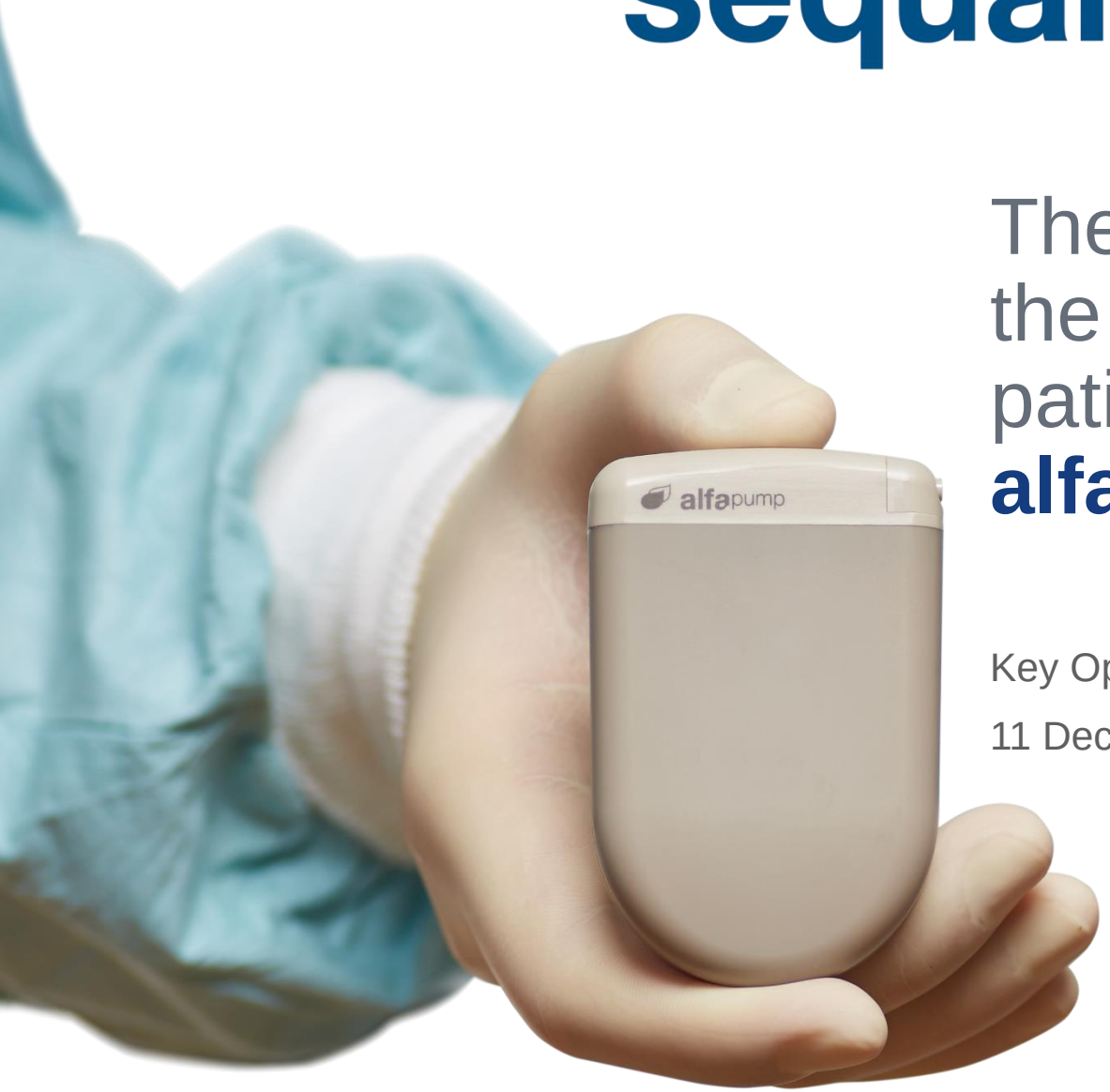
sequanamedical



The challenge of diuretic resistance in the management of heart failure patients and the potential for **alfa**pump® DSR therapy

Key Opinion Leader Webinar with Jeffrey Testani, MD, MTR

11 December 2020

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- The **alfa**pump® system has not yet received regulatory approval in the United States and Canada. Any statement in this presentation about safety and efficacy of the **alfa**pump® system does not apply to the United States and Canada. In the United States and Canada, the **alfa**pump® system is currently under clinical investigation (POSEIDON Study) and is being studied in adult patients with refractory or recurrent ascites due to cirrhosis. For more information regarding the POSEIDON clinical study see www.poseidonstudy.com.
- The DSR therapy is still in development and it should be noted that any statements regarding safety and efficacy arise from ongoing pre-clinical and clinical investigations which have yet to be completed. The DSR therapy is not currently approved for clinical research in the United States or Canada. There is no link between the DSR therapy and ongoing investigations with the **alfa**pump® system in Europe, the United States or Canada.

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Agenda and Presenters

09:00 – Ian Crosbie, CEO Sequana Medical

- Welcome and Introduction

Ian Crosbie, CEO

09:05 – Dr. Jeffrey Testani, Associate Professor at Yale University and Heart Failure Scientific Advisor of Sequana Medical

- Cardio-Renal Syndrome and Diuretic Resistance: Mechanism and Clinical Implications
- **alfa**pump® DSR – Potential Chronic Therapy for Heart Failure Patients with Fluid Overload that are Not Well Controlled on Diuretics

Dr. Jeffrey Testani, MTR

09:35 – Ian Crosbie, CEO

- Proven **alfa**pump platform in the Management of Fluid Overload
- Key Upcoming Milestones

Dr. Oliver Gödje, CMO

09:40 – Q&A

The challenge of diuretic resistance in the management of heart failure patients: The potential for **alfa**pump® DSR therapy

Jeffrey M. Testani, M.D., M.T.R.

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Yale SCHOOL OF MEDICINE

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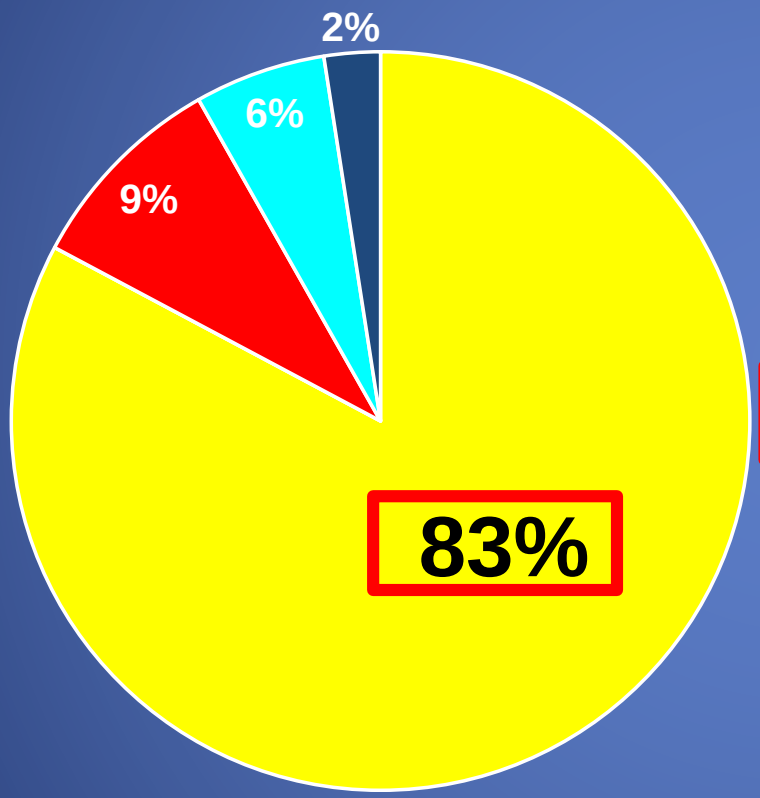
Congestion is the major cause of and therapeutic target in HF Hospitalization

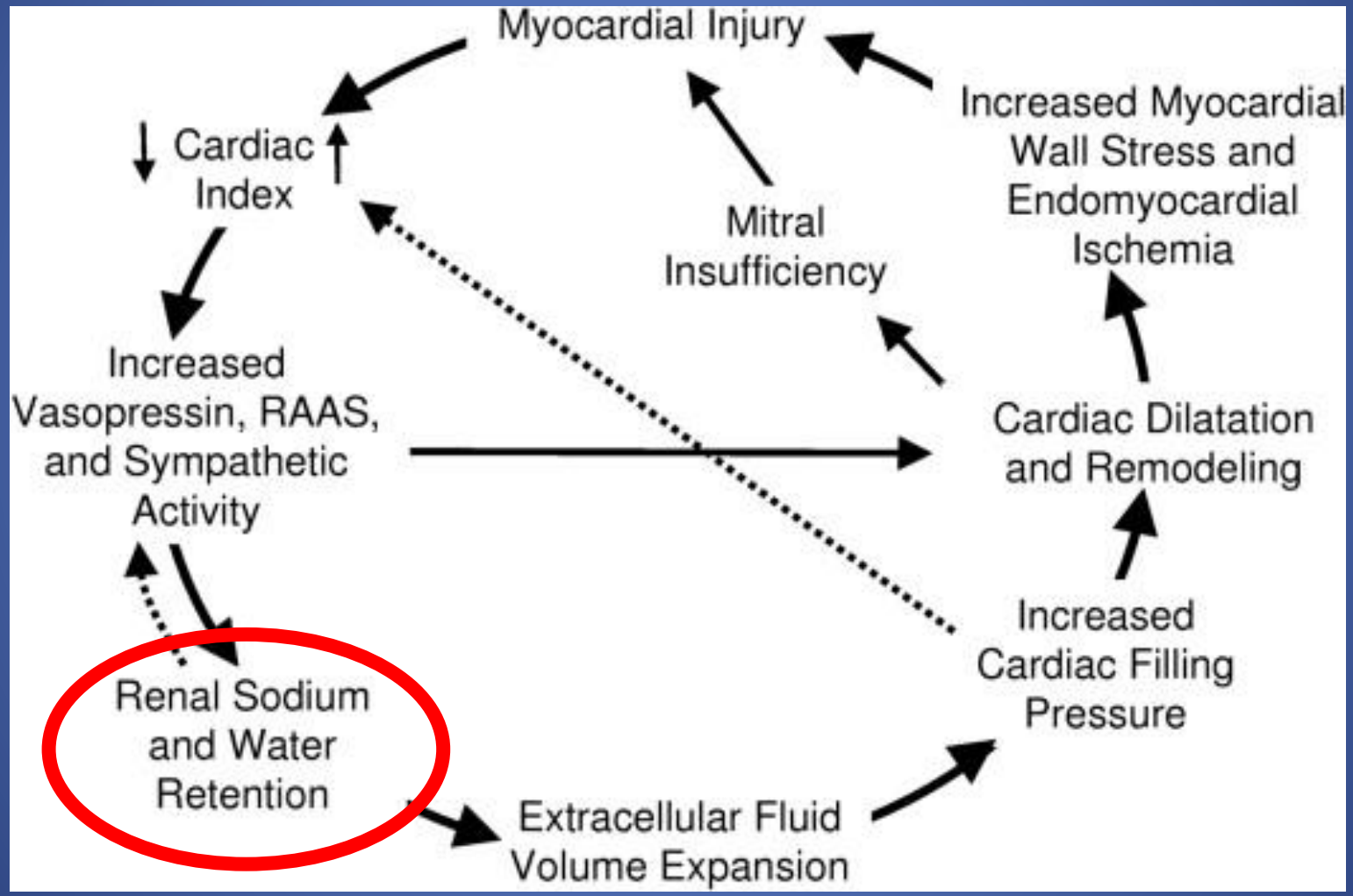


N=3,580

- Volume Overload or Pulmonary Edema
- HTN HF
- Cardiogenic Shock
- Right heart failure

Adapted from Nieminen, M et al *Eur Heart J* 2006

Congestion is the disease, not just a nuisance symptom



Schrier, *Seminars in Nephrology* 2011;31:503

Volume overload is prognostically incredibly important in heart failure any way you measure it

- Physical exam
- Bioimpedance
- Natriuretic peptides
- IVC collapse
- Blood volume
- Weight gain
- Swan-Ganz parameters

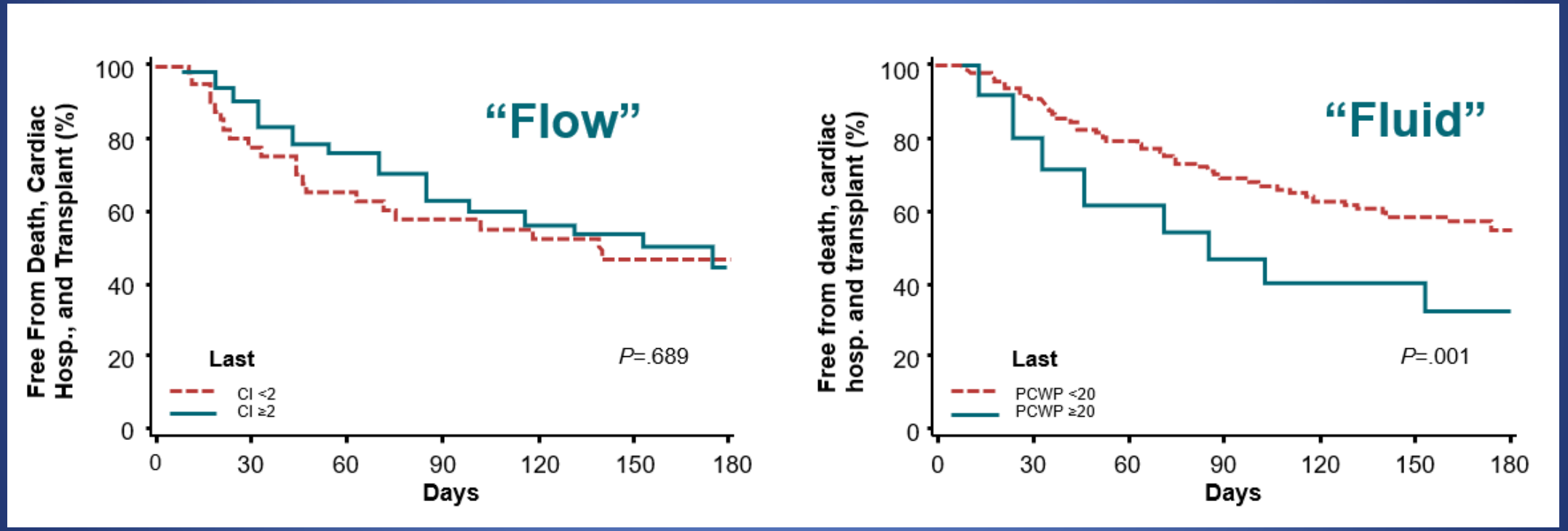
Journal of Cardiac Failure Vol. 22 No. 3 2016

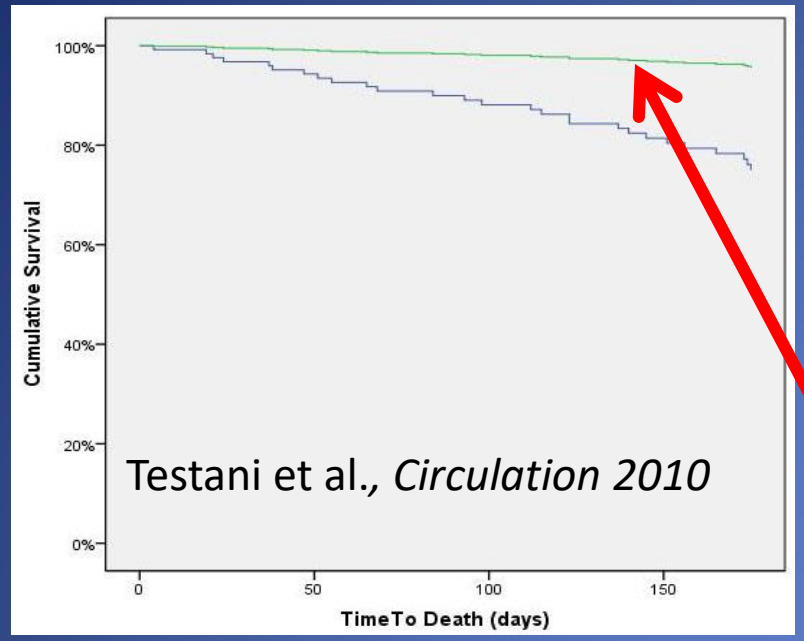
Clinical Investigation

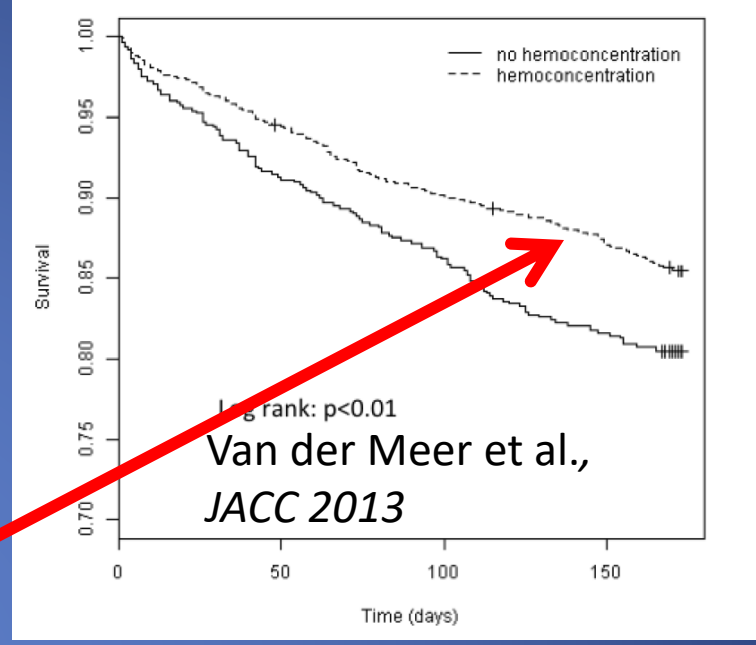
Hemodynamic Predictors of Heart Failure Morbidity and Mortality: Fluid or Flow?

LAUREN B. COOPER, MD,[1,2] ROBERT J. MENTZ, MD,[1,2] SUSANNA R. STEVENS, MS,[1] G. MICHAEL FELKER, MD, MHS,[1,2] CARLO LOMBARDI, MD,[3] MARCO METRA, MD,[3] LYNNE W. STEVENSON, MD,[4] CHRISTOPHER M. O'CONNOR, MD,[1,2] CARMELO A. MILANO, MD,[1,5] CHETAN B. PATEL, MD,[1,2] AND JOSEPH G. ROGERS, MD[1,2]

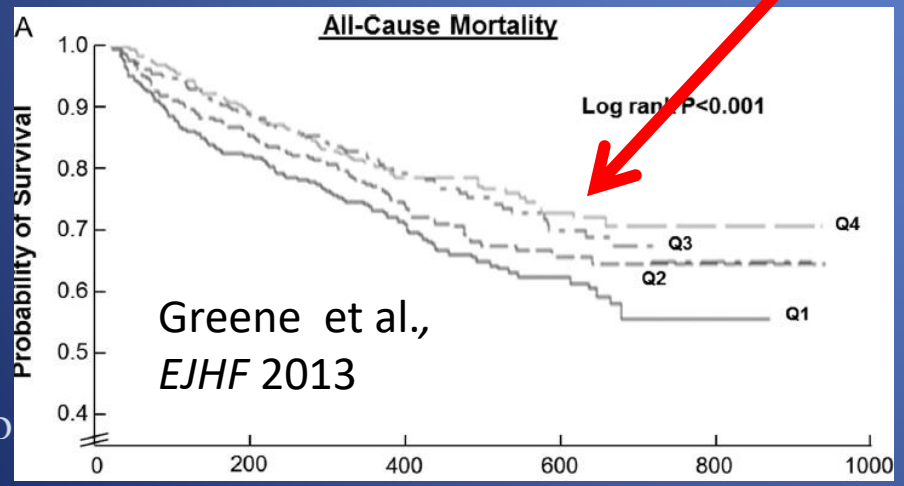
Durham, North Carolina, USA; Brescia, Italy; Boston, Massachusetts, USA

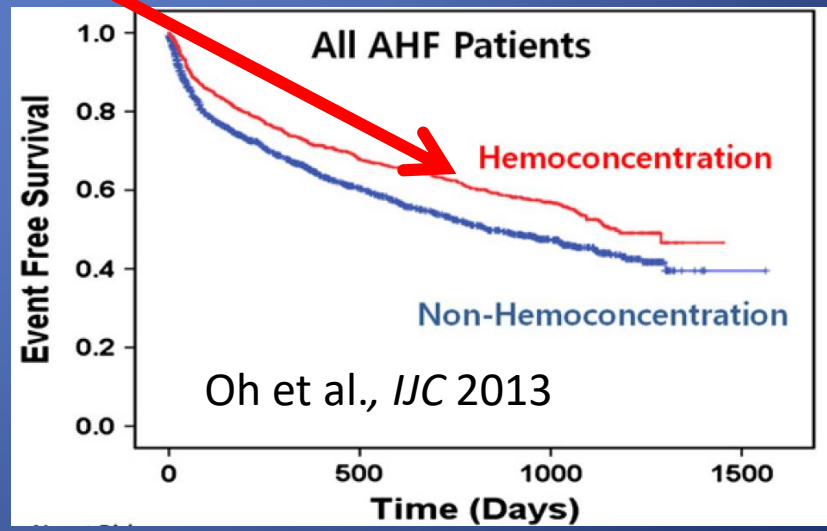

"Flow"
Free From Death, Cardiac Hosp., and Transplant (%)
100
80
60
40
20
0
0
30
60
90
120
150
180
Days
Last
CI <2
CI ≥2
P=.689
"Fluid"
Free from death, cardiac hosp. and transplant (%)
100
80
60
40
20
0
0
30
60
90
120
150
180
Days
Last
PCWP <20
PCWP ≥20
P=.001





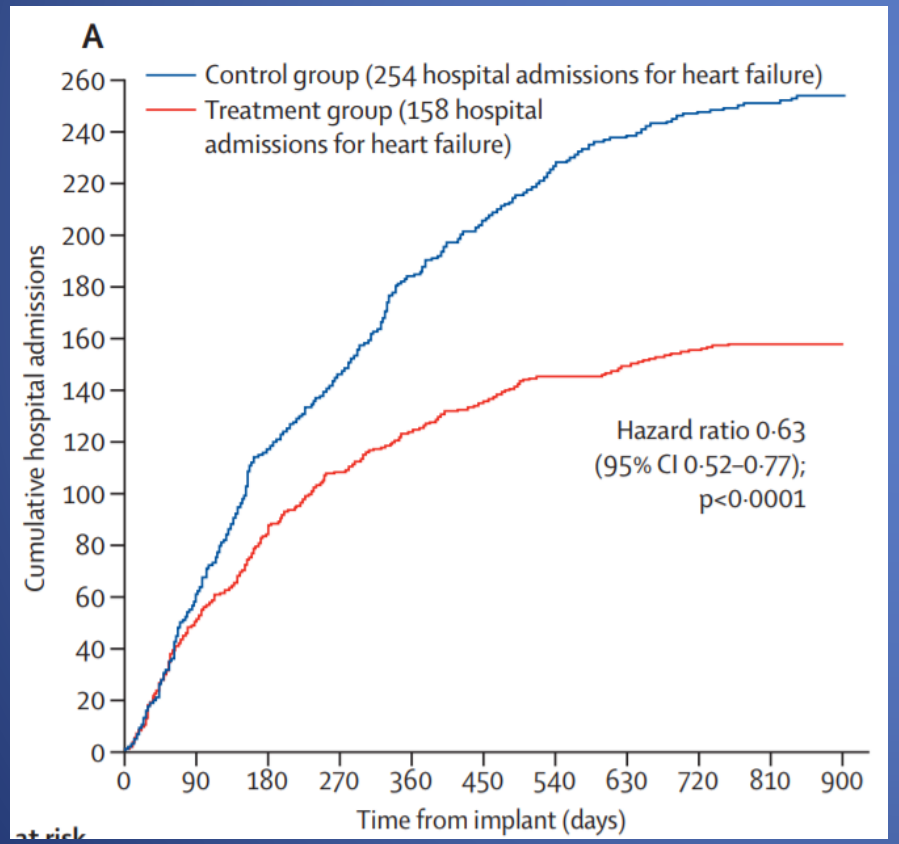
Aggressive diuresis is associated with improved survival



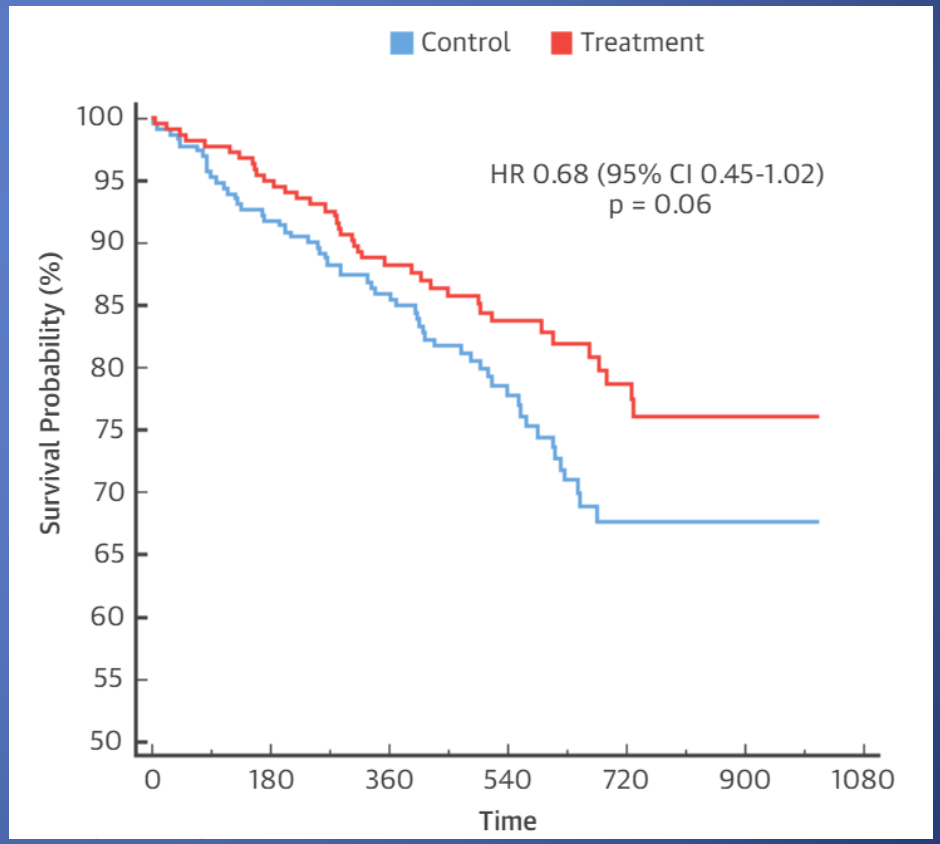


CHAMPION trial of cardioMEMS illustrates the importance of chronic volume management

Rehospitalization



Death

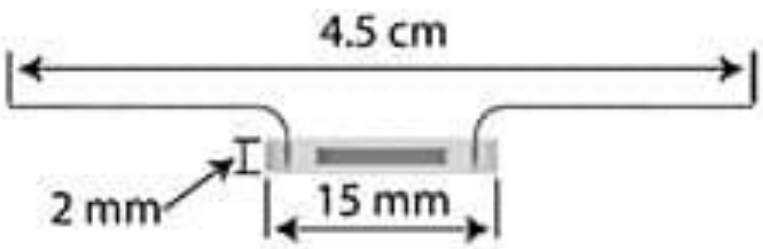


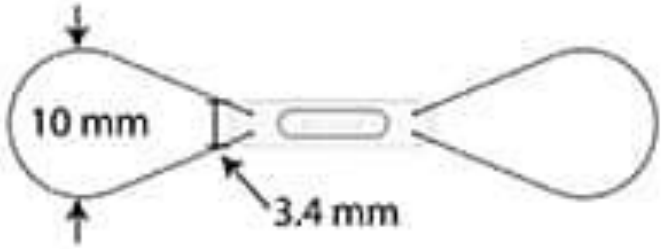
Yale SCHOOL OF MEDICINE

Abraham, Lancet 2011

Givertz, JACC 2017

CARDIOMEMS TECHNOLOGY

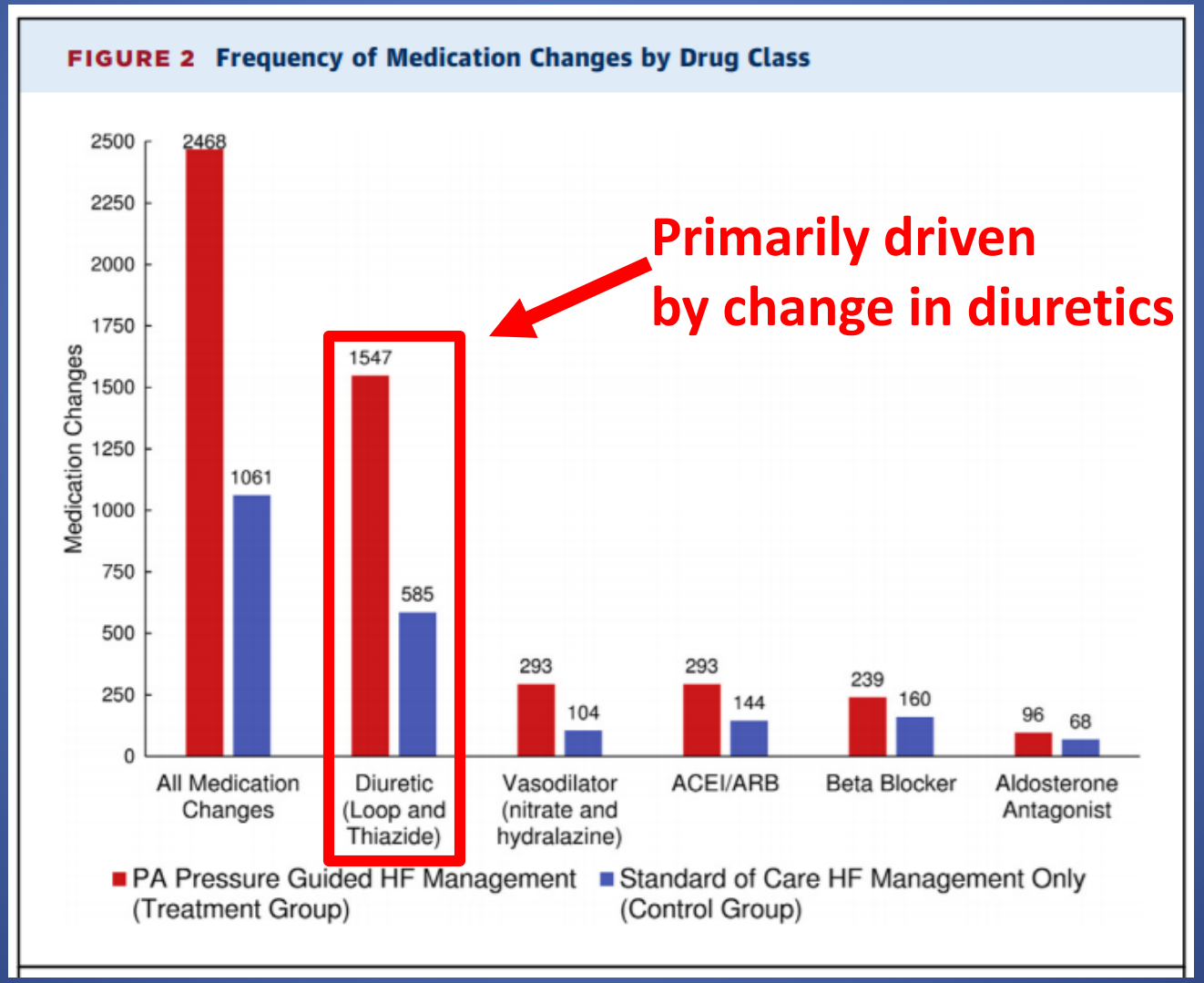




St. Jude Medical website

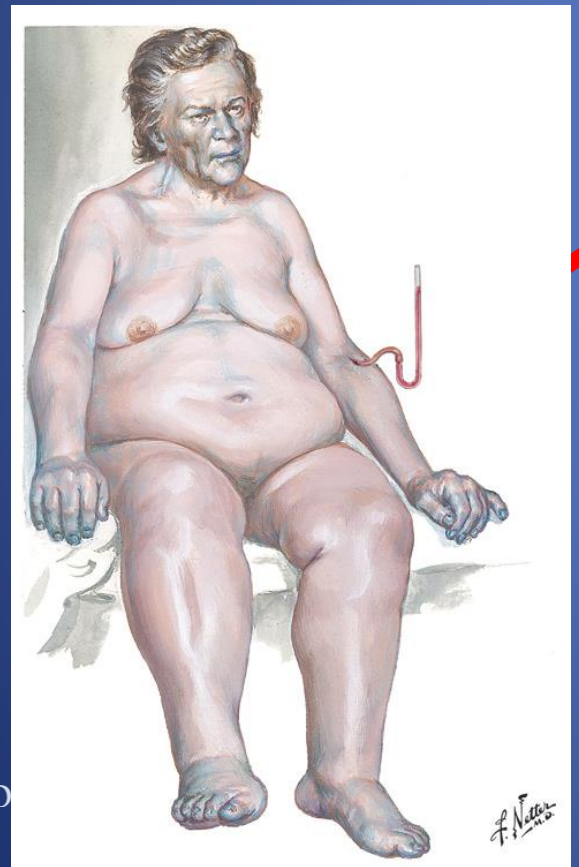
NW HEART FAILURE COLLABORATIVE
Project ECHO

Having the sensor in the patient has no direct therapeutic value….it's the medication changes



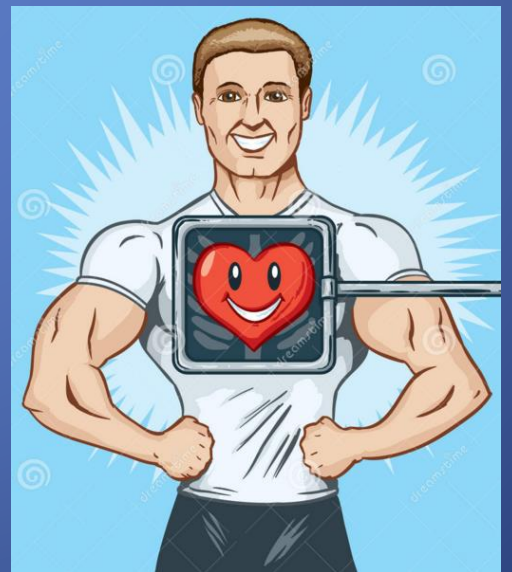
Costanzo, JACC:HF 2016

Volume=Bad

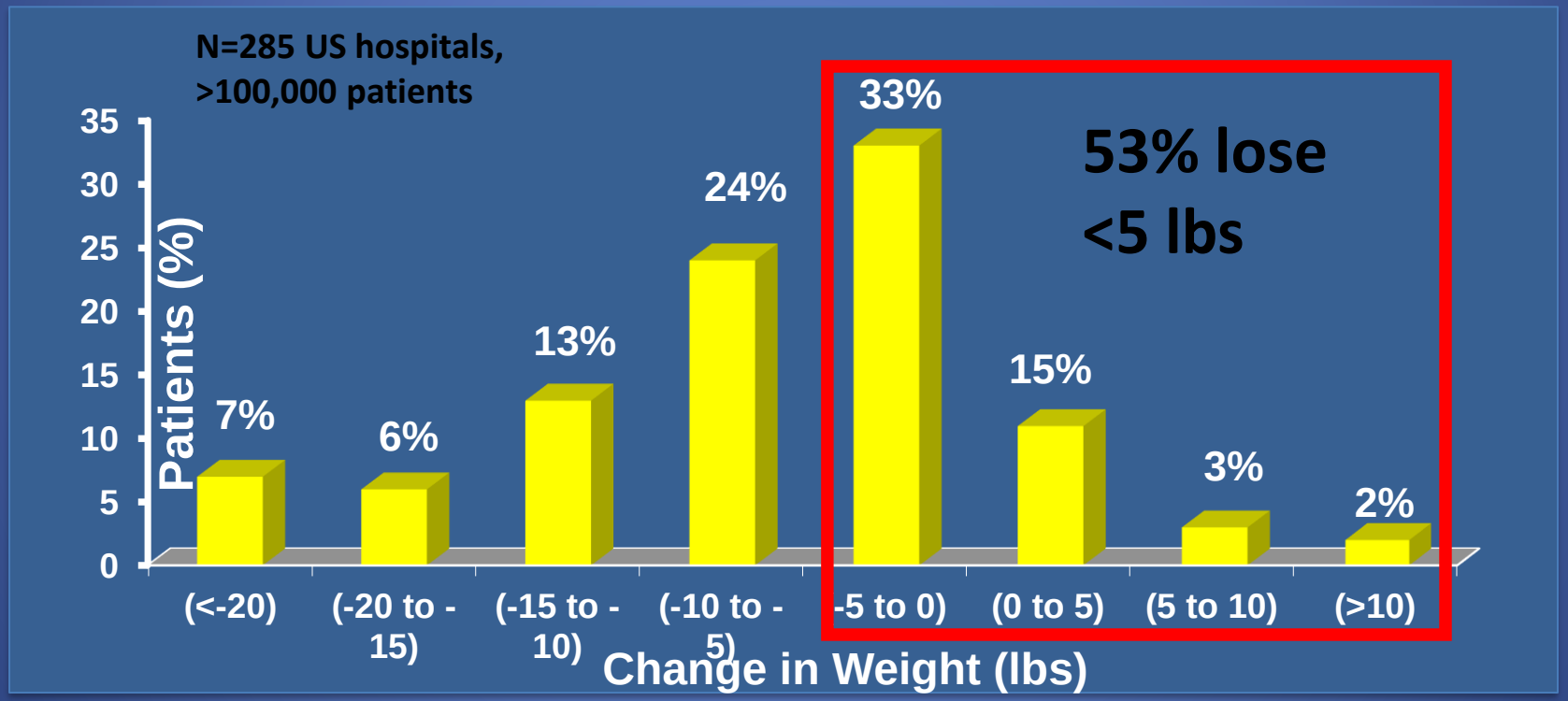


Give a little Lasix

Live forever



We actually do a terrible job actually removing fluid from decompensated HF patients



Fonarow GC. Rev Cardiovasc Med. 2003

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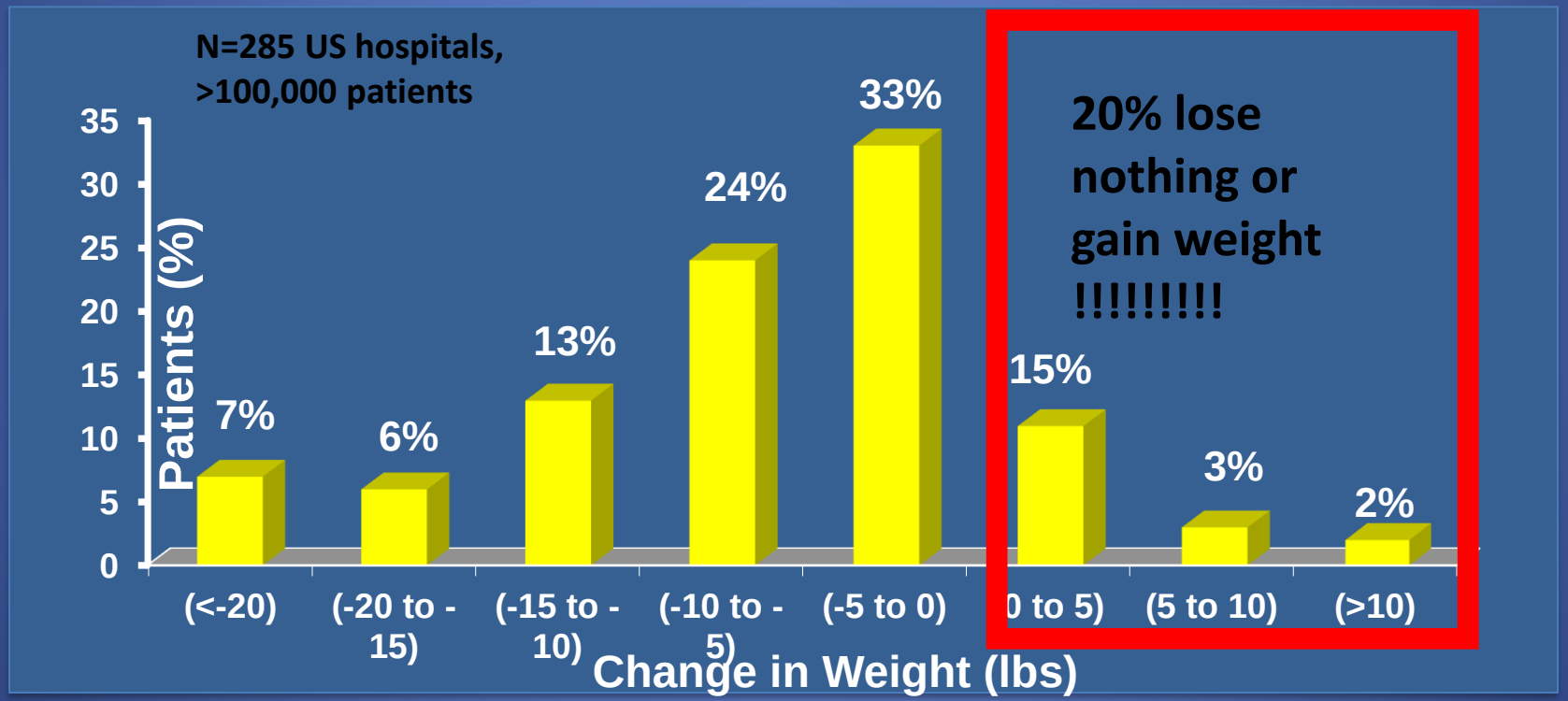


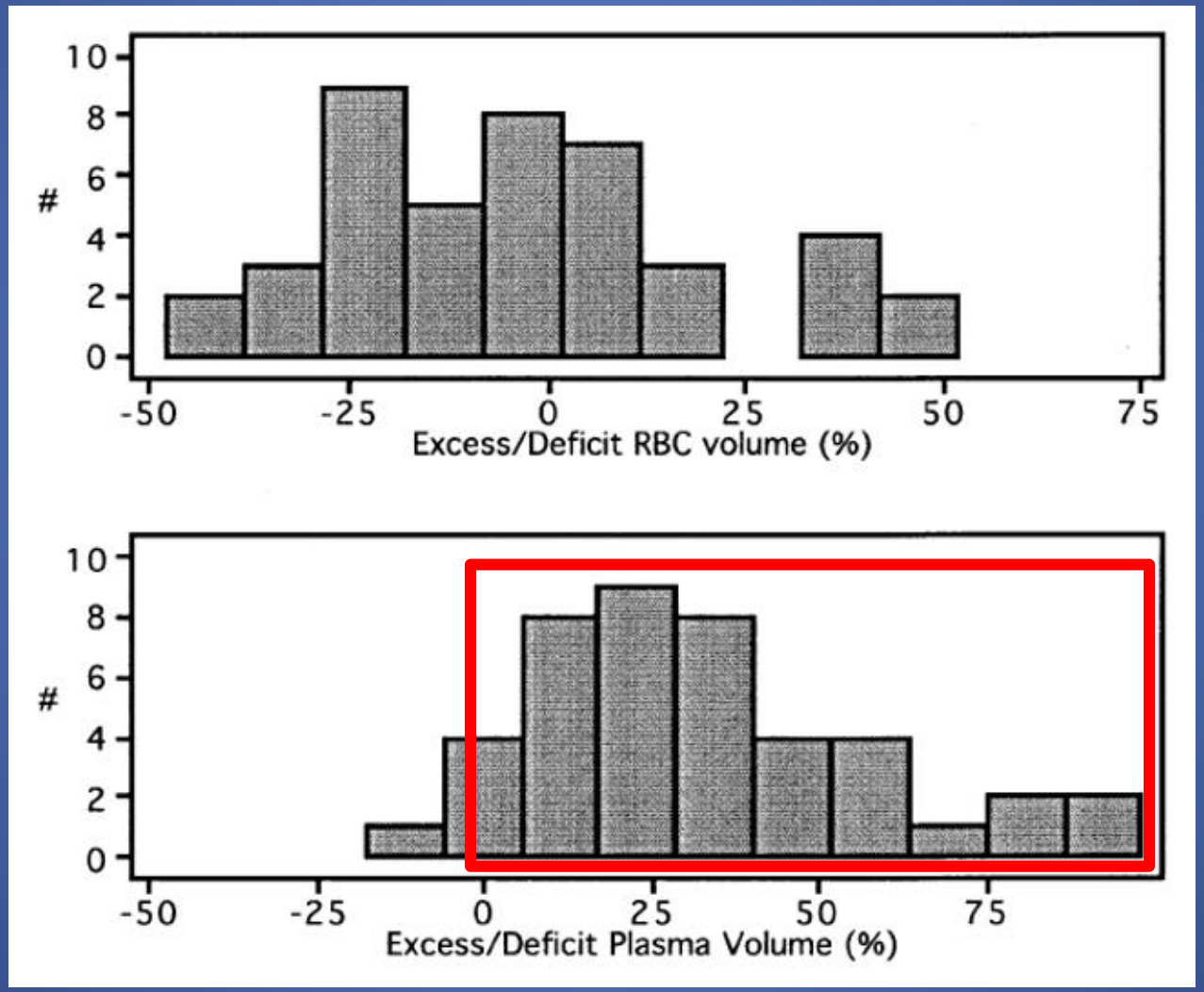
Fonarow GC. Rev Cardiovasc Med. 2003

Poor management of volume status also true in outpatients

Relation of Unrecognized Hypervolemia in Chronic Heart Failure to Clinical Status, Hemodynamics, and Patient Outcomes

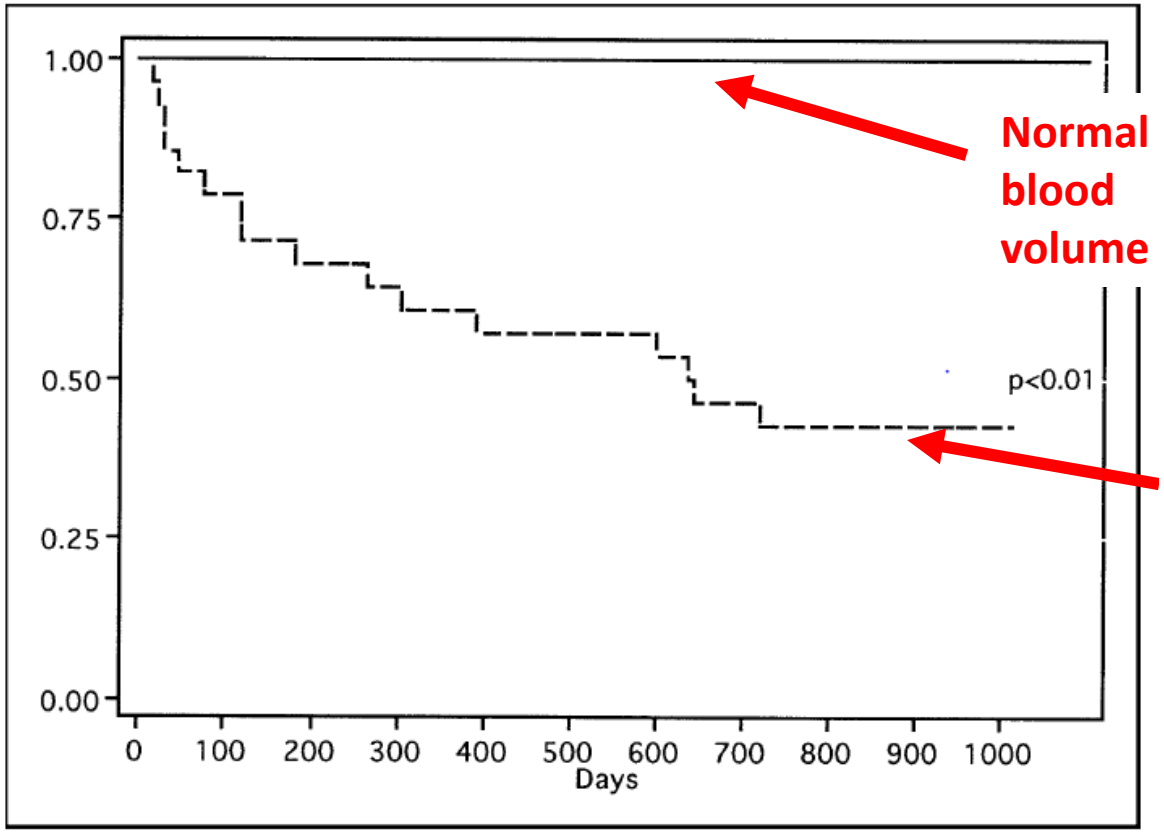
Ana Silvia Androne, MD, Katarzyna Hryniewicz, MD, Alhakam Hudaihed, MD, Donna Mancini, MD, John Lamanca, PhD, and Stuart D. Katz, MD, MS

Blood volume determined in non-edematous stable outpatients



Androne, AJC 2004

Not too surprising, mortality was worse in the expanded blood volume group



Normal blood volume

Increased blood volume

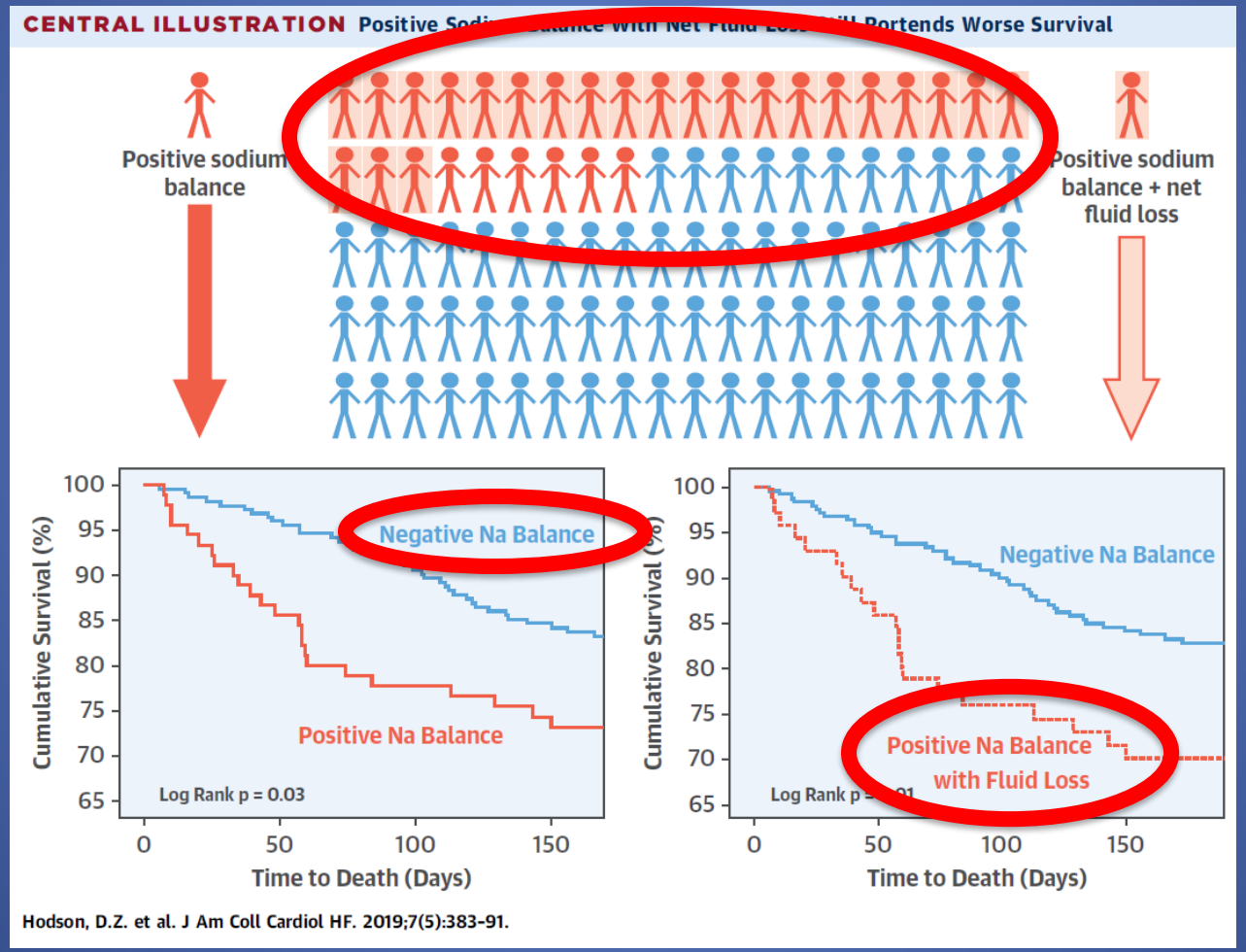
FIGURE 3. Kaplan-Meier plot of proportion of patients with hypervolemia surviving without urgent transplantation over time *(dashed line)* and in patients with normovolemia or hypovolemia *(solid line)*.

Androne, AJC 2004

We talk about “volume overload” but it’s really all about the sodium

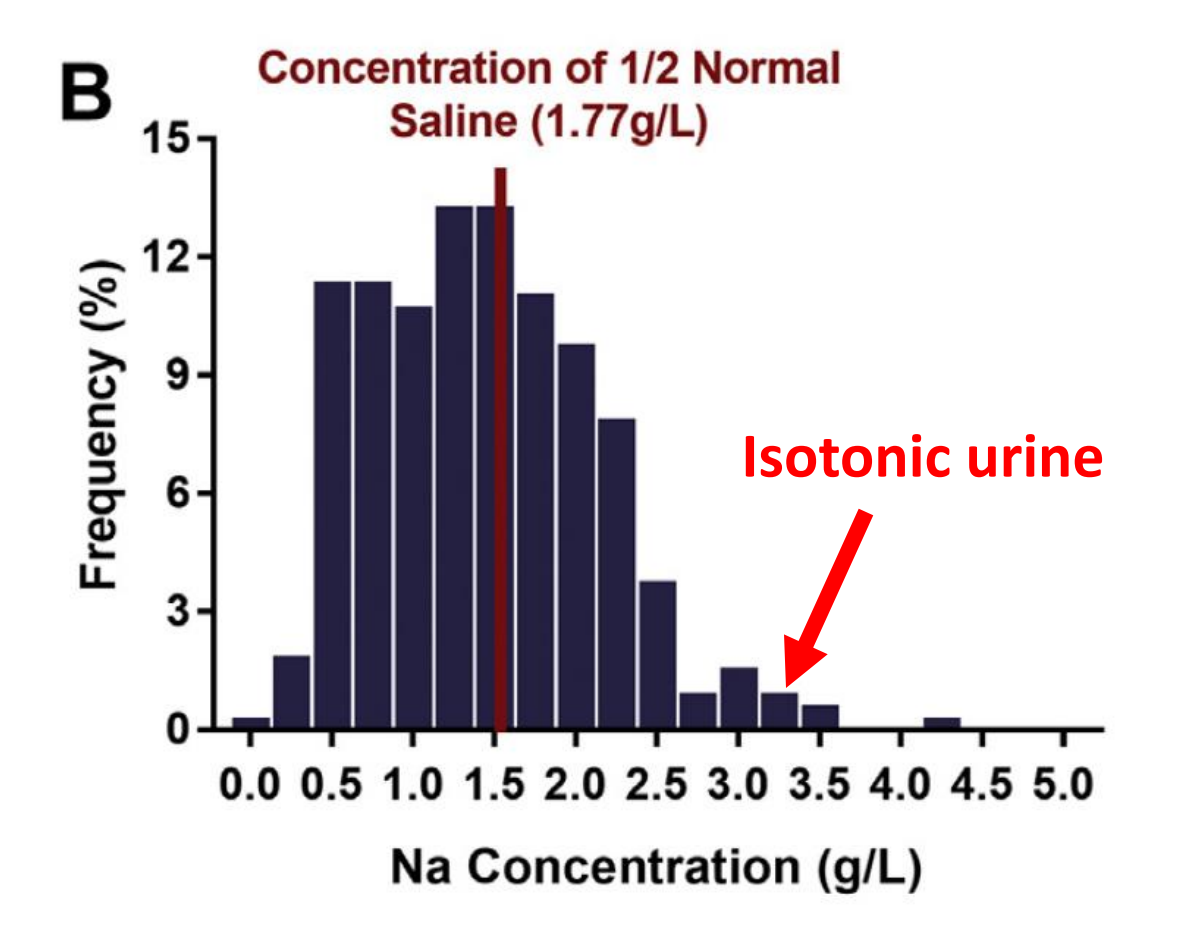
- Sodium is the key driver of extracellular volume expansion
  - The kidney regulates extracellular volume by the quantity of sodium it reabsorbs
    - The fluid follows the sodium as the major extracellular osm
  - The kidney regulates water excretion primary to keep plasma osmolarity constant
  - Thus targeting sodium removal is key

It's actually all about the sodium



Hodson, D.Z. et al. J Am Coll Cardiol HF. 2019;7(5):383-91.

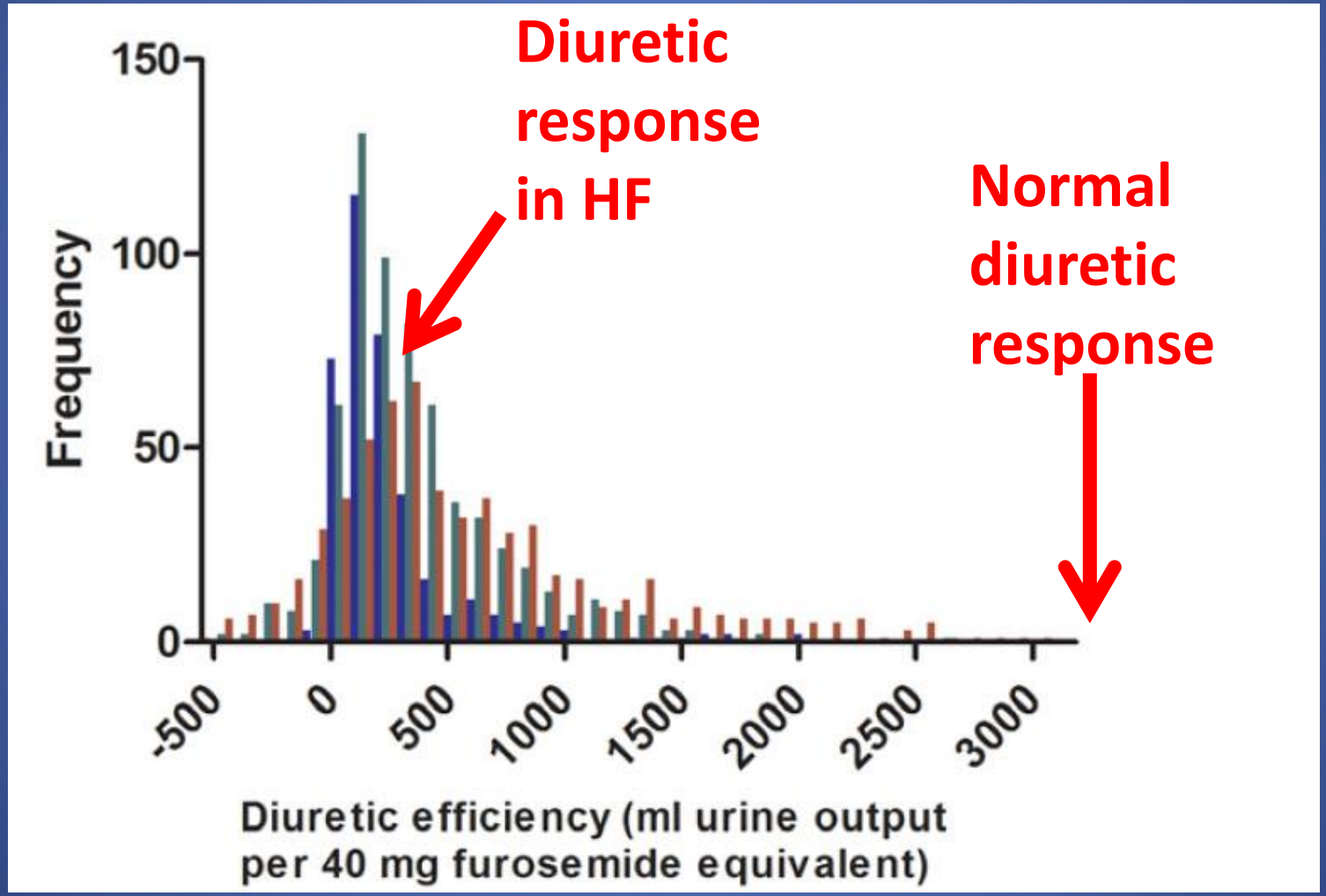
Furosemide results in dilute “watery” urine



Hodson, JACC:HF 2019

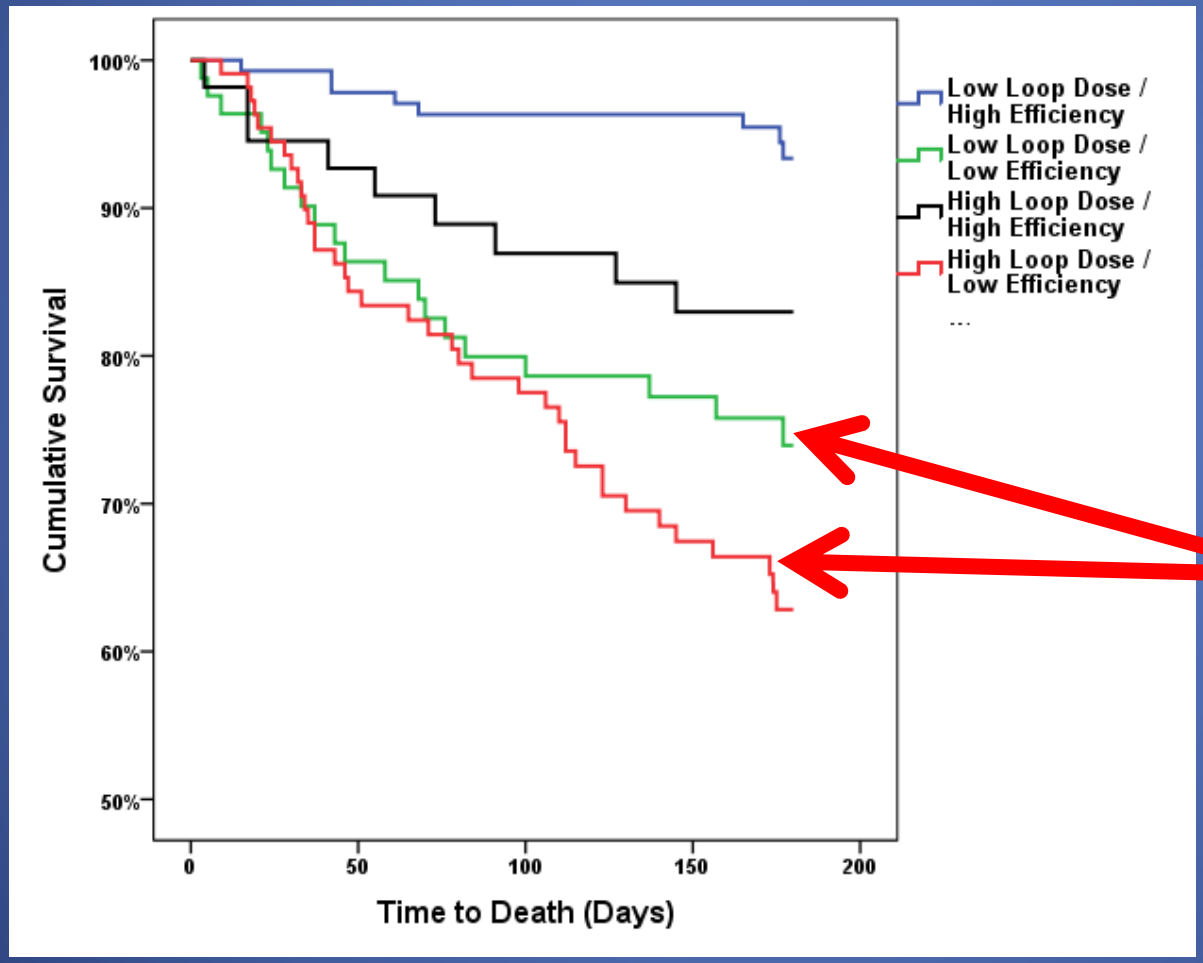
If sodium/volume overload is so important, why is it we have so much untreated volume overload?

Diuretic resistance is nearly ubiquitous



Testani et al, Circ HF 2014

Diuretic resistance is associated with mortality



Diuretic resistance with either high or low loop dose

Testani et al, Circ HF 2015

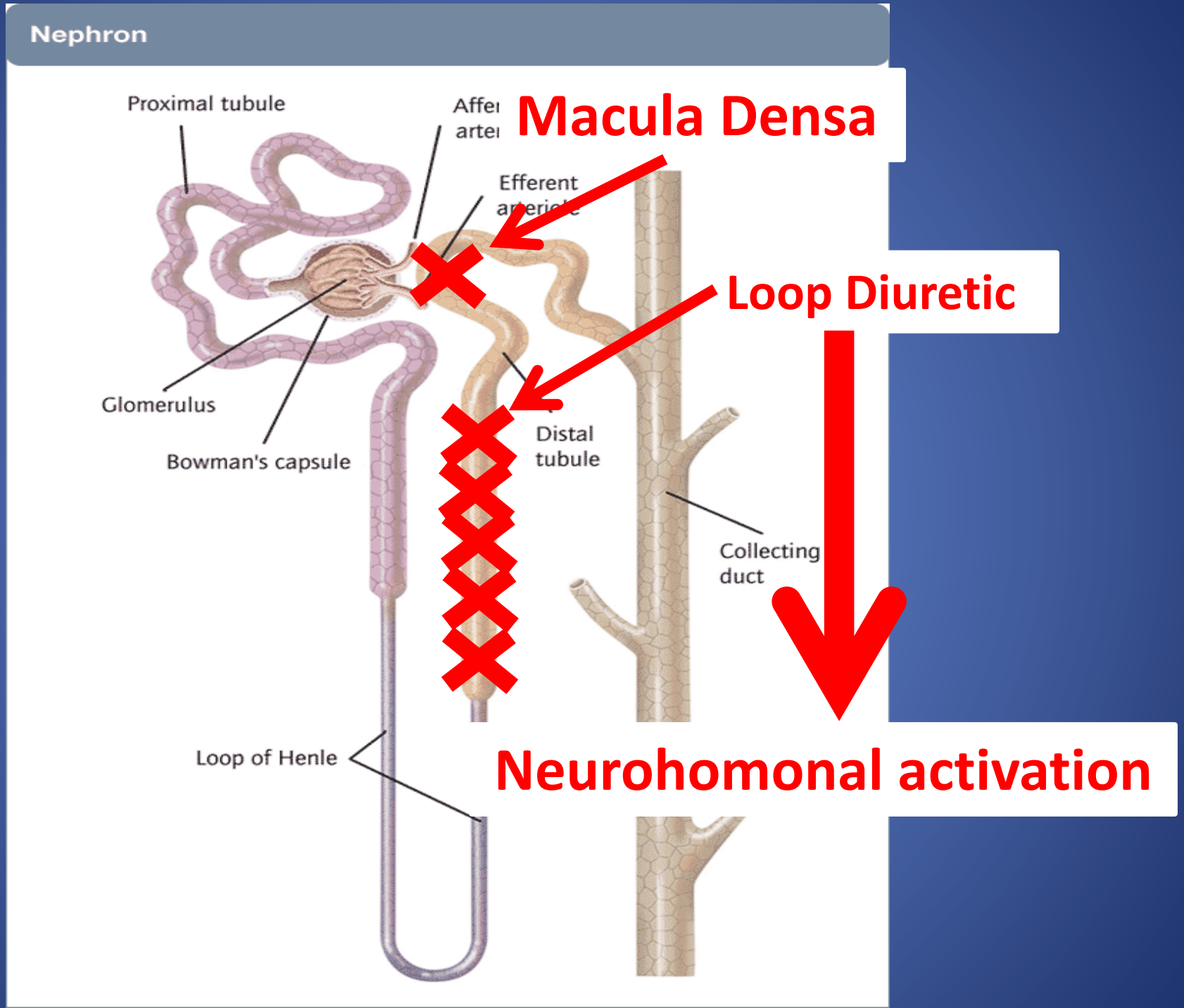
How do we treat this diuretic resistance

- …..more diuretics
- Unfortunately there is a large body of literature showing diuretics are associated with
  - Mortality
  - Rehospitalization
  - Kidney dysfunction
  - Electrolyte abnormalities
- These are dose dependent associations
  - The more diuretic you give the worse the patients seems to do

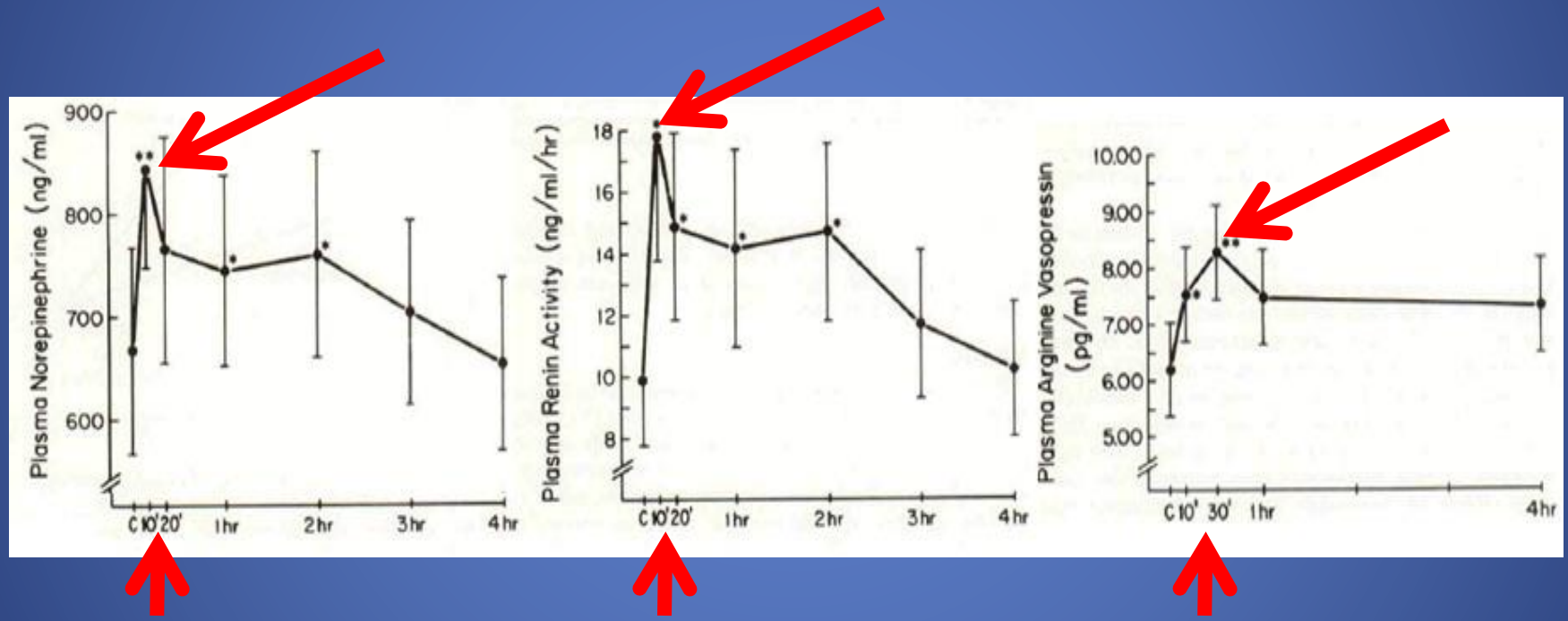
Some of this association may be causal

- The kidney “sees” salt through chloride entry into the macula densa through the Na-K-2Cl cotransporter
- This is the same transporter that loop diuretics antagonize

Francis et al, *Ann Intern Med* 1985;103:1

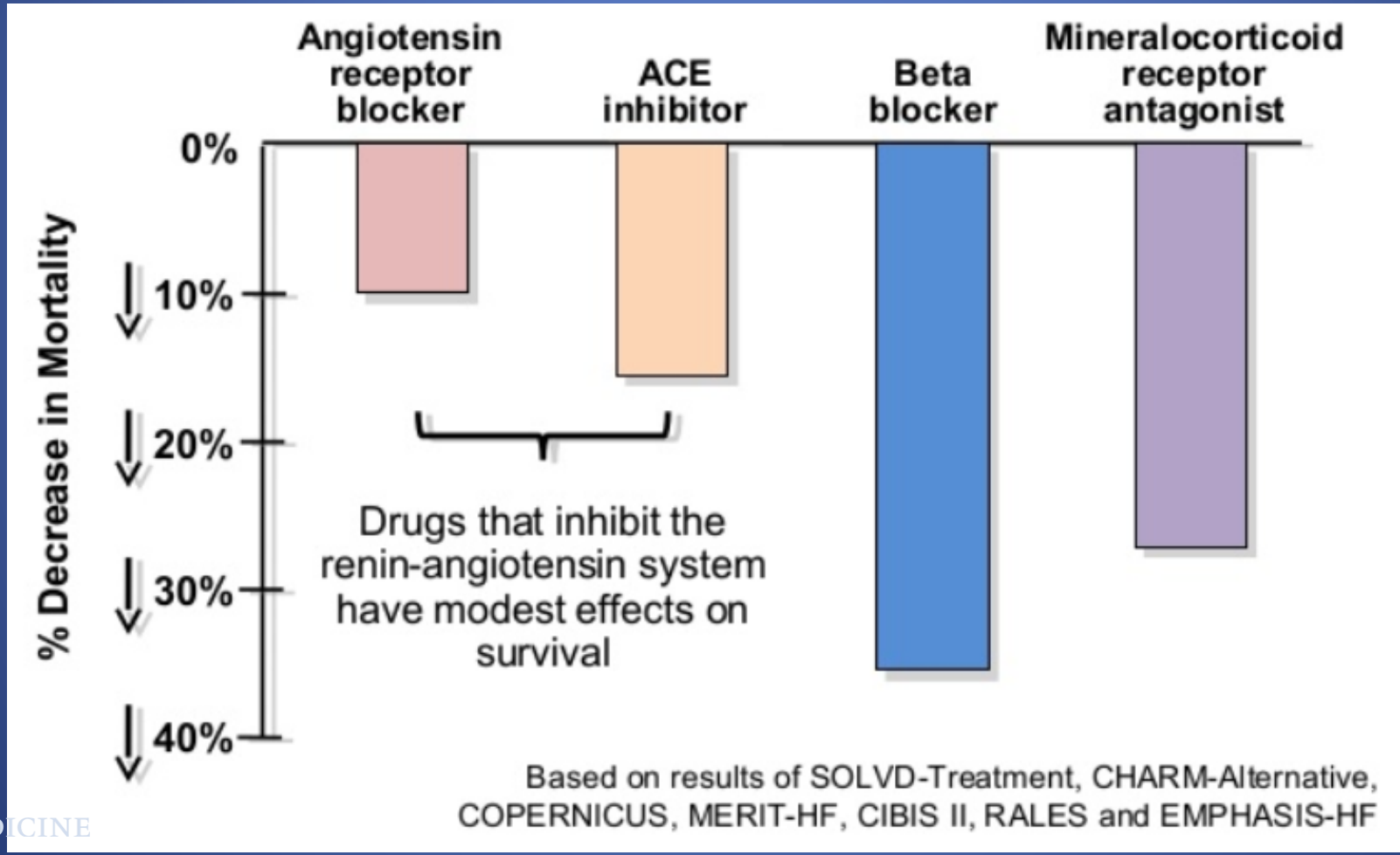

Nephron
Proximal tubule
Macula Densa
Efferent
Loop Diuretic
Glomerulus
Bowman's capsule
Distal
tubule
Collecting
duct
Loop of Henle
Neurohomonal activation

Net result is neurohormonal activation



Francis et al, *Ann Intern Med* 1985;103:1

Neurohormonal activation is critical in HF: most of our proven therapies block it

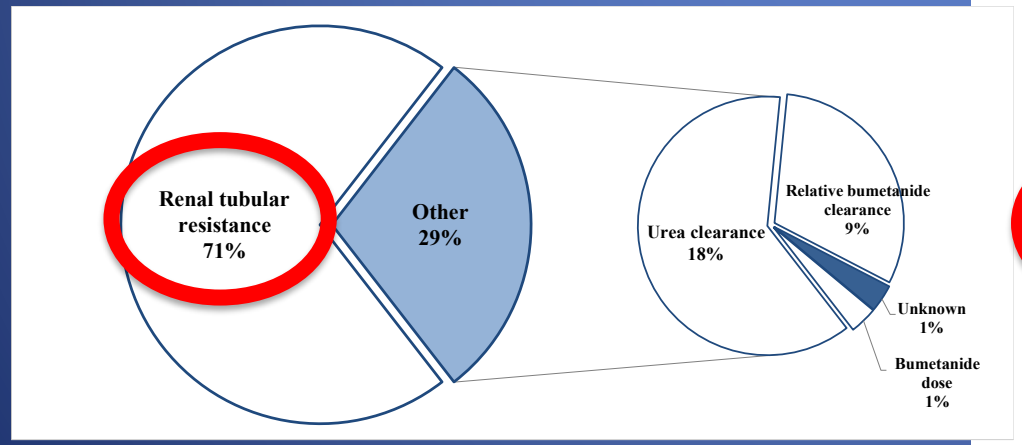


So why do we see so much diuretic resistance?

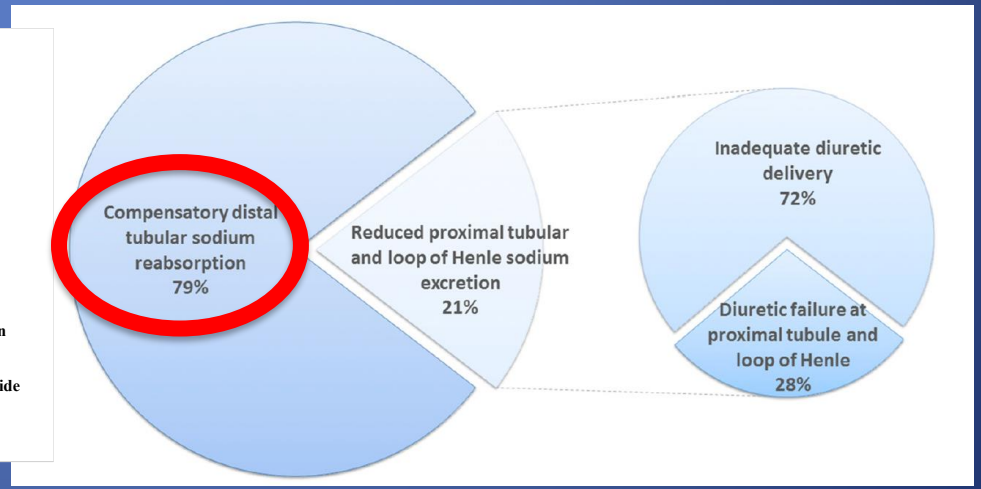
- Teleology: A human is basically a bag of salt and water
  - Our ability to exist outside of the ocean depended on millions of years of evolution developing a system to keep the right amount of salt and water in this bag
- Given that human life can not exist if this system does not accomplish the above, the complexity and redundancy of this system is profound

Mechanism for diuretic resistance in HF: It's really "acute renal success"

- Diuretic is getting to the site of action
  - And in most patients it is blocking sodium reabsorption at the site of action
- Renal tubules downstream are just pumping all the salt back into the patient
  - This is exactly what the kidney is designed to do when it thinks the organism is dehydrated



Ter Maaten, EJHF 2017



Rao, JASN 2017

Which recent strategies have had positive clinical trials and improved our care of volume overload in HF?

- …..essentially none of them
- Closest was the DOSE-AHF trial
  - Technically negative study as primary endpoint (global assessment of symptoms) was not significant (p=0.06)
- **Design**: Randomized study of high dose vs. low dose furosemide
  - High dose strategy was 2.5X home diuretic dose (mg per mg)
  - Low dose strategy was 1X home dose
- **DOSE trial results**:
  1. More Lasix makes you pee a bit more than less Lasix
     - 4.9L vs. 3.6L net fluid loss
  2. More Lasix results in a higher rate of worsening renal function
     - 40% increase in >0.3 mg/dl increase in creatinine
  3. No difference in death or rehospitalization

List of recent failed “novel” agents

- Adenosine antagonists
- High dose nesiritide
- Low dose nesiritide
- Vasopressin antagonists
- Ularitide
- Renal dose dopamine
- Serelaxin
- An array of additional drugs and devices you never heard of

Mechanism of current (and failed) therapies?

Standard therapies (e.g., High dose lasix)

Kidney

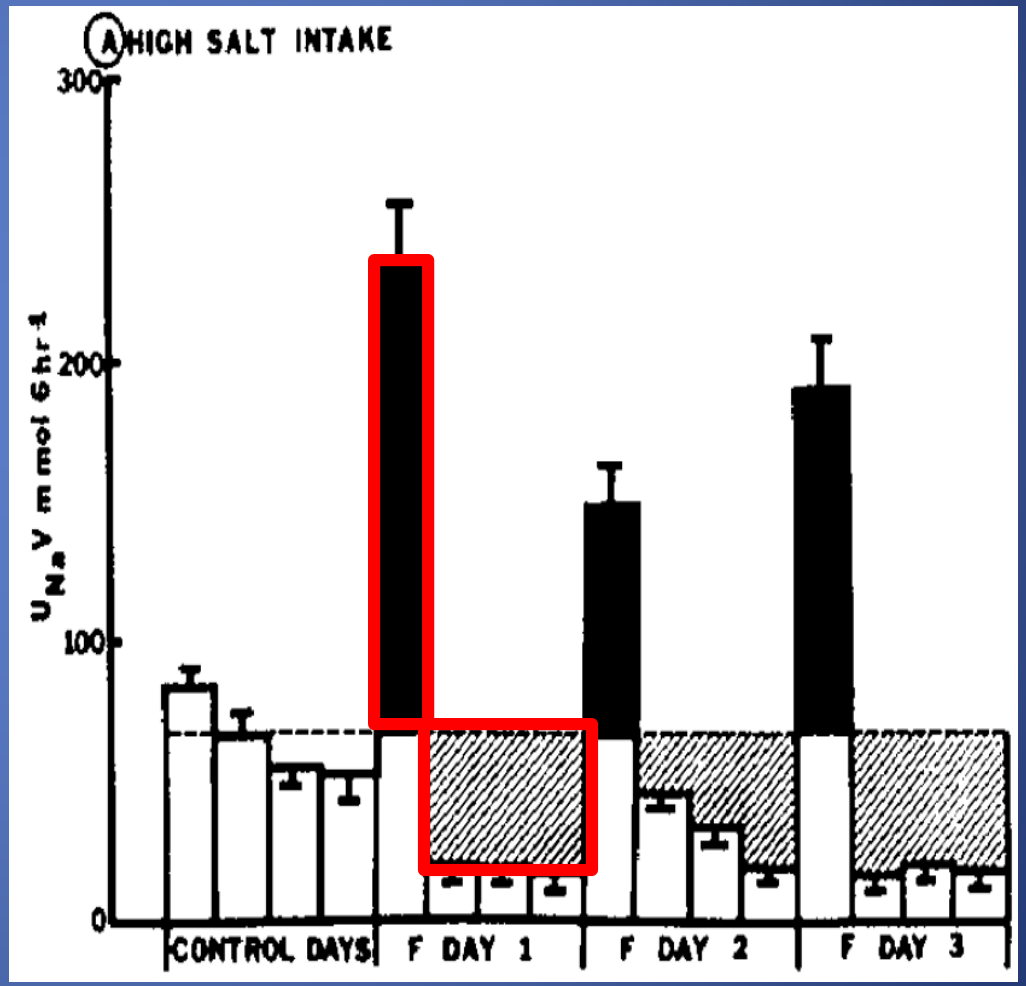
"Novel" cardiorenal medications and devices

Current therapies

- We don’t have time to review why all the “novel” therapies failed
  - My short answer is they are all too distal in the sodium avidity pathway and the kidney outsmarts them
- I will briefly review some of the traditional therapies that are commonly used in clinical practice

Continuous loop diuretic infusion

Traditional teaching is that this works primarily by avoiding post-diuretic period of sodium retention



Wilcox, *J Lab Clin Med*. 1983 Sep;102(3):450-8.

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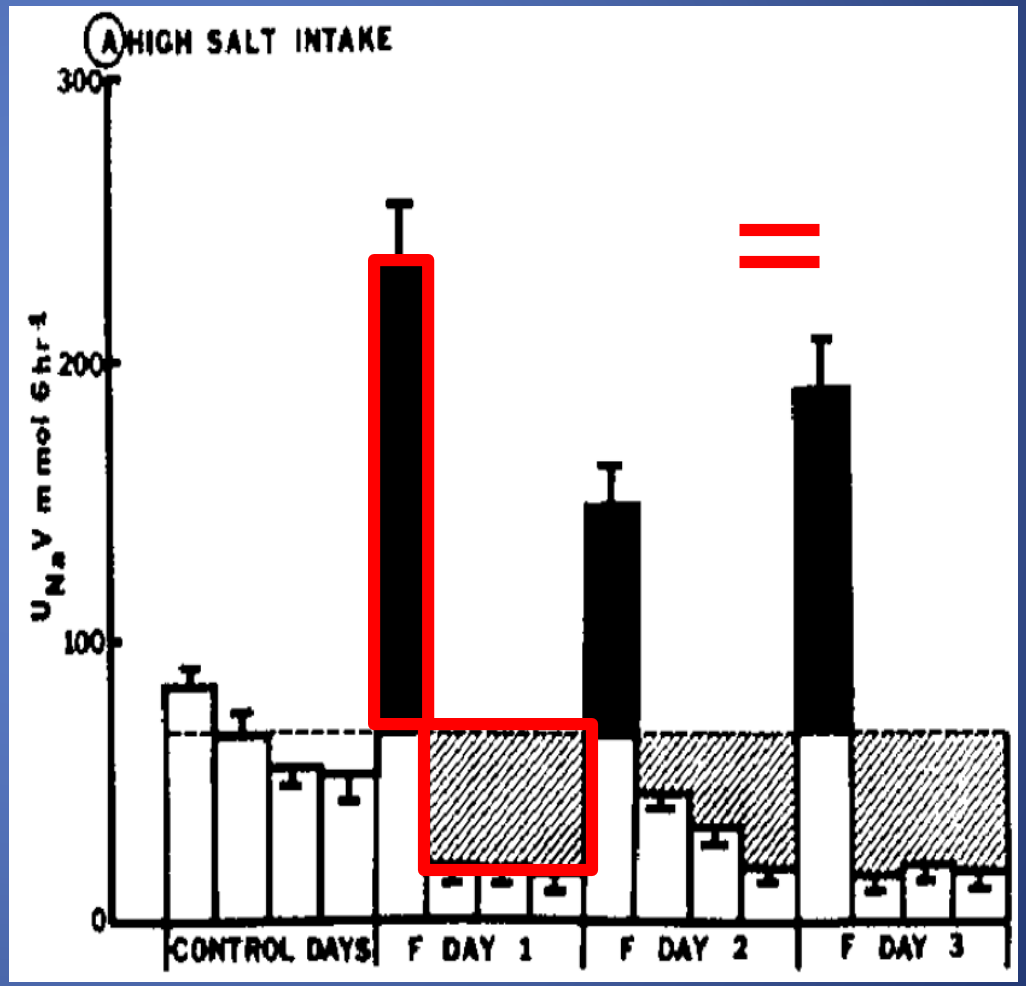
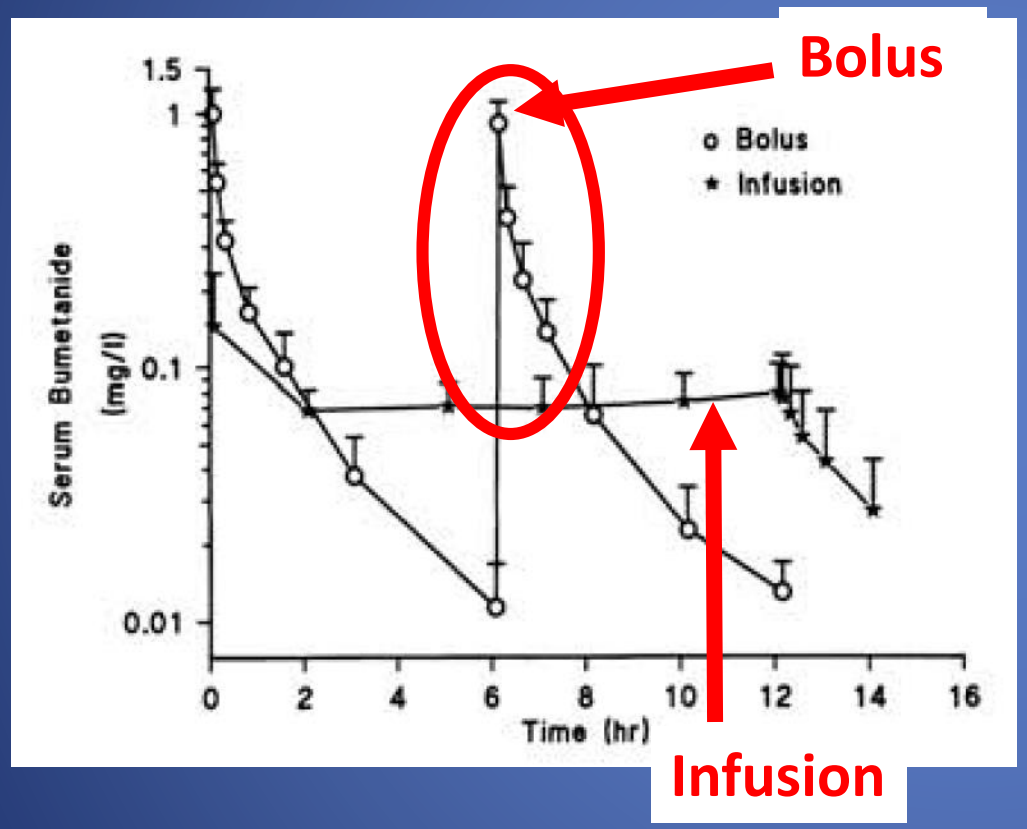
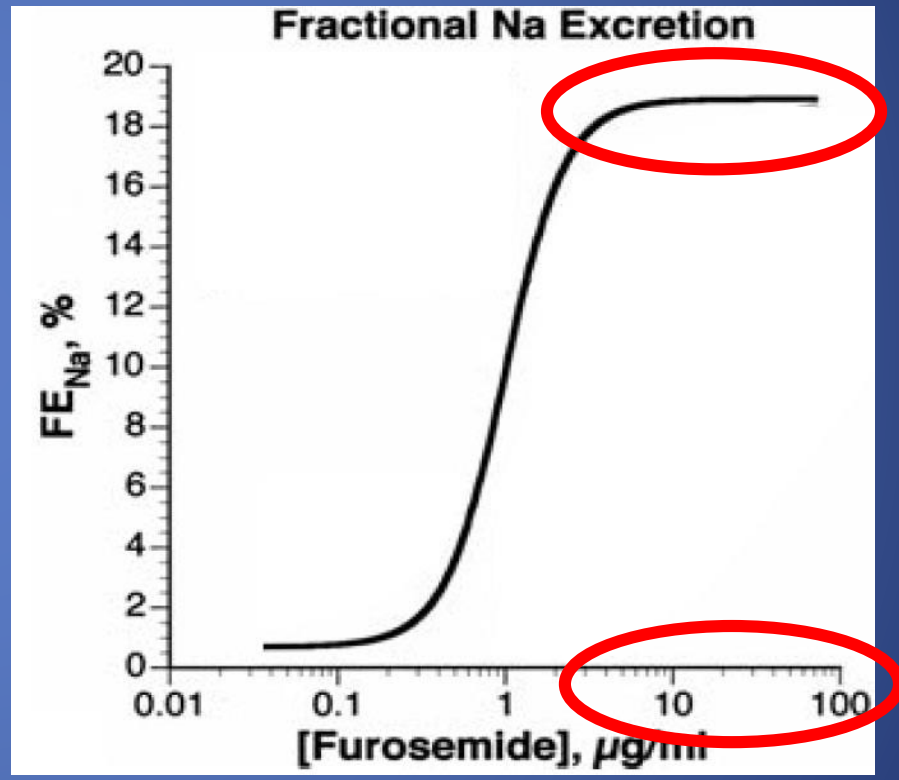


Wilcox, *J Lab Clin Med*. 1983 Sep;102(3):450-8.

Infusion "wastes" less diuretic with the high concentrations after a bolus





Rudy, *Annals of Internal Med*, 1991

Adapted from Ellison, *Cardiology*. 2001;96(3-4):132-43.

Results of the DOSE trial:

- Double blind randomized trial of continuous infusion vs. bolus (n=308).
- Net fluid output at 72 hours:
  - Bolus: 4.24 L
  - Continuous: 4.25L
- No significant difference in LOS, dyspnea, freedom from congestion at 72 hours, treatment failure
- Post hoc analysis:
  - Patients with the highest baseline diuretic requirement (i.e. those with diuretic resistance) actually did the worst with continuous infusion

Felker, *N Engl J Med*. 2011 Mar 3;364(9):797-805

DOSE trial is not the only trial to show less than spectacular results:

Table 1
Characteristics of the randomized controlled trials included in the meta-analysis

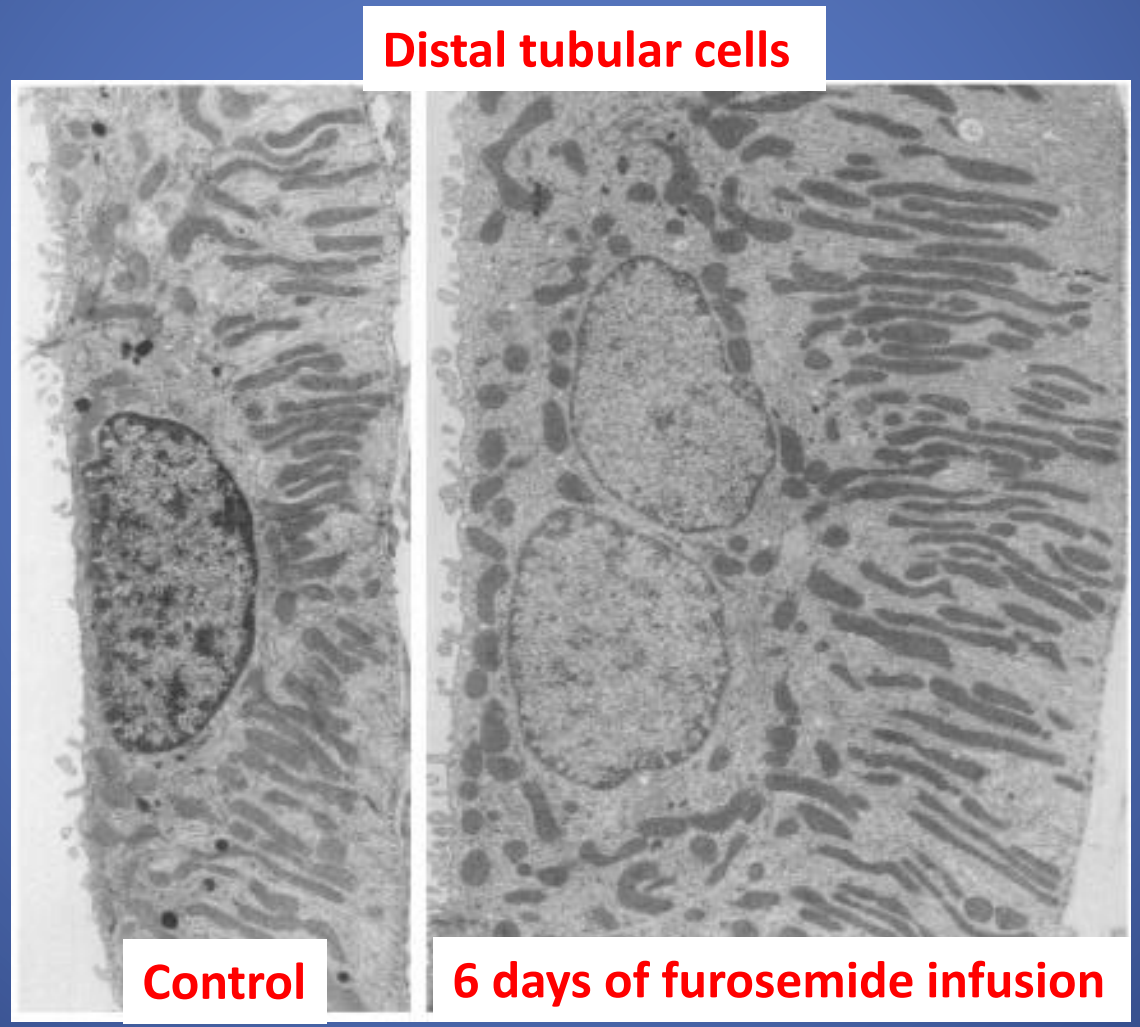
Author	Year	Population	Clinical setting	Study design	No. of patients	Mean age (y)	Loop diuretic	Duration of intervention (h)	Loading dose[a]	Prescribed furosemide (or equivalent) dose (mg/d)		Jadad score
										Continuous infusion	Intermittent infusion	
Copeland et al [14]	1983	Adults	Cardiac surgery	Parallel-arm	18	NR	Furosemide	12	No	90[b]		1
Rudy et al [12]	1991	Adults	Chronic kidney disease	Cross-over	8	40.8	Bumetanide	12	Yes	960[b]		1
Singh et al [34]	1992	Children	Cardiac surgery	Parallel arm	20	1.9	Furosemide	24	Yes	4.9[c]	6.2[c]	1
Lahav et al [20]	1992	Adults	Heart failure (classes III and IV[d])	Cross-over	9	74.1	Furosemide	48	Yes	90-120[b]		1
Dormans et al [5]	1996	Adults	Heart failure (classes III and IV[d])	Cross-over	20	71.0	Furosemide	8	Yes	690[b]		1
Kramer et al [19]	1996	Adults	Heart failure (classes II and III[d])	Cross-over	8	53.4	Torsemide	24	Yes	200[b]		1
Luciani et al [32]	1997	Children	Cardiac surgery	Parallel arm	26	0.3	Furosemide	24	Yes	2.5[c]	6.8[c]	1
Klinge et al [33]	1997	Children	Cardiac surgery	Parallel arm	46	2.8	Furosemide	72	No	2.1[c]	1.6[c]	2
Aaser et al [3]	1997	Adults	Heart failure (classes II and III[d])	Cross-over	8	54.0	Furosemide	24	No	145[b]		1
Schuller et al [23]	1997	Adults	Medical intensive care unit	Parallel arm	33	64.0	Furosemide	24	Yes	320	320	1
Pivac et al [7]	1998	Adults	Heart failure (classes III and IV[d])	Cross-over	20	62.2	Furosemide	24	No	80[b]		1
Mojtahedzadeh et al [21]	2004	Adults	Medical intensive care unit	Parallel arm	22	NR	Furosemide	36	Yes	320	320	1
Ostermann et al [22]	2007	Adults	Medical and surgical intensive care unit	Parallel arm	56	64.0	Furosemide	72	Yes	221	576	5
Sanjay et al [13]	2008	Adults	Chronic kidney disease	Cross-over	42	53.6	Furosemide	4	Yes	360-1440[b]		2
Kunt et al [15]	2009	Adults	Cardiac surgery	Parallel arm	100	65.6	Furosemide	24	No	240[b]		4
Allen et al [4]	2010	Adults	Acute decompensated heart failure	Parallel arm	41	59.5	Furosemide	24	No	162[b]		3
Thomson et al [8]	2010	Adults	Acute decompensated heart failure	Parallel arm	56	55.5	Furosemide	86-112	No	197	172	3
Felker et al [6]	2011	Adults	Acute decompensated heart failure	Parallel arm	308	66.0	Furosemide	72	No	160	198	5

Alqahtani, J Crit Care, 2014

So why didn't it work?

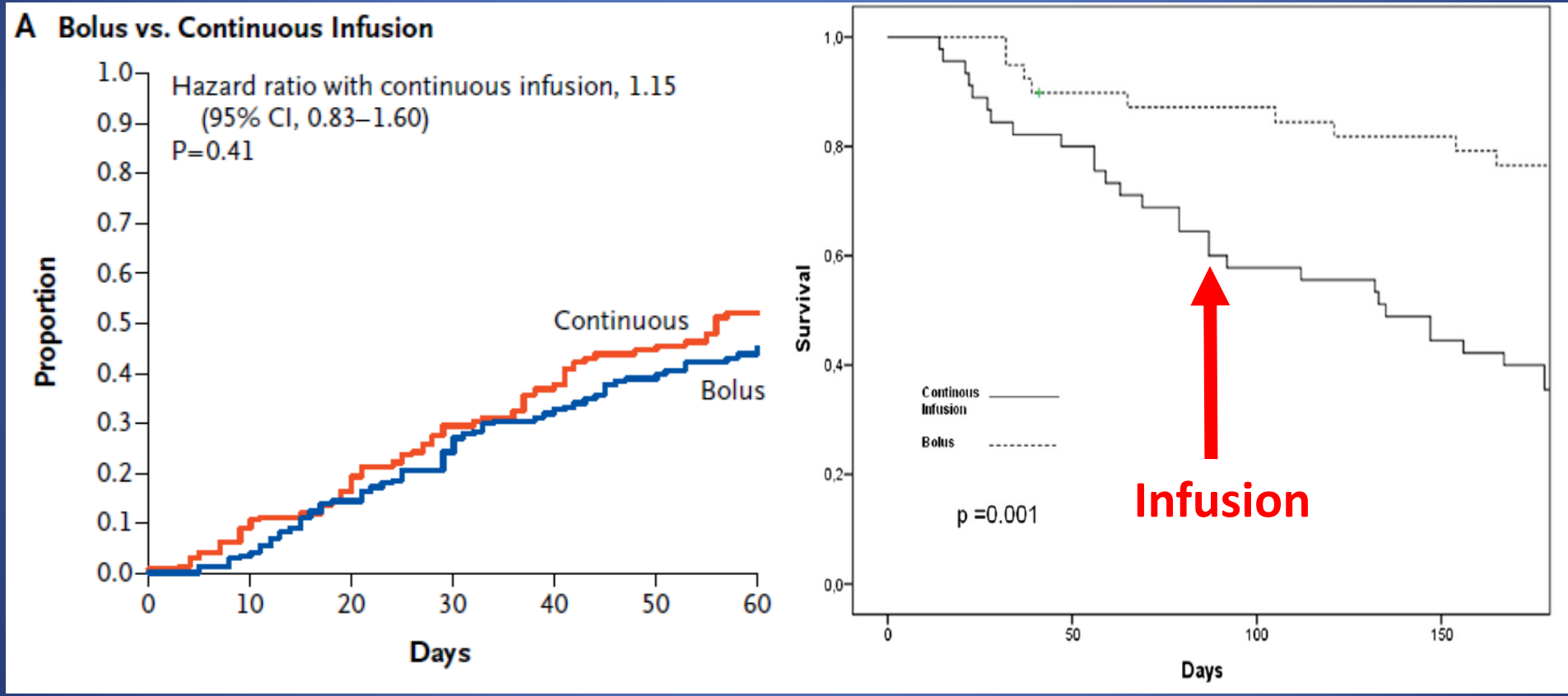
- Lasix is a poison as far as the kidney is concerned so it fights back

Continuous exposure of the kidney to loop diuretic causes massive structural remodeling



Kaissling B Am J Physiol. 1985 :F374-81.

Possibly worsened outcomes!



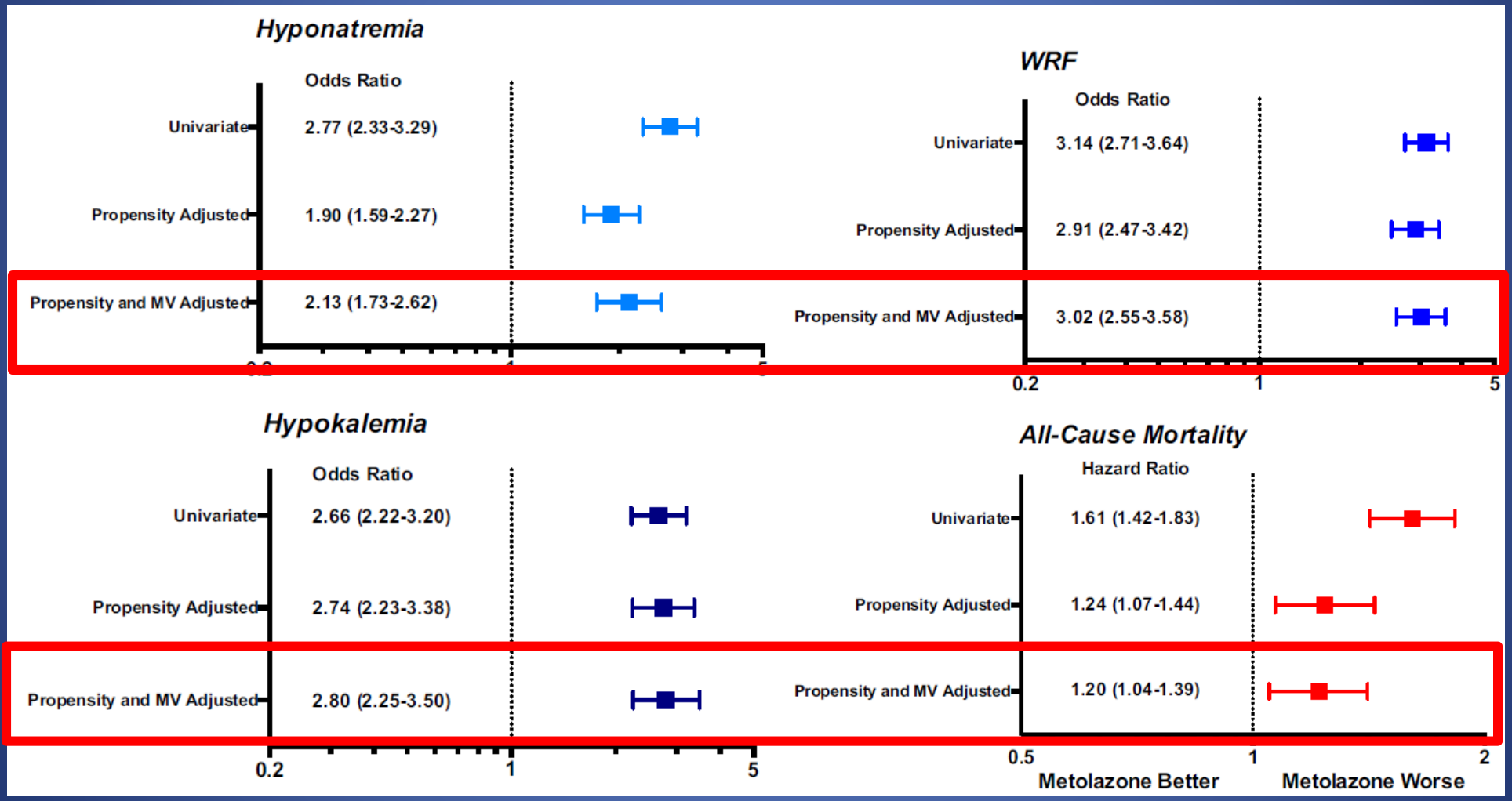
Felker, *NEJM*. 2011 Mar 3;364(9):797-805

Palazzuoli, *Crit Care*. 2014 Jun 28;18(3):R134

What do we do when high dose loop diuretic doesn't work: Adjuvant thiazides

- Observational data on thiazides found associations between thiazide use and:
  - Deterioration in renal function
  - Hyponatremia
  - Severe hypokalemia
  - Increased death/rehospitalization
- Some of this is driven by confounding by indication
  - Only the sickest patients receive thiazides

We have not been able to prove this…..



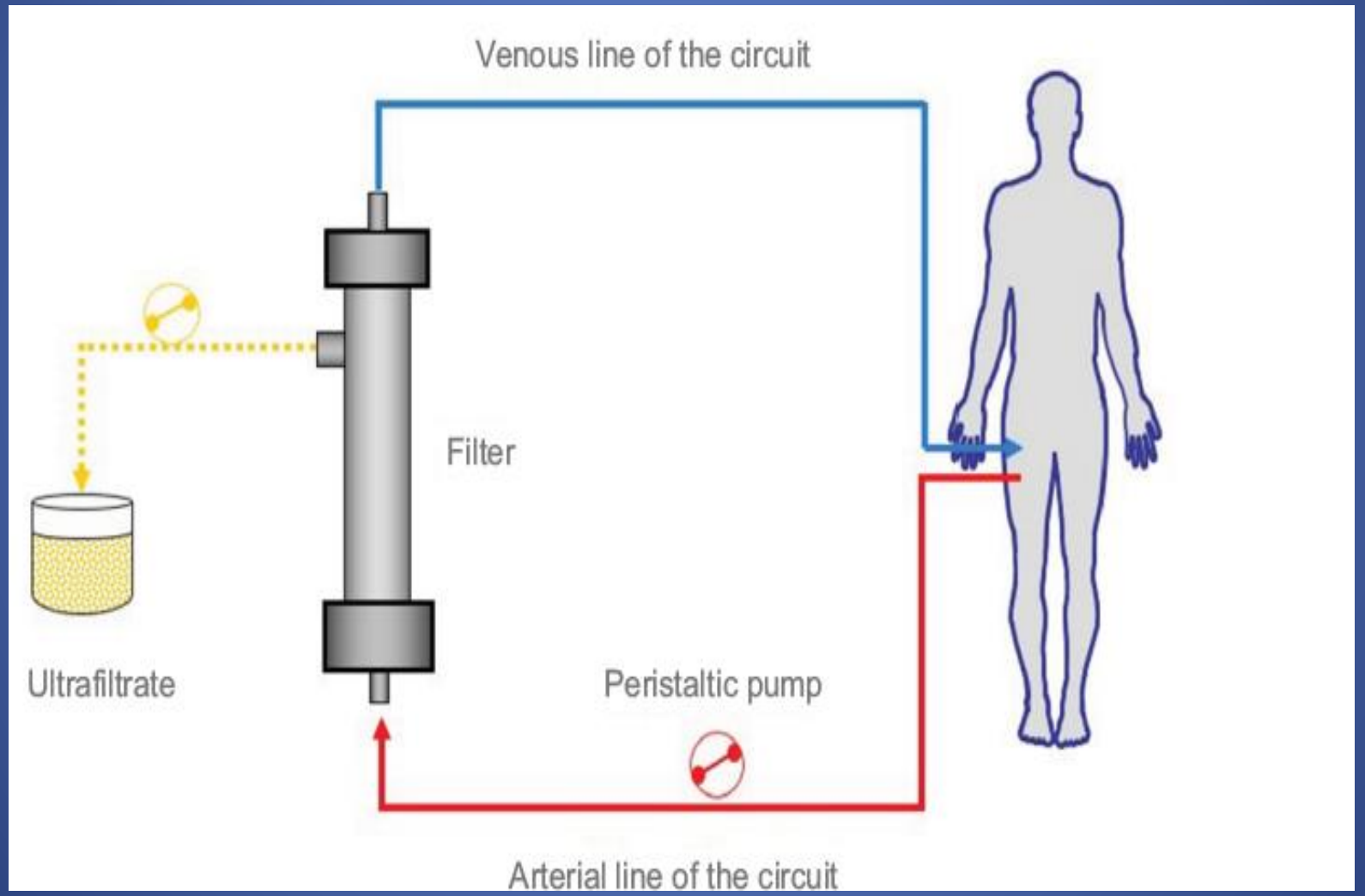
Yale SCHOOL OF MEDICINE

Brisco-Bacik, JAHA 2018

Summary so far

- Volume overload is the primary driver of HF symptoms, hospitalization, and quite possibly mortality
- Despite billions in pharma research, no new therapies have been successful
- As a result, we continue to rely on loop diuretics despite
  - Direct dose dependent adverse effects
  - Rapid development of resistance
- We really need a non-renal method to control sodium and volume overload

The first non-renal volume management therapy for HF: Ultrafiltration



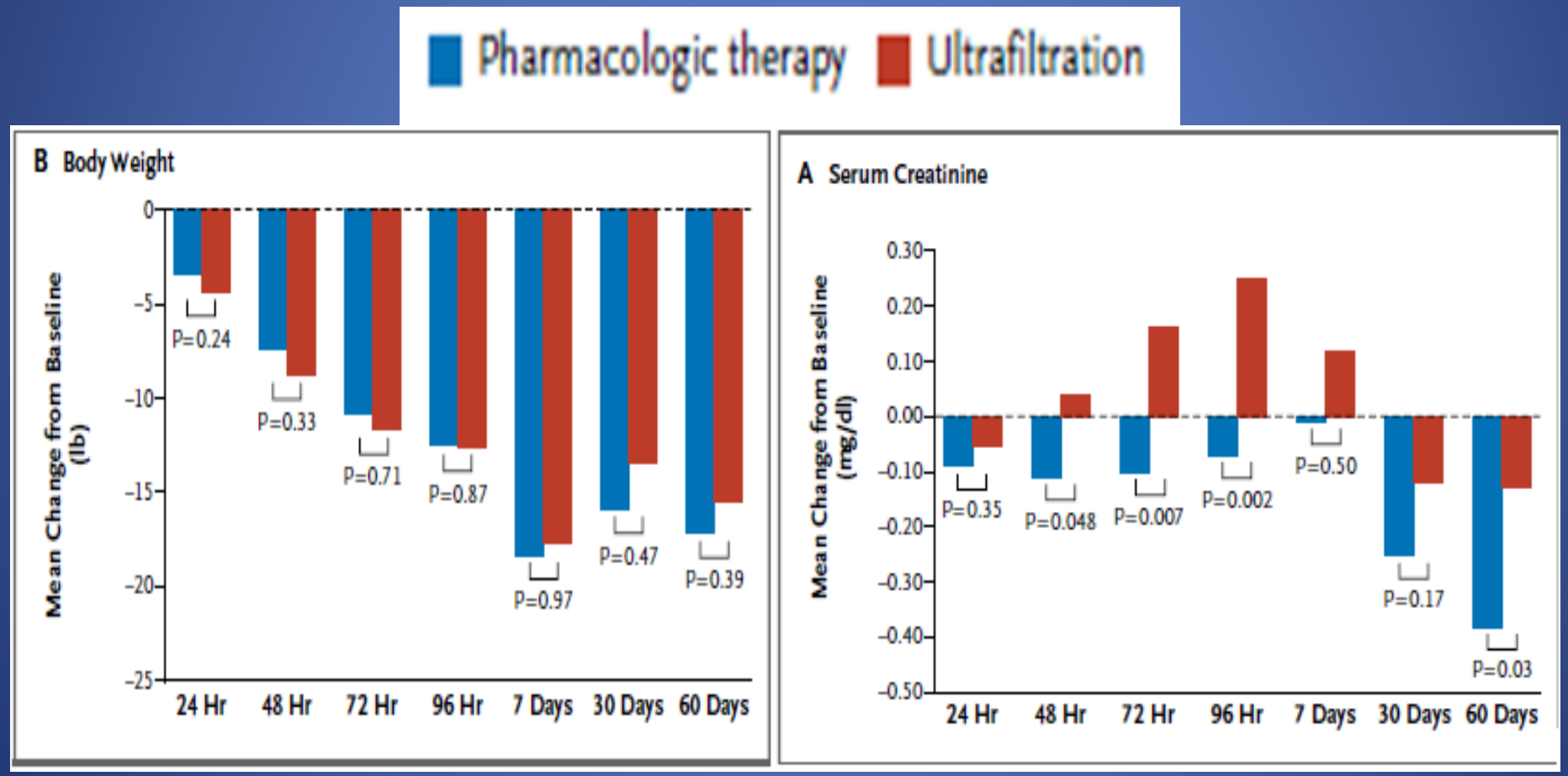
The first non-renal volume management therapy for HF: Ultrafiltration (UF)

- Pros:
  - Non-renal approach to sodium removal
    - Thus not dependent on the kidney "cooperating" to get sodium out
  - High sodium content fluid removed
  - Large quantities of sodium can be removed
- Cons:
  - Requires venous access with high blood flow rate (usually large bore central)
    - Makes chronic therapy very challenging
  - High nursing demands to operate with traditional UF systems available in most hospitals
    - ICU level care with 1:1 nursing ratio
  - High consumable costs
  - Rate of fluid removal independent of excess amount of fluid patient has
    - This can lead "overshooting" with hemodynamic and renal complications

CARRESS HF dampened enthusiasm for UF:

- Demonstrated how hard this therapy was to use
- Despite this being conducted in the premiere HF centers of excellence
  - Delay of 8 hours from randomization to initiation of UF
  - UF was only 40 out of the 96 planned hours
  - ~10% of patients included in the intention to treat analysis for UF never actually received UF
  - 30% of subjects received intravenous diuretics during UF period

Results: Similar weight loss with worse renal function



Bart, *N Engl J Med*. 2012:2296-304

My diuretic resistance algorithm:

Maximize loop diuretic dose
(Bumetanide 12.5mg TID)

↓

Maximize Thiazide diuretic
(metolazone 10mg TID)

↓

Maximize other segment blockade
(spironolactone 100mg TID, acetazolamide 1000mg BID,
±empagliflozin 25 QD, ± amiloride 10 BID)

↓

Dopamine 3 mcg/kg/min

↓

Hypertonic saline

↓

Ultrafiltration Hospice

The peritoneum is an alternative “membrane” that can be used for ultrafiltration

- The peritoneal membrane is a large surface area natural membrane in the body that can be used for dialysis (toxin removal) or ultrafiltration (fluid and solute removal)
- Peritoneal dialysis (PD) is a commonly utilized for therapy for patients with ESRD which utilizes the peritoneal membrane

ESRD: End Stage Renal Disease

Why is peritoneal dialysis (PD) not used more frequently in HF?

- Standard PD has several limitations:
  - Large volumes (~8 to 10 liters) and long dwell times with the patient connected to PD cycler
  - External catheter with infection risks
  - Dialysis stigma

- Only modest fluid and sodium removal with standard PD solutions
  - PD is designed primary to “clean” the blood rather than remove sodium

Can we use the peritoneal membrane more efficiently to directly remove sodium in HF patients?

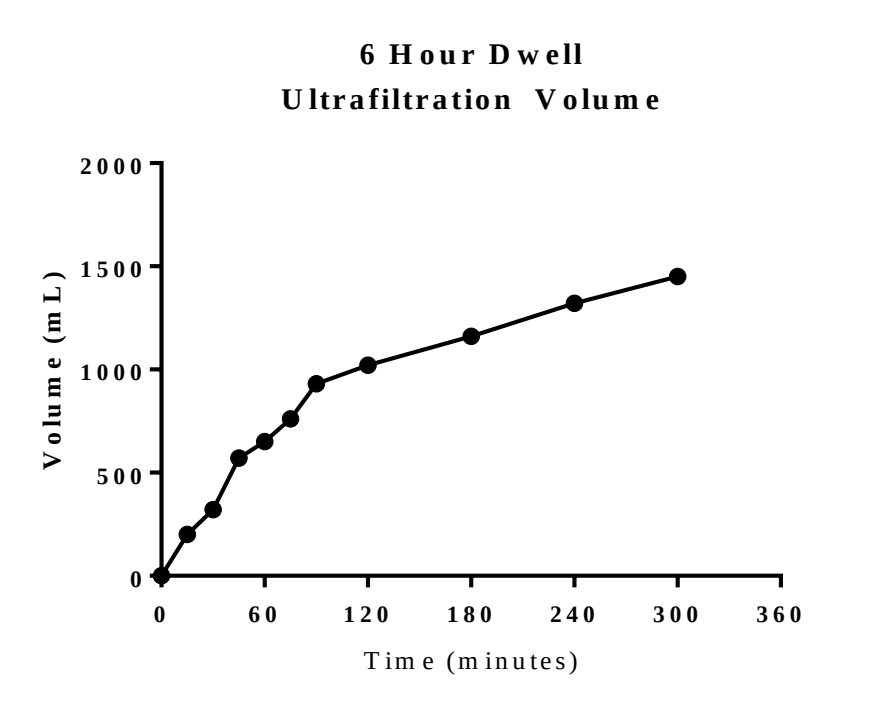
- Most HF patients have acceptably functioning kidneys
  - No need to “clean” the blood
- Standard PD solutions have ~7.5 grams of salt per liter
  - Nearly isotonic to plasma (~132 mmol/L)
  - Very small gradient for sodium to diffuse

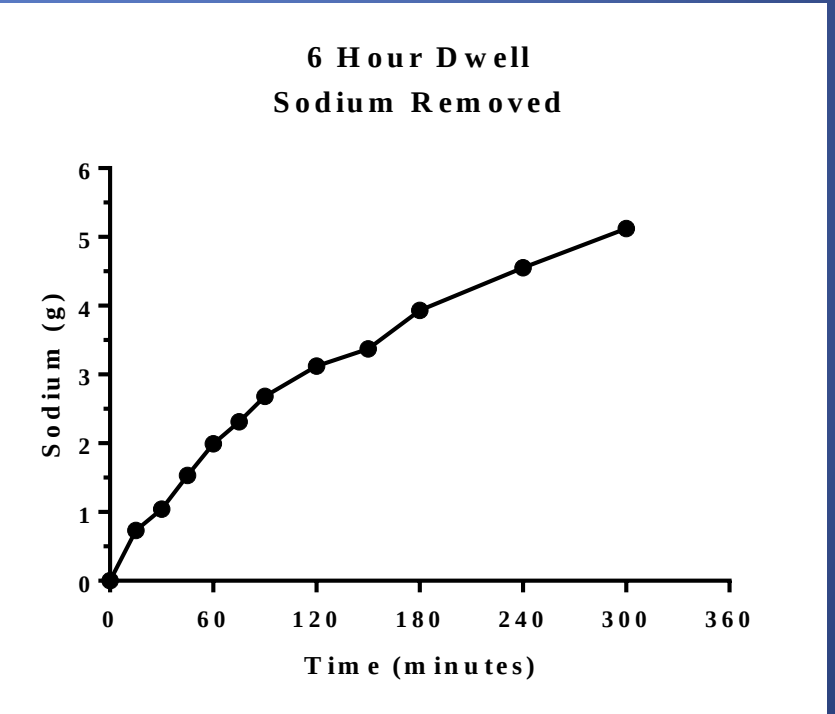
Direct Sodium Removal (DSR) concept

- The salt is necessary in traditional PD solutions to make them safe to use to clean the blood
  - This is not needed for most HF patients
- With a zero sodium solution, we should be able to get much more sodium removal with less volume than standard PD fluid
  - In addition to ultrafiltration, we can capitalize on diffusion down a huge concentration gradient (~140mmol/L vs. 0 mmol/L)
- Lower volume of fluid allows for alternatives to the standard PD catheter to get fluid in and out of peritoneum

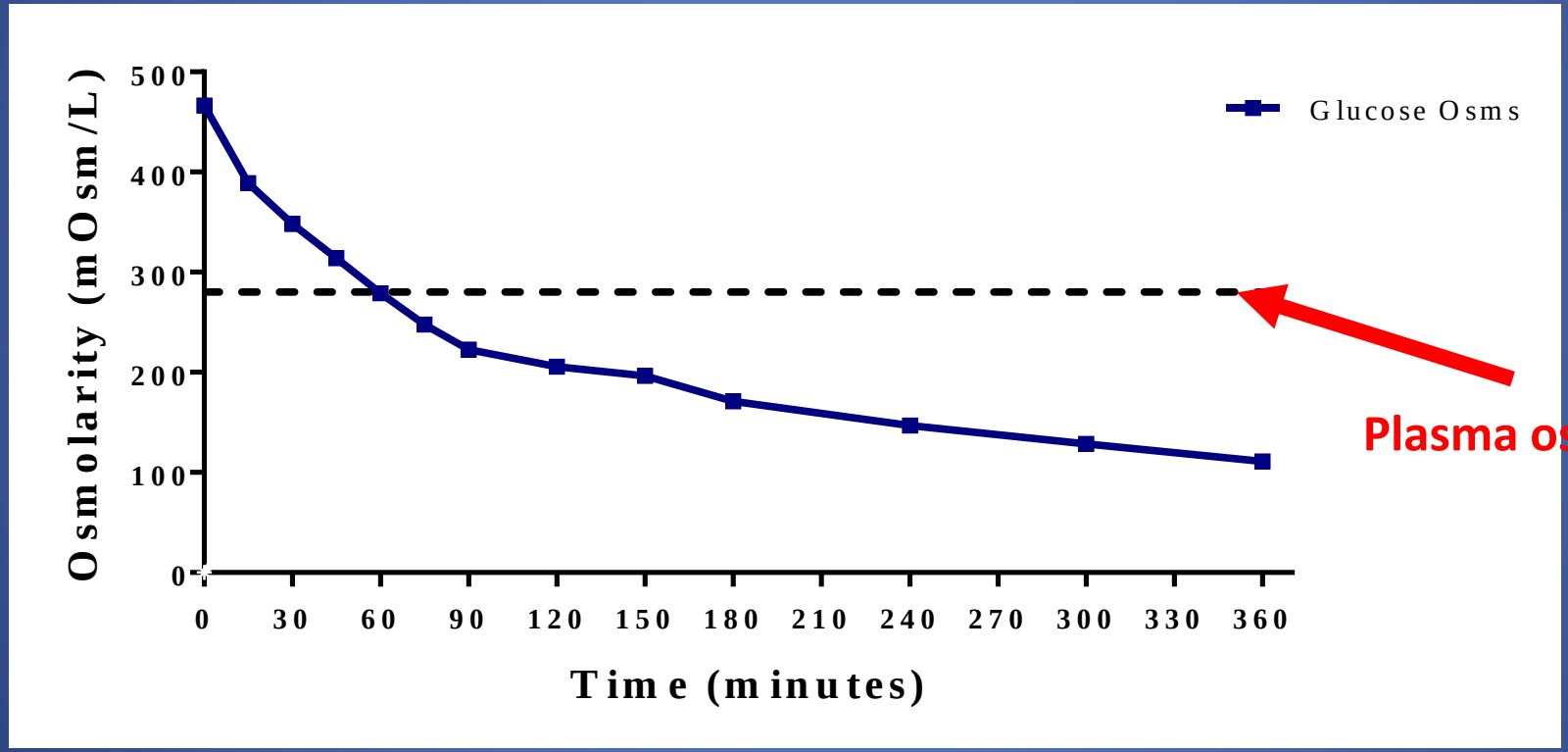
DSR: Proof of concept porcine experiment

- 1L instillation of 10% dextrose in water, zero sodium
- Dwell time of 6 hours

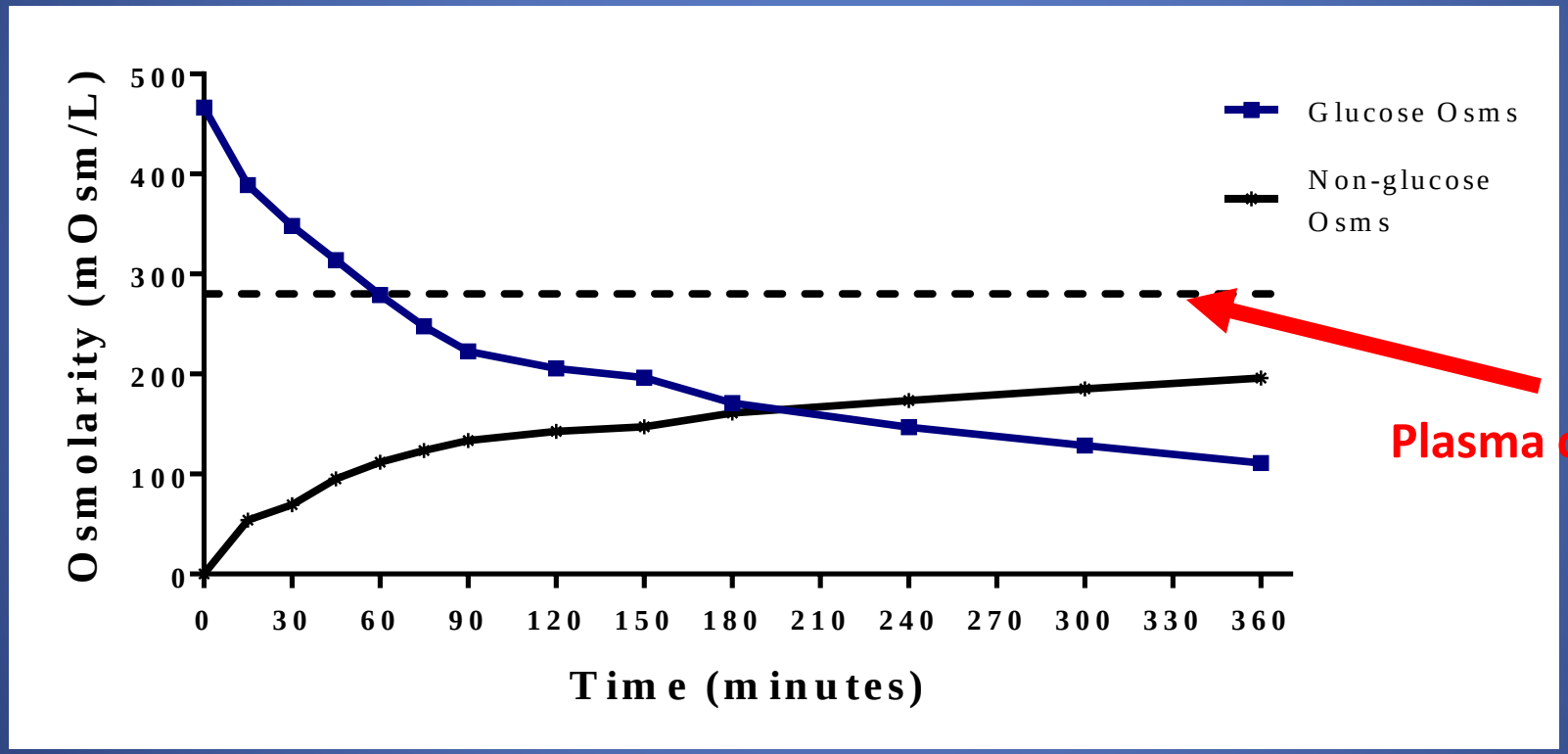




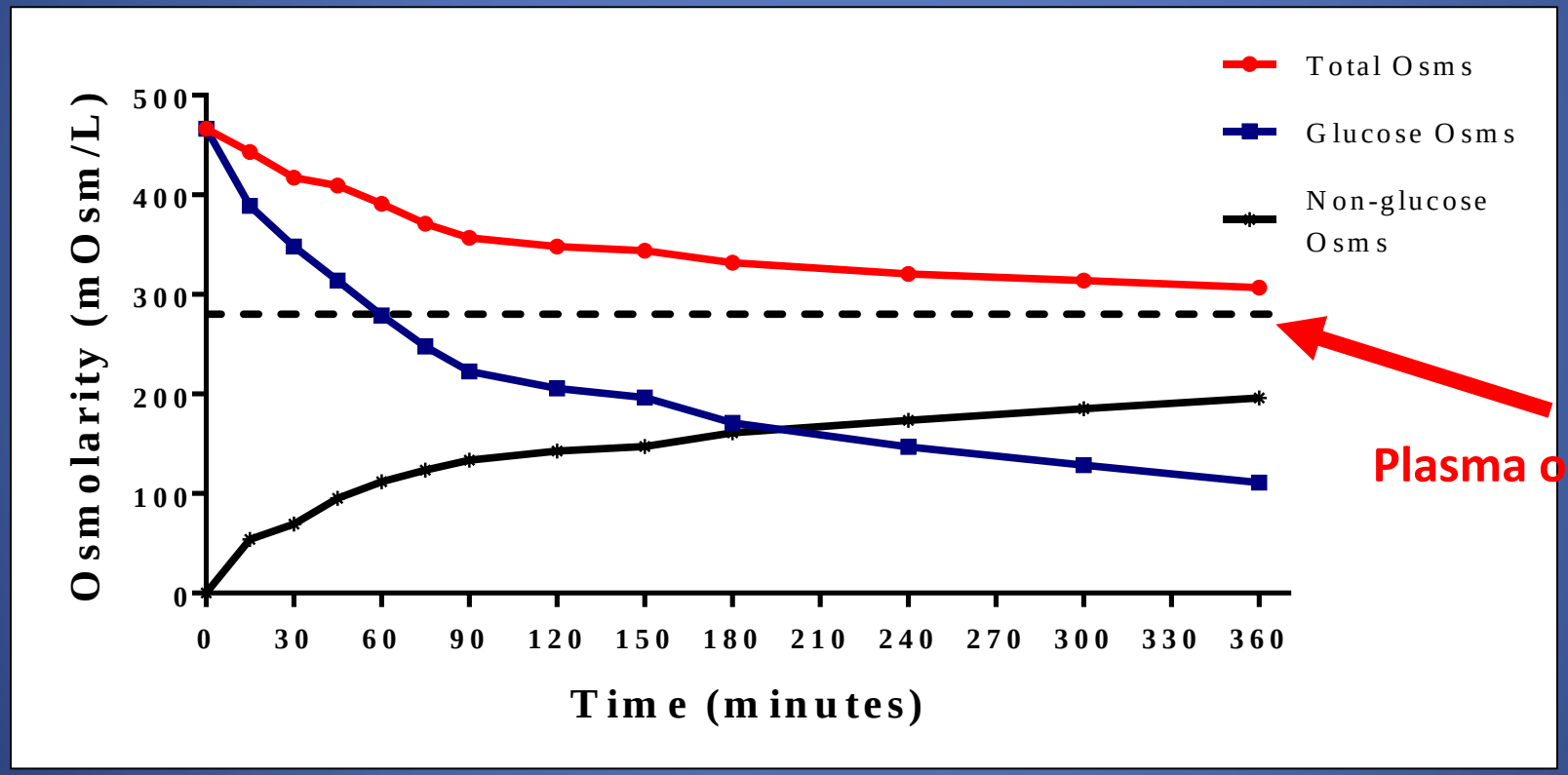
DSR: Osmotic gradient is maintained over time



DSR: Osmotic gradient is maintained over time

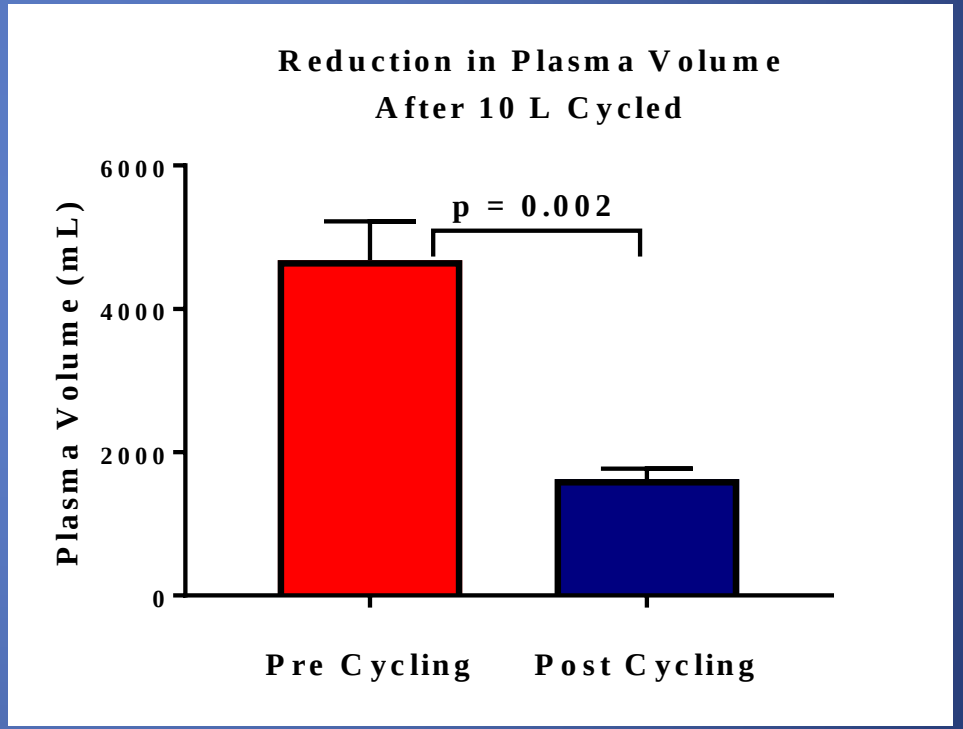


DSR: Osmotic gradient is maintained over time

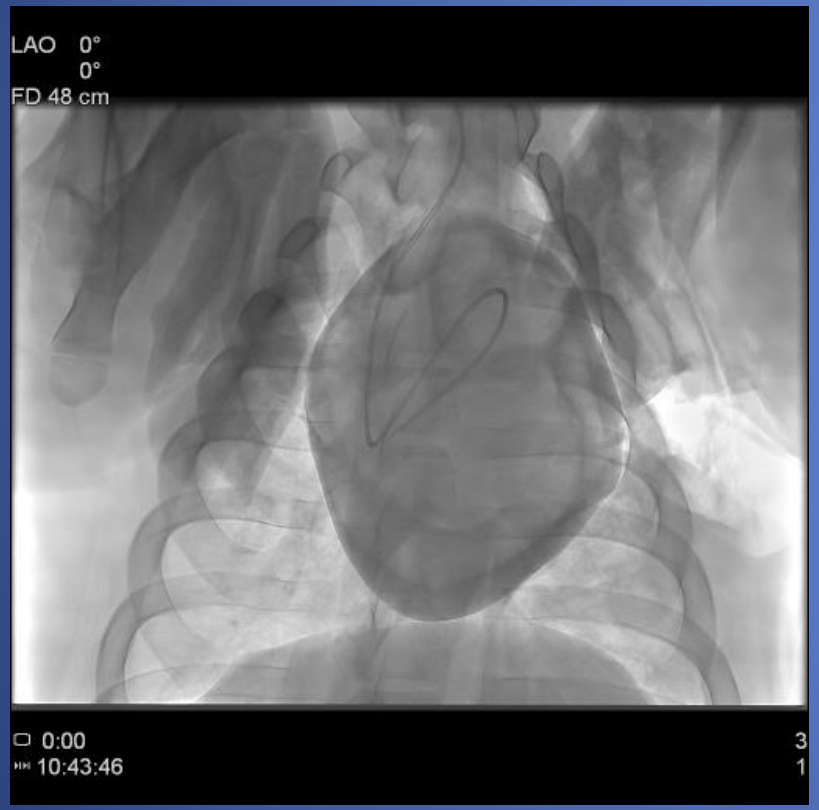


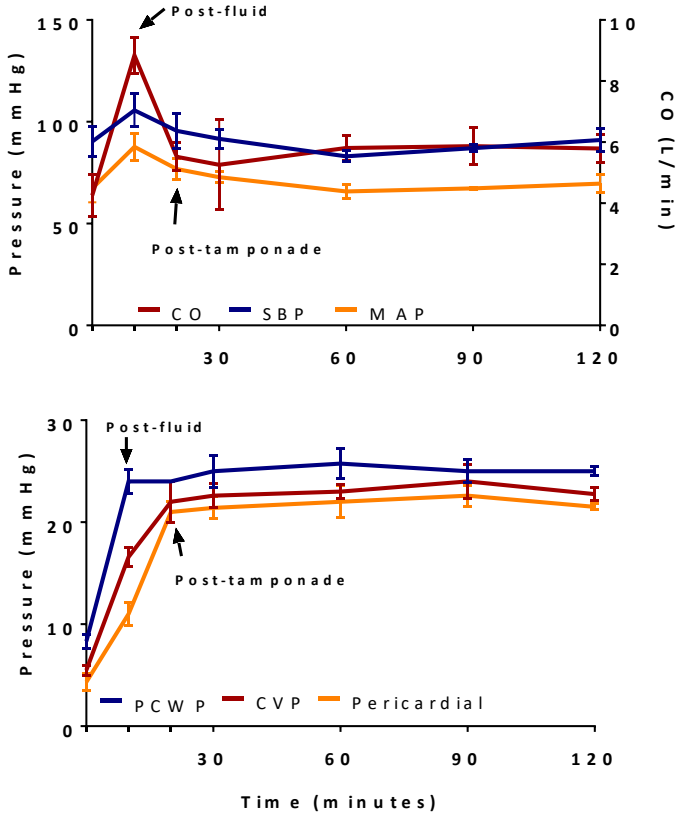
DSR: Huge quantities of sodium can be removed

- 10L of 10% dextrose cycled over 6 hours
- 52.8 +/- 8.2 g of salt was removed
- 65% reduction in plasma volume

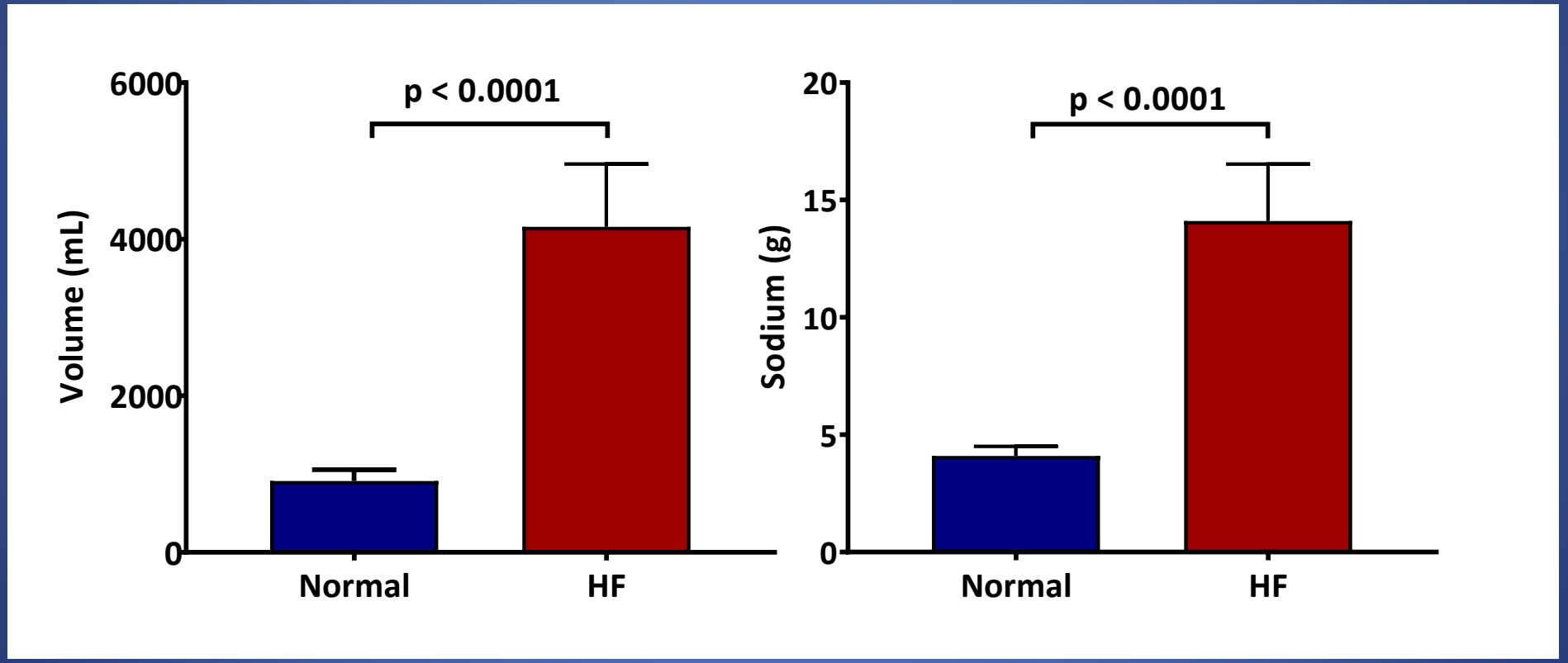


What happens in HF?





Substantially greater UF and salt removal in setting of HF



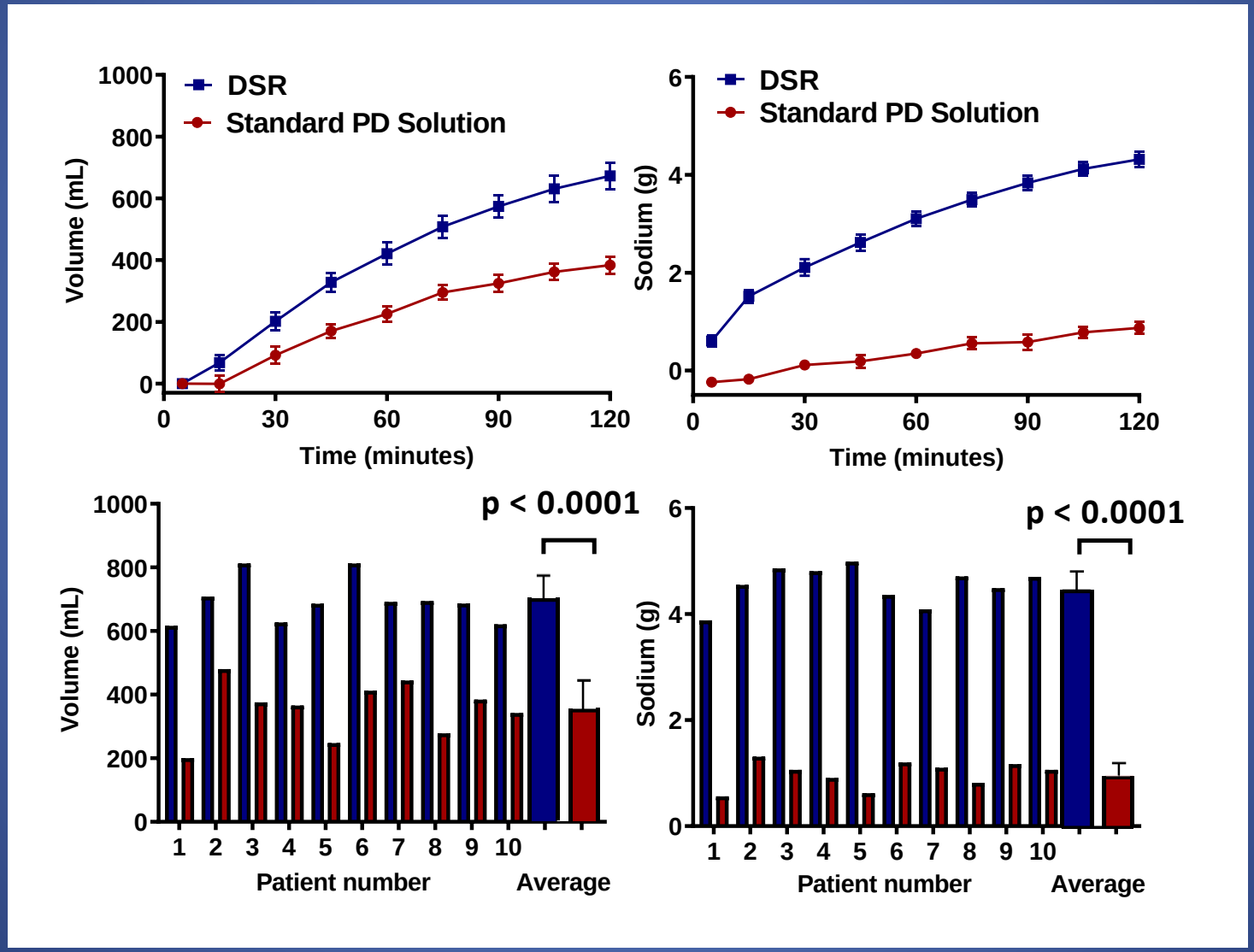
DSR first in human proof of concept: Design

- **Design:**
  - Randomized open label crossover of DSR vs. standard PD solution
  - Conducted in prevalent PD patients rather than normal subjects due to the risks of PD catheter placement
- **Intervention:**
  - DSR solution: Sodium free 10% dextrose
  - Standard PD solution: 4.25% dextrose standard PD solution (Dianeal, Baxter)
    - Both solutions are approximately 500 mOsm/L
    - 4.25% dextrose PD solution is the “strongest” commercially available product
  - One liter of either solution was infused into the peritoneum and left to dwell for 2 hours
  - Crossover to the alternate solution one week later
- **Endpoints:**
  - Primary: Safety/tolerability defined as completion of the 2-hour dwell without significant discomfort or AE
  - Secondary efficacy endpoint: Difference in sodium removal between DSR solution and standard PD solution

Primary endpoint: Safety and tolerability

- Primary endpoint:
  - All patients completed the 2 hour dwell without adverse event or significant discomfort causing protocol discontinuation
- Mild cramping during fluid instillation lasting <30 minutes occurred in 2 patients
  - One had cramping with DSR solution only
  - One had cramping with both solutions
  - Most patients stated instillation of the DSR solution felt the same as their standard PD solution
- Negligible removal of non-target solutes
  - Potassium (5.7 mmol)
  - Magnesium (1.1 mmol)
  - Phosphorus (2.0 mmol)
  - Calcium (1.7 mmol)
- Stable plasma electrolytes
- Absence of significant or sustained hyperglycemia

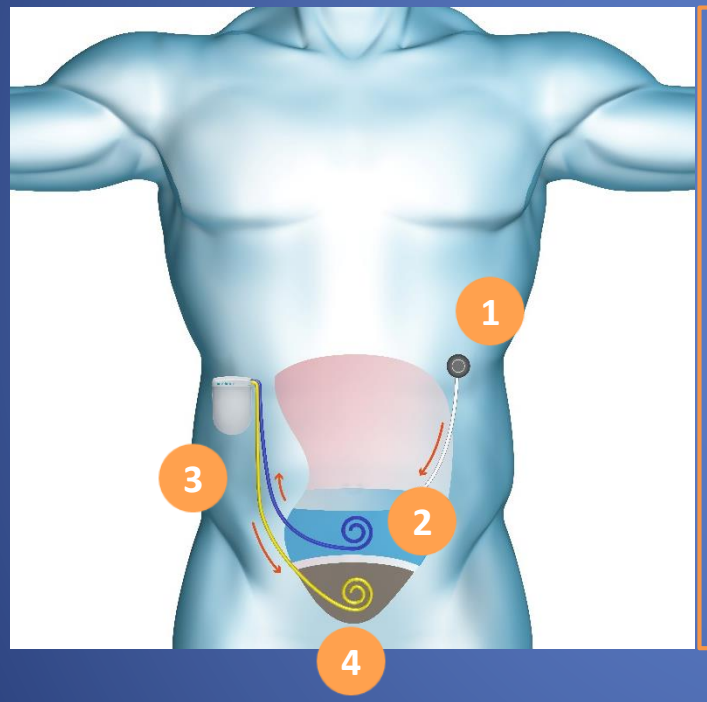
Secondary efficacy endpoint:
Sodium removal was substantially greater with DSR



Proof of concept conclusion

- These data provide proof of concept that Direct Sodium Removal with a sodium-free peritoneal solution is feasible in humans
- Safety/tolerability:
  - Well tolerated
  - Minimal off target solute removal
  - Did not result in significant electrolyte disturbances or prolonged or severe hyperglycemia
- Efficacy:
  - Substantial sodium removal
    - Nearly 5 grams of sodium with a 2 hour treatment

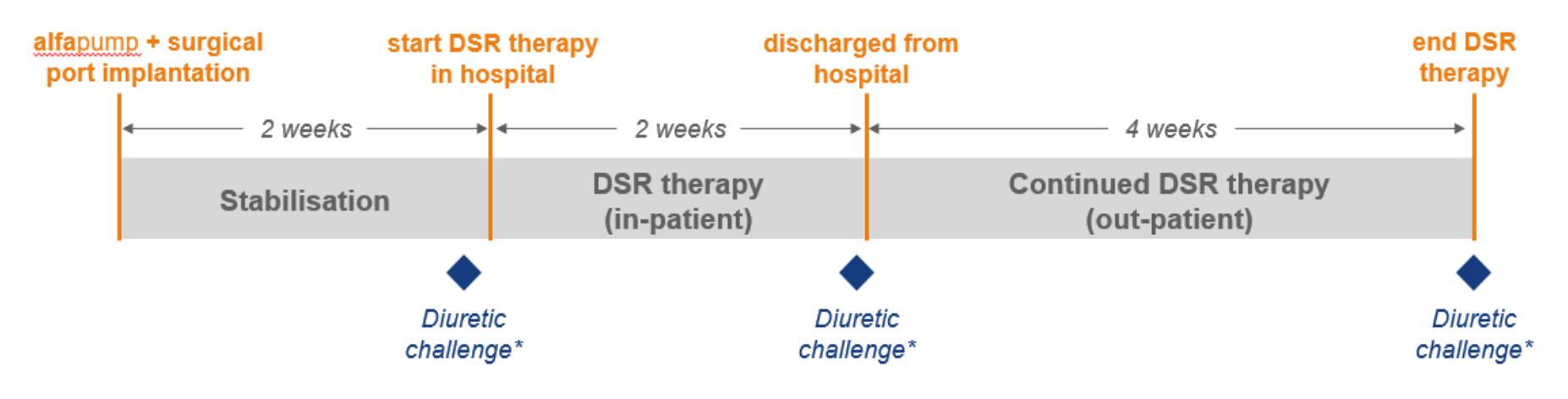
alfapump® DSR – Potential chronic therapy for heart failure patients with fluid overload not well controlled on diuretics



1. Administration of sodium-free DSR infusate to peritoneal cavity via implanted port
2. Sodium diffuses into DSR infusate
3. **alfa**pump pumps sodium-rich DSR infusate into the bladder
4. Body eliminates excess fluid through osmotic ultrafiltration and urination

RED DESERT study design

Repeated dose proof-of-concept study of alfapump® DSR in up to 10 diuretic-resistant heart failure patients



* intravenous dose of 40mg dose furosemide

Safety:	absence/rate of device, procedure and/or therapy related serious adverse events
Feasibility:	ability of the **alfa**pump DSR to maintain a neutral sodium balance and maintain euvolemia
Exploratory:	impact of DSR to restore response to diuretics (diuretic challenge)

RED DESERT Interim results

- 5 participants have completed the study
- Main findings:
  - Repeated dose **alfa**pump® DSR is well tolerated
  - Majority of patients lost weight and had reduction in natriuretic peptide levels
    - Despite volume loss all signs point toward improved renal function which is the opposite of what we see with diuretics
  - Loop diuretic response actually normalized in the majority of patients by the end of the study
  - Improved global sodium avidity of the patient
    - Most patients were not requiring full dose DSR by the end of therapy
    - Improvement in diuretic response durable for months in many patients
- Overall these preliminary findings provide optimism that **alfa**pump DSR therapy is fundamentally improving the cardio-renal substrate of the patient

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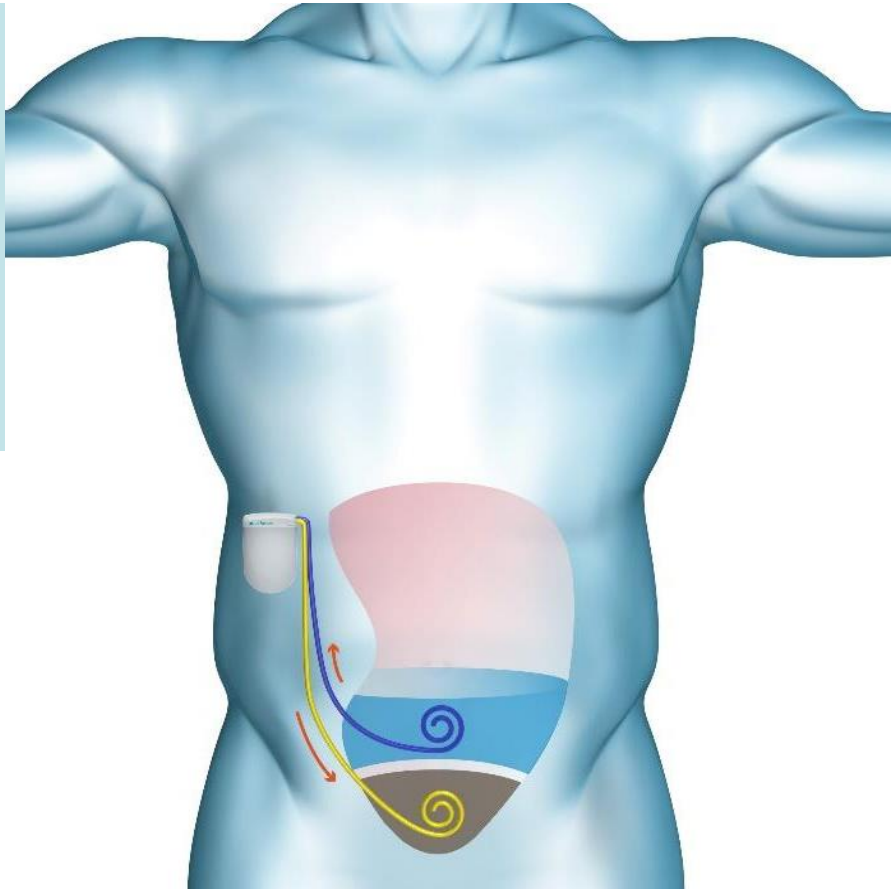
Innovators in the management of fluid overload

liver disease – malignant ascites – heart failure

Proven alfapump® platform in the management of fluid overload

alfapump – **Liver disease / NASH**

- ✓ CE mark + key clinical practice guidelines
- ✓ FDA breakthrough device designation
- ✓ Over 800 implants to date
- ✓ POSEIDON pivotal study in North America ongoing



Proven alfapump® platform in the management of fluid overload

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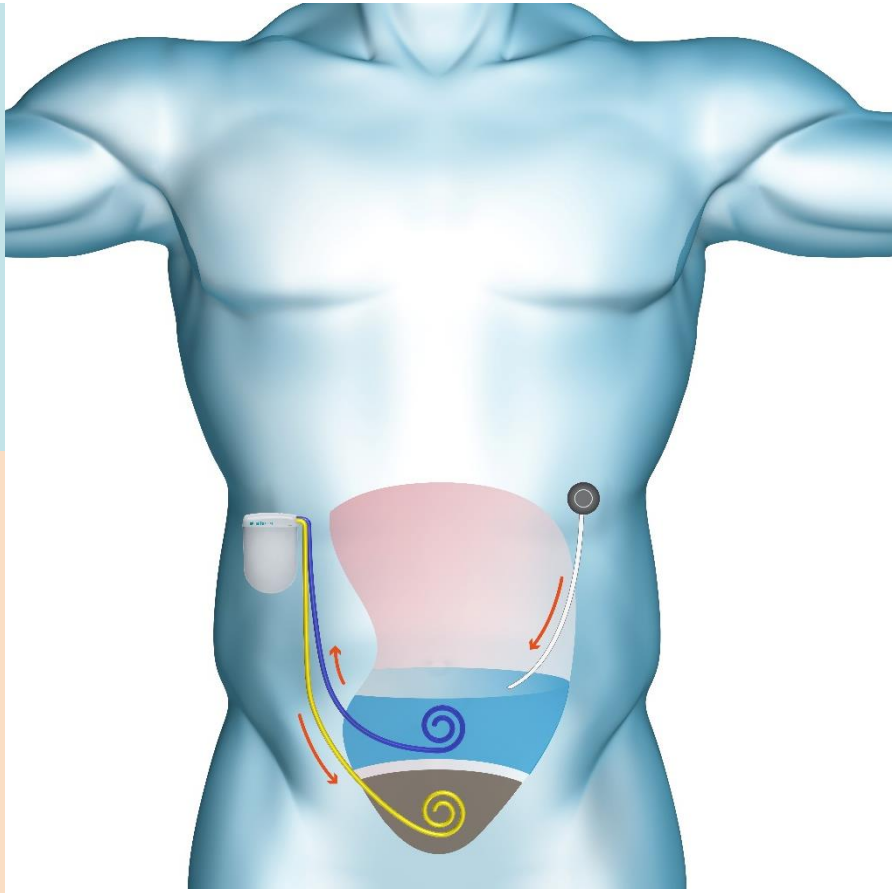
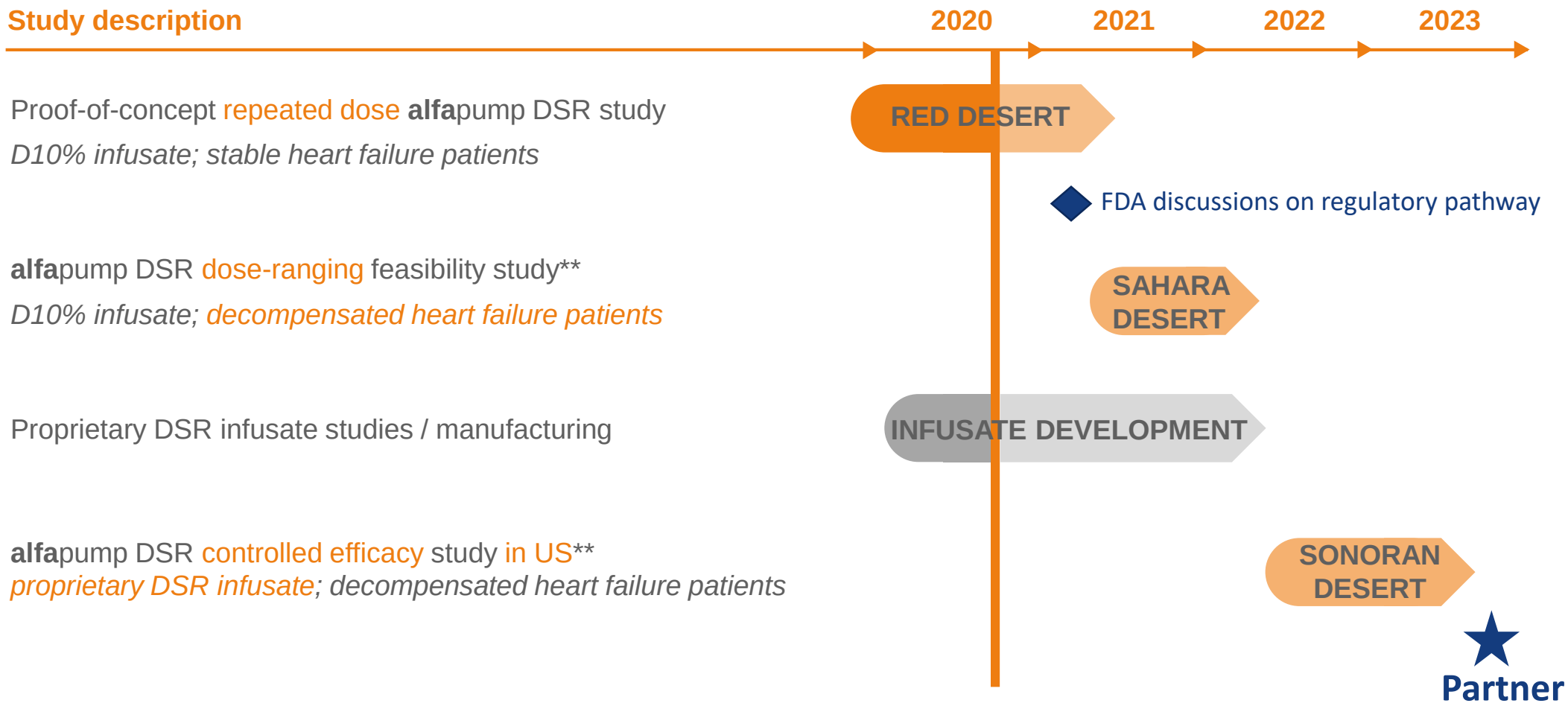
alfapump DSR – Heart Failure

- ✓ Built on proven **alfa**pump platform
- ✓ Clinical proof-of-concept of Direct Sodium Removal (DSR)
- ✓ Results published in *Circulation*
- ✓ RED DESERT repeated dose study ongoing

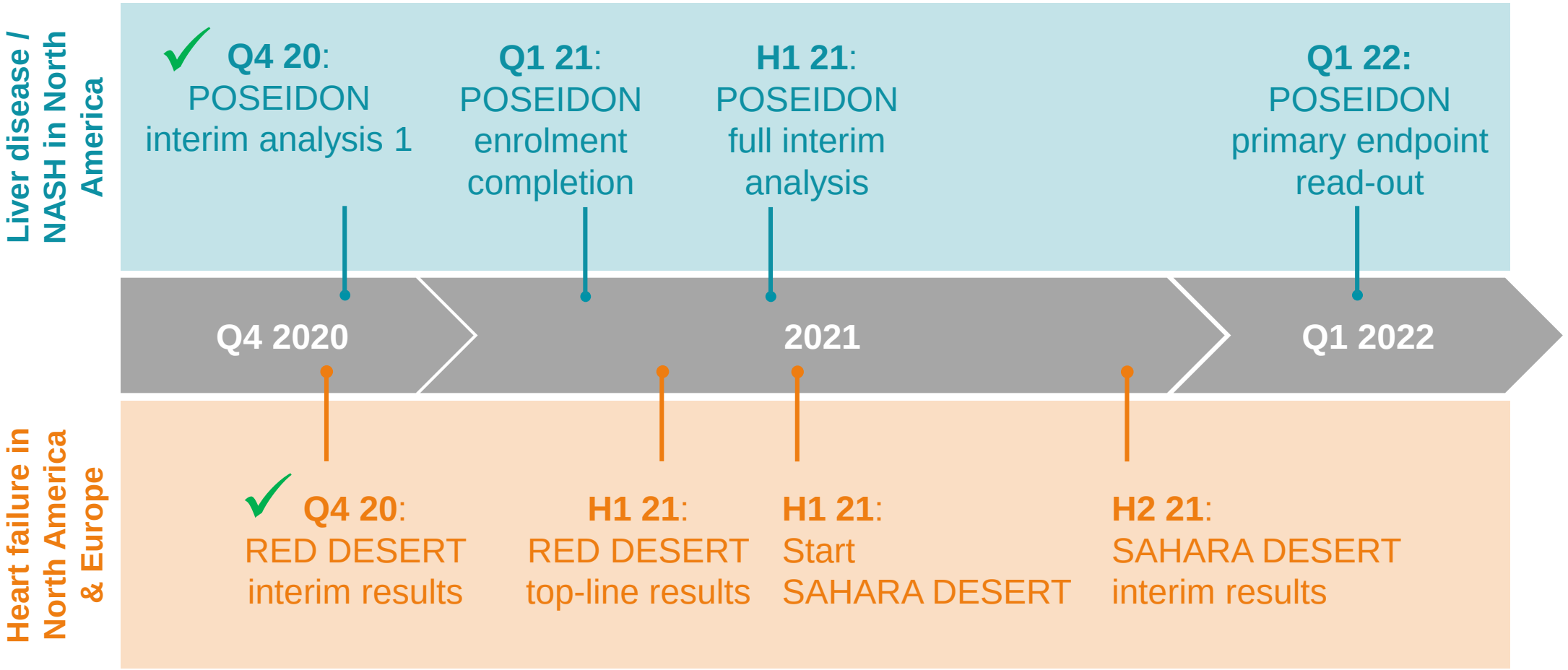


alfapump® DSR development strategy*



** Timelines subject to further developments related to the ongoing COVID-19 pandemic*
*** Subject to change and/or feedback from applicable regulatory authorities*

Expected core value drivers & outlook



Note: Presented timelines are subject to further developments related to the COVID-19 pandemic

Q&A

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