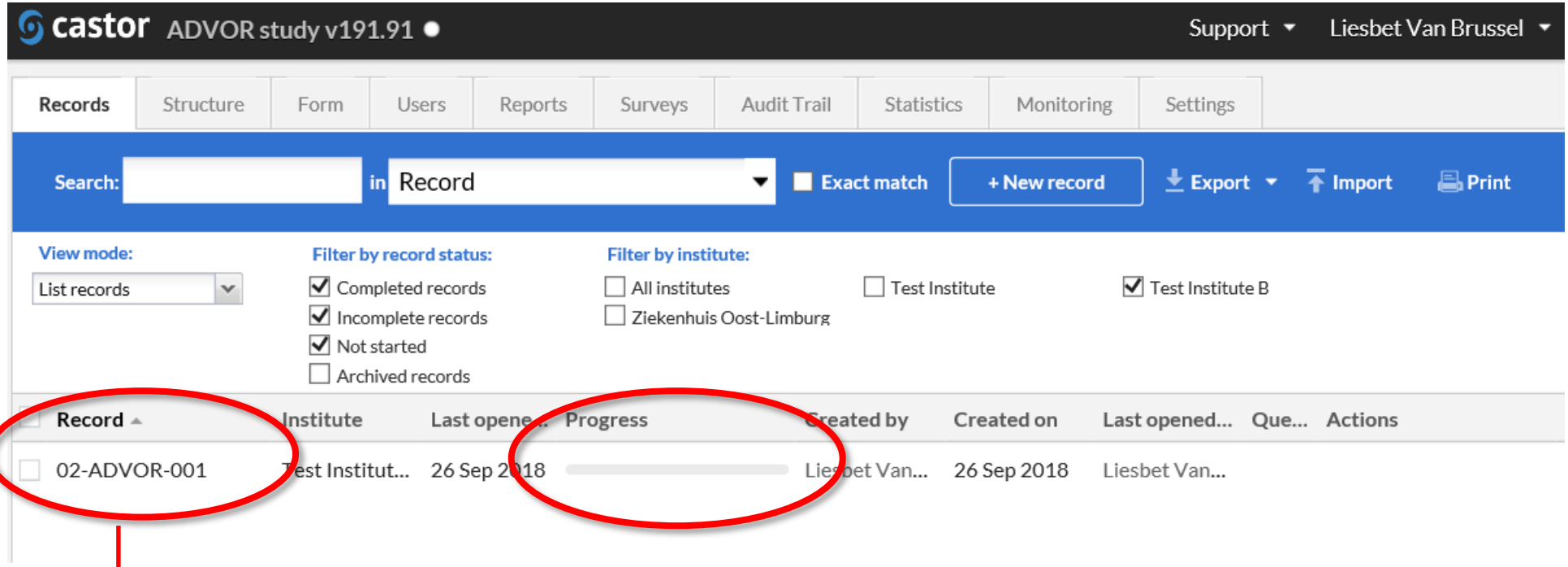
Accessing ADVOR



Add new subject

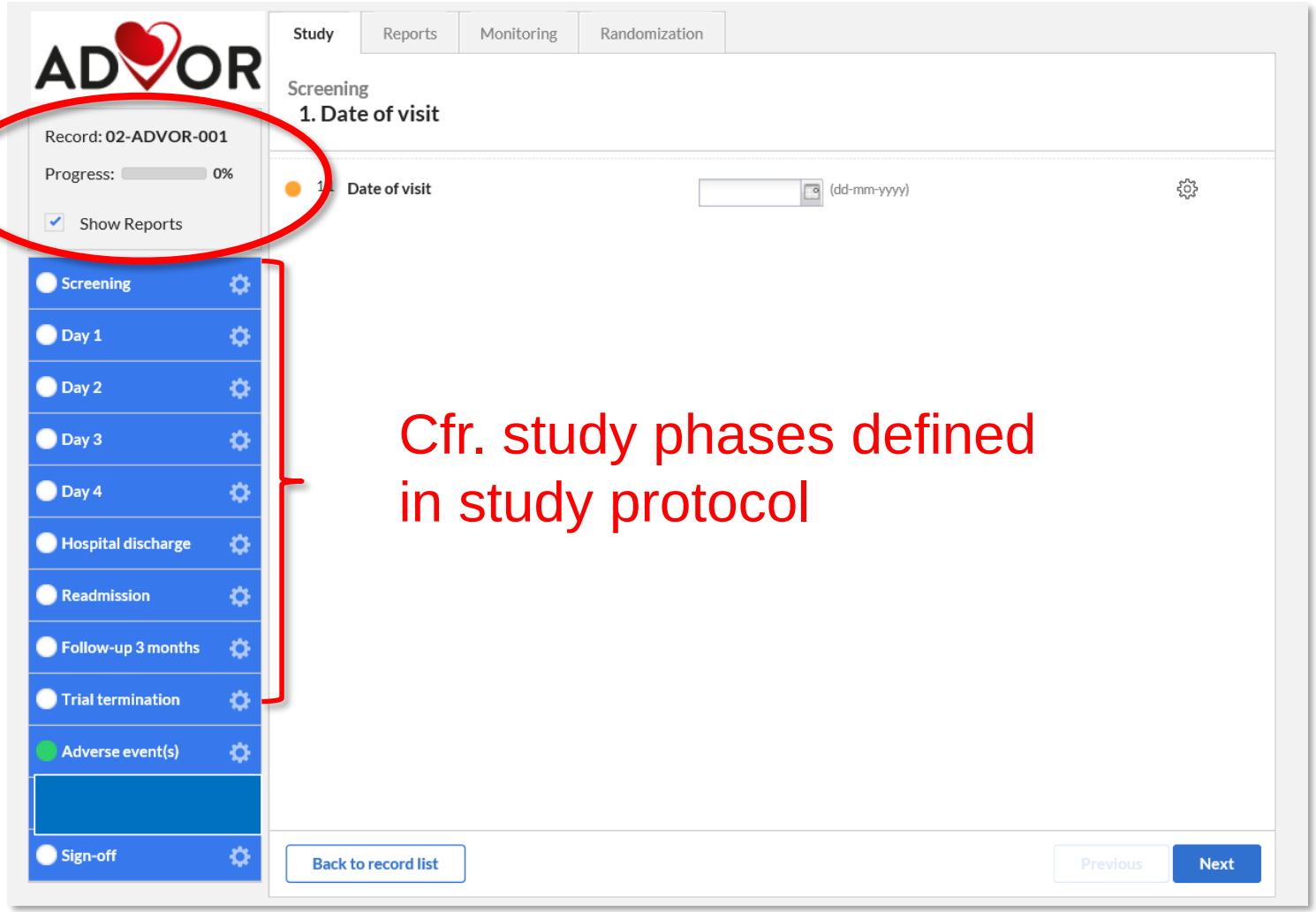


Add new subject



= **subject number in eCRF**
automatically completed

Entering study data



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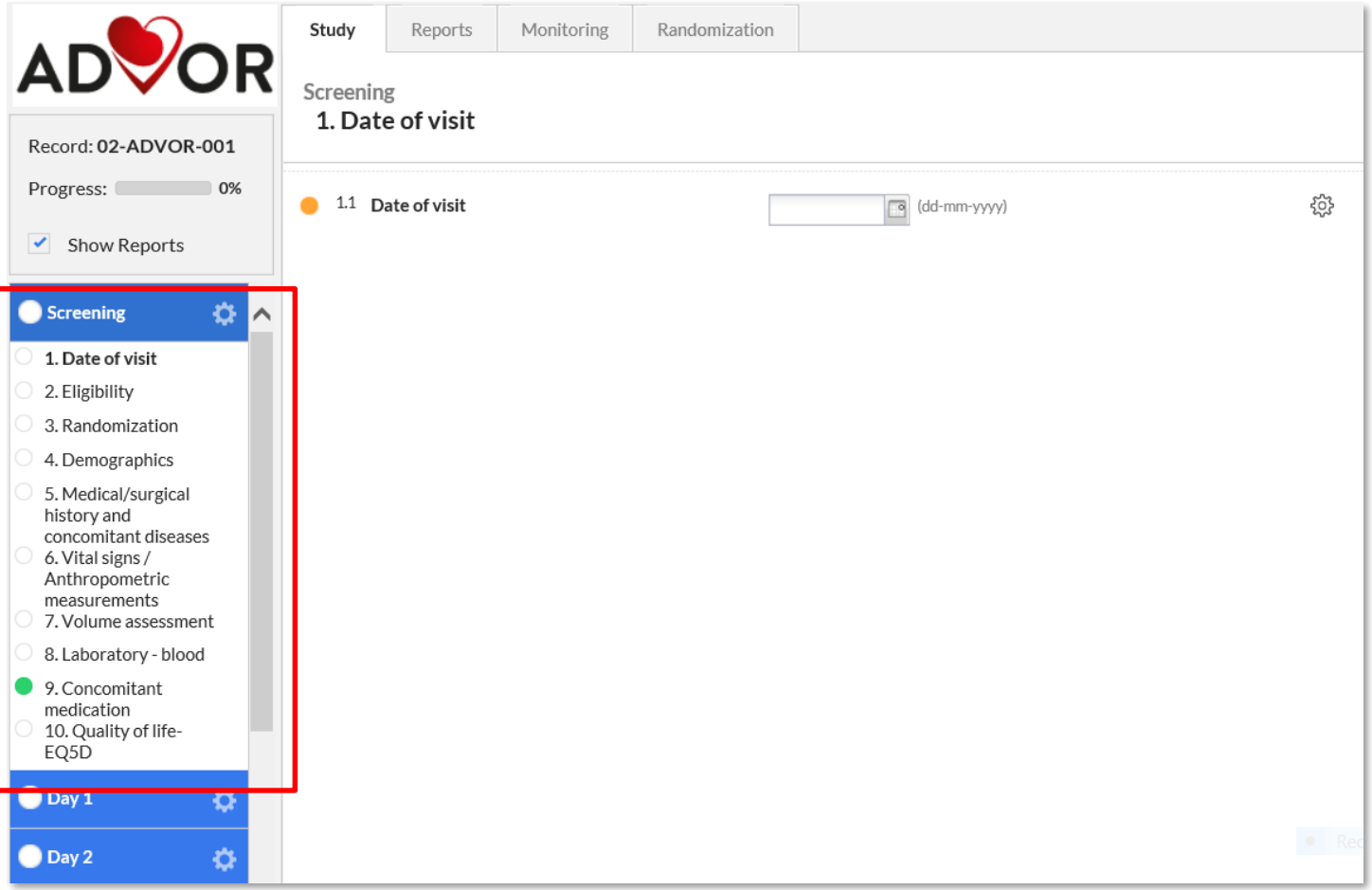
Entering study data



ADVOR

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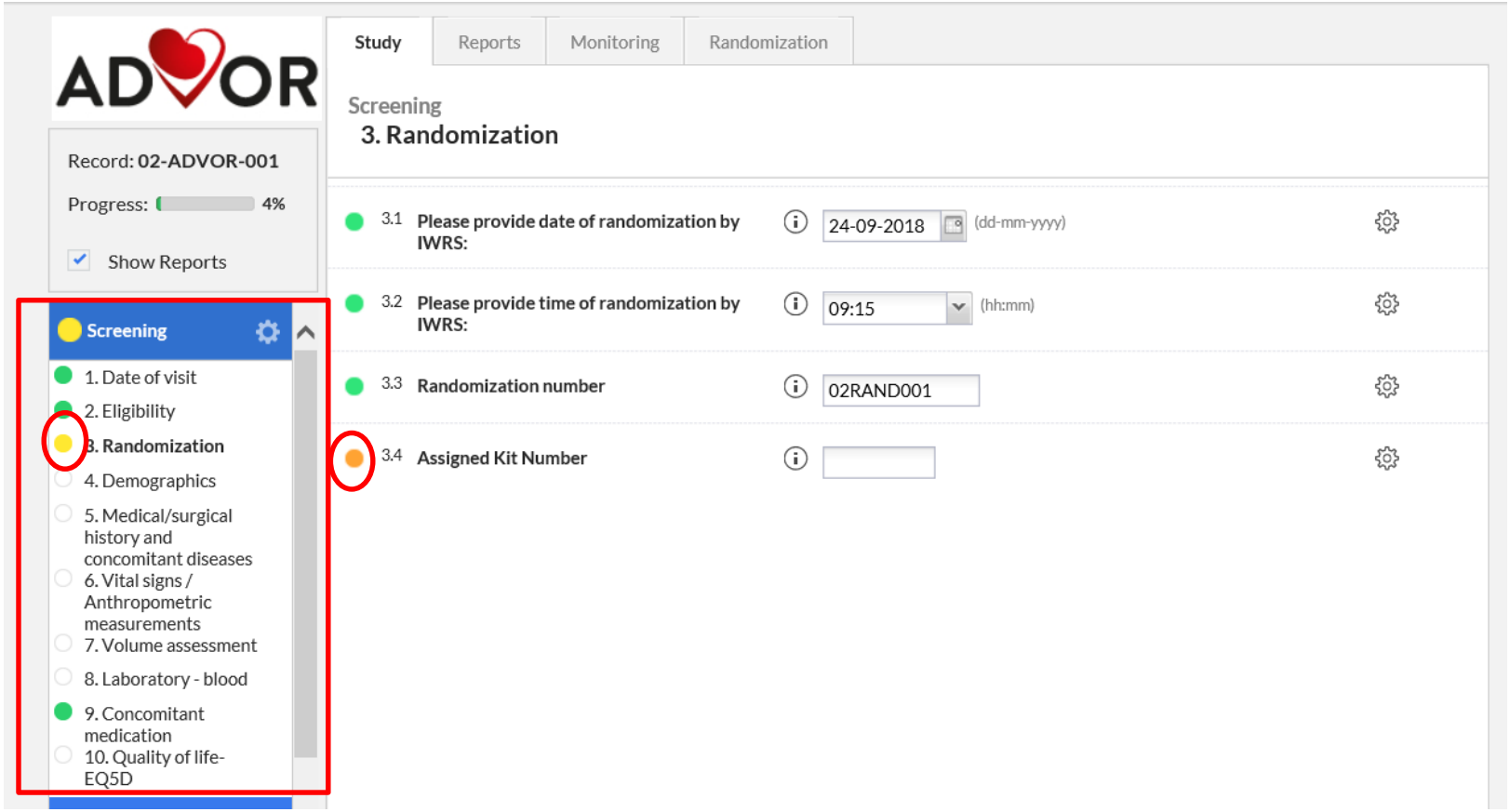
Entering study data



ADVOR

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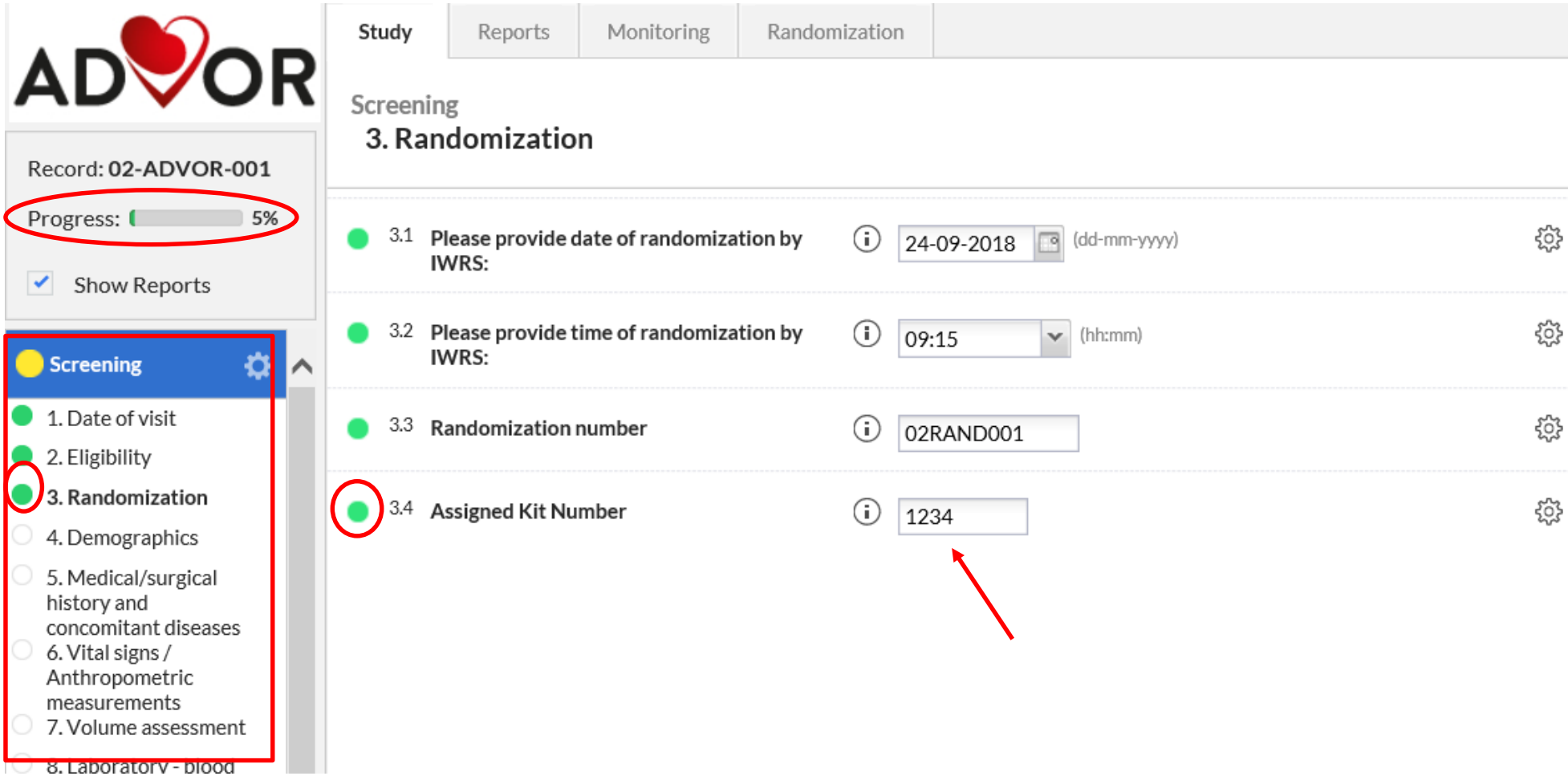
Entering study data



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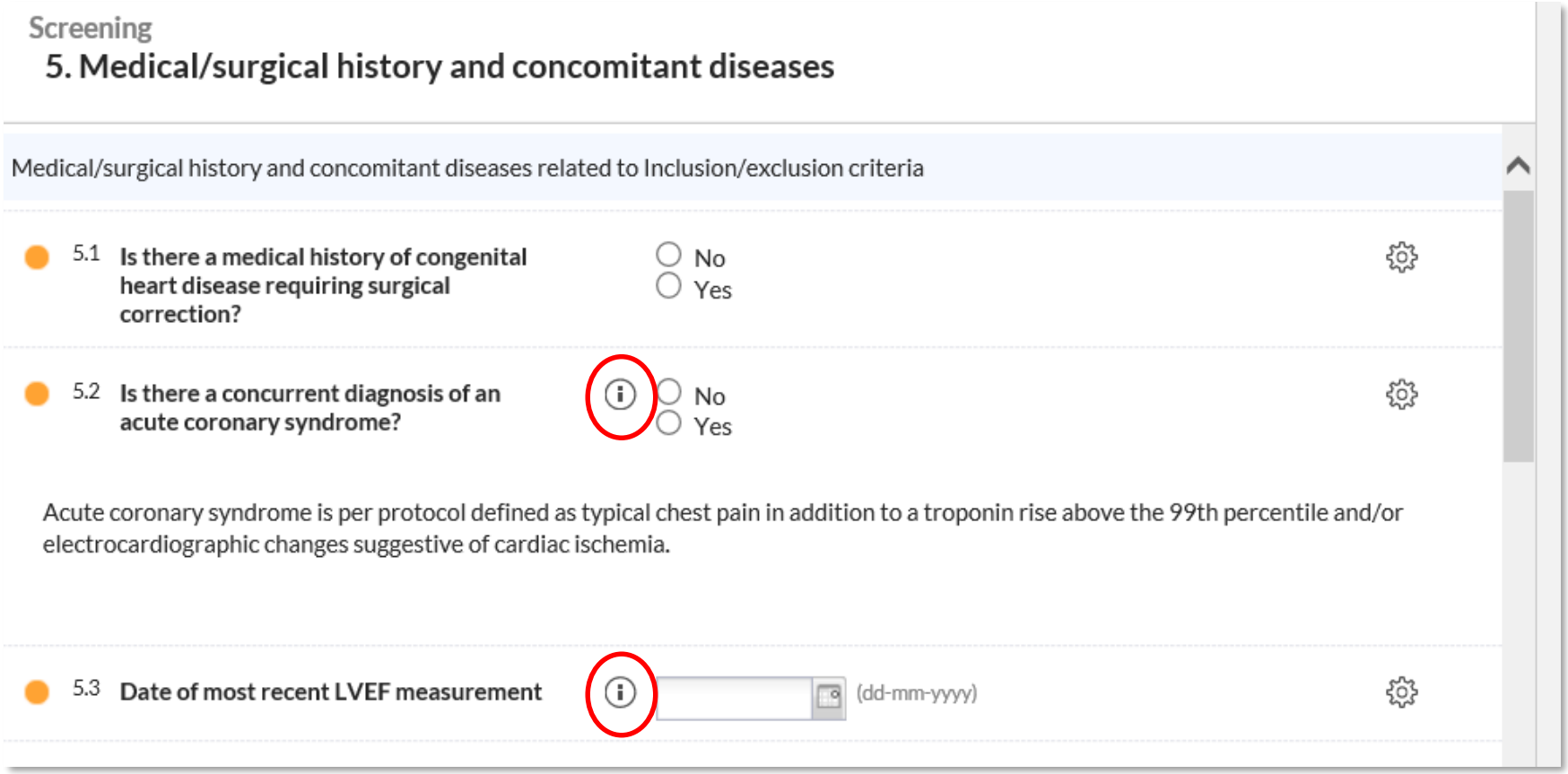
Help!? – Additional information



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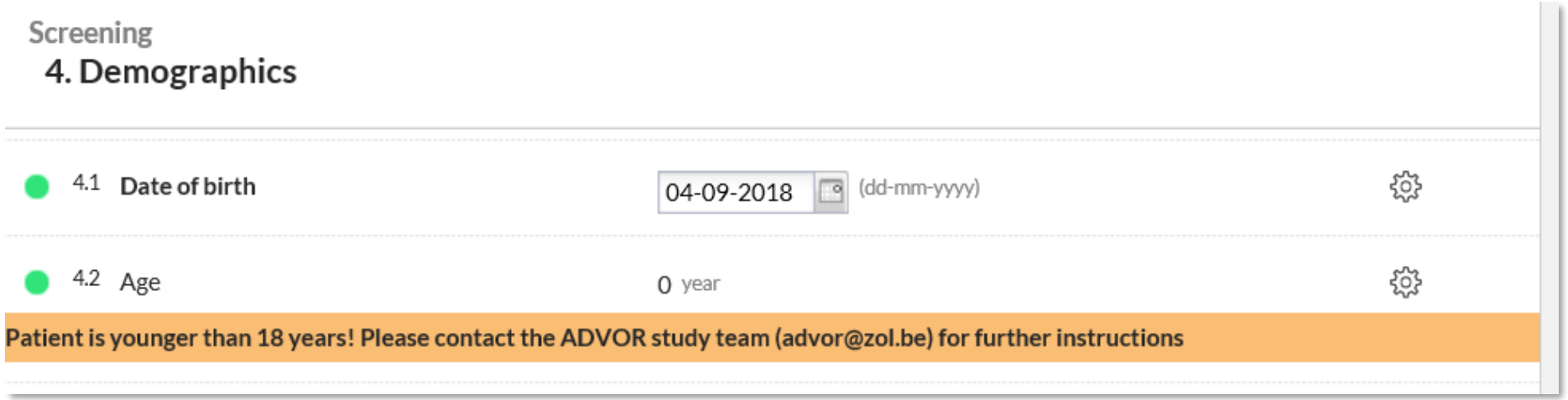
Help!? – warnings and messages



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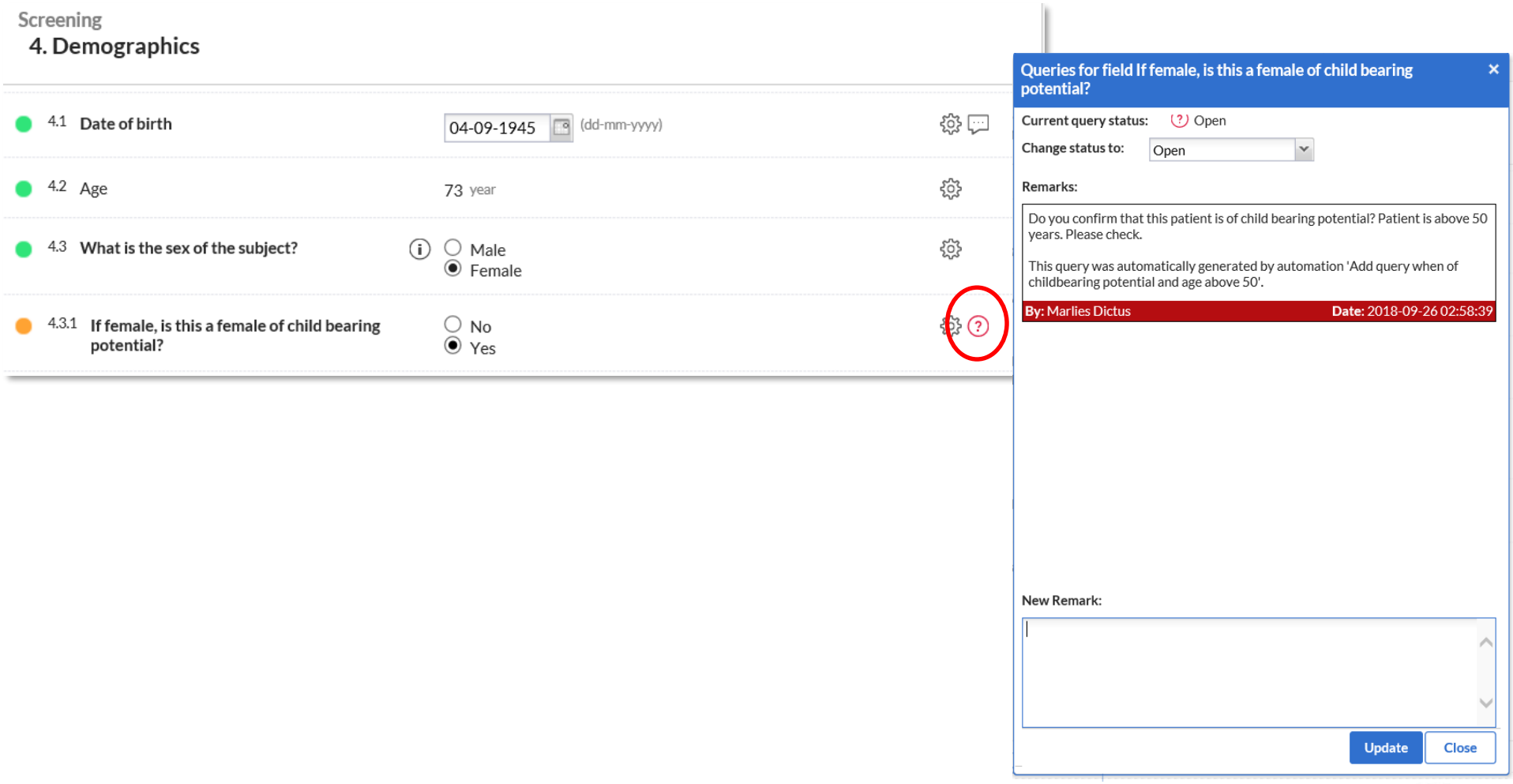
Help!?

- Manual
  - CRF Completion guidelines
- ADVOR team
  - advor@zol.be
  - 089/ 32 73 25

Data quality – auto queries



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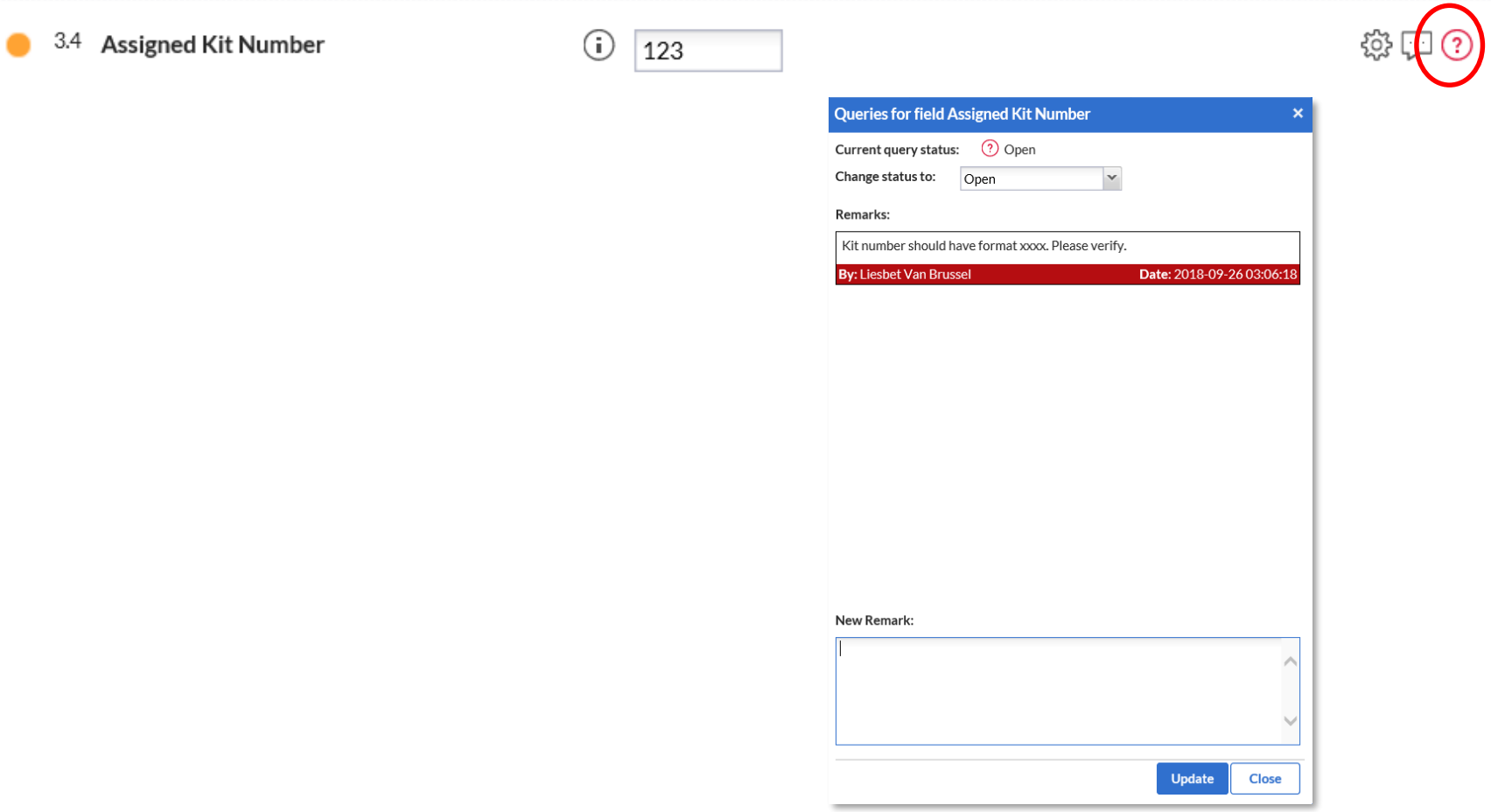
Data quality – manual queries



Questions?

Link demo data management systems

https://acc.tenalea.net/ctcm/dm/

https://data.castoredc.com

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Agenda

13:30	• Introduction KCE & ZOL AV
13:45	• Study and protocol presentation
15:15	• Data management
15:45	• Coffee break
16:00	• Study practicalities
16:25	• EDGE
16:40	• Q&A

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Study practicalities

- Study timelines
- ADVOR manuals/guidelines/forms

Study timelines

Presenter: Marlies Dictus

Current status

- Central EC approval
- Collection of site start-up documents
- Finalization of contracts

- First site initiation visits as of October 2018 (starting at ZOL Genk)

Expected start of accrual: October 2018

Participating centers

23 hospitals in Belgium

- Flanders
- Brussels
- Wallonia

(academic and non-academic)

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Study timelines

ADVOR manuals/guidelines/forms

Presenter: Marlies Dictus

Overview manuals and guidelines

Documentation	Content
Manual Of Operations	Practical guidelines for study start-up and conduct
Safety guidelines	Guidelines on handling of safety data
CRF completion guidelines	Guidelines on Castor EDC and eCRF completion
Lab manual (sub-study)	Guidance on the sub-study practicalities

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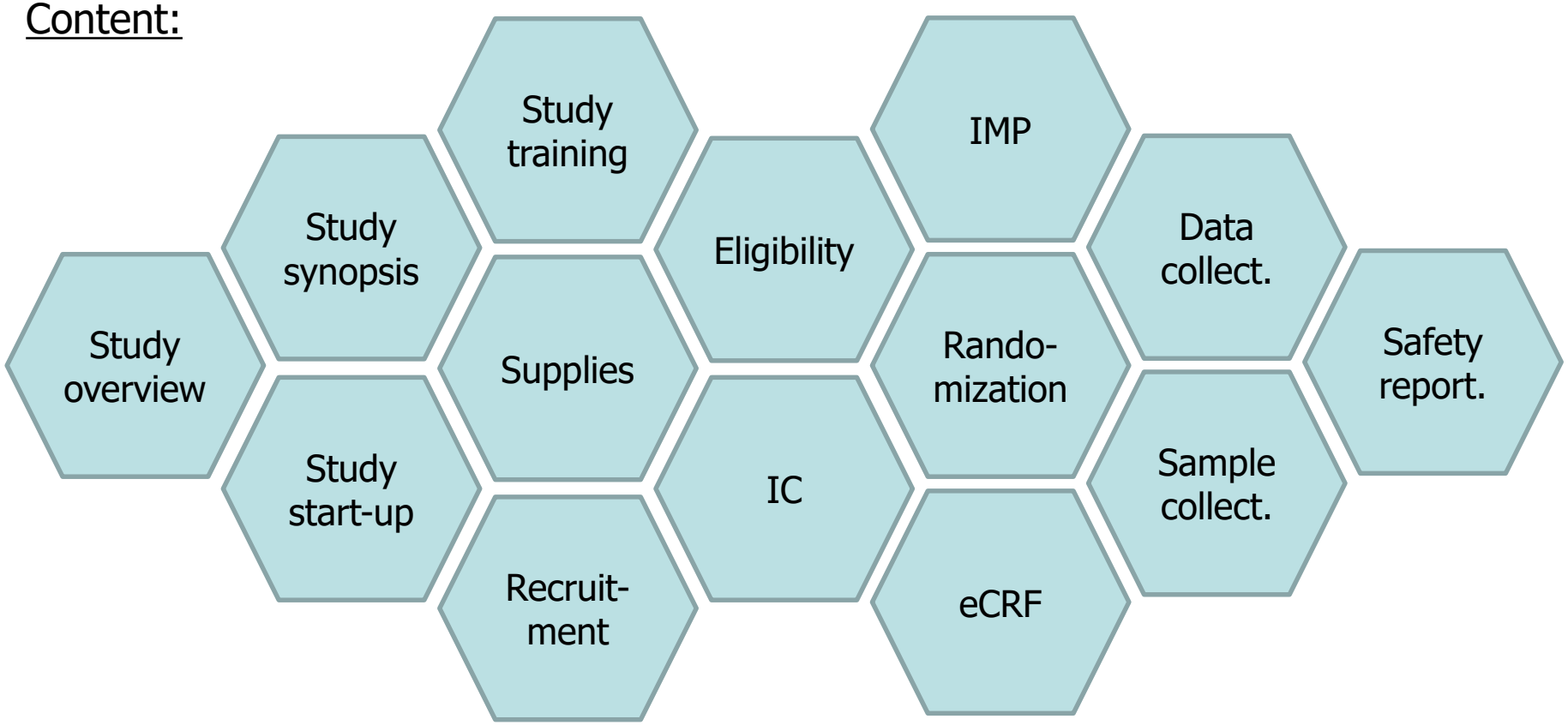
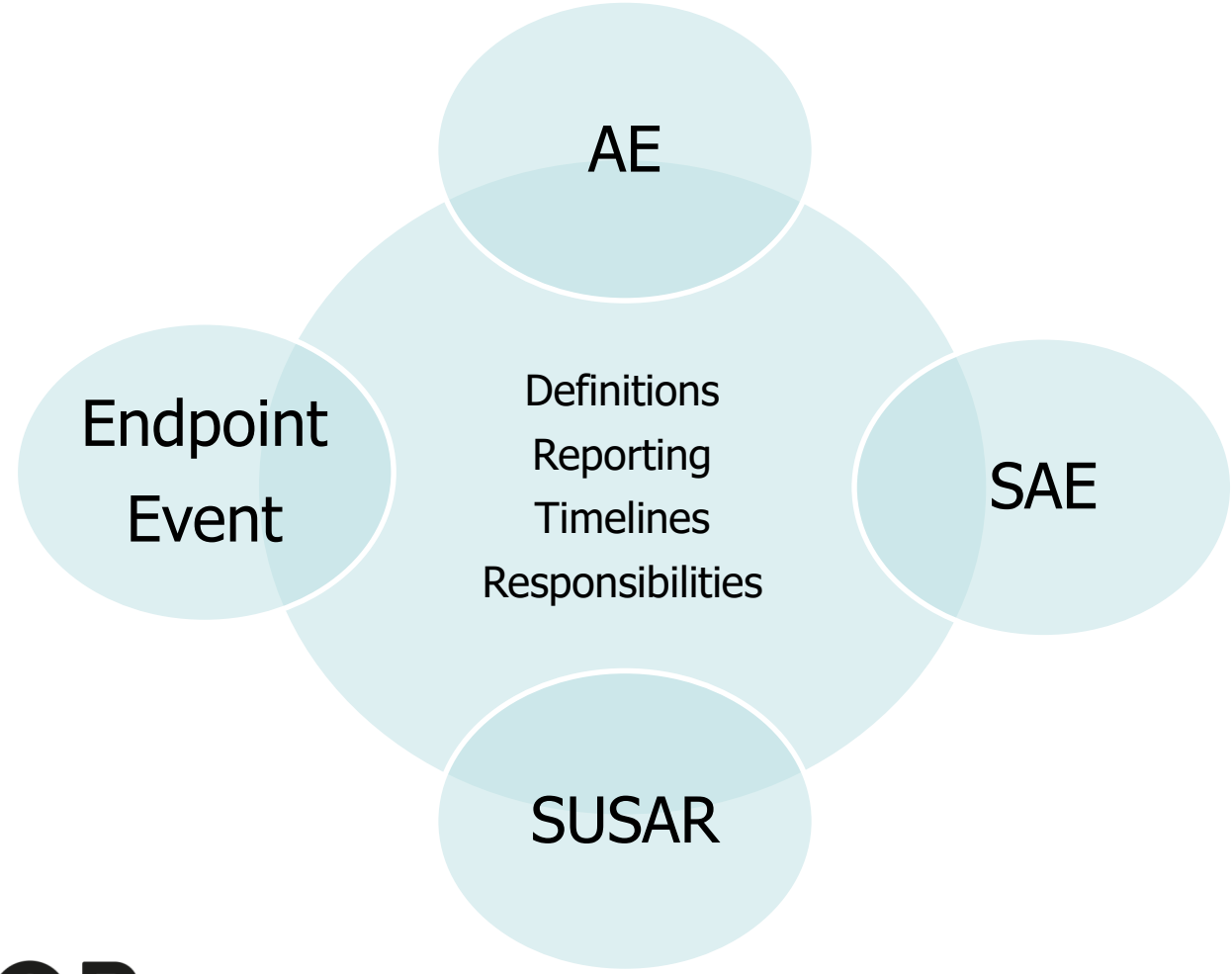
Manual Of Operations (MOO)

Content:



Safety guidelines



CRF completion guidelines

General guidelines

CASTOR EDC

Completion schedule

Study - specific guidelines

Lab manual (sub-study)

! Only applicable if your site is participating to the laboratory sub-study !

- Contact information
- Supplies
- Schedule
- Sample processing
- Shipping procedure
- Resupply

Overview study specific forms and documents

Documentation	Content
Inclusion and exclusion form	Checklist of inclusion and exclusion criteria
Investigator worksheet	Daily checklist for investigator and documentation of volume assessment
Study coordinator worksheet	Work document for Study Coordinator on all assessments that should be performed/documented for the patient
Patient card	Card patient always needs to carry to inform in case of urgency that he/she is participating in the study

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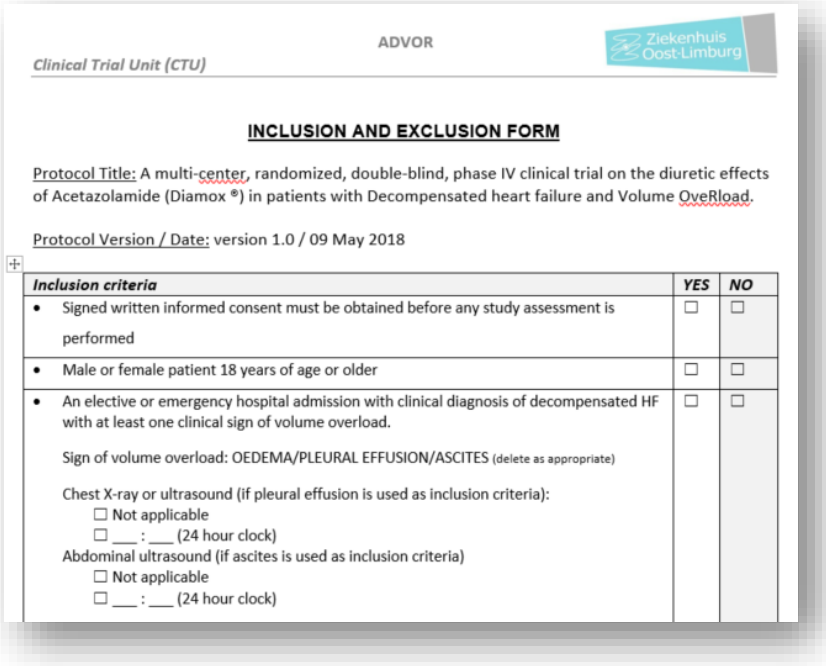
Inclusion and exclusion form

- Completed for each screened patient BEFORE randomization of the patient
- Signed and dated by Principal/Sub- Investigator to confirm eligibility of the patient



ADVOR

Clinical Trial Unit (CTU)

Ziekenhuis Oost-Limburg

INCLUSION AND EXCLUSION FORM

Protocol Title: A multi-center, randomized, double-blind, phase IV clinical trial on the diuretic effects of Acetazolamide (Diamox ®) in patients with Decompensated heart failure and Volume OveRload.

Protocol Version / Date: version 1.0 / 09 May 2018

Inclusion criteria	*YES*	*NO*
• Signed written informed consent must be obtained before any study assessment is performed	☐	☐
• Male or female patient 18 years of age or older	☐	☐
• An elective or emergency hospital admission with clinical diagnosis of decompensated HF with at least one clinical sign of volume overload. Sign of volume overload: OEDEMA/PLEURAL EFFUSION/ASCITES (delete as appropriate) Chest X-ray or ultrasound (if pleural effusion is used as inclusion criteria): ☐ Not applicable ☐ ___ : ___ (24 hour clock) Abdominal ultrasound (if ascites is used as inclusion criteria) ☐ Not applicable ☐ ___ : ___ (24 hour clock)	☐	☐

- ALL inclusion criteria should be 'YES'
- NONE of the exclusion criteria should be 'YES'

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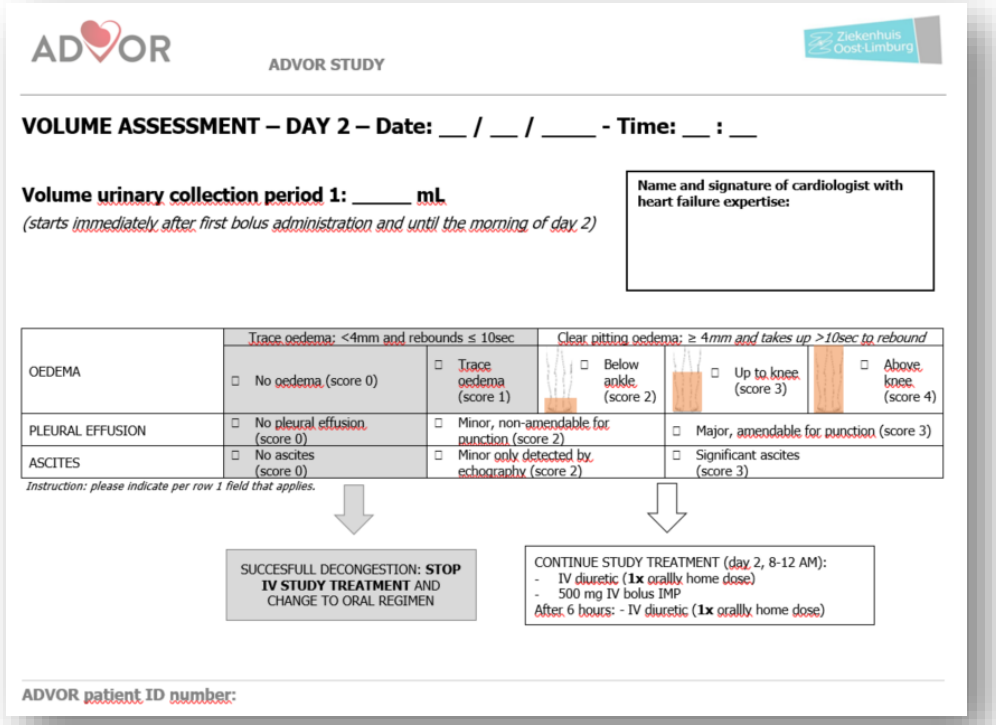
Investigator worksheet

- Work document for the investigator: daily action list – volume assessment
- Volume assessment = MANDATORY (to be signed off)
- Background therapy information sheet



ADVOR STUDY

VOLUME ASSESSMENT – DAY 2 – Date: __ / __ / ____ - Time: __ : __

Volume urinary collection period 1: _____ mL

(starts immediately after first bolus administration and until the morning of day 2)

Name and signature of cardiologist with heart failure expertise:

	Trace oedema: <4mm and rebounds ≤ 10sec		Clear pitting oedema: ≥ 4mm and takes up >10sec to rebound		
OEDEMA	☐ No oedema (score 0)	☐ Trace oedema (score 1)	☐ Below ankle (score 2)	☐ Up to knee (score 3)	☐ Above knee (score 4)
PLEURAL EFFUSION	☐ No pleural effusion (score 0)	☐ Minor, non-amendable for punction (score 2)		☐ Major, amendable for punction (score 3)	
ASCITES	☐ No ascites (score 0)	☐ Minor only detected by echography (score 2)		☐ Significant ascites (score 3)	

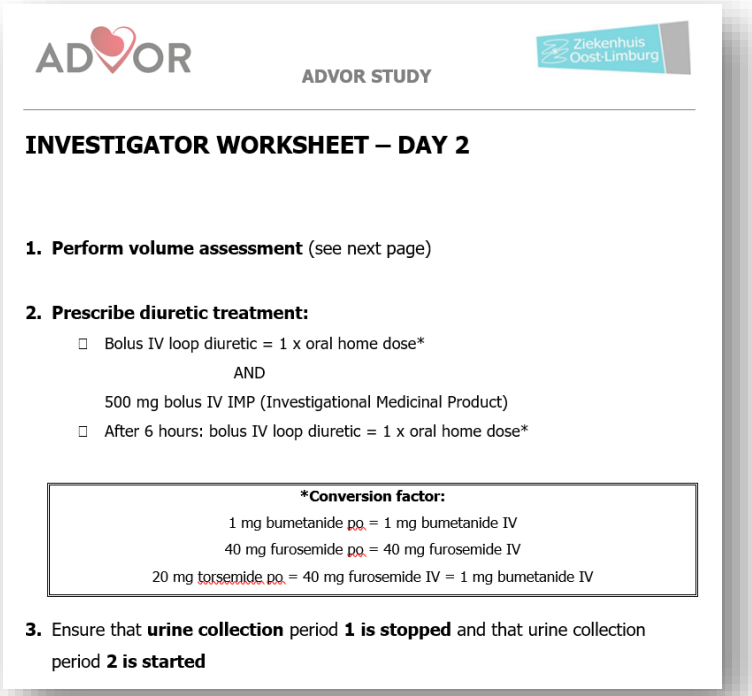
Instruction: please indicate per row 1 field that applies.

SUCCESFULL DECONGESTION: **STOP IV STUDY TREATMENT** AND CHANGE TO ORAL REGIMEN

CONTINUE STUDY TREATMENT (day 2, 8-12 AM):
- IV diuretic (**1x** orallly home dose)
- 500 mg IV bolus IMP

After 6 hours: - IV diuretic (**1x** orallly home dose)

ADVOR patient ID number:



ADVOR STUDY

INVESTIGATOR WORKSHEET – DAY 2

1. **Perform volume assessment** (see next page)

2. **Prescribe diuretic treatment:**
   - ☐ Bolus IV loop diuretic = 1 x oral home dose*
     AND
     500 mg bolus IV IMP (Investigational Medicinal Product)
   - ☐ After 6 hours: bolus IV loop diuretic = 1 x oral home dose*

***Conversion factor:**

1 mg bumetanide po = 1 mg bumetanide IV

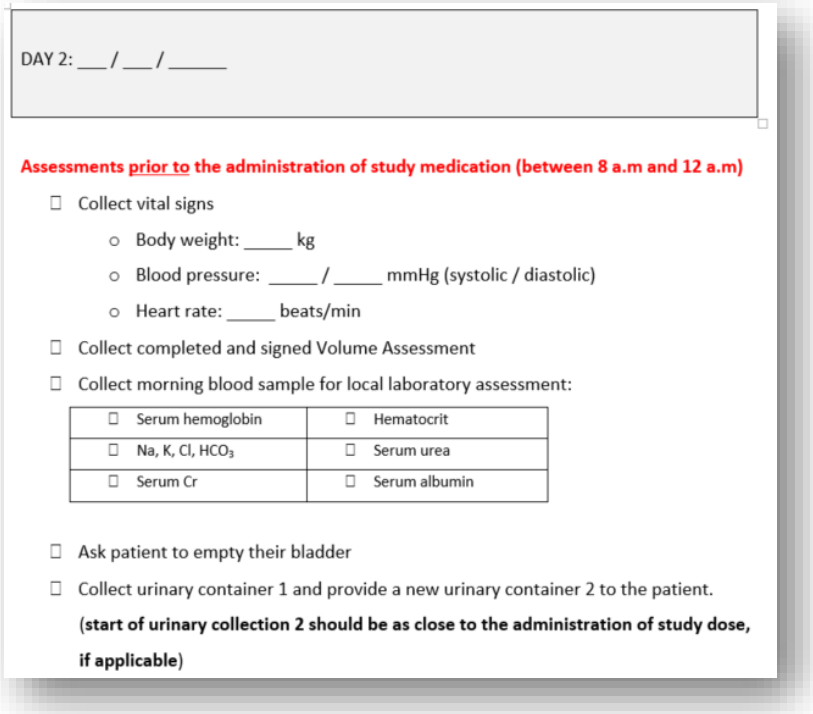
40 mg furosemide po = 40 mg furosemide IV

20 mg torsemide po = 40 mg furosemide IV = 1 mg bumetanide IV

3. Ensure that **urine collection** period **1 is stopped** and that urine collection period **2 is started**

Study coordinator worksheet

- Work document for the study coordinator that describes all assessments to be done and documented
- Not mandatory but very helpful (e.g. instructions, checklists, …)
- Can act as source documentation



DAY 2: ___ / ___ / _____

Assessments prior to the administration of study medication (between 8 a.m and 12 a.m)

- ☐ Collect vital signs
  - Body weight: _____ kg
  - Blood pressure: _____ / _____ mmHg (systolic / diastolic)
  - Heart rate: _____ beats/min
- ☐ Collect completed and signed Volume Assessment
- ☐ Collect morning blood sample for local laboratory assessment:

☐ Serum hemoglobin	☐ Hematocrit
☐ Na, K, Cl, HCO_3	☐ Serum urea
☐ Serum Cr	☐ Serum albumin

- ☐ Ask patient to empty their bladder
- ☐ Collect urinary container 1 and provide a new urinary container 2 to the patient. **(start of urinary collection 2 should be as close to the administration of study dose, if applicable)**

Patient card

- The card informs that the patient participates to the ADVOR clinical study
- Details of the patient and treating physician are written on the card
- Important in case of urgent deblinding, accident, …

! The patient always needs to carry this card with him/her !


PATIENTENKAART/CARTE DE PATIENT
ADVOR STUDIE/ETUDE
Acetazolamide in Decompensated heart failure with Volume OveRload

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Deze persoon neemt deel aan een klinische studie. Voor informatie over deze studie, spoedeisende deblindering of bij een ongeval, neem contact op met de behandelende arts (zie achterzijde).

Cette personne participe à un essai clinique. Pour tout information concernant cet essai, en cas de nécessité urgente d'ouvrir le code de randomisation ou en cas d'accident, veuillez contacter le médecin traitant (voir au verso).

Draag deze kaart altijd bij u.
Veuillez garder cette carte en permanence sur vous.

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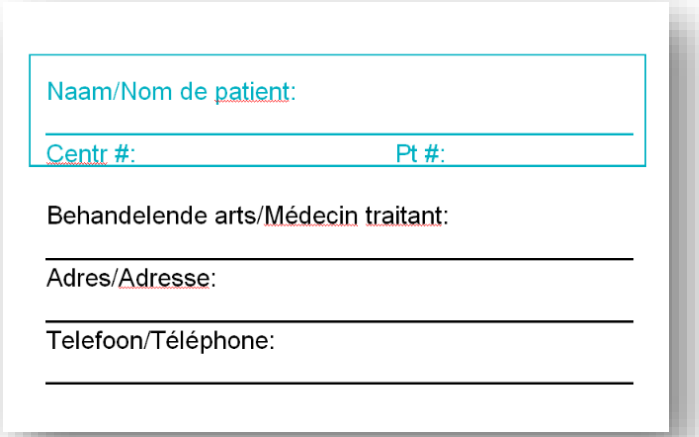
Naam/Nom de patient:

Centr #: Pt #:

Behandelende arts/Médecin traitant:

Adres/Adresse:

Telefoon/Téléphone:

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Overview study logs

Documentation	Content
Screening log	Log of all screened subjects
Enrollment log	Log of all patients that are enrolled in the study
Subject identification log	Identification of all patients: link between the personal data and the anonymized study ID number
IMP accountability log	Log of IMP receipt, dispense, return and/or destruction
Site delegation and responsibility log	Log of all people at site working on the study with their roles and delegated tasks
Study training log	Log of all trainings given on site for the study
Monitoring log	Log of all monitoring visits performed on site
Temperature log	Recording of daily temperature of storage IMP
Substudy shipment document	Log of available samples in the freezer and shipment of samples (only when participating to the substudy)
Site identification log	Localization of all source and study related documents

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IMP accountability log

IMP/IMD ACCOUNTABILITY LOG			□ Blinded Document □ Unblinded Document[1]
Site Principal Investigator:	**Site ID:**		**STUDY:**
IMP/IMD Name:	**Doses:**		**Dosage Form:**
Units Per Container:	**Storage Requirement (refer to product label):[2]**		

Receipt or Dispense Date[3] dd/mmm/yyyy	□ Lot Number □ Kit Number □ Container Number □ Other (specify) _____ Or Shipment ID #[4]	Study Subject ID Number (SSID)[5]	Quantity of Containers Received (R) or Dispensed (D)[6]	Balance (Containers)[7]	Staff Initials[8]	Monitor Initials[9]	Subject Returns[10]			Disposition[11]				Comments[12]
							Quantity of Units Returned (NR for not returned)	Date Returned dd/mmm/yyyy	Staff Initials	Return (R) to Sponsor / Designee or Destroy (D)	Date of Disposition dd/mmm/yyyy	Staff Initials	Monitor Initials	

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Site delegation and responsibility log

Study Site number: _____Principal Investigator: _____

Name	Initials	Role*	Delegated tasks	Signature	From **	PI initials and date	To	PI initials and date

*Role: Includes but is not limited to Sub-Investigator (SI), Study Coordinator (SC), Pharmacist, lab technician, etc.

**By initialing this document, the PI confirms that the relevant staff member was trained for the required delegated activities and will operate under PI surveillance. Training in project-specific tasks must be completed prior to performing any associated study procedures which differ from normal clinical practice and should be documented in the project-specific training log.

1. Obtain Informed Consent	6. AE causality	11. Break IP Blind	16. Sign CRF
2. Medical History	7. Prescribe and/or titrate IP	12. Draw Lab samples	17. Randomization
3. Perform Physical Exam	8. Prepare IP	13. Process Lab samples	18. Other, specify _____
4. Confirm Eligibility of subjects	9. Dispense IP	14. CRF completion and corrections	19. Other, specify _____
5. Safety Review and oversight	10. Administer IP	15. Sign DM queries	20. Other, specify _____

General

- All documentation will be provided and explained during site initiation visit
- ADVOR study team available for all your questions

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Any questions?

THANK YOU FOR YOUR ATTENDANCE!