

How to Adjust Heart Failure Therapy When Kidney Function Declines

The Egyptian Society of Cardiology
44th Annual Congress “CardioEgypt 2017”
Tuesday, February 21st 2016

Eric J. Velazquez, MD, FACP, FACC, FAHA, FASE

Professor of Medicine
Director, Cardiac Diagnostic Unit & Echocardiography Laboratories
Director, Late Phase Cardiovascular Trials
Duke University Health System & Duke Clinical Research Institute



Disclosures

- **Research Grants**
 - *NHLBI*
 - *Amgen*
 - *Novartis*
 - *Pfizer*
 - *Alnylam*
- **Consultant**
 - *Novartis*
 - *Amgen*
 - *Merck*





How to Adjust HF Therapies When Kidney Function Declines

- Definitions
- Epidemiology
- Prior studies
- Guidelines
- Take Home Points

3

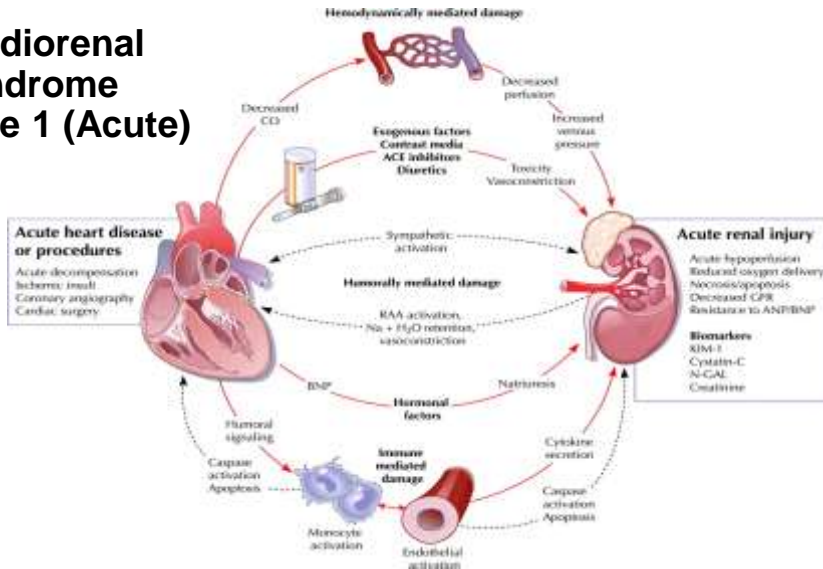


CRS Classification

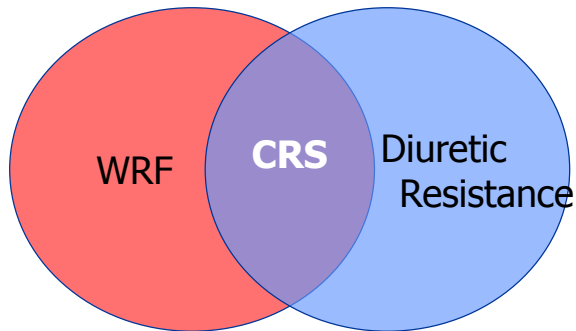
- ★ • **CRS Type 1:** Acute cardio-renal syndrome
 - *ADHF w worsening renal function/diuretic resistance*
- **CRS Type 2:** Chronic cardio-renal syndrome
 - *Chronic HF complicated by CKD*
- **CRS Type 3:** Acute reno-cardiac syndrome
 - *Acute renal glomerular disease leading to HF*
- **CRS Type 4:** Chronic reno-cardiac syndrome
 - *Advanced CKD leading to cardiac abnormalities (LVH, etc)*
- **CRS Type 5:** Systemic disease effects cardiac and renal function as a secondary phenomenon
 - *Amyloidosis leading to HF and RF*

Ronco C, et al. JACC 2008

Cardiorenal Syndrome Type 1 (Acute)



Cardio-renal Syndrome in Acute HF Patient



Persistent or worsening congestion associated with worsening renal function despite appropriate treatment



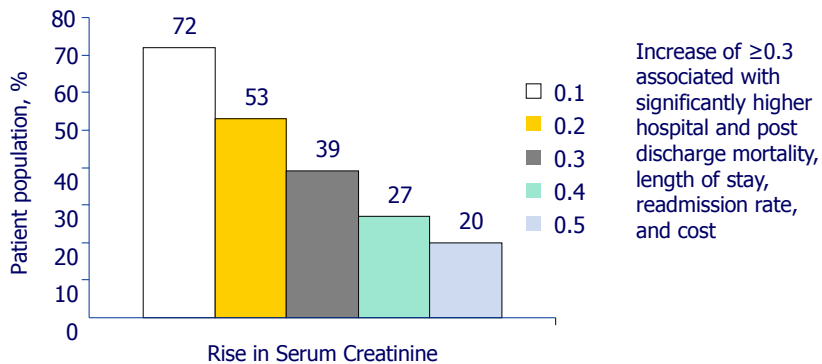
Some Thoughts on Nomenclature: WRF ≠ AKI!

- Worsening Renal Failure (WRF)
 - Generally equated with change in laboratory parameter of renal function (e.g., serum creatinine)
 - May or may not be associated with other signs of renal dysfunction (like urine output)
 - May or may not be associated with true renal injury
- Acute Kidney Injury (AKI)
 - Loss/injury to nephron units
 - May be subclinical (ie., AKI can occur without a change in serum creatinine or urine output)



Prevalence of WRF in ADHF

Multicenter, retrospective chart review of 1002 patients



Gottlieb SS, et al. J Card Fail. 2002



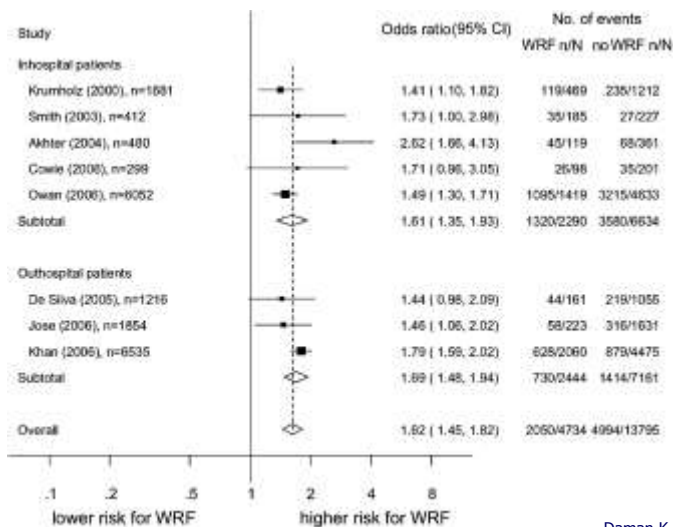


Prevalence of WRF in ADHF

Report	Year	N	WRF(%)	Definition
Gottlieb SS	2002	1002	39%	≥0.3mg/dl
Smith GL	2003	412	45%	≥0.3mg/dl
Owen TG	2006	6052	21-25%	>0.3mg/dl
Costanzo MR	2007	200	20-22%	>0.3mg/dl
Logeart D	2008	416	37%	>0.28mg/dl
Nohria A	2008	433	29.5%	≥0.3mg/dl



Association of WRF on Outcomes: Meta-Analysis

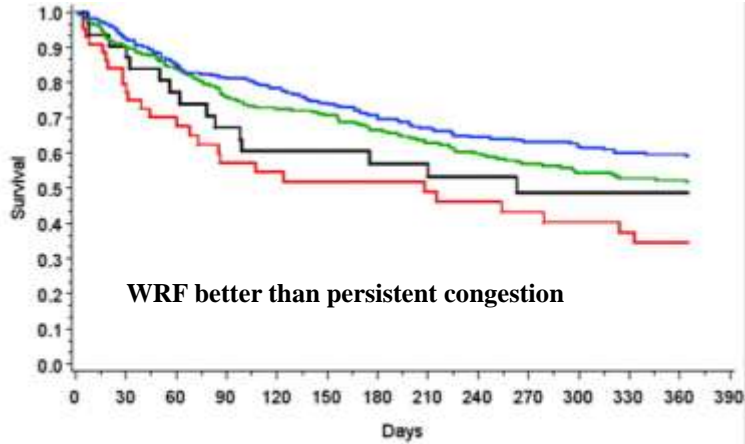


Daman K, et al. JCF 2007





Trade-offs Between WRF and Congestion in AHF

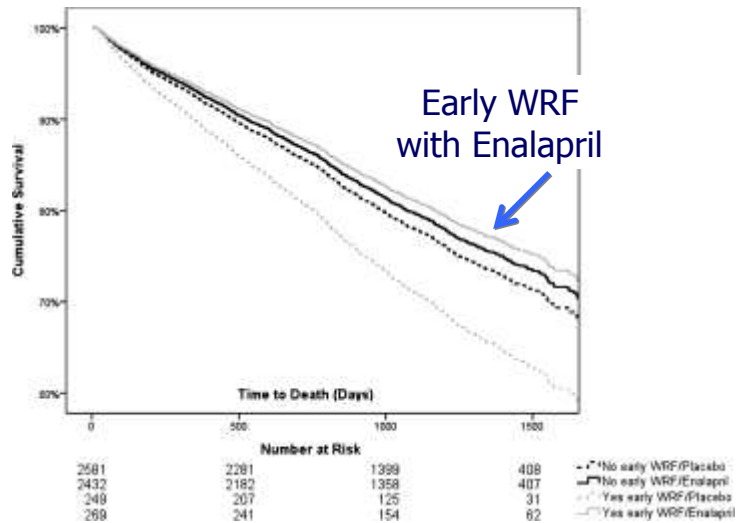


WRF/Cong	44	35	27	22	20	18	16	15	15	14	13	12
No WRF/Cong	31	28	23	20	18	16	15	15	14	13	11	11
WRF/No Cong	253	227	209	183	159	138	120	103	87	72	59	49
No WRF/No Cong	286	244	219	205	182	177	166	149	144	140	124	103

Metra M, et al. Circulation HF 2012



Worsening Renal Function & Outcomes: Depends on Therapy

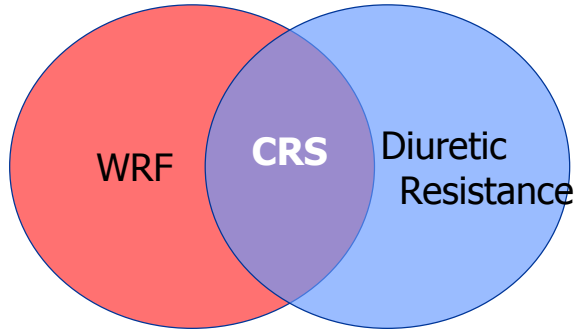


Testani JM, et al. Circ Heart Fail 2011;4:685-691





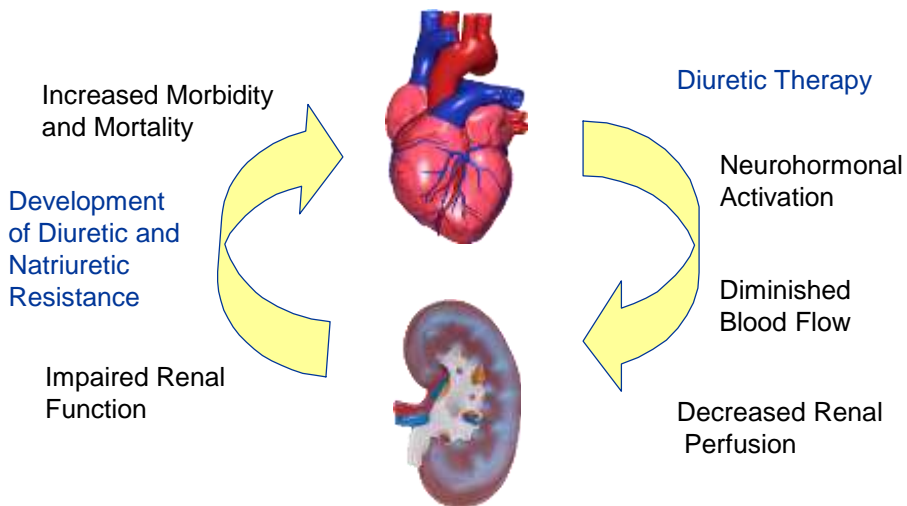
Cardio-renal Syndrome in Acute HF Patient



Persistent or worsening congestion associated with worsening renal function despite appropriate treatment



Challenges of Cardiorenal Syndrome of HF





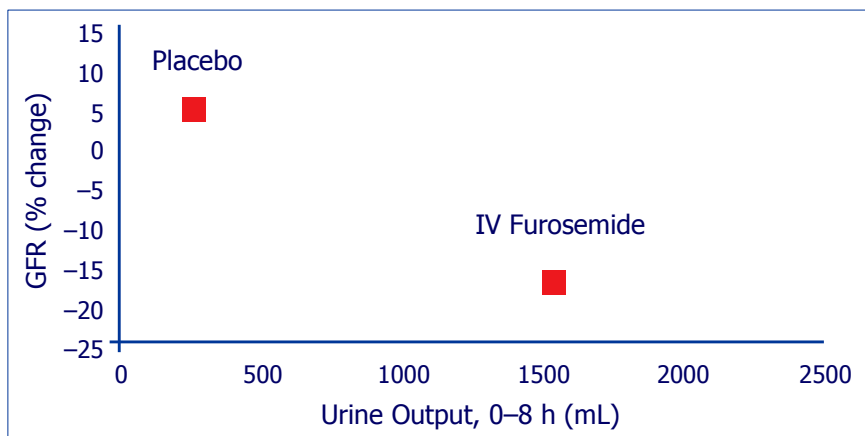
Acute Effects of IV Diuretics in Heart Failure

- Inc. heart rate
- Inc. SVR
- Inc. LV filling pressures
- Inc. norepinephrine, renin, vasopressin

Francis, et al. Ann Intern Med. 1985



Diuretic Therapy Significantly Decreases Glomerular Filtration Rate*



N = 16; NYHA II (19%) and III (81%); mean baseline creatinine clearance, $108 \pm 51 \mu\text{g/mL}$.

*GFR was estimated using a 7-hour creatinine clearance.

Gottlieb SS, et al. Circulation. 2002;105:1348-1353





Dose Response and Diuretic Resistance



What is Diuretic Resistance?

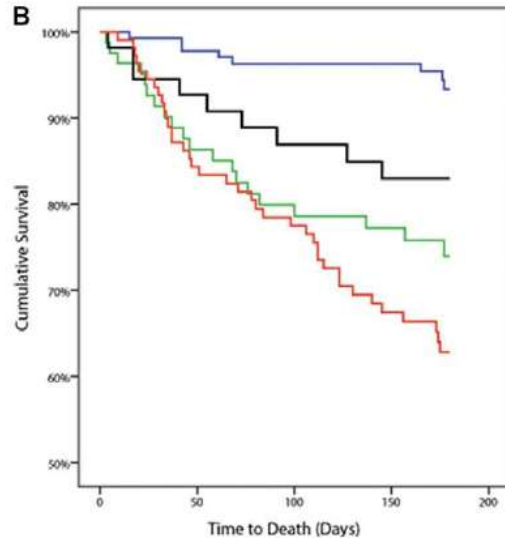
“A clinical state in which diuretic response is diminished or lost before the therapeutic goal of relief from edema has been reached.” Kramer, Am J Med, 2009

- It is a relative phenomenon—all patients with HF have some degree of diuretic resistance
- It complicates therapy and is associated with poor prognosis
- Risk factors: CKD, hyponatremia, RAAS activation, HF severity





Diuretic efficiency more important than dose



Low Loop/High DE

High Loop/High DE

Low Loop/Low DE

High Loop/Low DE

Testani, Circ HF 2014

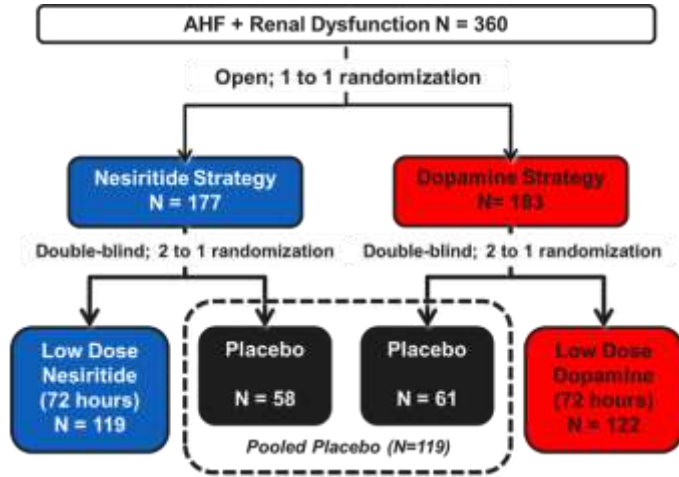


Dealing with Diuretic Resistance

- Ambulatory setting
 - Give more
 - Change to alternative loop diuretic
 - Add adjunct
 - Try parenteral diuretics
 - Hospitalize
- Inpatient setting
 - Give more
 - Change to alternative route (e.g., continuous infusion)
 - **Facilitated diuresis (add adjuncts)**
 - Hemodynamic approaches



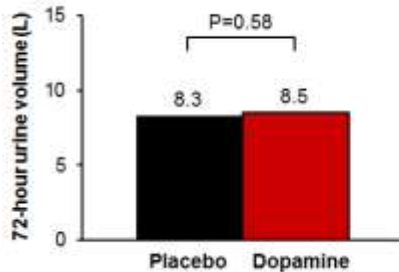
ROSE Study Design



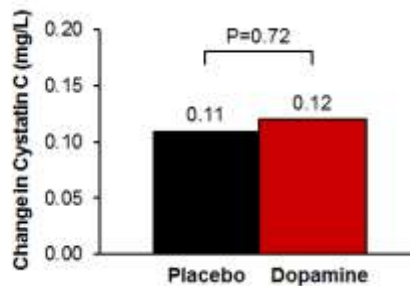
Standardized Diuretic Dosing For 1st 24 hours
2.5 x Outpt Furosemide Equivalent in Divided (BID) IV Doses

Low Dose Dopamine: *Co-primary End-points*

72 Hour Urine Volume



Change in Cystatin-C





Safety Endpoints: Renal Dose Dopamine

Study Drug Tolerance	Dopamine (n=122)	Placebo (N = 119)	P Value
Study drug d/c - Hypotension	0.9%	10.4%	<0.001
Study drug d/c - Tachycardia	7.2%	0.9%	<0.001
Study drug d/c – Any Cause	23%	25%	0.72



CARRESS-HF



- Randomized trial to evaluate the effects of ultrafiltration vs. stepped pharmacologic care in ADHF with cardiorenal syndrome
- Primary endpoint:
 - *Change in serum creatinine and weight assessed at 96 hrs considered together as a bivariate outcome*

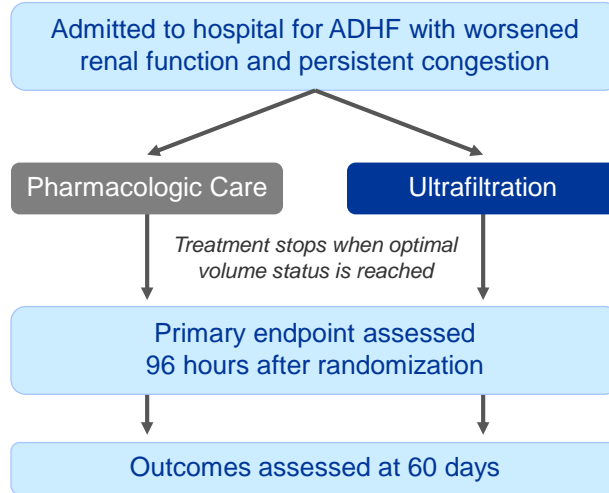


Presented: AHA 2012 Late Breaking Clinical Trial





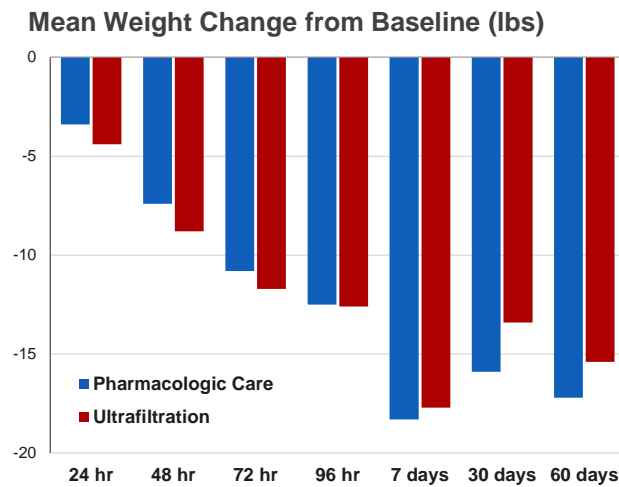
CARRESS-HF: Study Design



Bart B NEJM 2012



Change in Weight



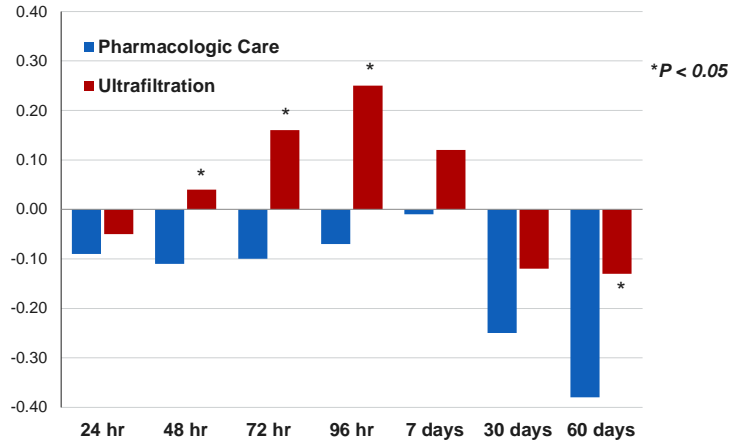
Bart B NEJM 2012





Change in Creatinine

Mean Creatinine Change from Baseline (mg/dL)

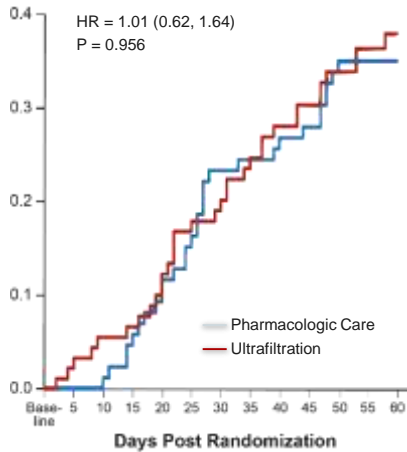


Bart B NEJM 2012

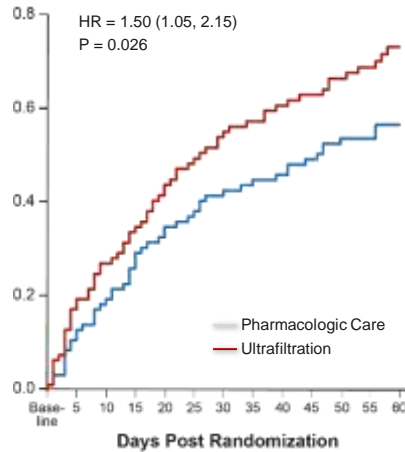


60-day Event Rates

Death or HF Rehospitalization



Death or Serious Adverse Event



Bart B NEJM 2012





ACC/AHA HF Guidelines - Diuretics

- The 2013 ACCF/AHA Guideline for the Management of Heart Failure made a Class 1 recommendation that *“diuretics are recommended in patients with HF and reduced EF with evidence of fluid retention, unless contraindicated, to improve symptoms. (Level of Evidence: C).”*
- *“Appropriate use of diuretics is a key element in the success of other drugs used for the treatment of HF. The use of inappropriately low doses of diuretics will result in fluid retention. Conversely, the use of inappropriately high doses of diuretics will lead to volume contraction, which can increase the risk of hypotension and renal insufficiency.”*



2016 ESC Guidelines – Diuretics in ADHF

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





Take Home Points

- " ADHF in the setting of kidney dysfunction is common – confluence of worsening renal function and diuretic resistance
- WRF during HF therapy must be considered in the context of the overall clinical picture
 - *Not a license to stop HF disease modifying drugs*
 - *Decongestion is more important than WRF*
- Diuretic resistance is real, more loop is generally ok
- Effective facilitated diuresis approaches lacking
- If congestion and kidney dysfunction persist or worsen during ADHF
 - *individualize care; consider hemodynamic monitoring*

