Torasemide

ΙΩΑΝΝΗΣ Γ. ΓΡΙΒΕΑΣ, MD,PHD
ΝΕΦΡΟΛΟΓΟΣ

athens-NEPHROLOGY

"Cardiorenal" for 100 Years

- Sir Thomas Lewis (1881-1945)

A Clinical Lecture

ON

PAROXYSMAL DYSPNOEA IN CARDIO-RENAL PATIENTS:

WITH SPECIAL REFERENCE TO "CARDIAC" AND "URAEMIC" ASTHMA.

DELIVERED AT UNIVERSITY COLLEGE HOSPITAL, LONDON, NOVEMBER 12TH, 1913.

BY THOMAS LEWIS, M.D., D.SC., F.R.C.P.

ASSISTANT PHYSICIAN AND LECTURER IN CARDIAC PATHOLOGY, UNIVERSITY COLLEGE HOSPITAL; PHYSICIAN TO OUT-PATIENTS, CITY OF LONDON HOSPITAL.

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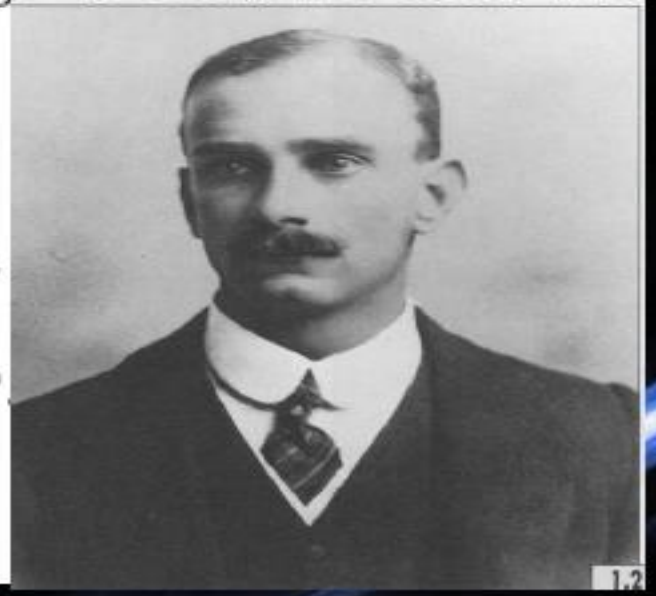
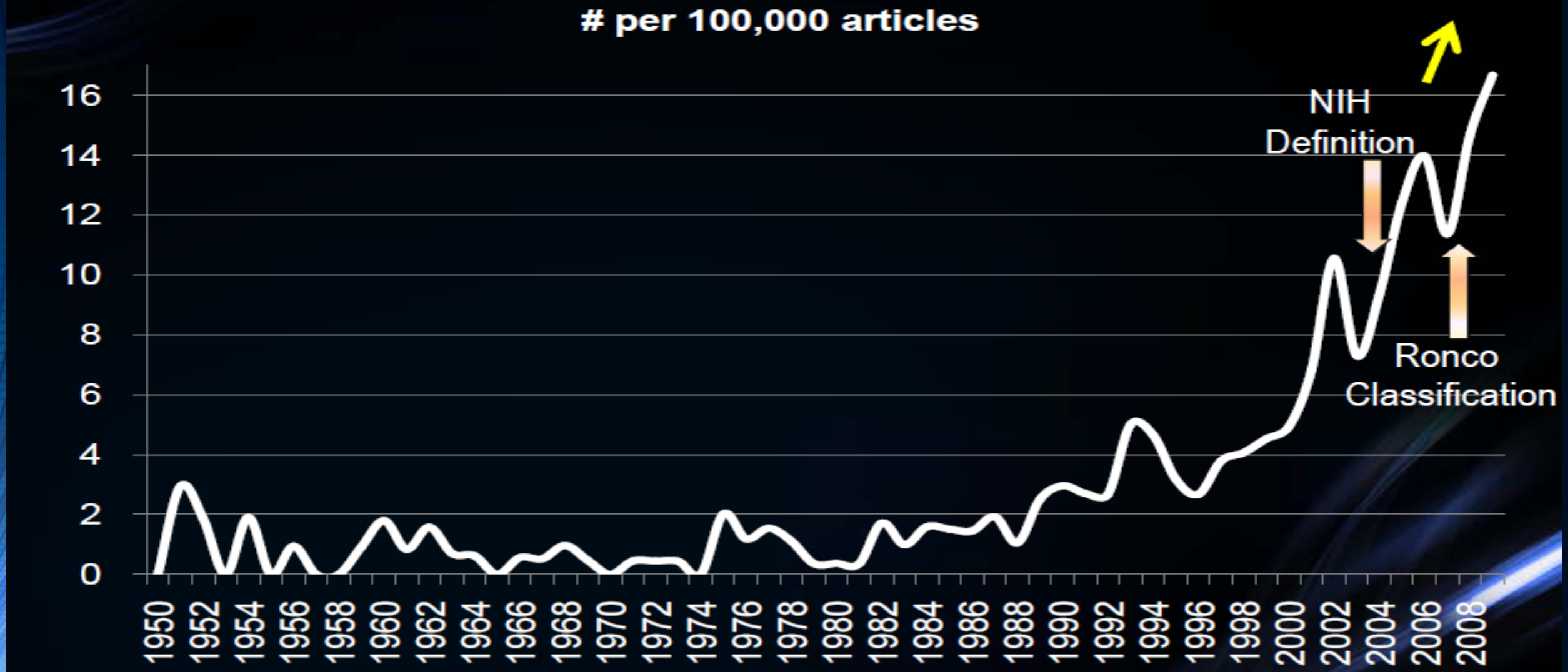


Lewis T., Br Med J 1913;2:1417-

PubMed Trend



Arthur C. Guyton

(1919) – (2003)

"Father" of Modern Cardiovascular Physiology

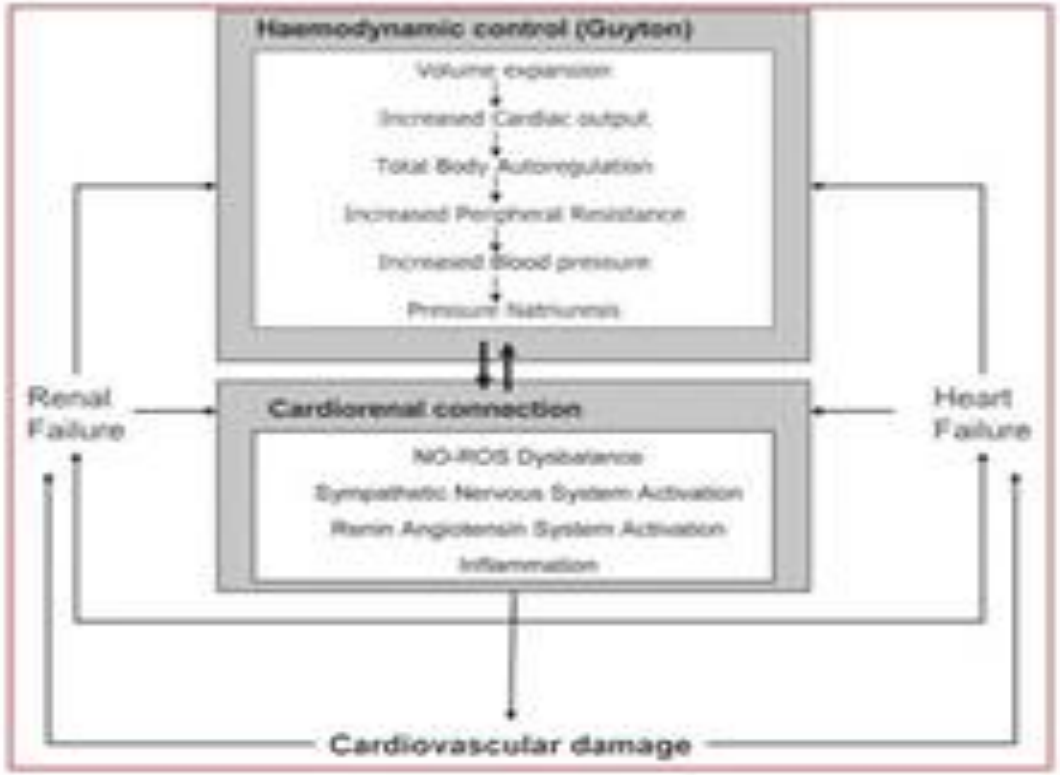
In 1950, Dr. Guyton did research that proved that the cardiac output was controlled by the body tissues' need for oxygen and not by the heart itself. In addition, he developed a computer model of the circulatory system and used it to demonstrate that the kidneys provided a long-term control of the blood pressure. He dedicated most of his research to the heart-kidney interactions.

GUYTON MODEL REVISITED

Bongartz, L., G. et al. Eur Heart J 2005;26:11-17

Severe cardiorenal syndrome represents a pathophysiological condition in which combined cardiac and renal dysfunction amplifies progression of failure of the individual organ, so that cardiovascular morbidity and mortality is increased.

Guyton has provided an excellent framework describing the physiological relationships between cardiac output, extracellular fluid volume control, and blood pressure. While this model is sufficient to understand systemic haemodynamics in combined cardiac and renal failure, not all aspects of the observed accelerated atherosclerosis, structural myocardial changes, and further decline of renal function can be explained.



Since increased activity of the renin-angiotensin system, oxidative stress, inflammation, and increased activity of the sympathetic nervous system seem to be cornerstones of the pathophysiology in combined chronic renal disease and heart failure, we have explored the potential interactions between these cardiorenal connectors. As such, the cardiorenal connection is an interactive network with positive feedback loops, which, in our view, forms the basis for the SCRS.

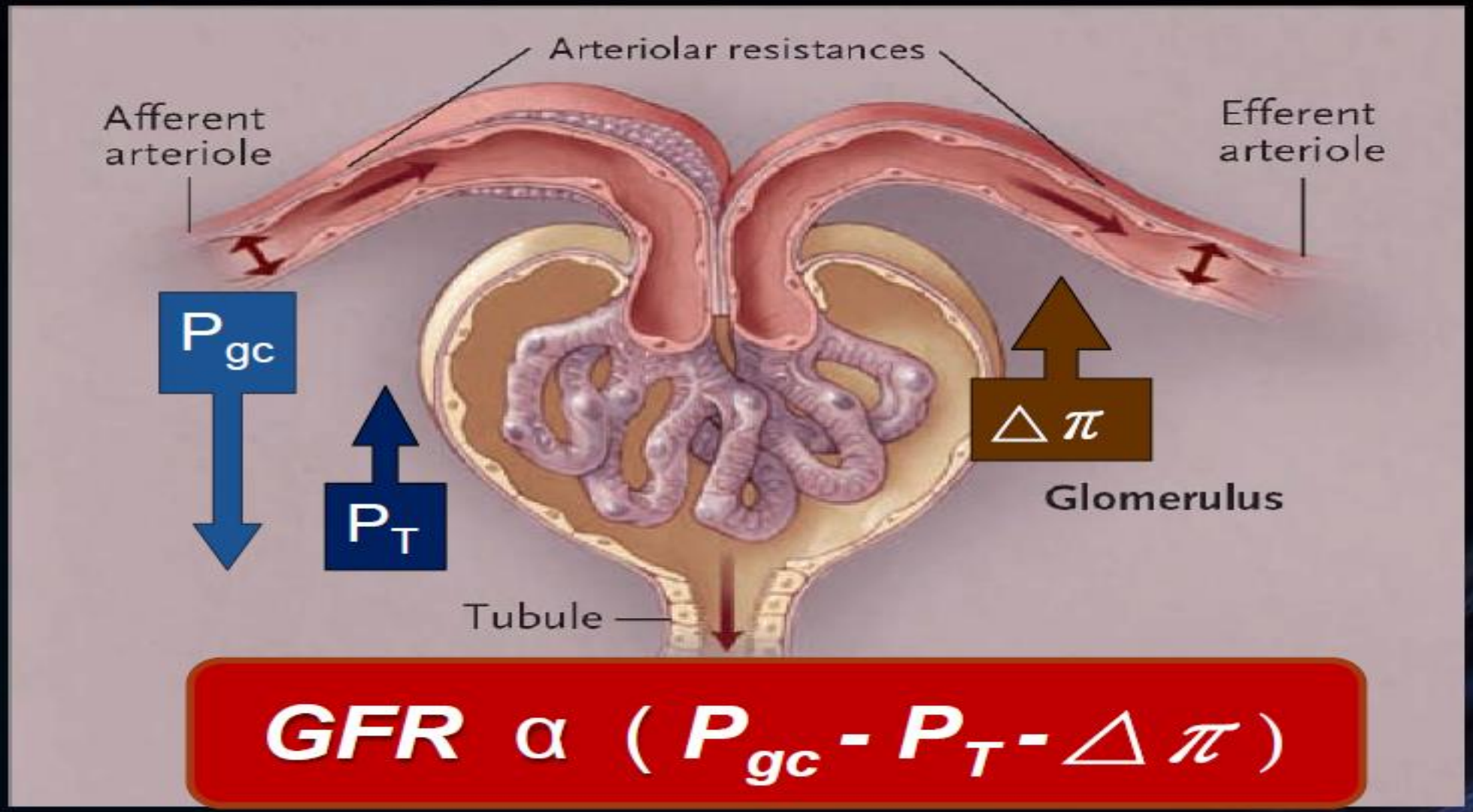
Working Definition (2004)

At its extreme, cardio-renal dysregulation leads to what is termed "cardio-renal syndrome" in which **therapy to relieve congestive symptoms of heart failure is limited by further decline in renal function**. It is clear that our current understanding of cardio-renal connections is inadequate to explain many of the clinical observations in heart failure or to direct its therapy.

NHLBI Working Group. http://www.nhlbi.nih.gov/meetings/workshops/cardiorenal-hf-hd.htm

P_{gc}: Glomerular pressure, P_T : Tubular pressure

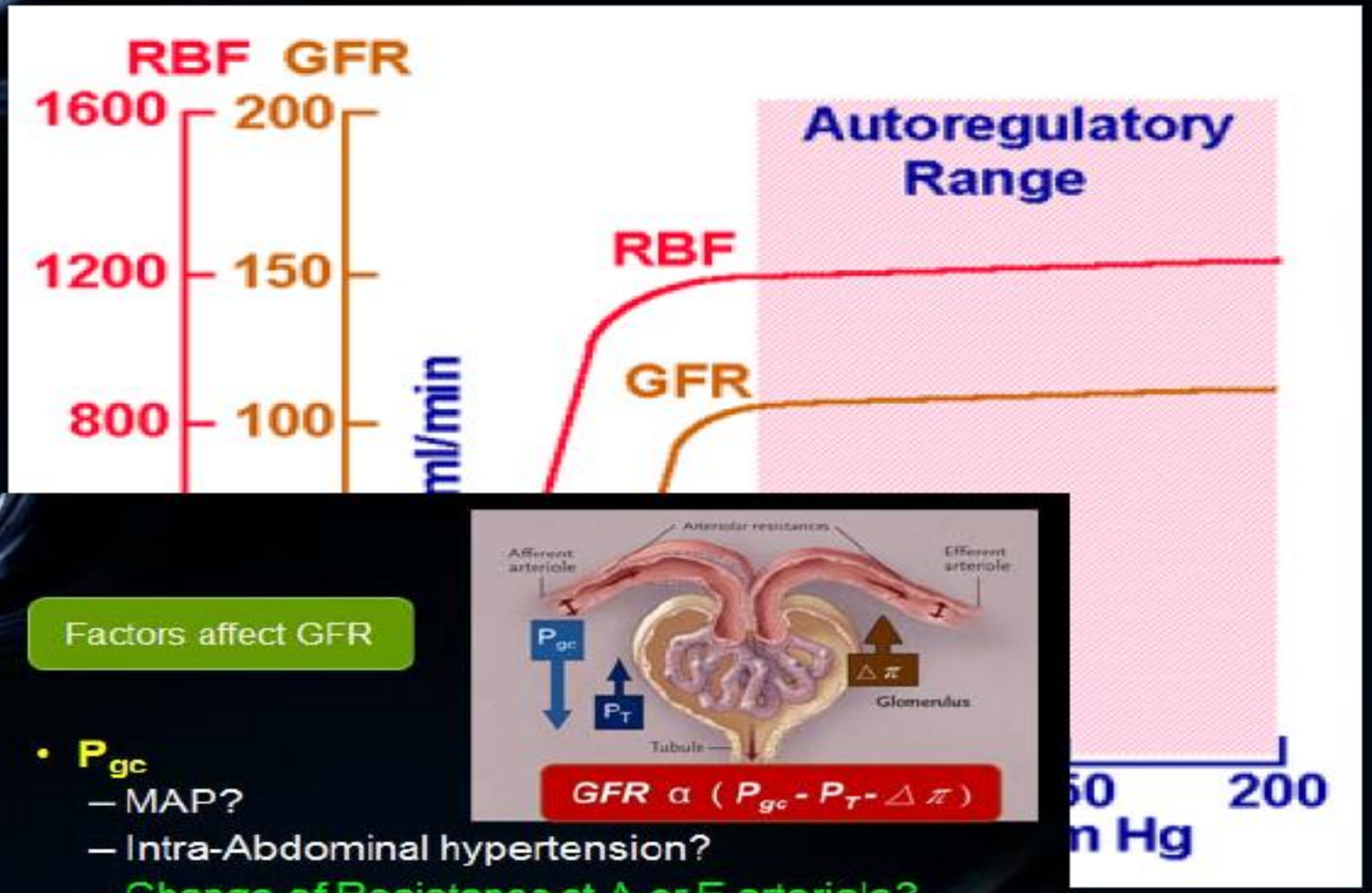
π_{gc}: Glomerular colloid p, π_T : Tubular colloid p



$$GFR \ \alpha \ (P_{gc} - P_T - \triangle \pi)$$

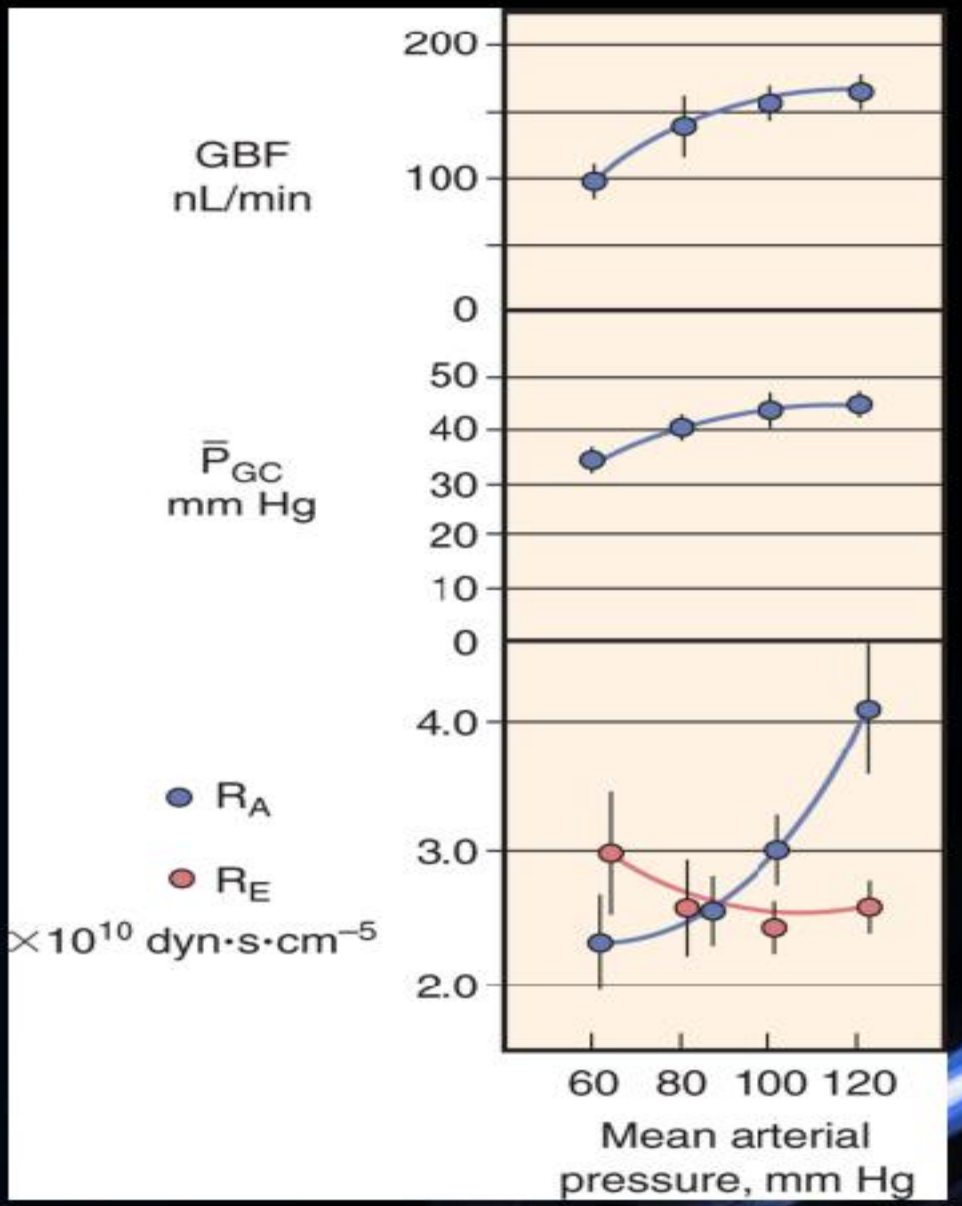
JG Abuelo et al, N Engl J Med 2007; 357(8): 797-805

Renal auto-regulation



Factors affect GFR

- P_{gc}
  - MAP?
  - Intra-Abdominal hypertension?
  - Change of Resistance at A or E arteriole?
- P_T
  - Intra-Abdominal hypertension?
  - Tubular obstruction?



Brenner and Rector's The Kidney, 8th ed
kumc.edu/ki/physiology/course/two/2_4.htm

Facts of Renal Physiology

- **Kidney-**
  - Weight- 0.5% of Body,
  - Receive 25% of cardiac output (50 times)
- **Kidney functions**
  - **B**alance of electrolytes, Plasma volume, Acid Base
  - **A**ctivation of Vitamin D
  - **S**ynthesis of Erythropoietin, Urokinase
  - **E**xcretion of Urea, Uric acid, Creatinine etc.
- **Transport types**
  - ***Passive***
    - Simple, channel mediated and facilitated diffusion, solvent drag
  - ***Active***
    - Primary and Secondary (Symports and Secondary Counter transport)

Facts related to Renal Physiology

- **Pressure difference** at Bowman's Capsule- 20mm Hg
- **Filter**= Plasma-Proteins
- **Volume** of
  - Filter- 180 liters
  - Urine- 1.5 liters (1%)
- **Kidneys**
  - Renal Blood Flow- 1200ml/min
  - Renal Plasma Flow- 650 ml/min
  - GFR- 120 ml/min
  - Reabsorb – Sodium, Chloride and Bicarbonates > 99% while Potassium about 85%

Terminology

- **Natriuresis-** increased sodium excretion
- **Kaliuresis-** Increased Potassium excretion
- **Diuretics-** Drugs which cause a net loss of Na^+ and water in urine. (Exception- Osmotic diuretics (Mannitol) don't cause natriuresis but produce diuresis

Loop Of Henle

- **Descending limb-**
  - Permeable to water
- **Thick ascending limb –**
  - Impermeable to water but
  - Permeable to sodium by **$Na^{+}K^{+}2Cl^{-}$ Co transport**
  - About **25%** of filtered sodium is absorbed here

RAAS in response to low BP, or Low Na

Renin-

- Angiotensinogen - Angiotensin I

ACE-

- Angiotensin II-

- Sympathetic, Aldosterone

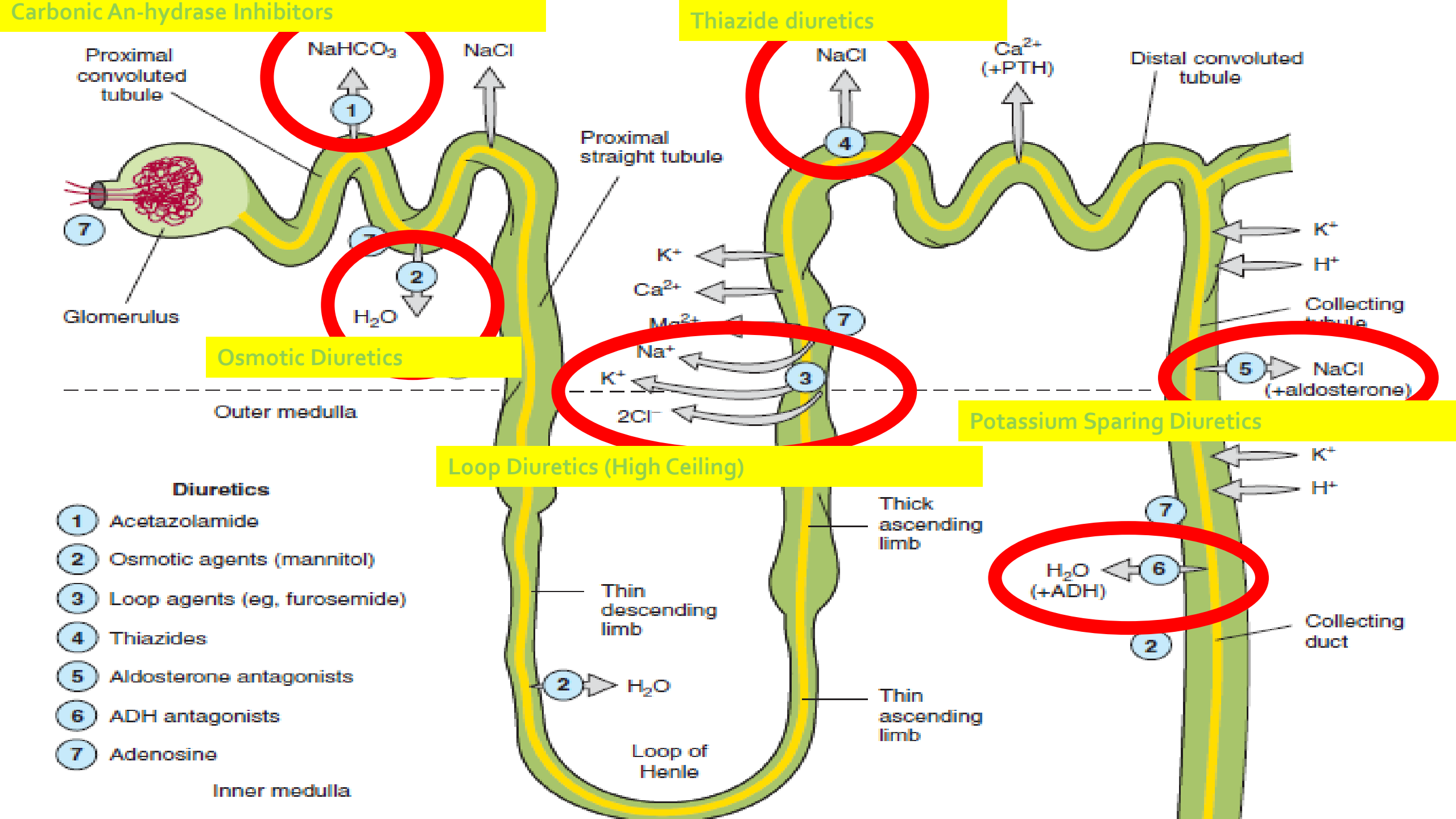
Vasoconstriction, Sodium and water retention,

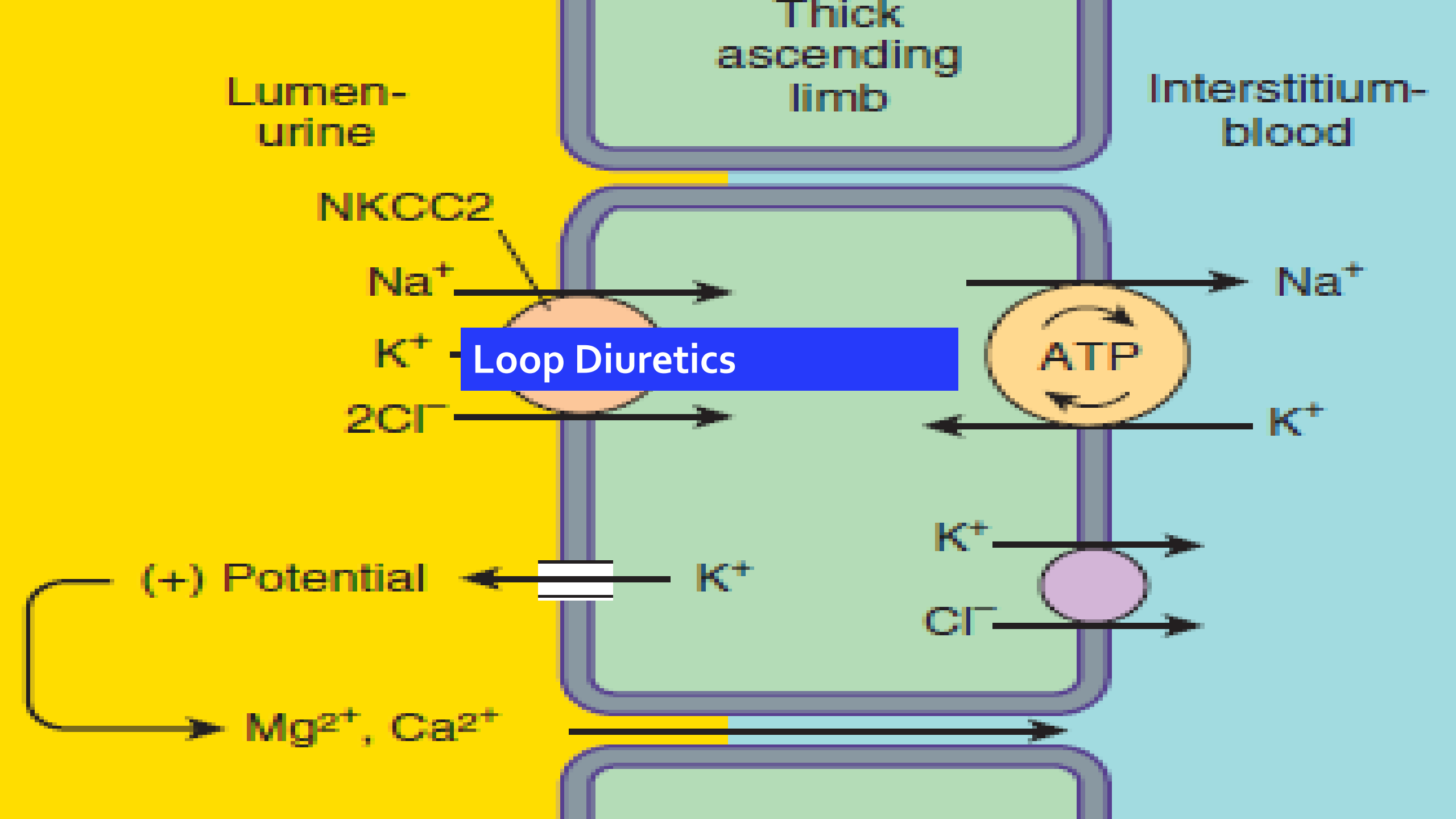
Nephron parts and their functions

SEGMENT	FUNCTION
Glomerulus	Formation of glomerular filtrate
Proximal convoluted tubule (PCT)	Reabsorption of 65% of filtered Na+/K+/ Ca2+, and Mg2+; 85% of $NaHCO_3$, (activity of Carbonic anhydrase enzyme) and nearly, 100% of glucose and amino acids. Iso-osmotic reabsorption of water., Secretion and reabsorption of organic acids and bases, including uric acid and most diuretics
Thin descending limb of Henle's loop	Passive reabsorption of water
Thick ascending limb of Henle's loop (TAL)	Active reabsorption of 25% of filtered $Na^+/K^+/2Cl^-$;, secondary re-absorption of Ca2+ and Mg2+
Distal convoluted tubule (DCT)	Active reabsorption of 4–8% of filtered Na^+ Cl^-; Ca2+ reabsorption under parathyroid hormone control
Cortical collecting tubule (CCT)	Na+ reabsorption (2–5%) coupled to K+ and H+ secretion (under **Aldosterone**)
Medullary collecting duct	Water reabsorption under **Vasopressin** control

Control of Renal Function

- **Sympathetic-** Increase Na reabsorption, Renin
- **RAAS- Renin in response to Low sodium, Low BP**
- **ADH –** Water reabsorption at collecting duct
- **Atrial Natriuretic Peptide/Factor-** Released when atrial pressure is high and causes solute and water diuresis and reduces blood volume and BP. Inhibits synthesis of Renin, Aldosterone, ADH and overcomes the long term persistent effect of aldosterone **(Opposite of RAAS)**
- **Prostaglandins-** maintain renal circulation


Carbonic An-hydrase Inhibitors
Thiazide diuretics
Osmotic Diuretics
Loop Diuretics (High Ceiling)
Potassium Sparing Diuretics
Proximal convoluted tubule
NaHCO3
NaCl
Glomerulus
H2O
Proximal straight tubule
NaCl
Ca2+ (+PTH)
Distal convoluted tubule
K+
H+
Collecting tubule
Na+
K+
2Cl−
NaCl (+aldosterone)
Outer medulla
Thick ascending limb
Thin descending limb
H2O
Thin ascending limb
Loop of Henle
H2O (+ADH)
Collecting duct
Inner medulla
Diuretics
1 Acetazolamide
2 Osmotic agents (mannitol)
3 Loop agents (eg, furosemide)
4 Thiazides
5 Aldosterone antagonists
6 ADH antagonists
7 Adenosine


Thick ascending limb
Lumen- urine
Interstitium- blood
NKCC2
Na+
K+
2Cl−
Loop Diuretics
ATP
Na+
K+
(+) Potential
K+
K+
Cl−
Mg2+, Ca2+

Pharmacotherapy in Congestive Heart Failure

Domenic A. Sica, MD
Editor

Drug Absorption in the Management of Congestive Heart Failure: Loop Diuretics

Compound Dissolution Characteristics, Site-Specific Absorption, and Food Effect. Among the loop diuretics the greatest treatment experience exists for the compound furosemide. Furosemide absorption is erratic with considerable intra- and intersubject variability in its bioavailability (expressed in terms of both rate and extent of absorption), particularly in relationship to its intake with food.[24–28] Although furosemide is nearly insoluble in water, this insolubility does not seem to be the exclusive cause of its erratic bioavailability in that a furosemide solution is not more completely absorbed than a tablet form.[24] Absorption of furosemide appears to be rate-limited by transmembrane transport and/or gastric emptying, not by its tablet dissolution rate per se.[29] Therefore, the poor solubility of furosemide does not explain its incomplete absorption, though this is not to discount the importance of its formulation as a determinant of day-to-day

Torsemide. Torsemide is extremely well absorbed after oral administration, with peak plasma concentrations in normal volunteers within 1 hour of its administration and an absolute bioavailability of approximately 80% in normal volunteers.[41,42] In CHF patients the bioavailability of torsemide is the same as that observed in normal volunteers with values approximating 90%.[40,43] This value indicates that there is little presystemic or first-pass metabolism for this compound.[44,45] However, there is a food-related decrease in absorption rate for torsemide as shown by a decrease in maximum concentration and an increase in time to peak drug concentration.[42]

Vargo et al.[40] examined the pharmacokinetics of torsemide (10 mg orally and intravenously) and furosemide (40 mg orally and 20 mg intravenously) in 16 patients with CHF (class II and III). Torsemide was rapidly absorbed in patients with CHF (time of maximum concentration, 1.1±0.9 hours [torsemide] vs. 2.4±2.5 hours [furosemide]) with an absolute bioavailability of 89%. More importantly, for both routes of administration the plasma concentration and urinary excretion rate-time curves were essentially the same for torsemide. This strongly suggests that the extent/rate of drug absorption for orally administered torsemide may allow it to be safely substituted for intravenous torsemide in the setting of subacute CHF deterioration. This stratagem has been demonstrated to have a significant pharmacoeconomic effect on the treatment of CHF.[46]

Cardiovascular Drugs and Therapy 1993;7:75–80

Torasemide in Advanced Renal Failure

J. Kindler
Department of Internal Medicine, Kreiskrankenhaus Marienhöhe, Würselen, Germany

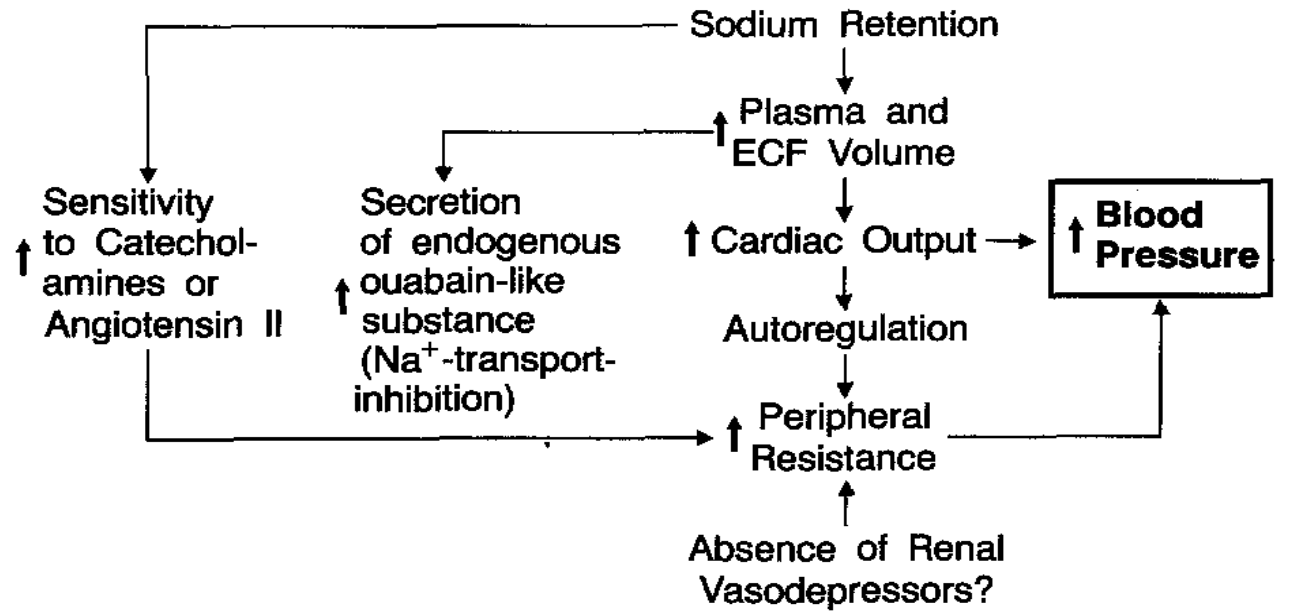


Fig 1. *Possible mechanisms for hypertension in patients with advanced chronic renal failure. ECF = extracellular volume.*

Cardiovascular Drugs and Therapy 1993;7:75–80

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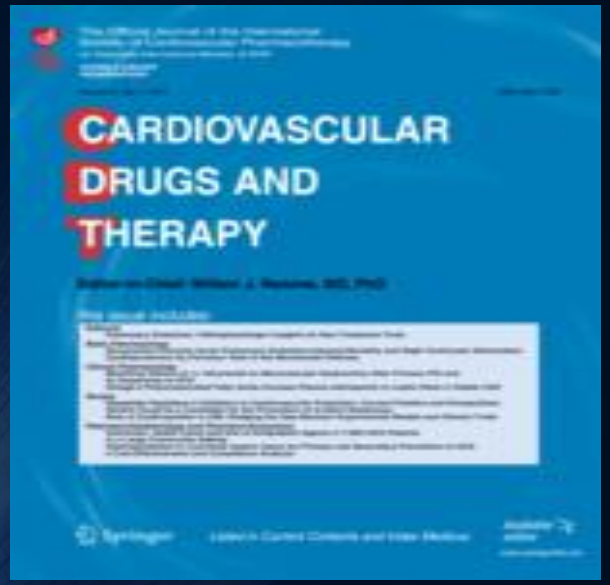

Table 1. *Requirements for an ideal loop diuretic in chronic renal failure*

- Increase of sodium and fluid excretion, even in end-stage renal disease
- Control of volume-dependent hypertension
- No decrease in glomerular filtration rate
- No substantial disturbances in potassium, magnesium, and calcium balance
- Independence of pharmacokinetic properties from renal function
- No extrarenal toxicity, even in high doses
- No elimination by hemodialysis

Kidney International, Vol. 64 (2003), pp. 632–640

A double-blind randomized crossover trial of two loop diuretics in chronic kidney disease

NINA VASAVADA, CHANDAN SAHA, and RAJIV AGARWAL

Division of Nephrology, Division of Biostatistics, and Division of Clinical Pharmacology, Department of Medicine, Indiana University School of Medicine, Indianapolis, Indiana; and Richard L. Roudebush VA Medical Center, Indianapolis, Indiana

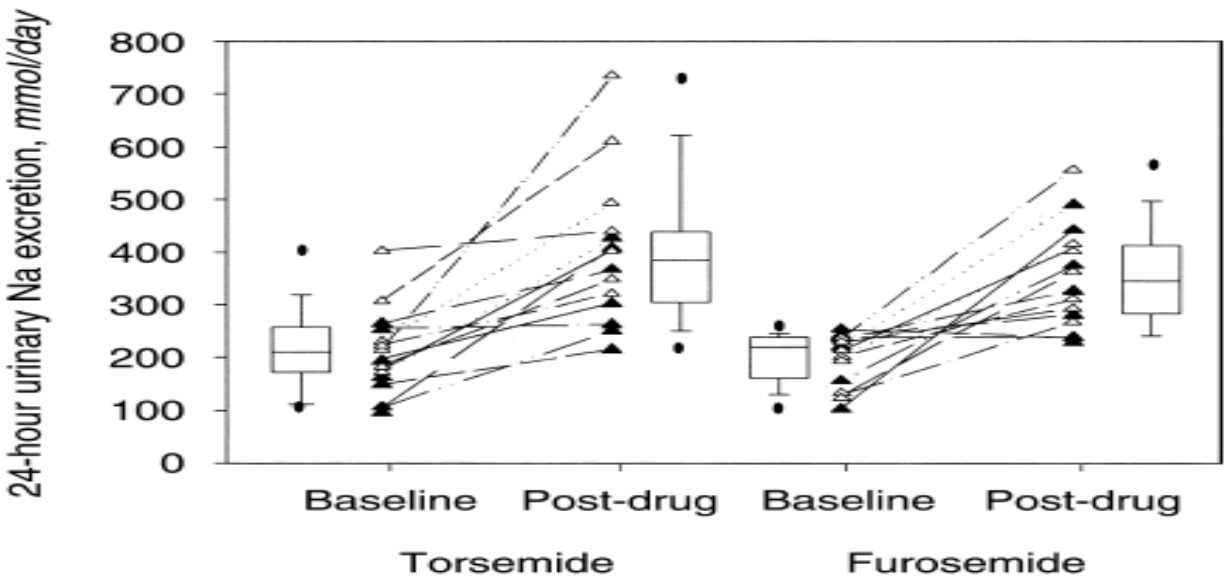

Fig. 2. Inpatient 24-hour urinary sodium excretions of torsemide (T) and furosemide (F) for each subject. Symbols are: (▲) subjects enrolled in the sequence T/F; (△) subjects enrolled in the sequence F/T. Box plots represents the median, 10th, 25th, 75th, and 90th percentiles of each data set.

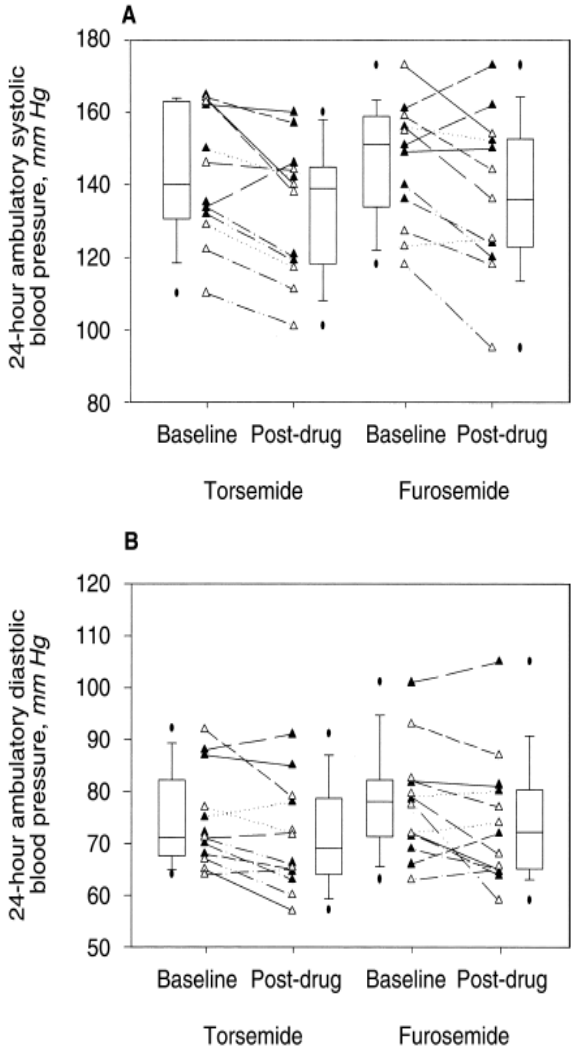

Fig. 3. Outpatient 24-hour ambulatory systolic (*A*) and diastolic (*B*) blood pressure responses of chronic torsemide (T) and furosemide (F) therapy for each subject. Symbols are: (▲) subjects enrolled in the sequence T/F; (△) subjects enrolled in the sequence F/T. Box plots represents the median, 10th, 25th, 75th, and 90th percentiles of each data set.

Kidney International, Vol. 64 (2003), pp. 632–640

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Division of Nephrology, Division of Biostatistics, and Division of Clinical Pharmacology, Department of Medicine, Indiana University School of Medicine, Indianapolis, Indiana; and Richard L. Roudebush VA Medical Center, Indianapolis, Indiana

European Journal of Heart Failure (2016) 18, 891–975
doi:10.1002/ejhf.592

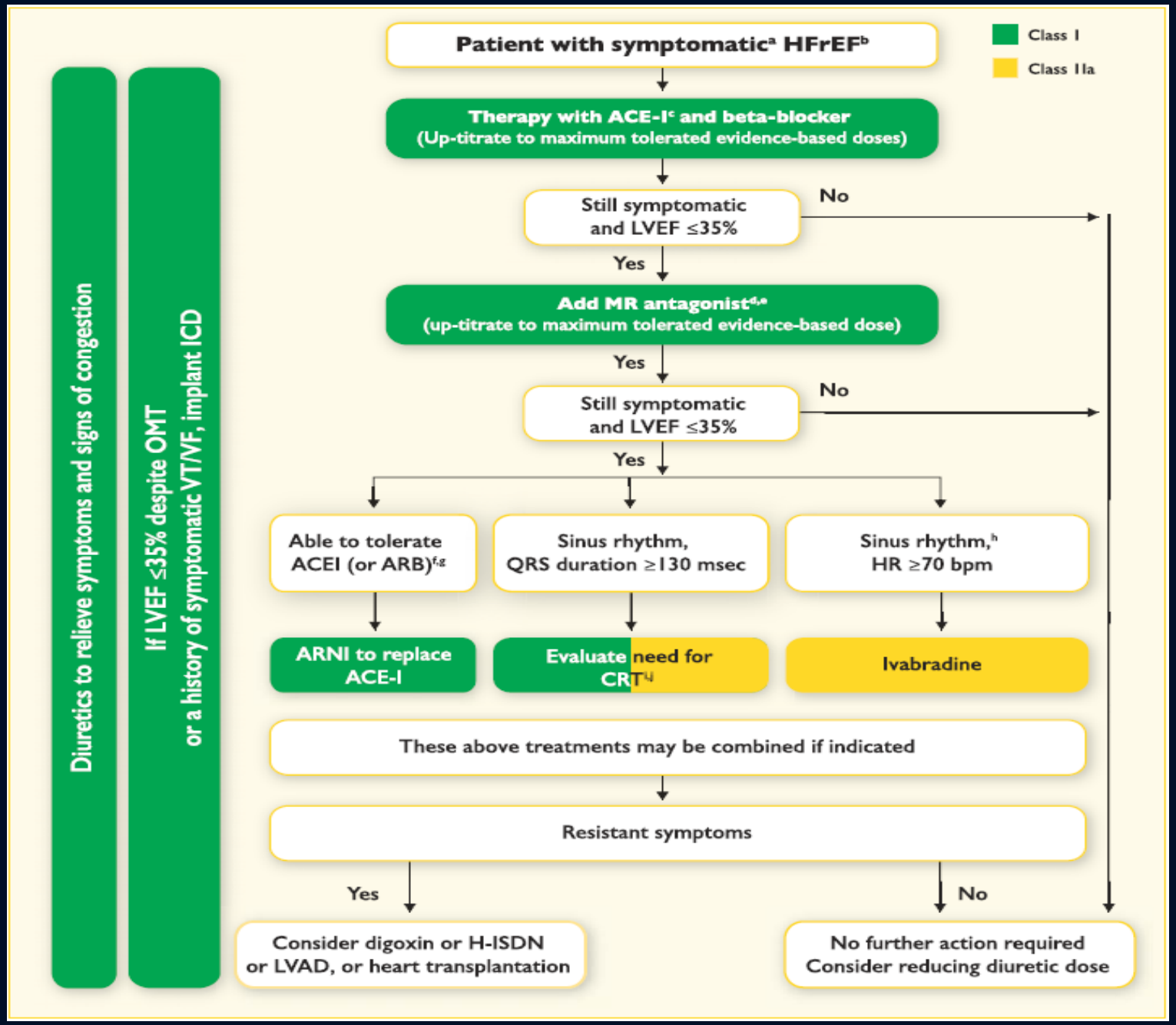
ESC GUIDELINES

2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure

The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)

Developed with the special contribution of the Heart Failure Association (HFA) of the ESC

ESC Guidelines 2016: Therapeutic Algorithm in Patients with Symptomatic HFrEF



Ponikowski P, et al. Eur J Heart Fail 2016;18:891-975

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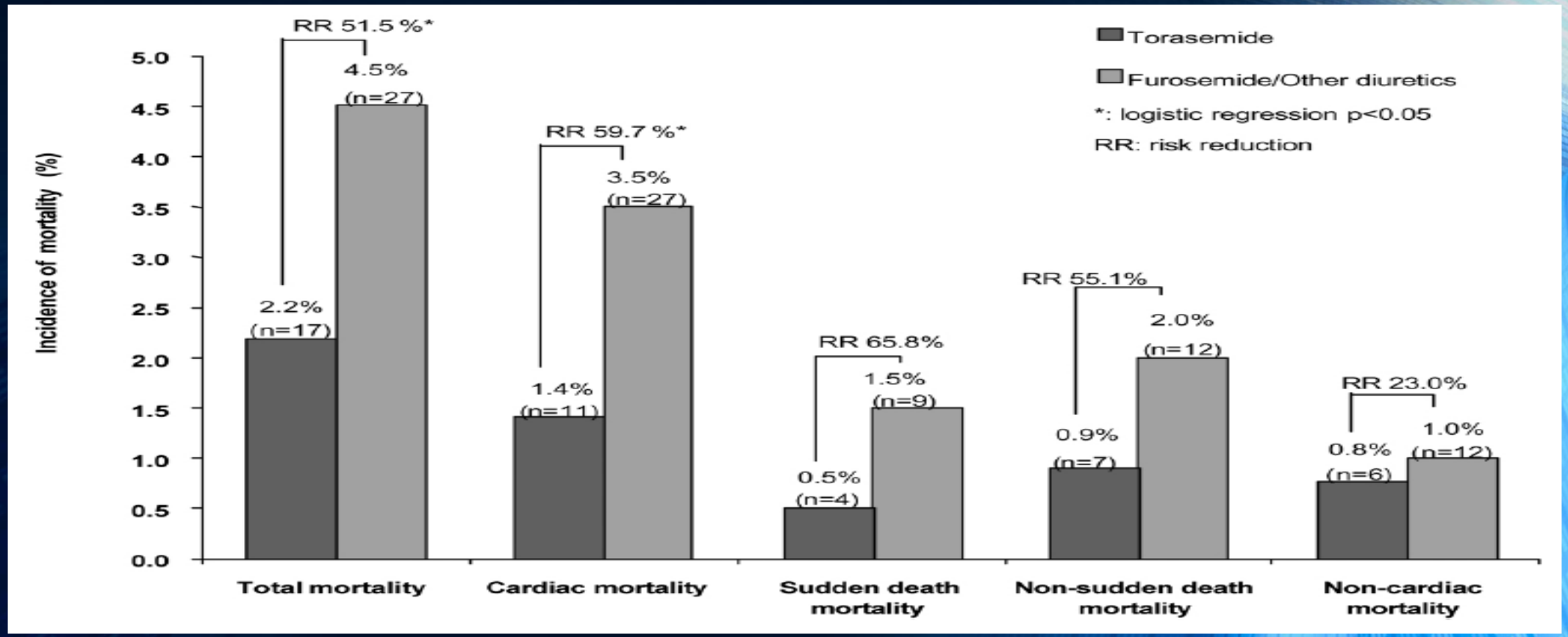
Table 7.3 Doses of diuretics commonly used in patients with heart failure

Diuretics	Initial dose (mg)		Usual daily dose (mg)	
Loop diuretics[a]				
Furosemide	20–40		40–240	
Bumetanide	0.5–1.0		1–5	
Torasemide	5–10		10–20	
Thiazides[b]				
Bendroflumethiazide	2.5		2.5–10	
Hydrochlorothiazide	25		12.5–100	
Metolazone	2.5		2.5–10	
Indapamide[c]	2.5		2.5–5	
Potassium-sparing diuretics[d]				
	+ACE-I/ ARB	-ACE-I/ ARB	+ACE-I/ ARB	-ACE-I/ ARB
Spironolactone/ eplerenone	12.5–25	50	50	100–200
Amiloride	2.5	5	5–10	10–20
Triamterene	25	50	100	200

Torasemide in chronic heart failure: results of the TORIC study

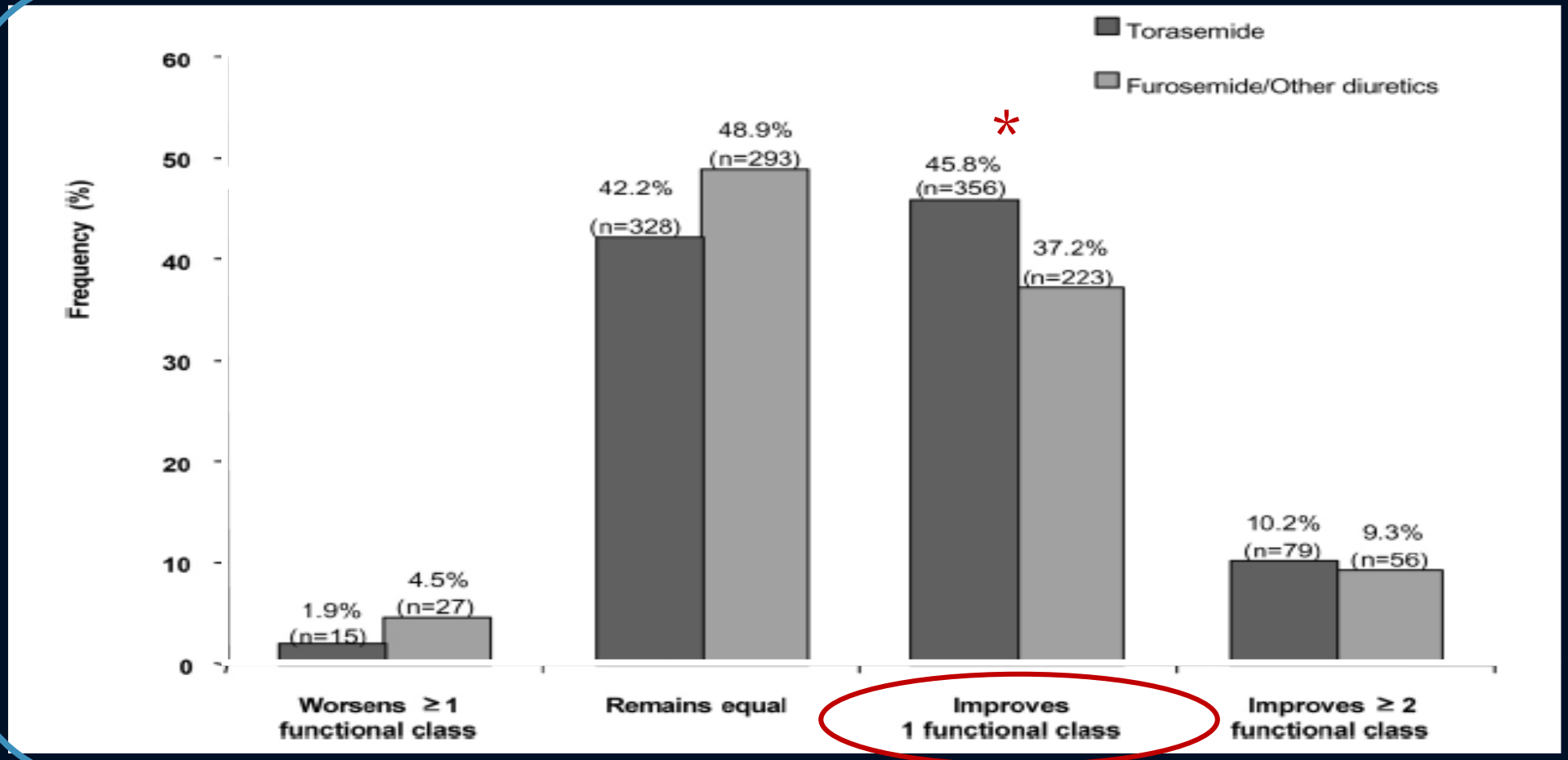
Juan Cosín[a], Javier Díez[b,*], on behalf of the TORIC investigators

[a]*Cardiocirculatory Research Unit, Research Center, University Hospital La Fe, Valencia, Spain*
[b]*Division of Cardiovascular Pathophysiology School of Medicine and Department of Cardiology and Cardiovascular Surgery, University Clinic, University of Navarra, Pamplona, Spain*



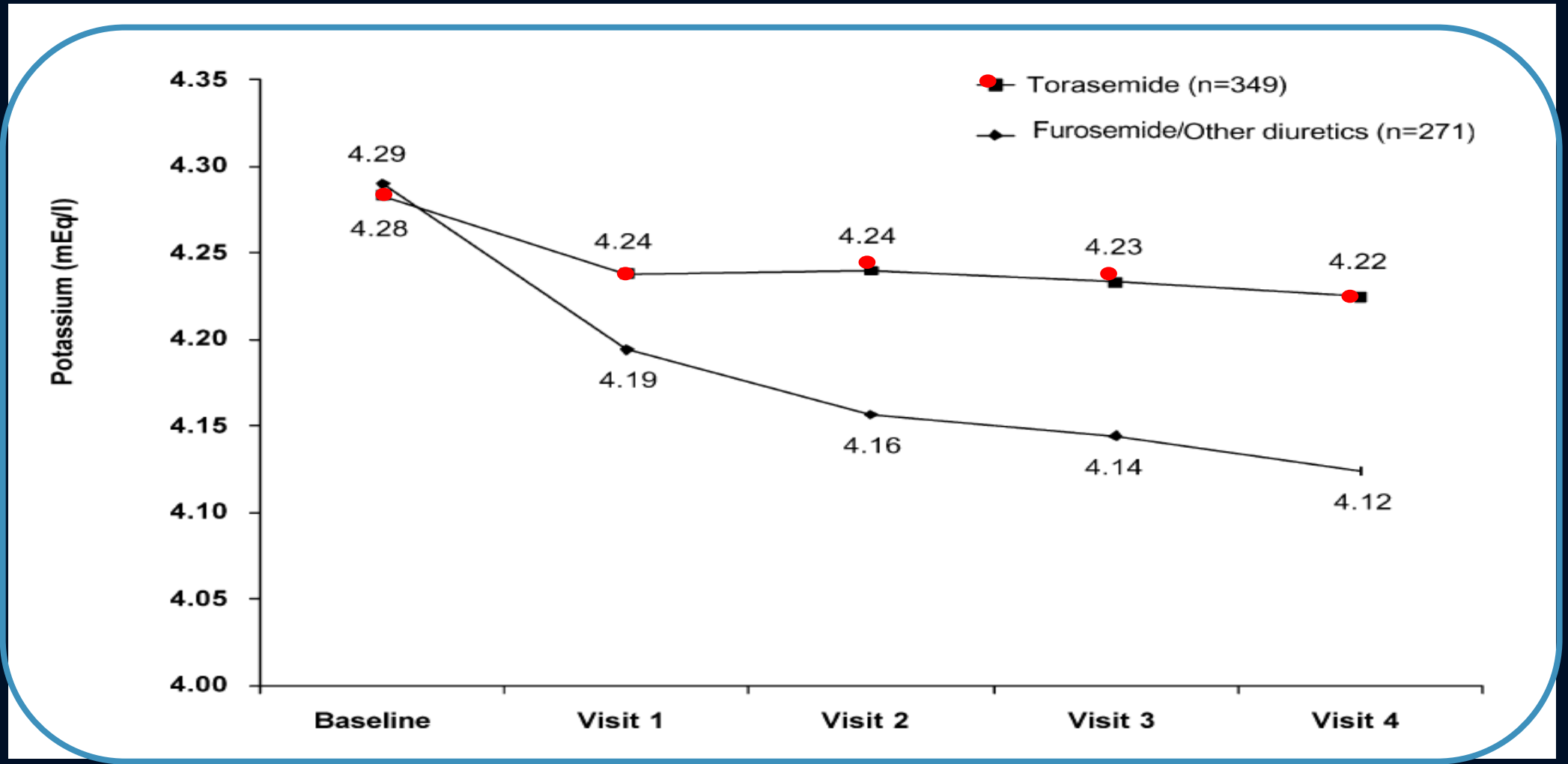
The European Journal of Heart Failure 2002;4:507–513

The TORIC Study: Changes in NYHA Class



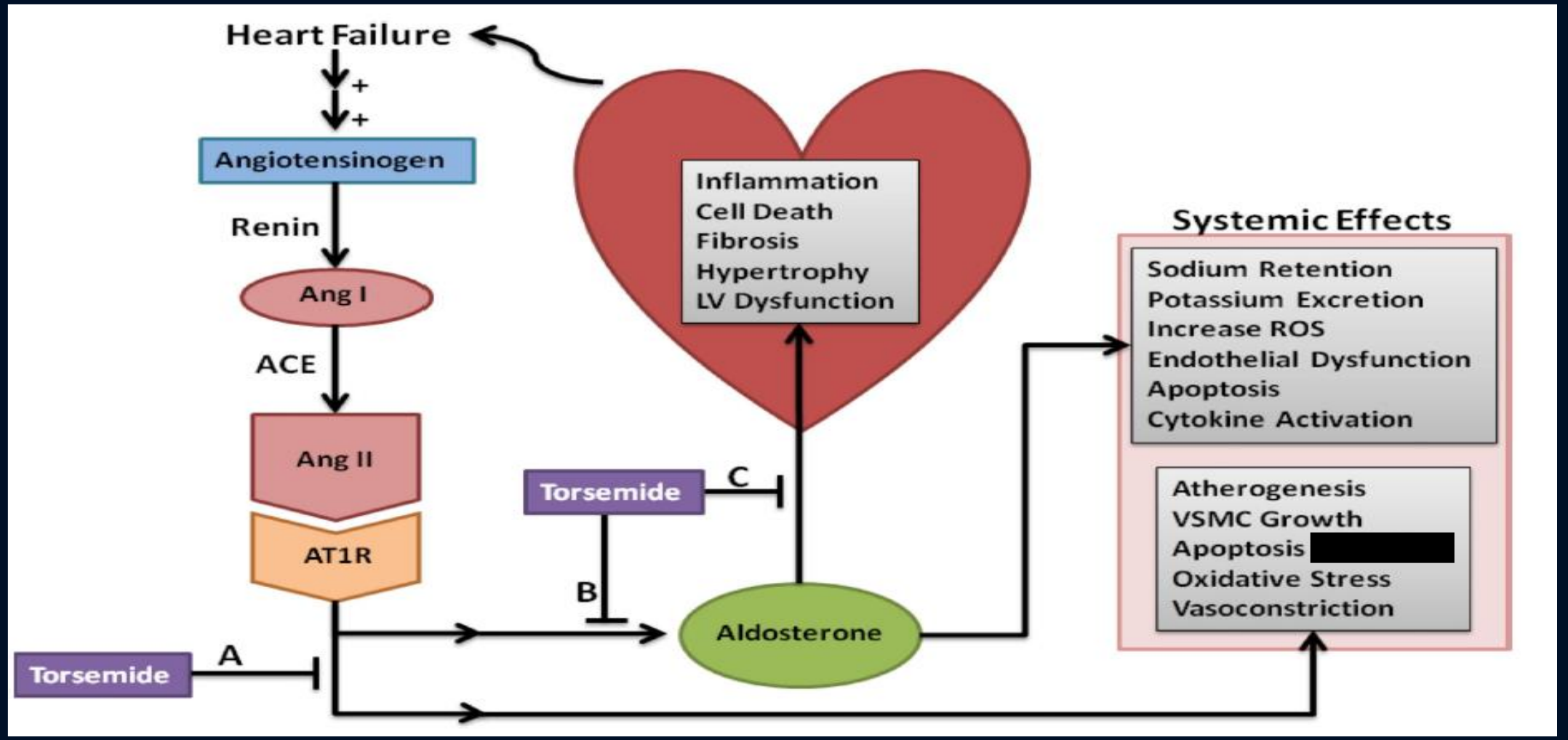
Cosin, et al. European Journal of Heart Failure 2002; 4: 507–513

The TORIC Study: Mean Serum Potassium Levels



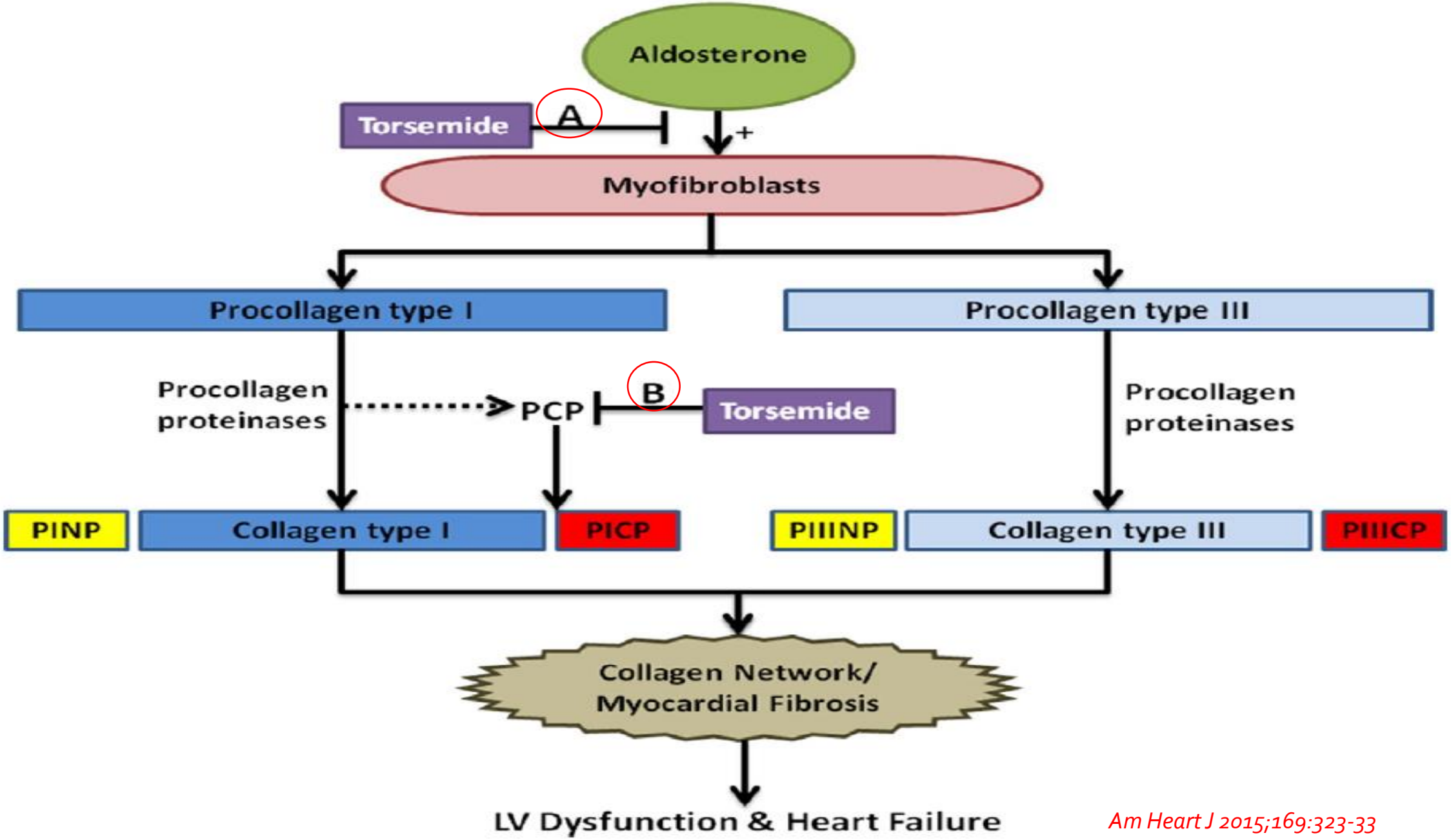
Cosin, et al. European Journal of Heart Failure 2002; 4: 507–513

Potential Effects of Tor(a)semide on RAAS



Buggey, et al. Am Heart J 2015 ; 169: 323–333

Potential effects of torsemide on myocardial fibrosis



Am Heart J 2015;169:323-33

Αντιαλδοστερονική δράση Τορασεμίδης

- Ιδιότητες ανταγωνιστή της δράσης της αλδοστερόνης – μείωση της έκκρισης της

(αντίθετα η φουροσεμίδη αυξάνει τα επίπεδα και τη δραστηριότητα της αλδοστερόνης)

- Torsemide: ↑↑PRA, ↑↑ALDO

όμως παρατηρείται

άμεση αναστολή της δραστηριότητας των υποδοχέων της αλδοστερόνης στο μυοκάρδιο

Torsemide και ίνωση του μυοκαρδίου

⬇ δράσης της αλδοστερόνης

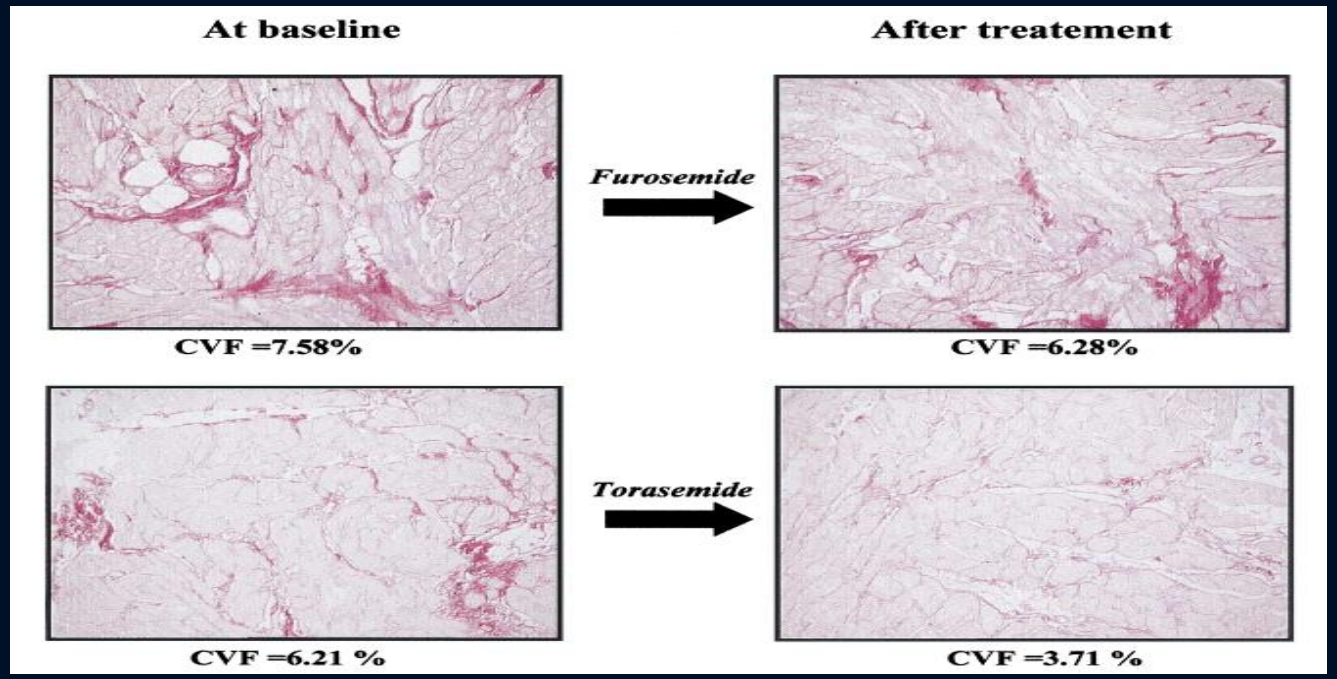
⬇ ίνωσης του μυοκαρδίου (vs φουροσεμίδη)

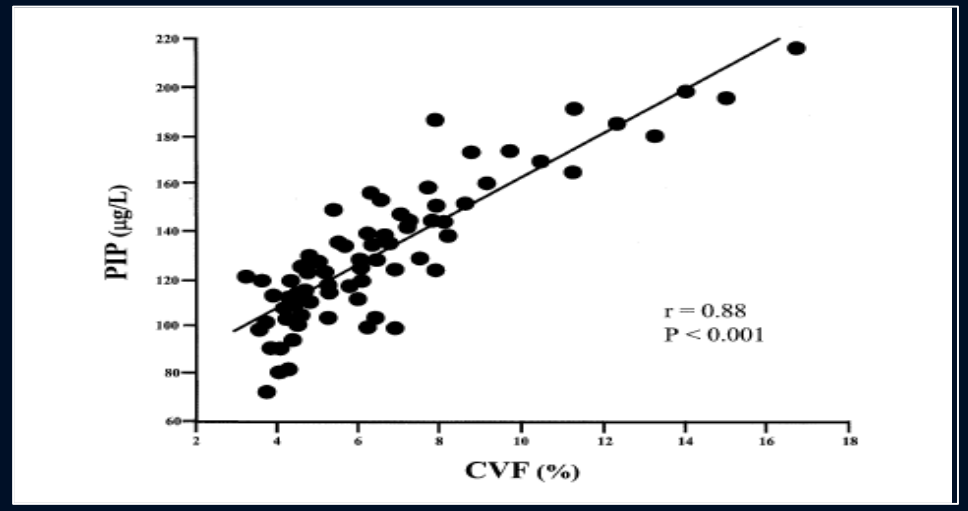
⬇ καλιούρησης

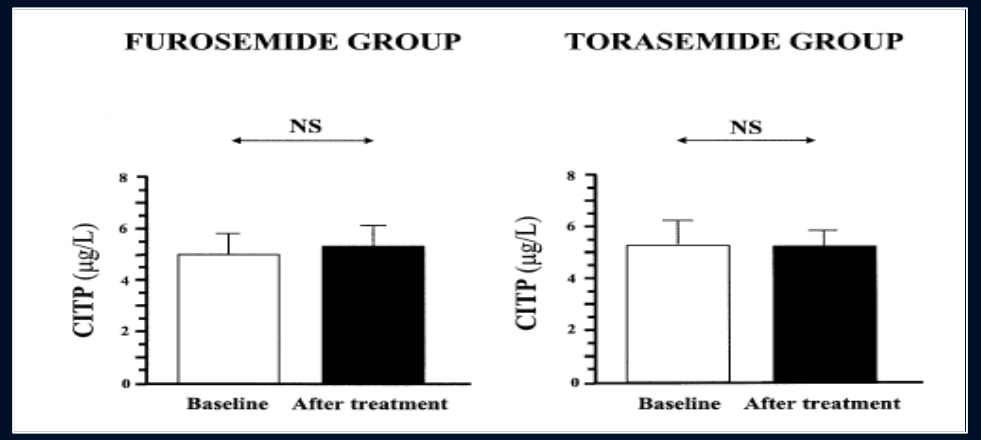
JACC 2004;43:2028

Effects of Loop Diuretics on Myocardial Fibrosis and Collagen Type I Turnover in CHF

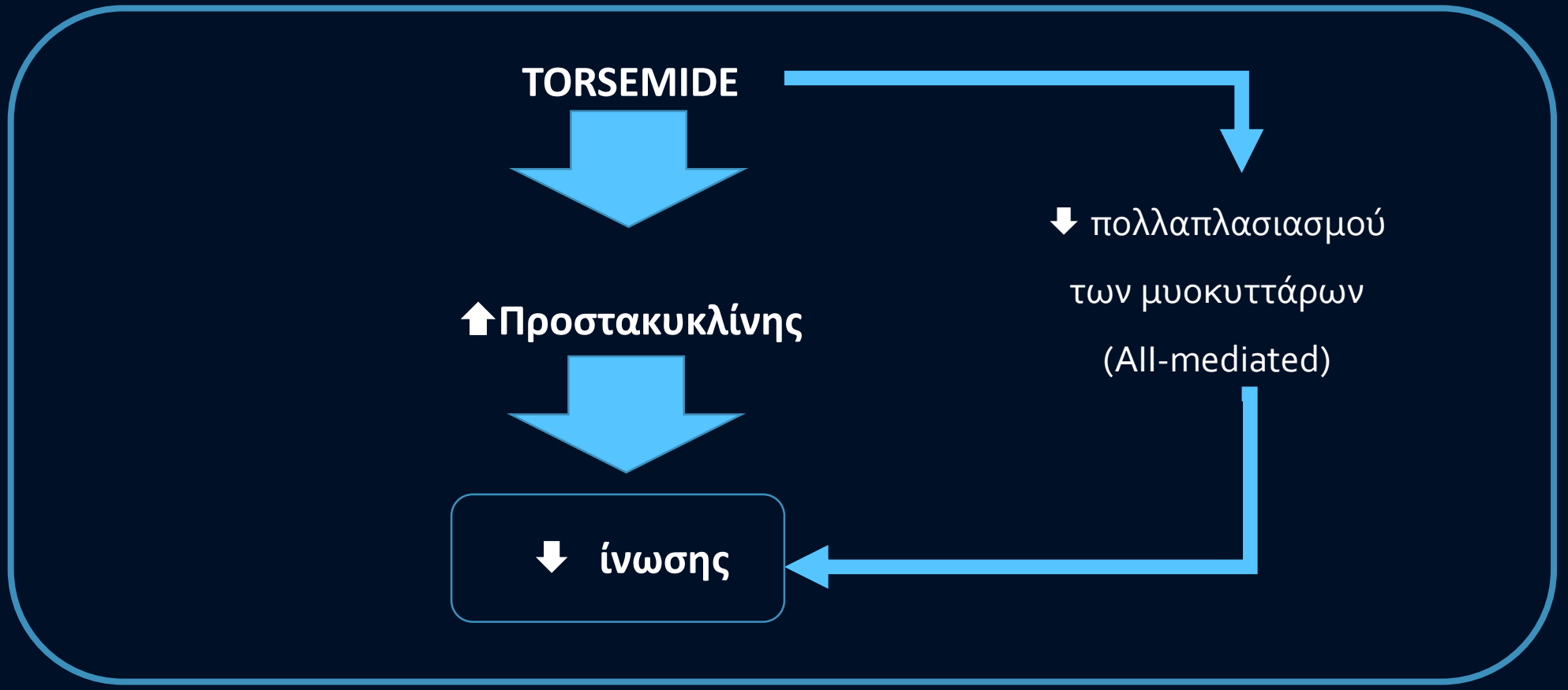
Pts with NYHA functional class II to IV CHF received either 10 -20 mg/day oral torasemide (n =19) or 20 to 40 mg/day oral furosemide (n=17), in addition to standard therapy for 8 months. At baseline and after 8 months, right septal endomyocardial biopsies were obtained to quantify collagen volume fraction (CVF). Serum carboxy-terminal peptide of procollagen type I (PIP) and serum carboxy-terminal telopeptide of collagen type I (CITP), indexes of collagen type I synthesis and degradation, respectively, were measured by specific radioimmunoassays.





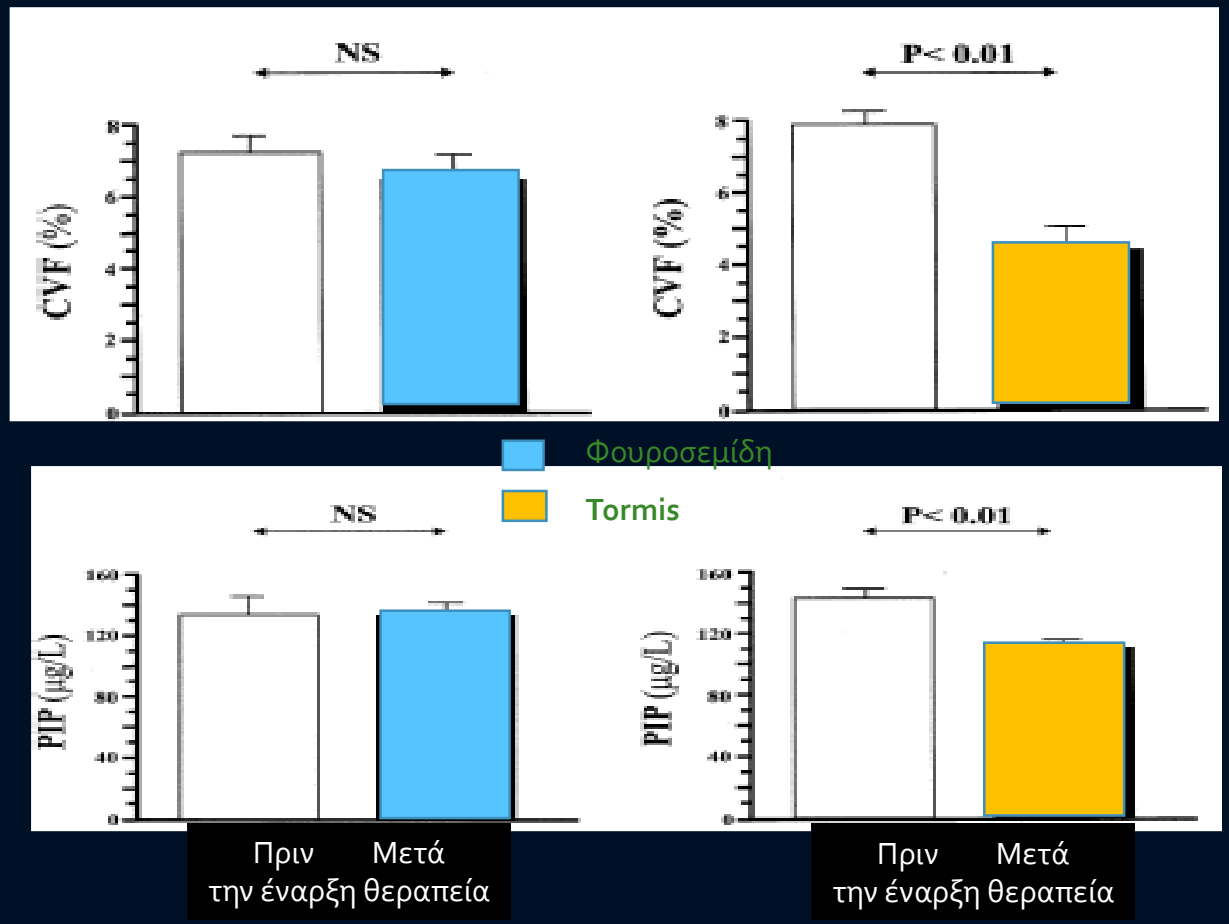


Lopez, et al. J Am Coll Cardiol 2004;43:2028 –35


TORSEMIDE
⬆Προστακυκλίνης
⬇ ίνωσης
⬇ πολλαπλασιασμού
των μυοκυττάρων
(AII-mediated)

Καρδιακή Ανεπάρκεια – Πλειοτρόπες δράσεις

Αποτελέσματα:



Ο CVF μειώθηκε με το Tormis (από 7,96% σε 4,48%) σημαντικά (p<0,01). Η διαφορά μεταξύ των δύο θεραπειών ήταν σημαντική (p<0,005)

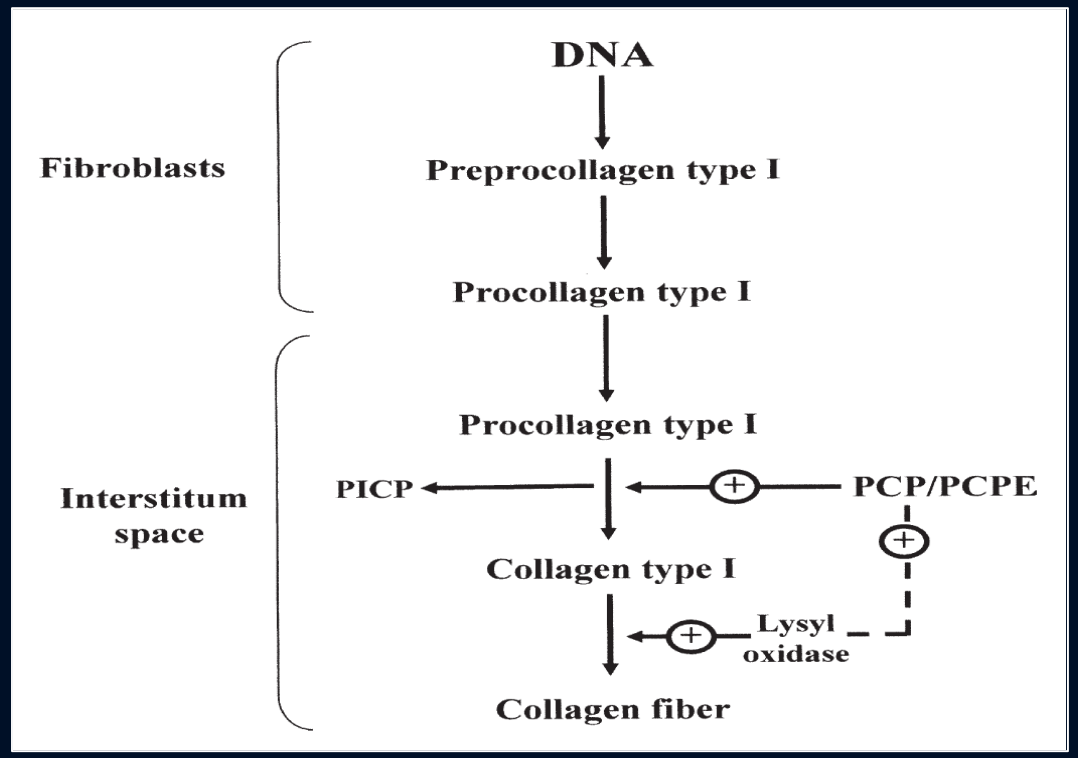
Ο PIP μειώθηκε με το Tormis (από 143 σε 111μg/l) σημαντικά (p<0,01). Η διαφορά μεταξύ των δύο θεραπειών ήταν σημαντική (p<0,01)

Το **Tormis** ασκεί ισχυρή, ευεργετική αντι-ινωτική επίδραση στο μυοκάρδιο

Lopez B. et al, J Am Coll Cardiol 2004;43

Identification of a Potential Cardiac Antifibrotic Mechanism of Tor(a)semide in CHF

CHF pts received either 10 to 20 mg/day oral torasemide (n =11) or 20 to 40 mg/day oral furosemide (n =11) in addition to their standard HF therapy. At baseline and after 8 months from randomization, right septal endomyocardial biopsies were obtained to analyze the expression of PCP by Western blot and the deposition of collagen fibers (collagen volume fraction [CVF]) with an automated image analysis system.



Parameters	Furosemide Group		Torasemide Group	
	Baseline	Treatment	Baseline	Treatment
CVF, %	7.90 ± 0.87	7.09 ± 0.59	8.29 ± 0.52	4.24 ± 0.24*†
α1(I) mRNA, AU	158 ± 19	37 ± 10‡	141 ± 38	61 ± 5‡
PCP zymogen, ADU	10,484 ± 626	13,489 ± 972‡	10,229 ± 1073	10,903 ± 776
PCP active form, ADU	21,616 ± 2,106	25,065 ± 892‡	24,485 ± 1812	23,596 ± 869
Full-length PCPE, ADU	0.37 ± 0.04	0.37 ± 0.05	0.34 ± 0.04	0.32 ± 0.04
36-kDa fragment PCPE, ADU	0.39 ± 0.05	0.33 ± 0.05	0.37 ± 0.05	0.26 ± 0.03‡
PICP, μg/l	144 ± 9	140 ± 8	147 ± 9	109 ± 3*†
MMP-1, ADU	1.04 ± 0.09	1.03 ± 0.08	1.09 ± 0.11	0.91 ± 0.08
TIMP-1, ADU	0.96 ± 0.09	1.18 ± 0.11	0.97 ± 0.02	0.94 ± 0.05

Data are expressed as the mean value ± SEM. *$p < 0.01$ versus values at baseline in the same group. †$p < 0.01$ versus values after 8 months of randomization in the furosemide group. ‡$p < 0.05$.

Lopez B. et al, J Am Coll Cardiol 2007;50:859–67

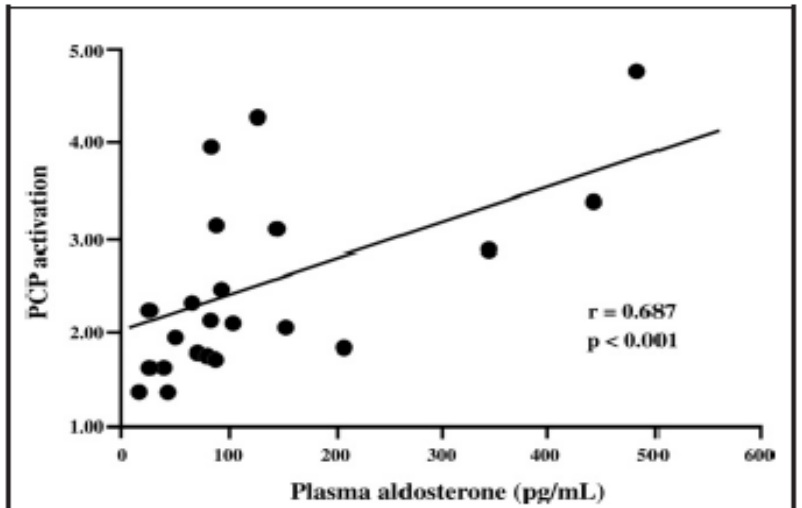


Figure 5 **Association Between Aldosterone and PCP Activation**

Positive correlation (y = 0.004x + 1.907) between plasma aldosterone and activation of myocardial PCP (as assessed by the ratio of PCP active form to PCP zymogen) in all patients with chronic heart failure. Abbreviations as in Figure 1.

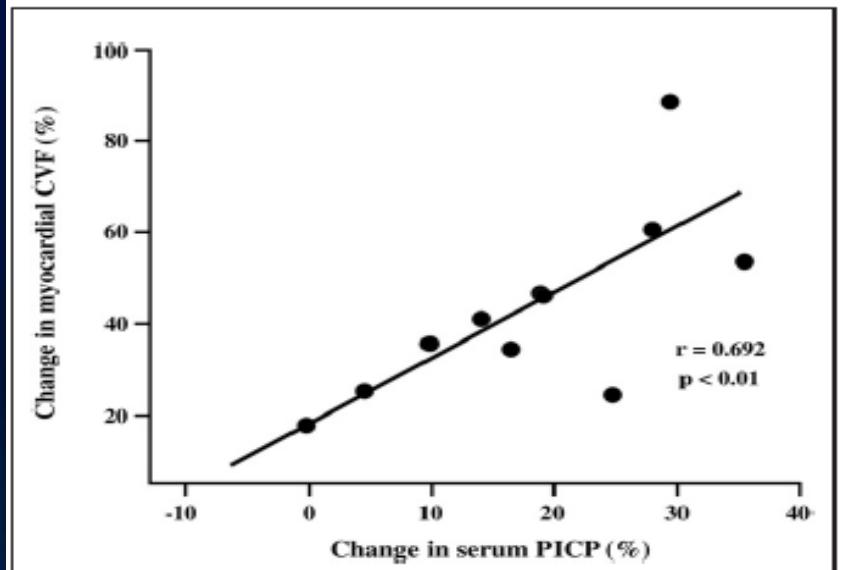


Figure 6 **Association Between PICP and CVF**

Positive correlation (y = 1.338x + 18.73) between the reduction in serum PICP and the reduction in myocardial collagen volume fraction (CVF) in patients with chronic heart failure treated with torasemide. Abbreviations as in Figure 1.

Journal of the American College of Cardiology
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Published by Elsevier Inc.

Vol. 50, No. 9, 2007
ISSN 0735-1097/07/$32.00
doi:10.1016/j.jacc.2007.04.080

Heart Failure

Identification of a Potential Cardiac Antifibrotic Mechanism of Torasemide in Patients With Chronic Heart Failure

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Pamplona and San Sebastián, Spain

Tor(a)semide Versus Furosemide in Acute Heart Failure: the ASCEND-HF Trial

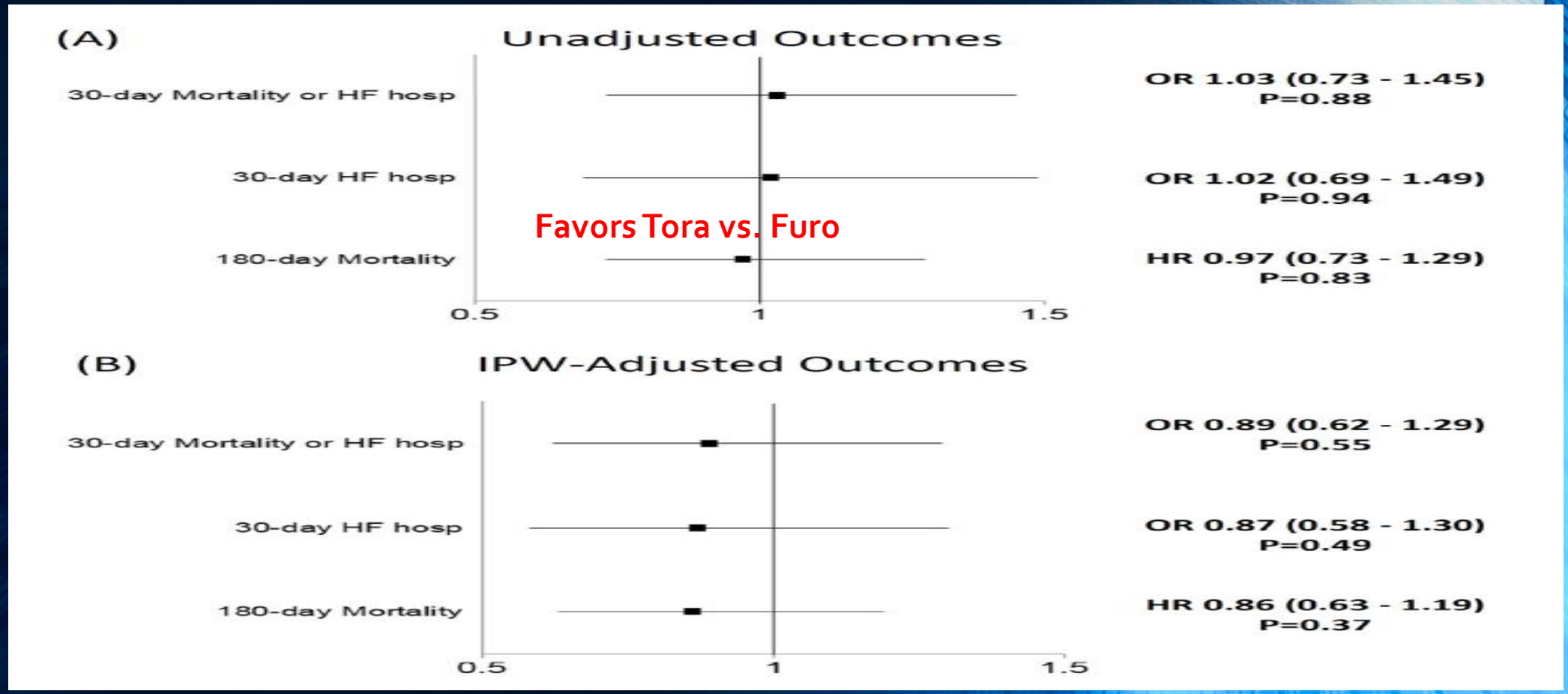
Patients with HF in ASCEND-HF discharged on either torsemide or furosemide. The relation between choice of diuretic at discharge with 30-day mortality or HF hospitalization and 180-day mortality were assessed. Of 7,141 patients in the trial, 4,177 patients were included in this analysis, of which 87% (n =3,620) received furosemide and 13% (n=557) received torsemide.

Characteristic	Furosemide (N=3620)	Torsemide (N=557)	P-Value
Age (years)	65 (54-75)	65 (54-74)	0.34
Women	1255 (34.7%)	179 (32.1%)	0.24
Heart failure history			
HF hospitalization within prior year	1476 (40.8%)	239 (42.9%)	0.35
Ischemic etiology	2228 (61.5%)	38 (69.5%)	<.001
Ejection fraction (%)	30 (20-35)	25 (20-35)	0.025
Ejection fraction ≥50%	346 (9.6%)	52 (9.3%)	0.87
NYHA Class			0.12
I	77 (2.6%)	8 (1.7%)	
II	501 (17.0%)	79 (16.6%)	
III	1572 (53.5%)	238 (50.0%)	
IV	791 (26.9%)	151 (31.7%)	
Laboratories and imaging			
Sodium (mmol/L)	139 (136-141)	138 (135-141)	<.001
Creatinine (mg/dL)	1.2 (1.0-1.5)	1.3 (1.1-1.6)	0.002
Blood urea nitrogen (mg/dL)	23 (17-34)	28 (19-39)	<.001
Hemoglobin (g/dL)	12.6 (11.3-13.9)	12.5 (11.2-14.0)	0.54
NT-proBNP (pg/mL)	4307 (2112-8770)	5345 (2661-9315)	0.006
X-ray indicating pulmonary congestion	2560 (78.1%)	329 (70.0%)	<.001
Baseline medications and devices			

Mentz, et al. Am J Cardiol 2016;117:404-411

Torsemide versus Furosemide in Patients with Acute Heart Failure (From the ASCEND-HF Trial)

Robert J. Mentz, MD[1,2], Vic Hasselblad, PhD[1], Adam D. DeVore, MD[1,2], Marco Metra, MD[3], Adriaan A. Voors, MD[4], Paul W. Armstrong, MD[5,6], Justin A. Ezekowitz, MBBCh[6], W.H. Wilson Tang, MD[7], Phillip J. Schulte, PhD[1], Kevin J. Anstrom, PhD[1], Adrian F. Hernandez, MD, MHS[1,2], Eric J. Velazquez, MD[1,2], and Christopher M. O'Connor, MD[1,2]



Am J Cardiol. 2016 February 1; 117(3): 404–411

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Highlights

- Furosemide is the most commonly used loop diuretic in heart failure (HF) patients despite data suggesting potential pharmacologic and anti-fibrotic benefits with torsemide.
- In this large international acute HF trial, a minority of patients received torsemide and commonly had indicators of more severe disease.
- After risk-adjustment, torsemide was associated with a non-significant reduction in 30 and 180-day events.

Am J Cardiol. 2016 February 1; 117(3): 404–411

Should torsemide be the loop diuretic of choice in systolic heart failure?

Future Cardiol. (2012) 8(5), 707–728

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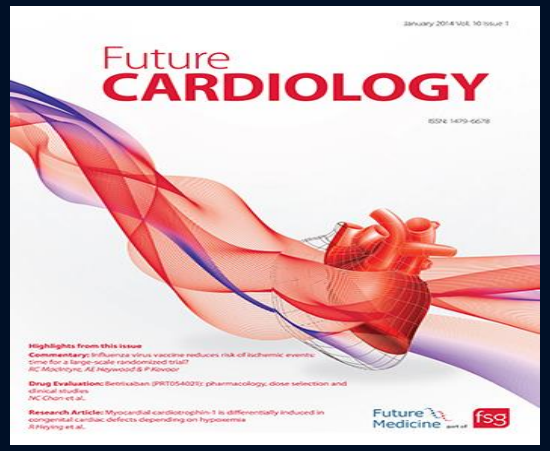

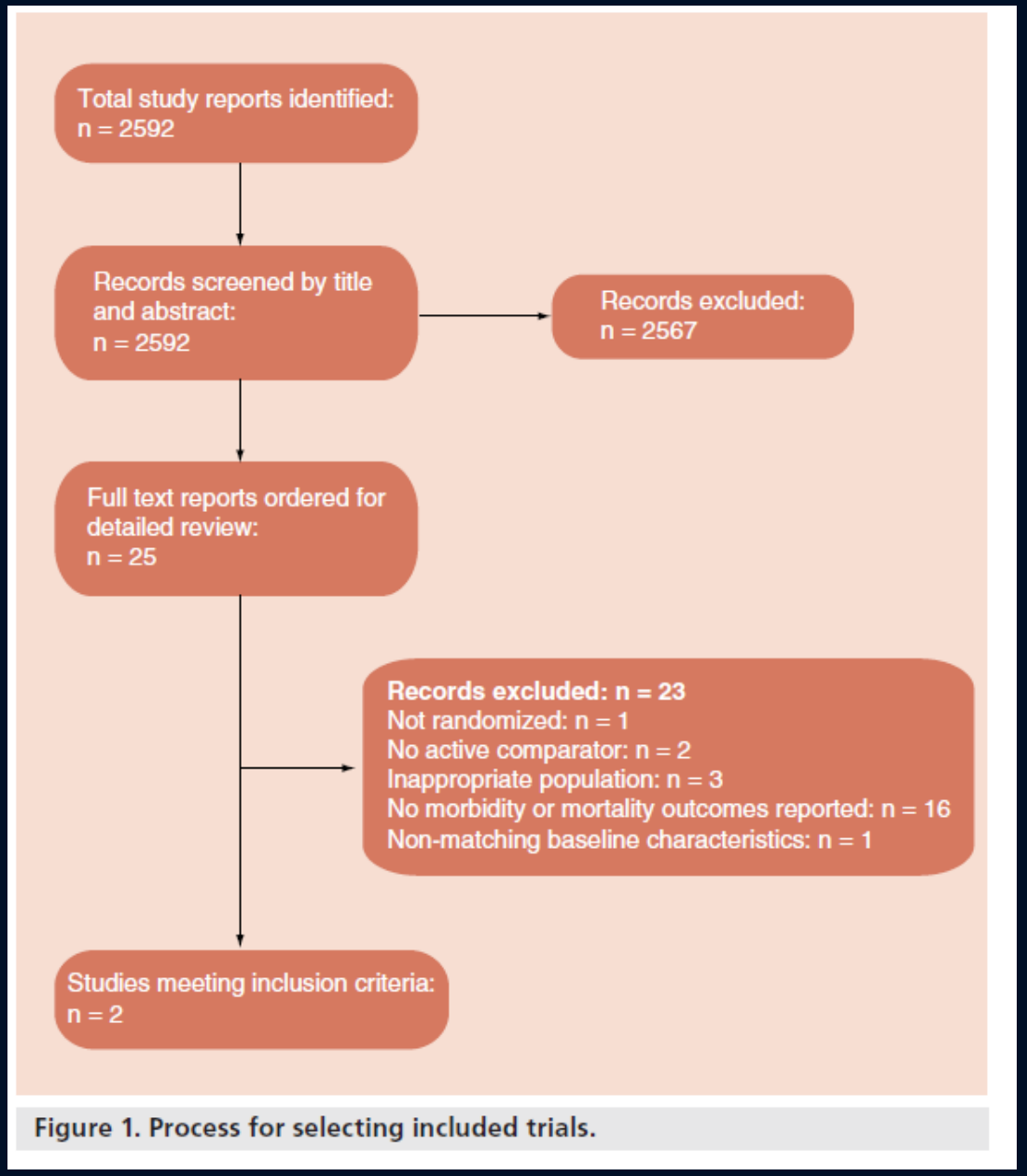

Figure 1. Process for selecting included trials.

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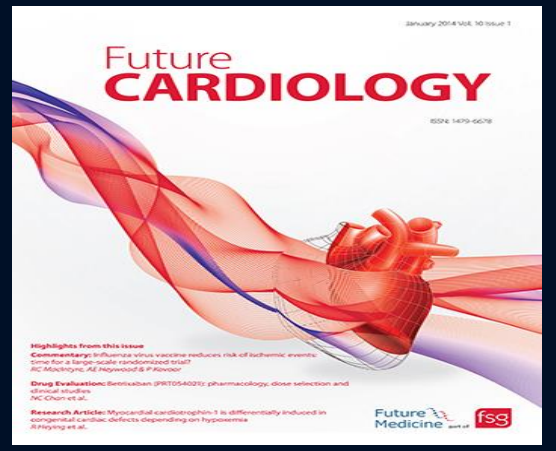

Table 1. Properties of loop diuretics.

Diuretic	Oral bioavailability	Initial dose (mg)	Maintenance dose (mg)	Max dose (mg)	iv. to p.o. conversion	Elimination	Duration of action (h)
Torsemide	80–100%	5–10 q.d.	10–20	200	1:1	80% liver 20% renal†	18–24
Furosemide	10–90%	20–40 q.d.–b.i.d.	40–240	600	1:2	50% renal (unchanged)‡ 50% renal (conjugation)‡	4–6
Bumetanide	80–100%	0.5–1 q.d.–b.i.d.	1–5	10	1:1	50% liver†	6–8

†More torsemide and bumetanide reaches the tubular fluid in patients with liver disease due to a prolonged half-life.
‡Furosemide accumulates in renal insufficiency due to a decrease in both urinary excretion and renal conjugation.
b.i.d.: Twice daily; iv.: Intravenous; p.o.: Per orum*; q.d.: Once daily.*
Data taken from [59–61].

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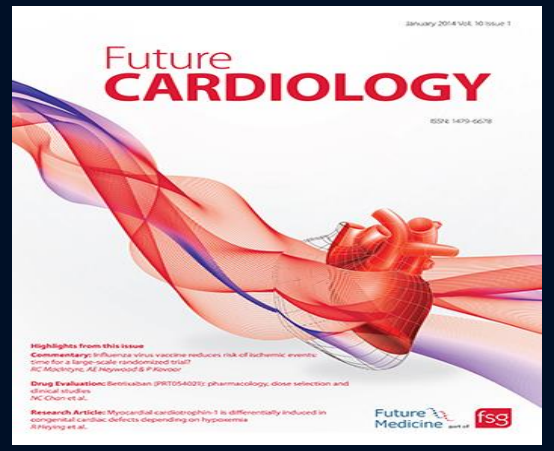


Study or subgroup	Torsemide Events	Torsemide Total	Furosemide Events	Furosemide Total	Weight (%)	Risk ratio IV, random (95% CI)
Murray *et al.* (2001) [48]	18	113	25	121	77.8	0.77 (0.45–1.33)
Muller *et al.* (2003) [36]	8	122	6	115	22.2	1.26 (0.45–3.51)
Total (95% CI)		235		236	100.0	0.86 (0.53–1.39)
Total events	26		31			

Heterogeneity: tau² = 0.00; χ^2 = 0.68, df = 1 (p = 0.41); I^2 = 0%
Test for overall effect: Z = 0.61 (p = 0.54)

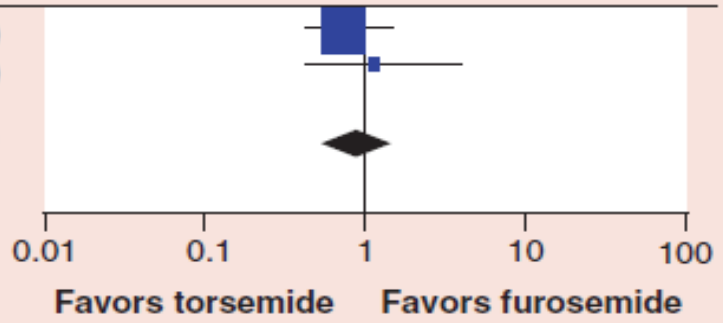
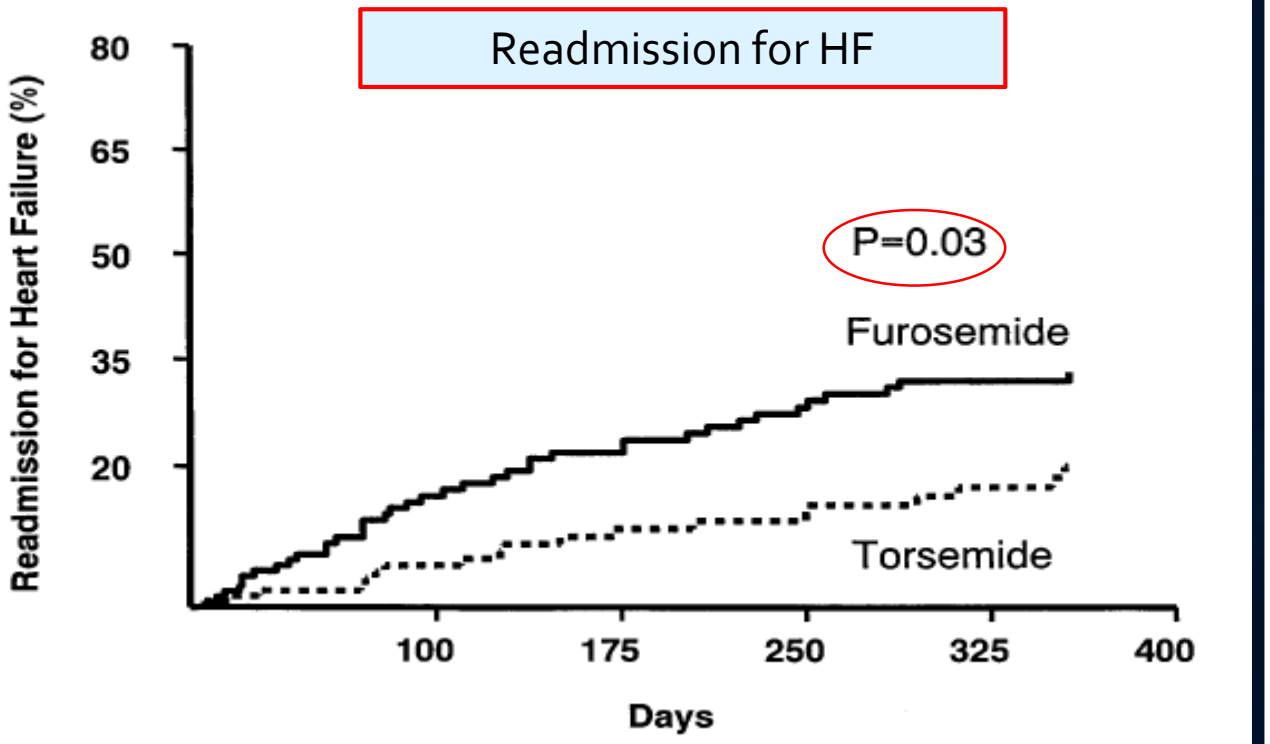
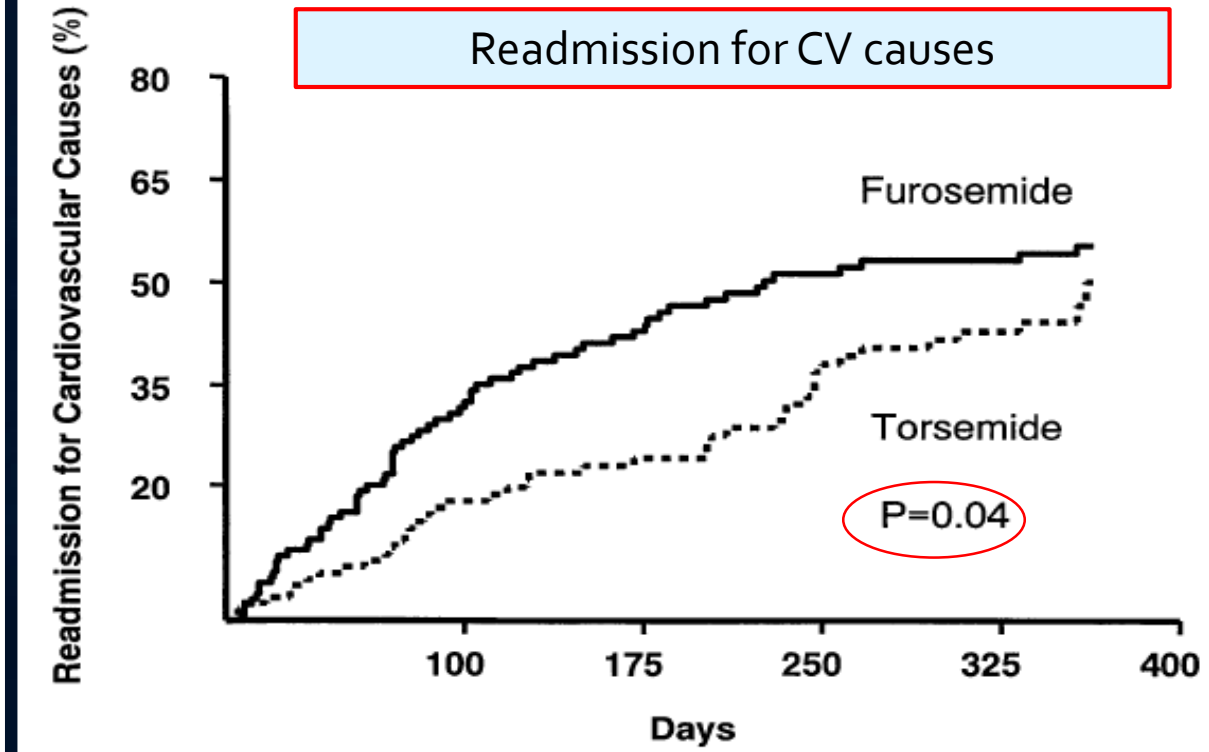


Figure 5. Forest plot of relative risks for mortality.
df: Degrees of freedom; IV: Inverse variance.

Open-label Randomized Trial of Torsemide Compared with Furosemide Therapy for Patients with Heart Failure





Compared with furosemide-treated pts, torsemide-treated pts were less likely to need readmission for heart failure or for all cardiovascular causes. Pts treated with torsemide had significantly fewer hospital days for heart failure ($P<0.02$). Improvements in dyspnea and fatigue scores from baseline were greater among pts treated with torsemide.

Murray, Am J Med. 2001;111:513–520

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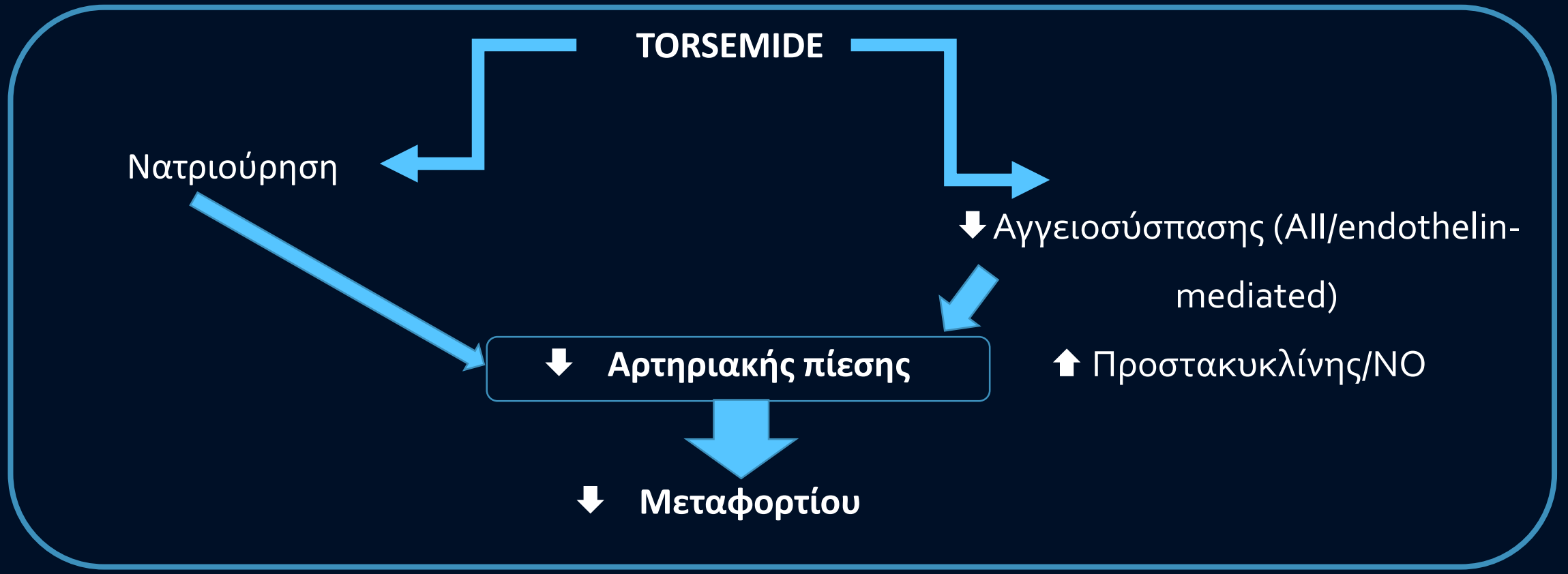
Executive summary

- A systematic review of randomized trials using OVID MEDLINE, Excerpta Medica, Web of Science, PubMed and Google Scholar was performed. Two randomized trials comparing furosemide with torsemide in 471 patients with systolic heart failure (HF) were identified. Compared with furosemide, torsemide significantly reduced HF readmissions (relative risk: 0.53, 95% CI: 0.33–0.84) and cardiovascular readmissions (relative risk: 0.77, 95% CI: 0.60–0.98) in patients with "at least 1 readmission".
- In direct comparison trials, torsemide significantly improves fatigue, reduces HF and cardiovascular-related hospital readmissions, reduces hospital stay, improves exercise tolerance, quality of life, urinations, urinary urgency, left ventricular function, humoral factors, cardiac sympathetic nerve activity, myocardial fibrosis, left ventricular remodeling, hypokalemia, diuresis, natriuresis, pulmonary congestion, edema, blood pressure and weight compared with furosemide.
- On a milligram-to-milligram basis, the natriuretic and chloruretic effects of torsemide are approximately eight-times that of furosemide.
- Compared to furosemide, torsemide has a longer half-life, longer duration of action, and a higher and less variable bioavailability.
- Compared to furosemide, torsemide significantly reduced total heart failure readmissions (relative risk: 0.41, 95% CI: 0.28–0.61; $p < 0.0001$), $I^2 = 0\%$.
- Compared to healthy individuals, the rate of absorption of torsemide and the subsequent diuretic effect, are not affected by congestive HF (CHF), whereas the absorption rate and diuretic effect of furosemide and bumetanide are reduced in CHF. Thus, torsemide retains its pharmacodynamic properties in patients with CHF regardless of the HF severity, whereas furosemide's pharmacodynamics (diuretic and natriuretic effects) are significantly diminished.
- Furosemide is metabolized in the kidneys leading to accumulation of furosemide but not torsemide in renal dysfunction. The resulting increased accumulation of furosemide in patients with lowered kidney function results in an increased risk of ototoxicity with furosemide compared with torsemide.
- Torsemide has antialdosterone, antifibrotic and vasodilatory properties. These properties are not shared by furosemide.
- Torsemide should be the loop diuretic of choice compared with furosemide in patients with systolic HF.

TORSEMIDE ΚΑΙ ΑΡΤΗΡΙΑΚΗ ΥΠΕΡΤΑΣΗ/ΚΑΡΔΙΑΚΗ ΑΝΕΠΑΡΚΕΙΑ



Περί Tormis

- Η τορασεμίδη είναι το πρώτο διουρητικό αγκύλης της κατηγοράς των πυριδινικών σουλφονουριών
- Η τορασεμίδη εμφανίζει αντιυπερτασική επίδραση (ακόμα και στα 2,5mg) ανεξάρτητη νατριούρησης, πιθανώς λόγω αναστολής Ang II ή ενδοθηλίνης 1 ή αύξησης της προστακυκλίνης και του NO.
- Τυχαιοποιημένες μελέτες έχουν δείξει μείωση του LVSV και αύξηση του EF λόγω της αντιυπερτασικής δράσης

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Balsam *et al. Trials* (2017) 18:36
DOI 10.1186/s13063-016-1760-z

Trials

STUDY PROTOCOL Open Access

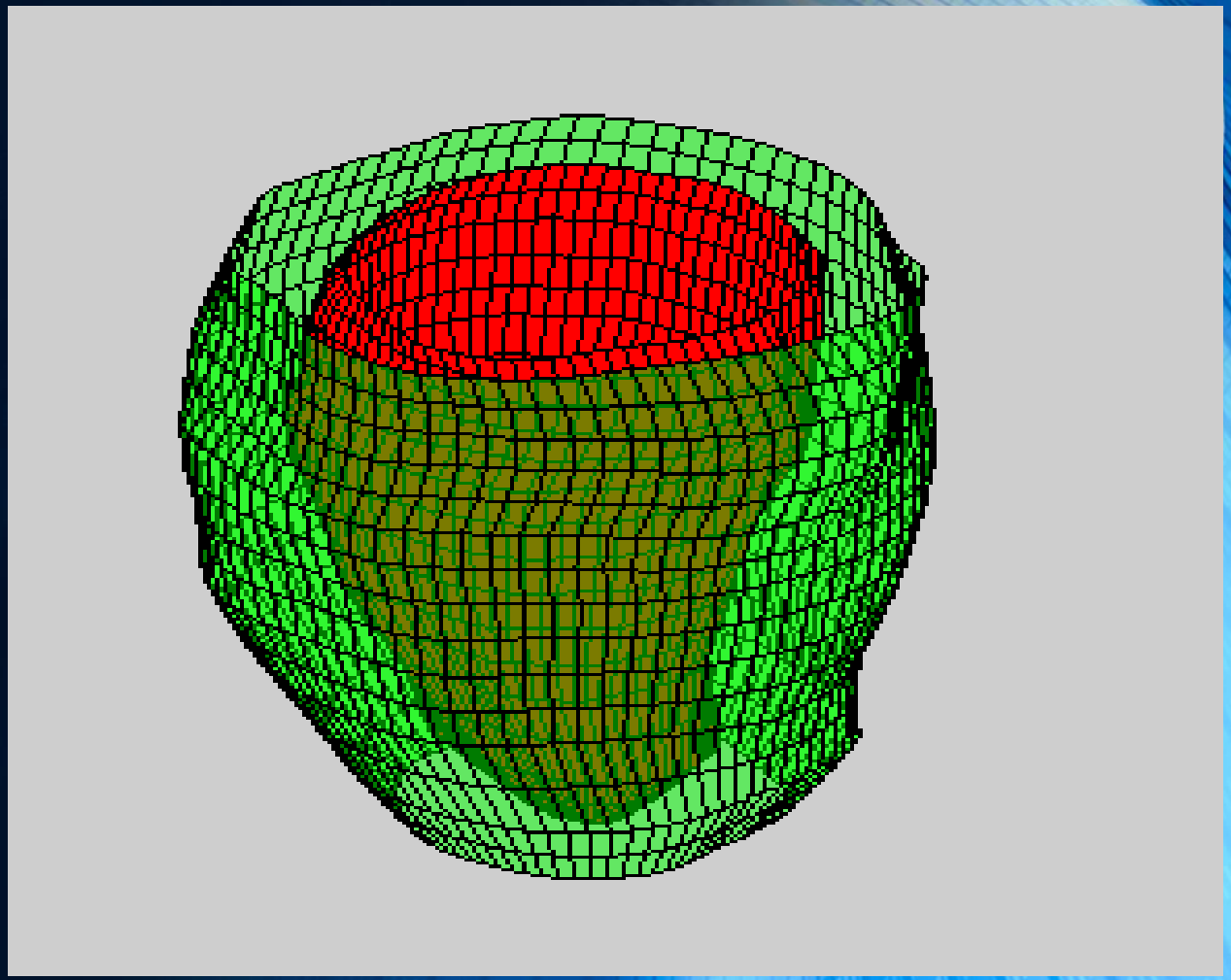
The impact of torasemide on haemodynamic and neurohormonal stress, and cardiac remodelling in heart failure – TORNADO: a study protocol for a randomized controlled trial

Paweł Balsam*, Krzysztof Ozierański, Agata Tymińska, Renata Główczyńska, Michał Peller, Anna Fojt, Andrzej Cacko, Bartosz Sieradzki, Elwira Bakuła, Maciej Markulis, Robert Kowalik, Zenon Huczek, Krzysztof J. Filipiak, Grzegorz Opolski and Marcin Grabowski

DIAGNOSIS

Chronic heart failure

A complex syndrome that can result from any structural or functional cardiac disorder that impairs the pumping ability of the heart



HF Clinic Patient

- RS is a 69 yr old gentleman recently referred to the HF team.
- He has a history of LV dysfunction with an EF of 20% due to IHD.
- He has had recent multiple admissions to hospital with worsening symptoms NYHA IV.
- He is now in NYHA III
- With PND, orthopnoea and pitting oedema to his knees
- He has LBBB on his ECG with a QRS of 160 ms

Medication

- During last admission beta blocker has been stopped due to symptomatic bradycardia.
- ACE I has been reduced due to worsening renal function and symptomatic hypotension.
- Spironolactone has been reduced due to hyperkalaemia

Further Management

- What next?

Treatment

- After discussion at the HF MDT, referred for Biventricular PPM (CRT) with ICD.
- He was brought into a pre assessment clinic and assessed and counselled by the HF nurse.
- He was admitted for CRT-D the next week

6 months later

- RS was followed up in the nurse Led HF clinic 2-4 weekly for assessment and titration of medication.
- Beta Blocker was reinstated and he is now tolerating 10 mg Bisoprolol.
- His ACE I was reintroduced and slowly titrated - now on 5mg Ramipril
- He is tolerating 50 mg Spironolactone
- His renal function is normal
- He is biventricular paced
- He is in NYHA II
- An echo was repeated showing an improvement with EF 35-40%
- He attends a cardiac rehab exercise class regularly
- He has not been admitted to hospital since his CRT-D was implanted

Case 2

- ED is a 67 yr old gentleman admitted to the medical ward with a history of breathlessness and bilateral ankle oedema. He has had a reduction in exercise tolerance over the last three months and has experienced PND and orthopnoea for a few days prior to admission.

Past Medical History

- STEMI 2008
- PPCI to LAD 2008
- HTN
- Hyperlipidaemia
- Arthritis

Drugs on admission

- Atenolol 25 mg od
- Perindopril 2 mg od
- Simvastatin 40 mg od
- Aspirin 75 mg od
- Piroxicam 20mg od

Social

- His wife has recently died and he now lives alone.
- He is retired
- He has two grown up daughters living in Manchester and Scotland.
- He drinks up to 5 pints of beer every Friday and Saturday night.
- He eats mainly microwave meals
- He is a current smoker of 5 cigarettes per day for 50 yrs.

Observations

- BP 160/90 mmHg
- HR 100bpm reg Sinus Rhythm
- Respirations 22/min
- Bilateral basal creps
- Third heart sound
- His ECG shows SR with anterior q waves
- His Chest x Ray shows Pulmonary oedema

Further Findings

- NT proBNP is raised on admission at 560pmol/L
- Echo carried out the day after admission shows impaired LV systolic function with an EF of 20% and severe AS
- He is referred to the HF team.

HF Review

- He is assessed the next day.
- Diagnosis LV dysfunction due to IHD and severe AS
- Stop Piroxicam
- PLAN: Change Atenolol to Bisoprolol 2.5 mg titrating up as tolerated, aim for a resting HR of <70 bpm
- Commence Furosemide
- Commence Spironolactone 12.5 mg titrating up to maximum tolerated dosage
- Aim to increase perindopril if BP and renal function will allow to the maximum tolerated dosage.
- Regular bloods for renal function

Life Style advice / Education

- Reduction in salt and advice on changing his diet from convenience foods
- Reduction in alcohol intake
- Highlight the importance of compliance of medication
- Explain possible symptoms and the importance of reporting any changes in symptoms to the HF team.
- Encourage stopping smoking, referral to cessation, give patches.

Discharge

- Mr Smith is discharged after 4 days on the medical ward, with a plan for FU in the HF clinic in 2 weeks.
- His U&E s were normal
- His HR was 70 bpm on 5 mg of Bisoprolol
- BP 120/80 on perindopril 4 mg
- His chest was clear

Follow up

- He was seen two weeks later in the HF clinic.
- His U&Es were checked showing his creatinine had increased to 161 umol/l and urea up to 15.4 umol/l
- He was reporting symptoms of increasing lethargy and dizziness
- His HR was 50bpm SR BP 100/50

Treatment plan

- Reduce Bisoprolol to 2.5 mg
- Reduced Perindopril back to 2 mg
- Plan to recheck U&E s in one week
- Readmitted with worsening HF symptoms
- Blood renal chemistry deteriorates further despite stopping ACEI – creatinine 288 umol/l
- Renal review

Ongoing management

- Joint care between HF team and renal team
- Started on haemodialysis
- Becomes euvolaemic with improvement in HF symptoms
- Discussed at HF MDT

Further progress

- Referred for consideration of TAVI in view of severe AS
- TAVI performed December 2013 Heart Hospital
- Repeat echo March 2014 shows improvement of LV function to 35%
- Now on 8mg perindopril, 7.5mg bisoprolol and 25mg spironolactone
- In NYHA class II

Aims of treatment of chronic heart failure

- The aims of therapy in heart failure are to:
  - Improve life expectancy
  - Improve quality of life
- The relative importance of these aims varies:
  - Between patients
  - Over time

NICE, 2003

Modern management

- The therapeutic approach in chronic heart failure due to systolic dysfunction consists of:
  - Non-pharmacological measures
    - Patient education
    - Avoid obesity
    - Dietary measures e.g. salt restriction if prescribed
    - Avoid excessive fluid intake
    - Smoking cessation
    - Exercise/rehabilitation
    - Influenza/pneumococcal vaccination
  - Pharmacological therapy
  - Devices and surgery

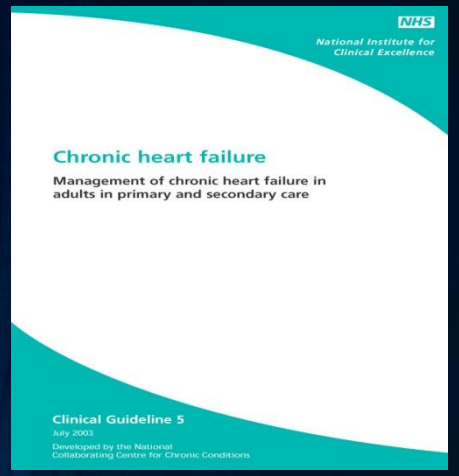
ESC, 2008

Treatment options for chronic heart failure

Drug therapy

- Diuretics
- Neurohormonal antagonists
  - ACE inhibitors
  - Beta blockers
  - Mineralocorticoid antagonists
  - Angiotensin II receptor blockers
- Ivabradine (If channel blocker)
- Digoxin
- Other drugs
  - Amiodarone
  - Nitrates/Hydralazine
  - Aspirin
  - Warfarin

Diuretic therapy



- Rapid relief of congestive symptoms and fluid retention, improving:
  - Breathlessness
  - Exercise performance
- May be titrated according to need following initiation of subsequent therapies
- No evidence for mortality benefit
- No effect on disease progression

"Diuretics should be routinely used for the relief of congestive symptoms and fluid retention in patients with heart failure, and titrated (up and down) according to need following initiation of subsequent heart failure therapies"

NICE, 2003

Use of oral diuretics

Drug	Initial dose (mg)	Maximum recommended daily dose (mg)
Loop diuretics		
Bumetanide	0.5–1.0	5–10
Furosemide	20–40	250–500
Torasemide	5–10	100–200
Thiazides*		
Bendroflumethiazide (bendrofluazide)	2.5	5
Indapamide	2.5	2.5
Metolazone	2.5	10
Potassium-sparing diuretic	+ACEI –ACEI	+ACEI –ACEI
Amiloride	2.5 5	20 40
Triamterene	25 50	100 200

*May be effective when added to loop diuretics when fluid retention is resistant, but can promote dramatic diuresis and disturbance in fluid balance and electrolytes. Patients must be closely monitored and specialist advice is required. ACEI=ACE inhibitor

Adapted from NICE et al. 2003.

NICE, 2003

Patient self-monitoring

- Patients can monitor their volume status by daily weighing and appropriate adjustment of their diuretic regimen
- Requires education and support
- Patients should be taught how to recognise early signs of decompensation and how to seek professional help
- Heart failure nurse usually most appropriate professional to 'train' patient

NICE, 2003

Other treatment options

Surgery and devices

- Cardiac resynchronisation therapy (CRT)
- Implantable cardioverter defibrillator (ICD)
- Coronary revascularisation (PCI/CABG)
- Transplantation
- Left ventricular assist device (LVAD)

- Other invasive therapies
  - Valve repair/replacement
  - Left ventricular aneurysmectomy

NICE, 2003

Should torsemide be the loop diuretic of choice in systolic heart failure?

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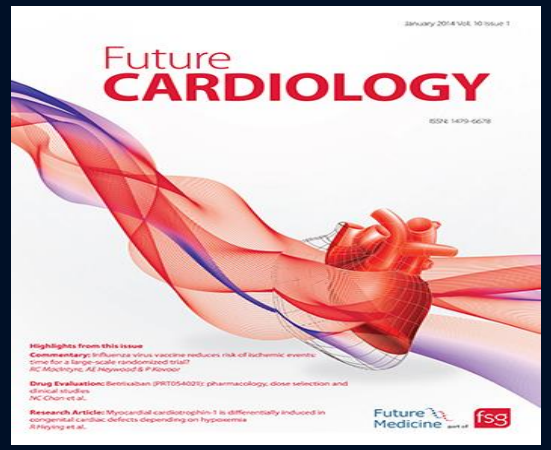


Future Cardiol. (2012) 8(5), 707–728

Box 1. Advantages of torsemide versus furosemide.

Pharmacological properties

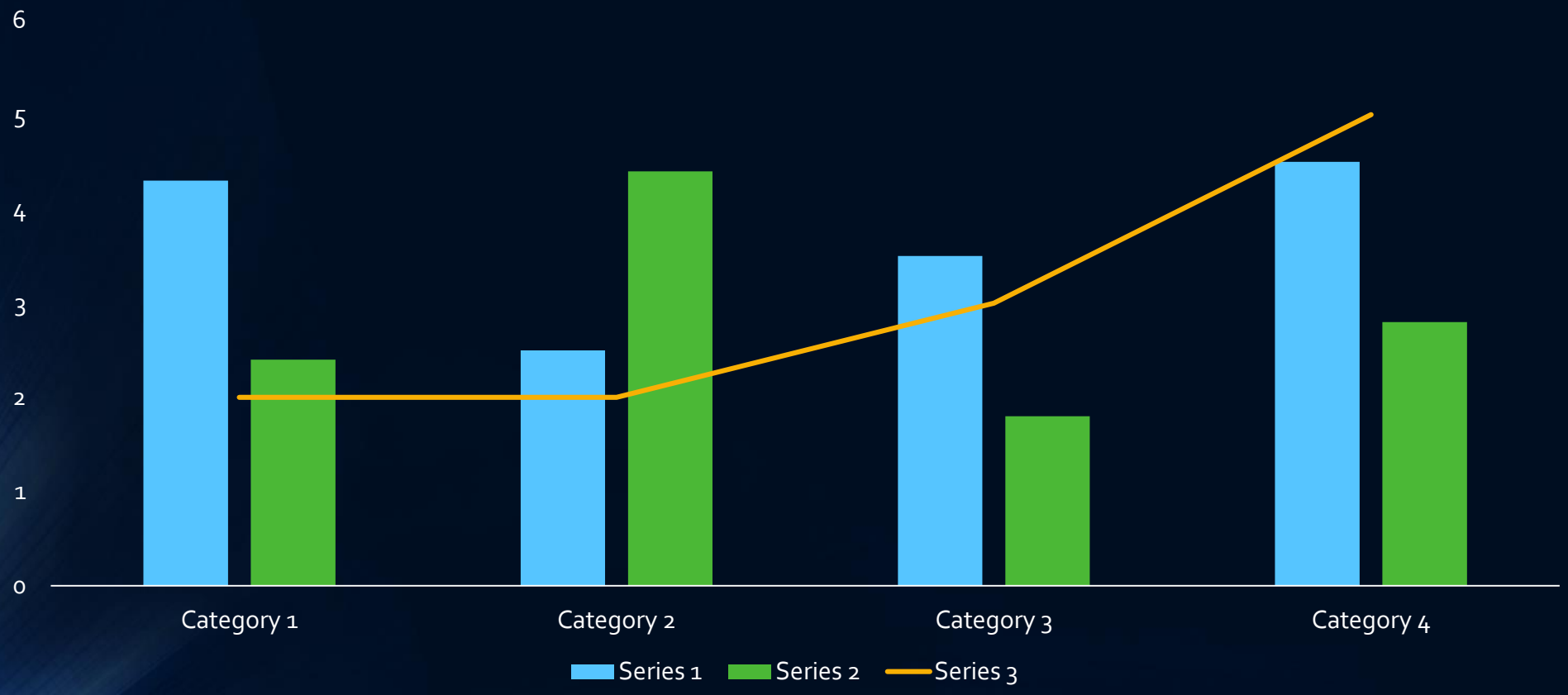
- Longer duration of action
- Quicker onset of action
- Greater and less variable bioavailability
- Food decreases fuorsemide's but not torsemide's diuretic activity (bioavailability, T_{max} and C_{max})
- Potassium-sparing effect
- Magnesium-sparing effect
- Less postdiuretic 'rebound effect' of sodium and water retention
- Less chance of ototoxicity: furosemide but not torsemide is metabolized by the kidneys and thus in renal dysfunction furosemide will accumulate, increasing the risk of ototoxicity
- Inhibition of the RAAS system: inhibition of angiotensin-II and aldosterone
- Greater binding to luminal tubular receptors
- Bioavailability is not affected by CHF or renal dysfunction
- On a milligram-to-milligram basis, the natriuretic and chloruretic effects of torsemide are approximately eight-times that of furosemide
- Torsemide is 97–99% protein bound whereas furosemide is 95% protein bound. A loop diuretic with greater than 95% protein binding limits its glomerular filtration. This allows the diuretic to stay trapped in the vascular space (bound to serum proteins) so that it can be consistently delivered to secretory sites of proximal tubule cells (i.e., more torsemide is delivered to the site of action versus furosemide due to higher protein binding)
- Hypoalbuminemic states (celiac disease, Crohn's disease, short bowel syndrome, liver dysfunction such as hepatitis, cirrhosis or hepatic carcinoma or nephrotic syndrome). A decrease in systemic albumin decreases the amount of medication bound to albumin in the blood, allowing more of the loop diuretic to be trapped in the interstitial space. This leads to less drug reaching the site of action in the tubular lumen. Furthermore, hypoalbuminemia increases renal glucuronidation and this increases furosemides metabolism (this will not occur with torsemide)

Clinical effects

- Greater effects on blood pressure
- Greater reduction in HF- and CV-related hospital readmissions
- Decreased length of hospital stay
- Better quality of life: less nocturia, micturition and urinary urgency
- Greater improvement in NYHA functional class (fatigue, heart size, leg edema, pulmonary congestion and ejection fraction are all improved significantly more with torsemide)
- Inhibits the sympathetic nervous system (norepinephrine): shows improvement in myocardial 123-iodine metaiodobenzylguanidine uptake and improves total defect score, washout rate and heart to mediastinum ratio
- Decreases cardiac fibrosis: offers the potential advantage of decreased sudden death from arrhythmias (due to cardiac fibrosis), improvement in cardiac function and improvements in NYHA functional class especially in patients with diastolic dysfunction (who are more affected by cardiac fibrosis)
- Increased compliance: once daily vs twice daily dosing
- Reduces thiazide diuretic induced potassium and magnesium loss
- Increased diuresis and natriuresis
- Increased glomerular filtration rate

CHF: Congestive heart failure; CV: Cardiovascular; HF: Heart failure; NYHA: New York Heart Association; RAAS: Renin–angiotensin–aldosterone system.

Title and Content Layout with Chart



Two Content Layout with Table

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Class	Group 1	Group 2
Class 1	82	95
Class 2	76	88
Class 3	84	90

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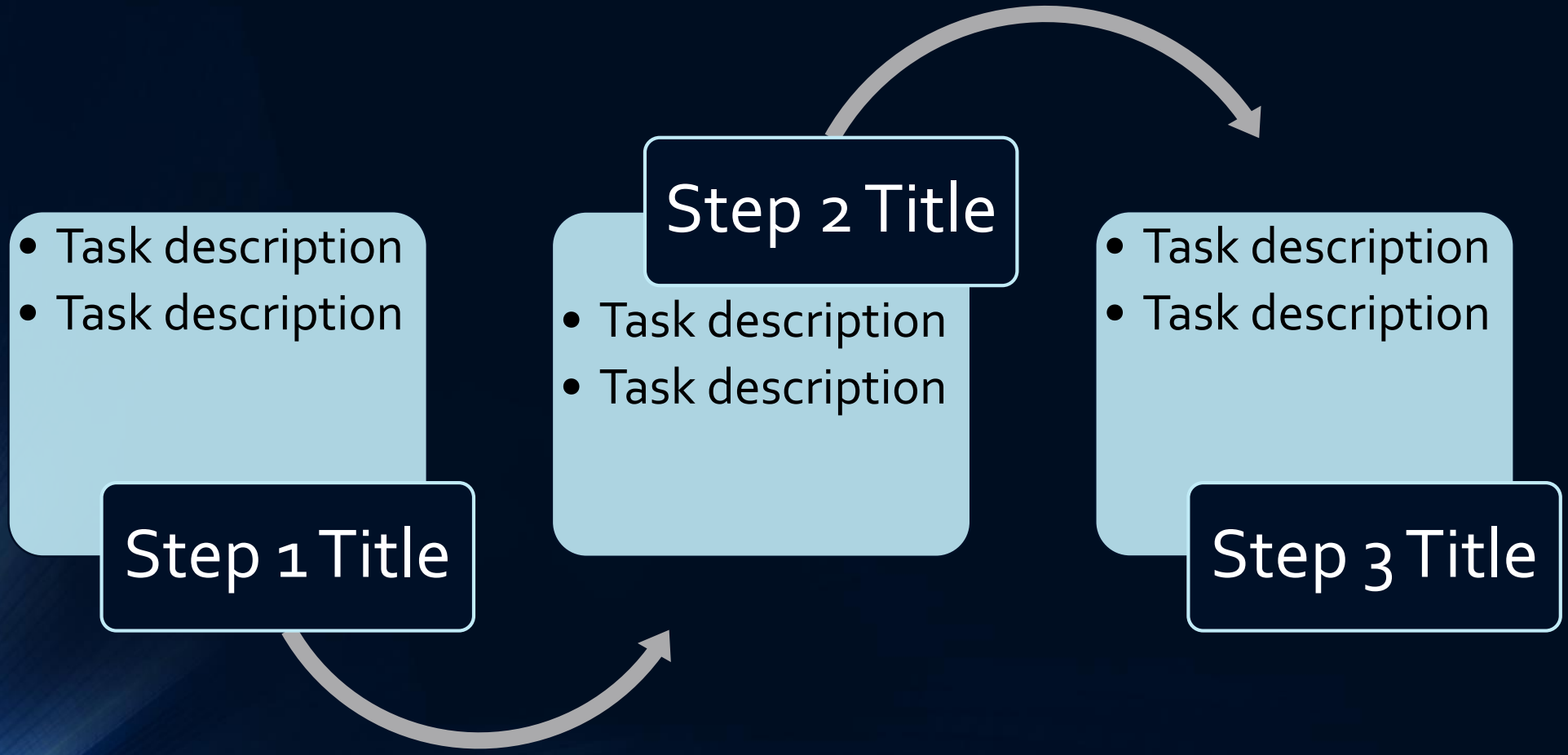

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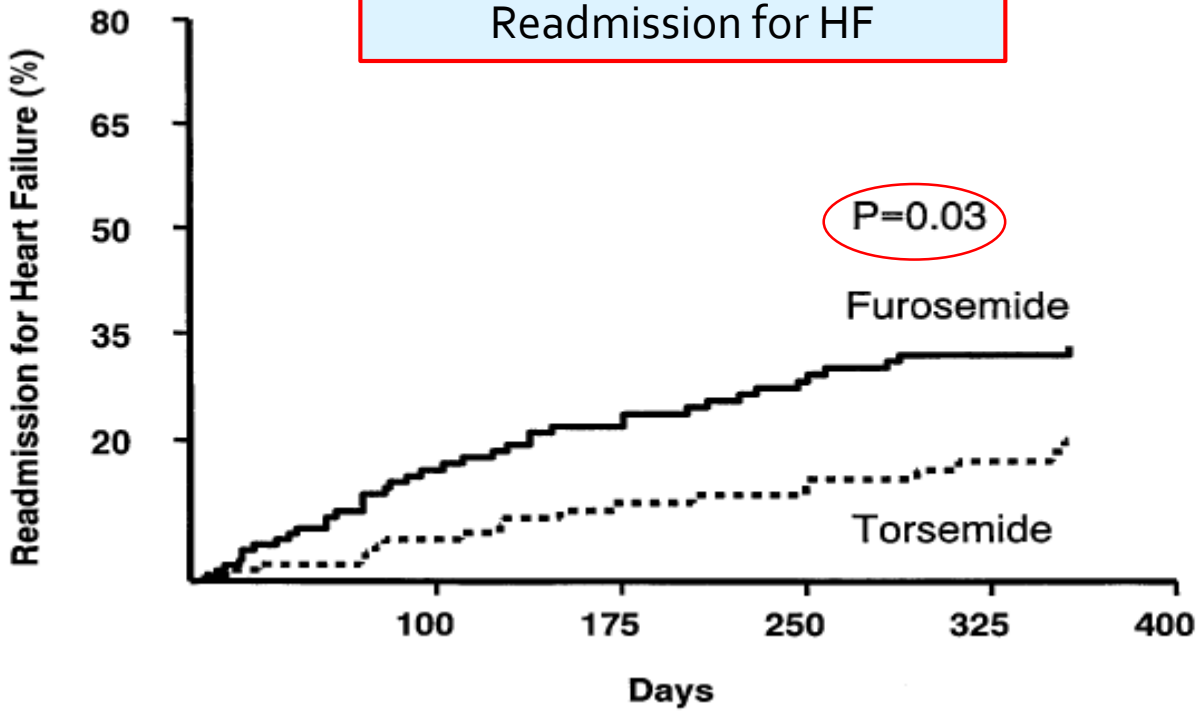
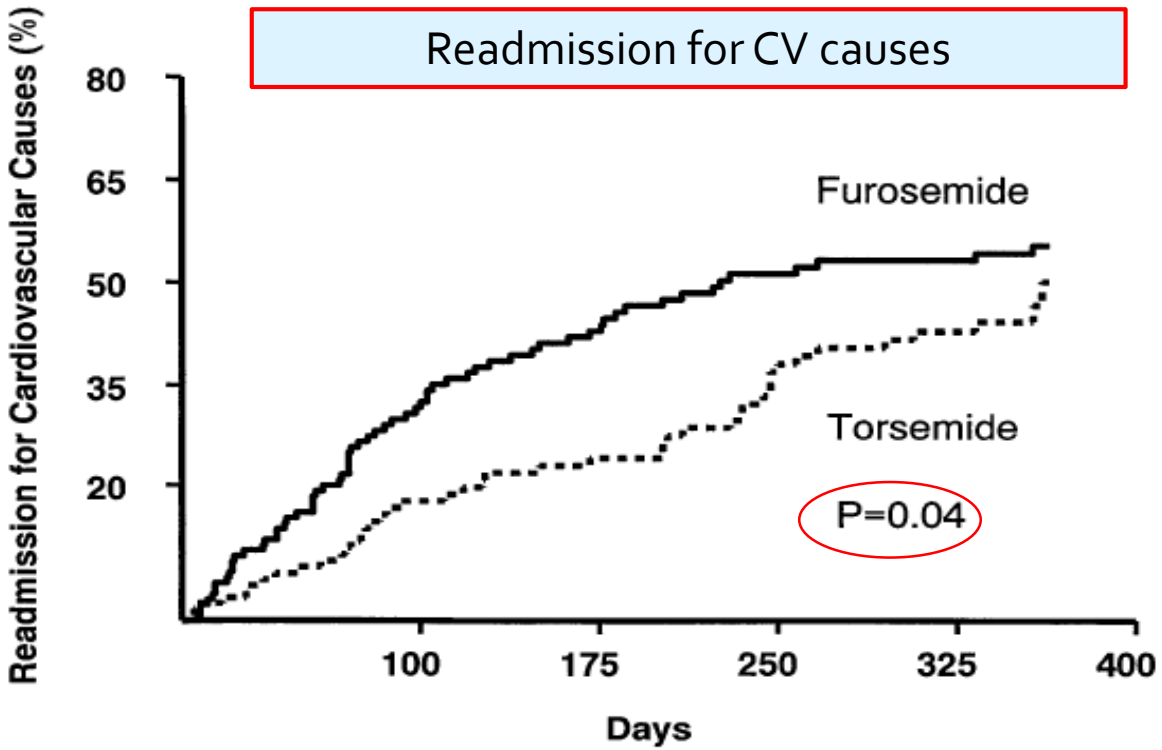
Open-label Randomized Trial of Torsemide Compared with Furosemide Therapy for Patients with Heart Failure

Readmission for HF



Readmission for CV causes



Compared with furosemide-treated pts, torsemide-treated pts were less likely to need readmission for heart failure or for all cardiovascular causes. Pts treated with torsemide had significantly fewer hospital days for heart failure (P<0.02). Improvements in dyspnea and fatigue scores from baseline were greater among pts treated with torsemide.

Murray, Am J Med. 2001;111:513–520

Title and Content Layout with List

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