

Pathophysiology of Hypertension and Pain Management

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American
Heart
Association.

Pathophysiology of Pain and Pharmacologic Treatment for Pain

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Disclosures

Dr. Choi has no disclosures.

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Outline

- Pathophysiology of pain management including pain pathways
- Overview of pharmacologic treatment for pain



Definition of Pain

“An unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage.”

– International Association for the Study of Pain

International Association for the Study of Pain (2021). Terminology. <https://www.iasp-pain.org/resources/terminology/>.





Pain is always a *personal* experience.

International Association for the Study of Pain (2021). Terminology. <https://www.iasp-pain.org/resources/terminology/>.





Pathophysiology of Pain

Perception of Stimulus

1. Transduction
2. Transmission
3. Modulation
4. Perception



Rene Descarte, 1662

Ringkamp, M, Dougherty, PM, Raja, SN. (2018). Anatomy and Physiology of the Pain Signaling Process. In H. Benzon (Ed.), *Essentials of Pain Medicine* (4th ed., pp. 3-10). Philadelphia: Elsevier.



Perception of Stimulus

1. Transduction
 - Peripheral terminals of primary afferent neurons
2. Transmission
 - Peripheral sensory cells in dorsal root ganglion (DRG) to spinal cord
 - Spinal neurons second order neurons project to thalamus, brainstem, diencephalon
 - Brainstem and diencephalon neurons form third component to cortical sites
3. Modulation
 - Dorsal horn of spinal cord including DRG
4. Perception
 - Cortex and subcortical regions

Ringkamp, M, Dougherty, PM, Raja, SN. (2018). Anatomy and Physiology of the Pain Signaling Process. In H. Benzon (Ed.), *Essentials of Pain Medicine* (4th ed., pp. 3-10). Philadelphia: Elsevier.



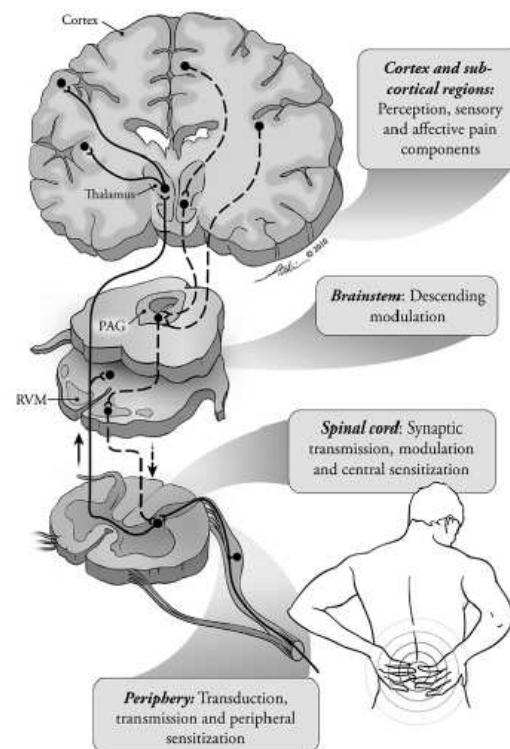
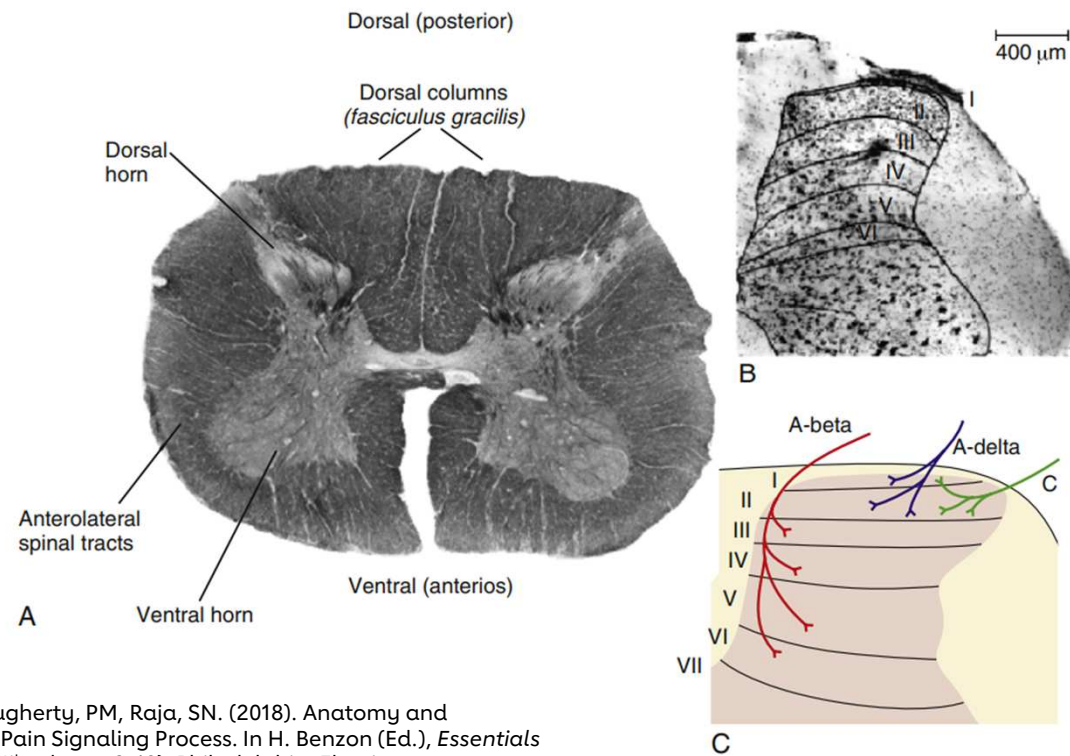
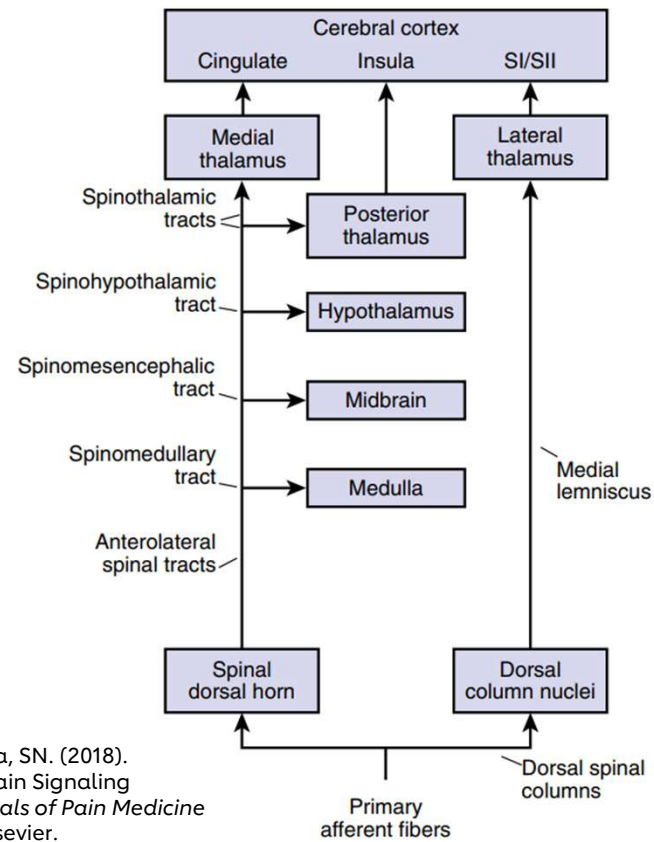


FIGURE 1-1 Schematic of pain-signaling mechanisms involved in transduction, transmission, modulation, and perception of pain. Ascending afferent and descending modulatory pathways are shown.

Ringkamp, M, Dougherty, PM, Raja, SN. (2018). Anatomy and Physiology of the Pain Signaling Process. In H. Benzon (Ed.), *Essentials of Pain Medicine* (4th ed., pp. 3-10). Philadelphia: Elsevier.



Ringkamp, M, Dougherty, PM, Raja, SN. (2018). Anatomy and Physiology of the Pain Signaling Process. In H. Benzon (Ed.), *Essentials of Pain Medicine* (4th ed., pp. 3-10). Philadelphia: Elsevier.



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Biases in Pain Treatment

INSIGHTS | DIVERSITY AND INCLUSION | HEALTH CARE | MEDICAL EDUCATION

How we fail black patients in pain

Janice A. Sabin, PhD, MSW

January 6, 2020



Sabin, JA. (2020). How we fail black patients in pain. AAMC. <https://www.aamc.org/news-insights/how-we-fail-black-patients-pain>.





Types of Pain

Pain	Description	Onset and Course	Distribution
Nociceptive	Sharp	Correlated with injury	Area of injury or trauma
Inflammatory	Achy, dull, stabbing	Progressive, affected by activity	Localized to the inflammation/ infection
Neuropathic	Burning, electric, shooting	Insidious, progressive	Radiates from nerve damage

Pinckard-Dover, HN, Choi, H, Petersen EA. (2022) Pharmacologic Treatment of Pain. In HR. Winn (Ed.) *Youmans and Winn Neurological Surgery* (8th ed., Pp.1484-1491). Philadelphia: Elsevier.





Types of Pain

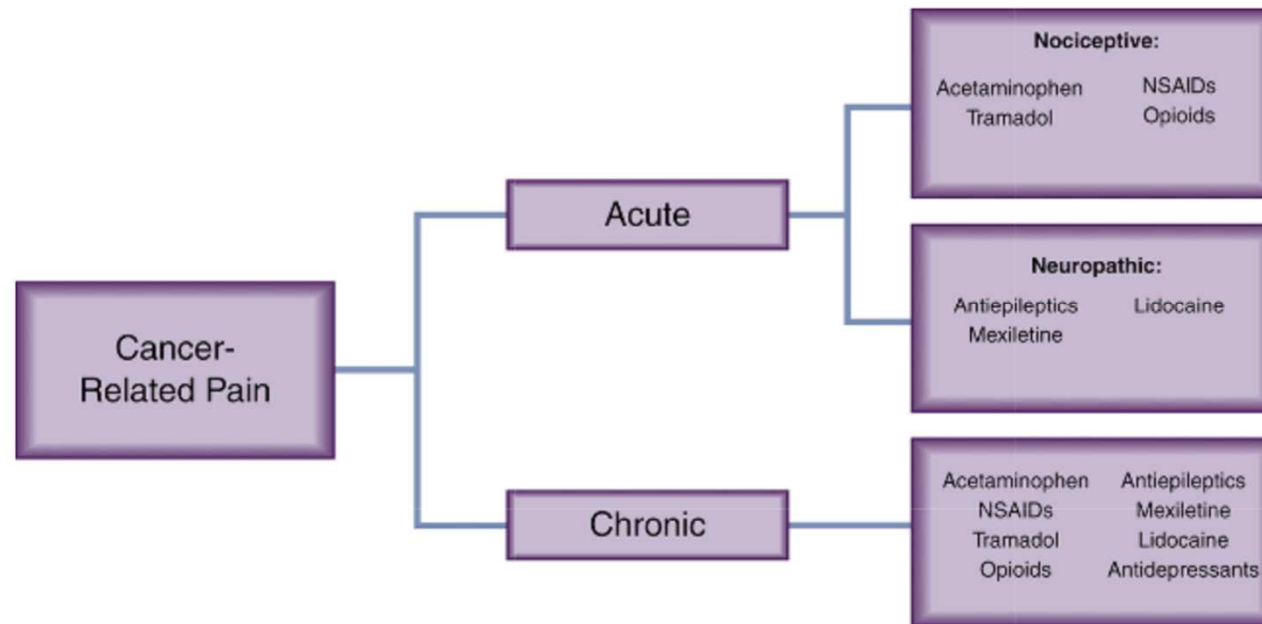
ACUTE vs. CHRONIC
CANCER vs. NON-CANCER



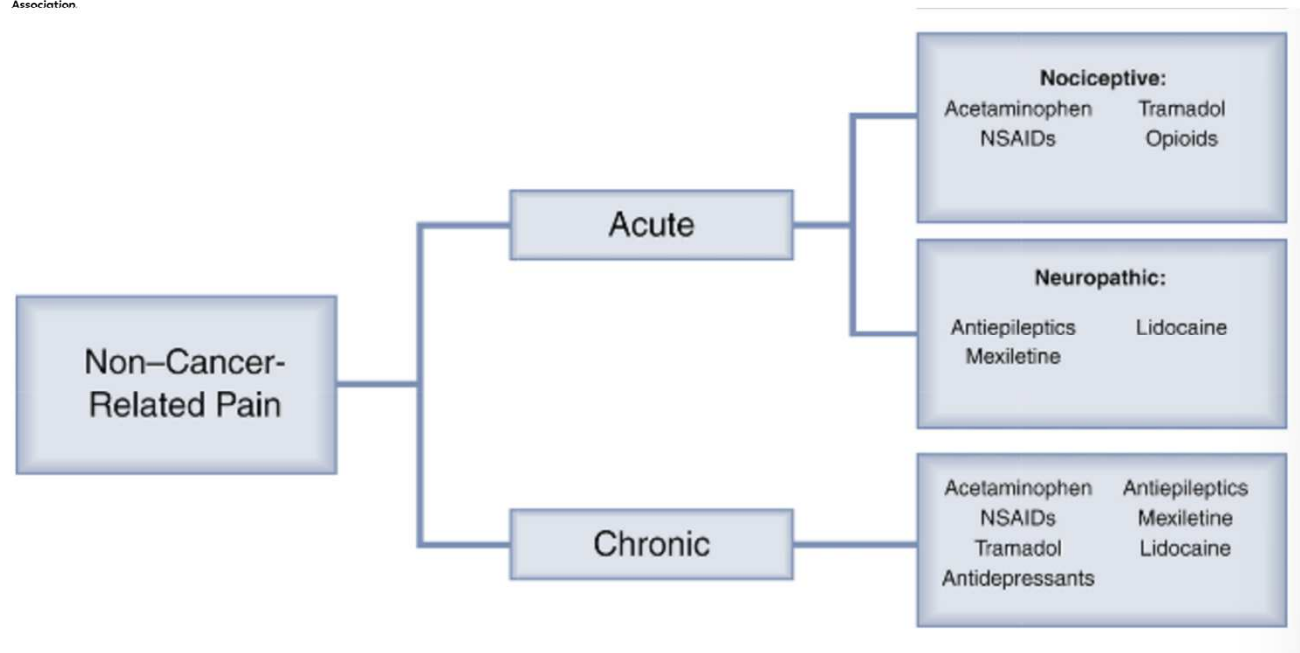
Pharmacologic Treatment of Pain

- Opioids
- Nonsteroidal Anti-inflammatory Drugs (NSAIDs)
 - Selective COX-2 inhibitors
 - Nonselective COX inhibitors
- Acetaminophen
- Antidepressants
 - Tricyclic antidepressants (TCAs)
 - Serotonin norepinephrine reuptake inhibitors (SNRIs)
 - Selective serotonin reuptake inhibitors (SSRIs)
- Antiepileptics
 - Calcium channel blockers
 - Sodium channel blockers
- Local anesthetics

Pinckard-Dover, HN, Choi, H, Petersen EA. (2022) Pharmacologic Treatment of Pain. In HR. Winn (Ed.) *Youmans and Winn Neurological Surgery* (8th ed., Pp.1484-1491). Philadelphia: Elsevier.



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Hypertension Pathophysiology and Non-Opioid Pain Management Considerations for Patients with Hypertension and/or Cardiovascular Disease in the Hospital

William B. White, MD
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University of Connecticut School of Medicine





Disclosures

- Cardiovascular safety consultant (CV endpoint committees and data safety committees): Astra-Zeneca, Bristol-Myers Squibb, Cerevel, Clarion, Clexio, JAZZ, Johnson & Johnson, Millenium-Takeda, Protalix, UCB
- Educational consultant: Wolter Kluwers and UpToDate
- Speaker's bureaus – NONE
- Stock ownership in pharmaceutical or device companies – NONE
- Patents related to lecture – None

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Blood Pressure Values

- Blood pressure is traditionally measured using an air-filled cuff around the arm (sphygmomanometer) with values expressed in millimeters of mercury (mmHg)
- Major blood pressure values derived from sphygmomanometry:
 - **SBP (systolic blood pressure)**: maximum within-cycle pressure in the arteries
 - **DBP (diastolic blood pressure)**: minimum within-cycle pressure in the arteries
 - **PP (pulse pressure)**: within-cycle pressure range
($PP = SBP - DBP$)
 - **MAP (mean arterial pressure)**: mean blood pressure for each cardiac cycle ($MAP = \frac{1}{3} PP + DBP$ [usually])

Izzo JL, Sica DA, Black HR, eds, and the Council for High Blood Pressure Research (American Heart Association). *Hypertension Primer: The Essentials of High Blood Pressure*. 4th ed. Philadelphia: Lippincott Williams & Wilkins; 2008:144–148, 335–338.





Ambulatory Blood Pressure Monitoring



ABPM devices are programmed to measure the patient's blood pressure at preset intervals throughout a 24-hour period

Advantages:

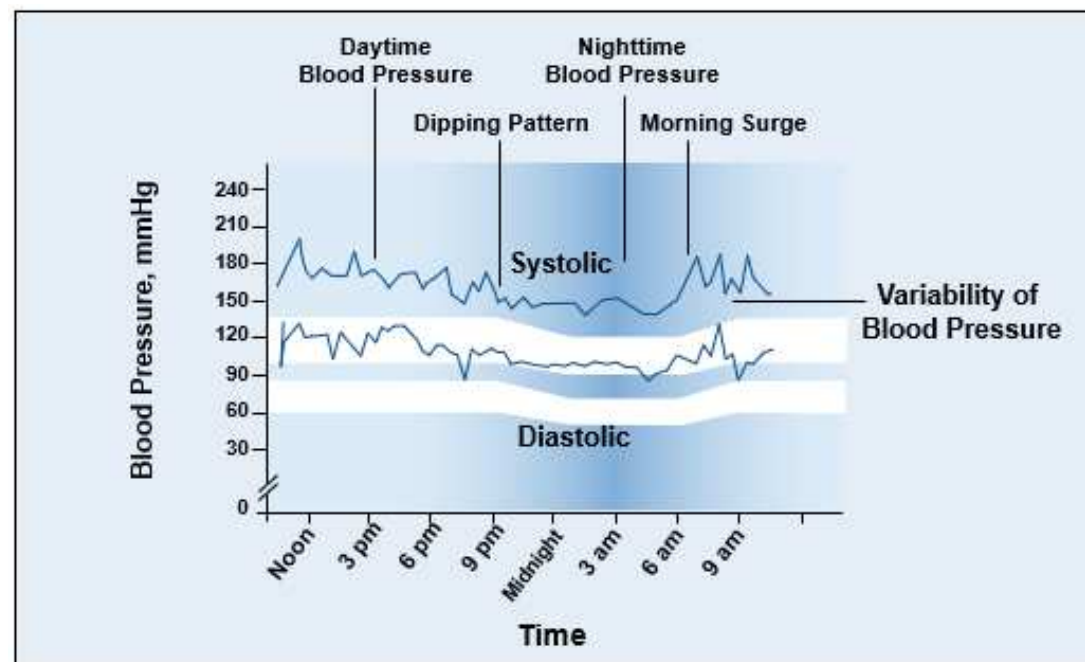
- Detects dipping patterns that may increase cardiovascular risk
- Elucidates subsets of hypertension (e.g., white coat hypertension (WCH), masked, borderline, and refractory hypertension)
- Multiple readings throughout the day may reveal patterns in blood pressure and periods when control is inadequate

Pickering TG, White WB. J Clin Hypertens. 2008;10:850–855





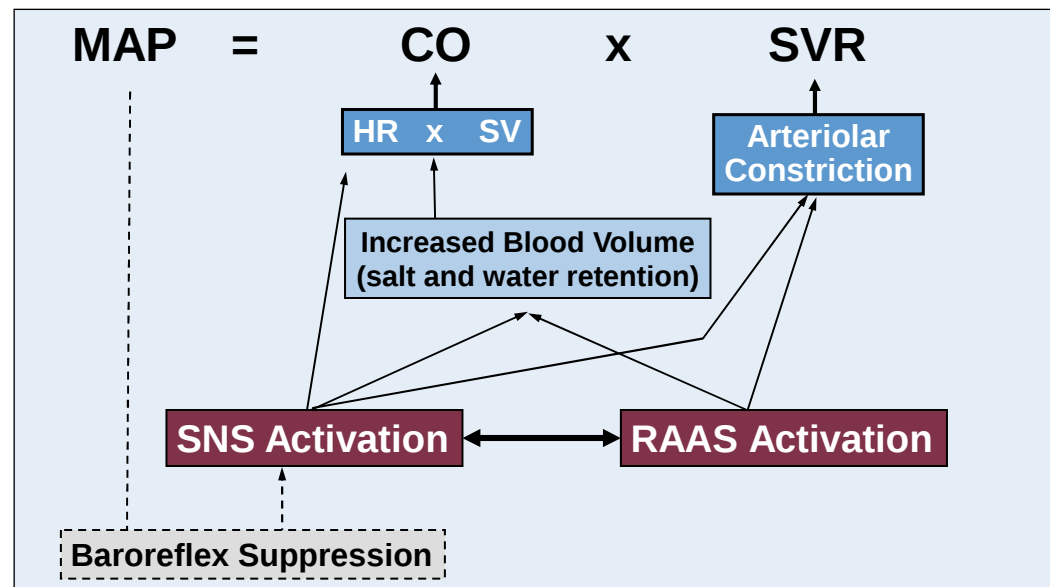
24-hour Blood Pressure Tracing With Hypertension



Reprinted with permission from Pickering TG et al. *N Engl J Med*. 2006;354:2368–2374.



Systemic Hemodynamics

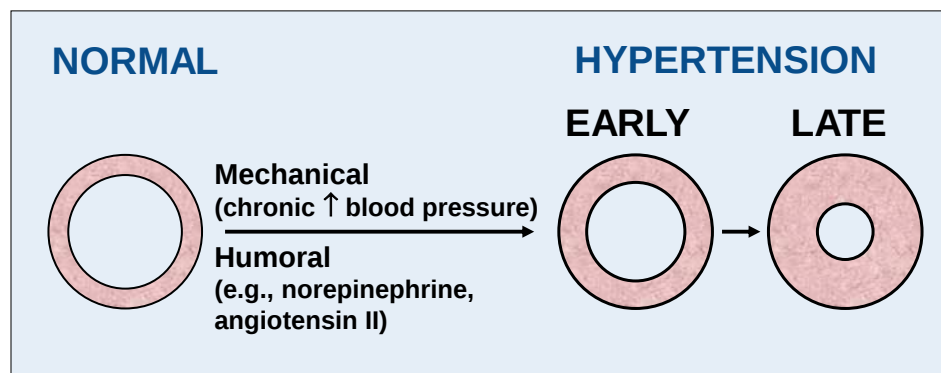


CO (cardiac output) SVR (systemic vascular resistance) HR (heart rate) SV (stroke volume)
 SNS (sympathetic nervous system) RAAS (renin-angiotensin-aldosterone system)

Izzo JL, Sica DA, Black HR, eds, and the Council for High Blood Pressure Research (American Heart Association). *Hypertension Primer: The Essentials of High Blood Pressure*. 4th ed. Philadelphia: Lippincott Williams & Wilkins; 2008:126–132, 443–450, 455–464.



Arteriolar Hypertrophy in Hypertension (Arteriolosclerosis)



Arteriolar smooth muscle hypertrophy causes

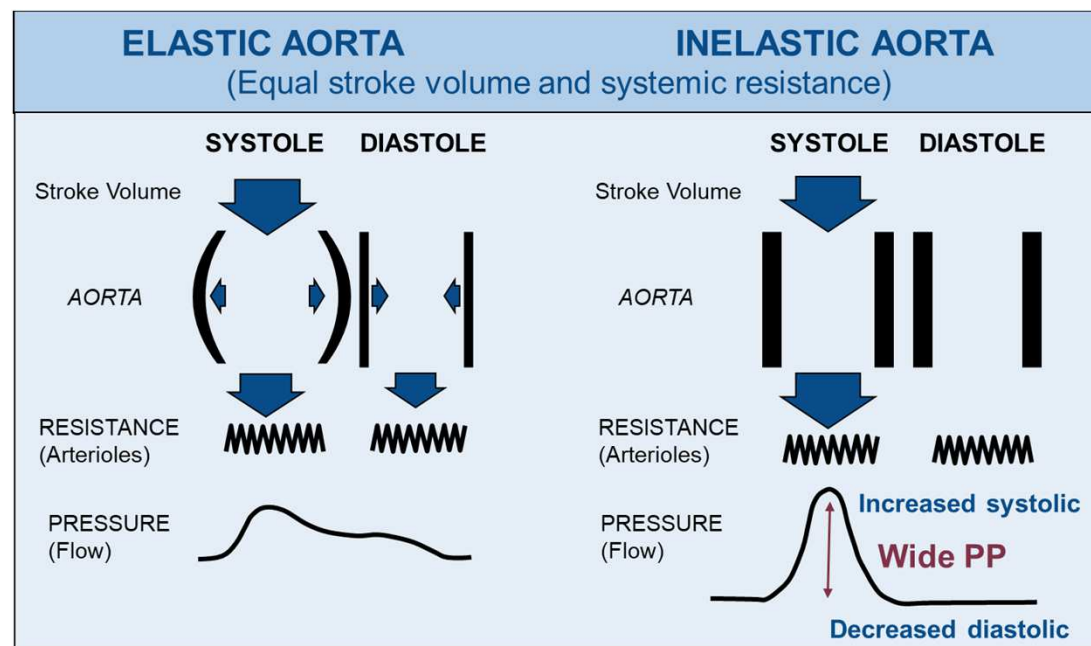
- ↑ wall thickness
- ↑ systemic vascular resistance (chronic)
- ↑ pressure-dependency of salt and water excretion (pressure natriuresis curve)

Izzo JL, Sica DA, Black HR, eds, and the Council for High Blood Pressure Research (American Heart Association). *Hypertension Primer: The Essentials of High Blood Pressure*. 4th ed. Philadelphia: Lippincott Williams & Wilkins; 2008:195–200.





Pathogenesis of Wide Pulse Pressure



Adapted from Victor RG, Kaplan NM. Systemic hypertension: mechanisms and diagnosis. In: Libby P, Bonow RO, Mann DL, Zipes, DP, eds. *Braunwald's Heart Disease*. 8th ed. Philadelphia, PA: Saunders Elsevier; 2008:1027–1048.



Blood Pressure Regulatory Systems

- Interactive regulatory systems integrate short-term and long-term cardiovascular and metabolic responses

SYSTEM	RESPONSE TIME
<u>SNS</u>	<u>Seconds to minutes</u>
RAAS	Minutes to hours
Kidney (salt and water balance)	Hours to days

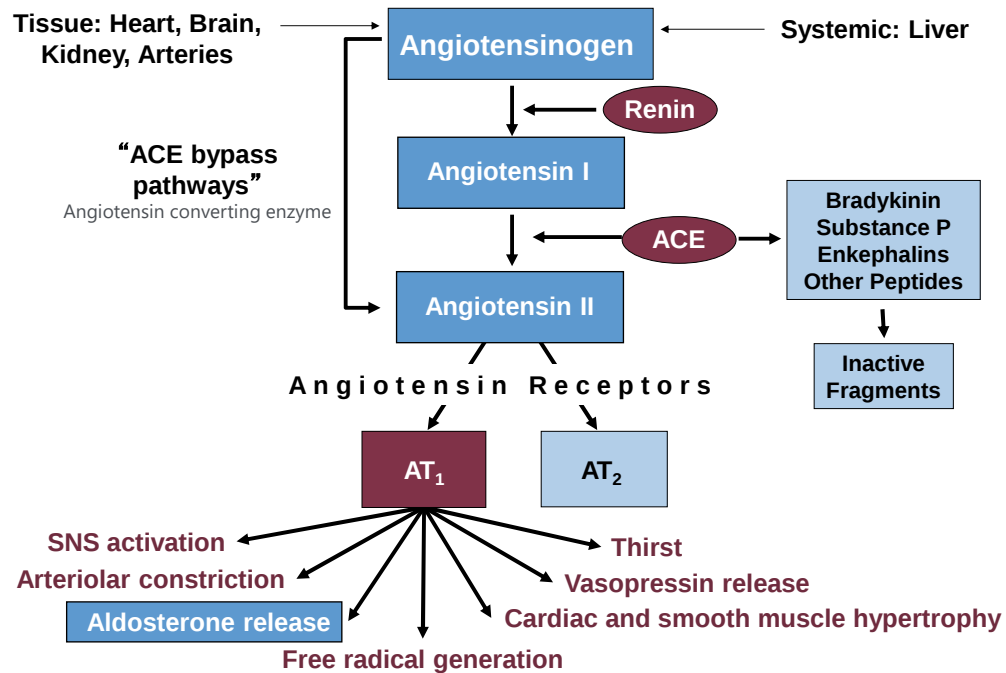
- These regulatory systems remain the major target of antihypertensive drugs

Izzo JL, Sica DA, Black HR, eds, and the Council for High Blood Pressure Research (American Heart Association). *Hypertension Primer: The Essentials of High Blood Pressure*. 4th ed. Philadelphia: Lippincott Williams & Wilkins; 2008:116–119, 126–132.





Angiotensin II Generation and Effects



Adapted from Schmieder RE. *Am J Hypertens*. 2005;18:720-730.





Salt-sensitivity

- Physiology
 - “Low renin states” (e.g., elderly) tend to be salt-sensitive but the condition also occurs in higher renin populations (e.g., obesity)
 - In research studies of salt-sensitivity, the exaggerated BP response to salt and water loading is due to increased vasoconstriction (or failure to adequately suppress vasoconstrictive systems)
- There is no routine clinical test for salt-sensitivity
- Probably about half of hypertensives are salt-sensitive
- Populations with increased salt-sensitivity:
 - Chronic kidney disease
 - Diabetics
 - African Americans
 - Elderly
 - Obese
 - Non-steroidal anti-inflammatory drug users

Izzo JL, Sica DA, Black HR, eds, and the Council for High Blood Pressure Research (American Heart Association). *Hypertension Primer: The Essentials of High Blood Pressure*. 4th ed. Philadelphia: Lippincott Williams & Wilkins; 2008:156–159.





SPRINT Primary Outcome and its Components Event Rates and Hazard Ratios

	Intensive		Standard		HR (95% CI)	P value
	No. of Events	Rate, %/year	No. of Events	Rate, %/year		
Primary Outcome	243	1.65	319	2.19	0.75 (0.64,0.89)	<0.001
All MI	97	0.65	116	0.78	0.83 (0.64,1.09)	0.19
Non-MI ACS	40	0.27	40	0.27	1.00 (0.64,1.55)	0.99
All Stroke	62	0.41	70	0.47	0.89 (0.63,1.25)	0.50
All HF	62	0.41	100	0.67	0.62 (0.45,0.84)	0.002
CVD Death	37	0.25	65	0.43	0.57 (0.38,0.85)	0.005

SPRINT Research Group. N Engl J Med 2015; 373:2103-2116





ACC/AHA Guidelines for BP Thresholds and Goals of Pharmacological Therapy in Patients With Hypertension According to Clinical Conditions

Clinical Condition(s)	BP Threshold, mm Hg	BP Goal, mm Hg
General		
Clinical CVD or 10-year ASCVD risk $\geq 10\%$	$\geq 130/80$	$< 130/80$
No clinical CVD and 10-year ASCVD risk $< 10\%$	$\geq 140/90$	$< 130/80$
Older persons (≥ 65 years of age; noninstitutionalized, ambulatory, community-living adults)	≥ 130 (SBP)	< 130 (SBP)
Specific comorbidities		
Diabetes mellitus	$\geq 130/80$	$< 130/80$
Chronic kidney disease	$\geq 130/80$	$< 130/80$
Chronic kidney disease after renal transplantation	$\geq 130/80$	$< 130/80$
Heart failure	$\geq 130/80$	$< 130/80$
Stable ischemic heart disease	$\geq 130/80$	$< 130/80$
Secondary stroke prevention	$\geq 140/90$	$< 130/80$
Secondary stroke prevention (lacunar)	$\geq 130/80$	$< 130/80$
Peripheral arterial disease	$\geq 130/80$	$< 130/80$

ASCVD indicates atherosclerotic cardiovascular disease; BP, blood pressure; CVD, cardiovascular disease; and SBP, systolic blood pressure.

Whelton P et al. Hypertension 2018 Table 23 



Choice of Initial Medication

COR	LOE	Recommendation for Choice of Initial Medication
I	A^{SR}	For initiation of antihypertensive drug therapy, first-line agents include thiazide diuretics, CCBs, and ACE inhibitors or ARBs.

SR indicates systematic review.

Whelton P et al. Hypertension 2018; 71: e46.





Choice of Initial Monotherapy Versus Initial Combination Drug Therapy

COR	LOE	Recommendations for Choice of Initial Monotherapy Versus Initial Combination Drug Therapy*
I	C-EO	Initiation of antihypertensive drug therapy with 2 first-line agents of different classes, either as separate agents or in a fixed-dose combination, is recommended in adults with stage 2 hypertension and an average BP more than 20/10 mm Hg above their BP target.
Ila	C-EO	Initiation of antihypertensive drug therapy with a single antihypertensive drug is reasonable in adults with stage 1 hypertension and BP goal <130/80 mm Hg with dosage titration and sequential addition of other agents to achieve the BP target.

Whelton P et al. Hypertension 2018; 71: e47. 



Causes of Secondary Hypertension With Clinical Indications

Common causes
Renal parenchymal disease
Renovascular disease
Primary aldosteronism
Obstructive sleep apnea
Drug or alcohol induced
Uncommon causes
Pheochromocytoma/paraganglioma
Cushing's syndrome
Hypothyroidism
Hyperthyroidism
Aortic coarctation (undiagnosed or repaired)
Primary hyperparathyroidism
Congenital adrenal hyperplasia
Mineralocorticoid excess syndromes other than primary aldosteronism
Acromegaly

Whelton P et al. Hypertension 2018; 71: e13–e115.





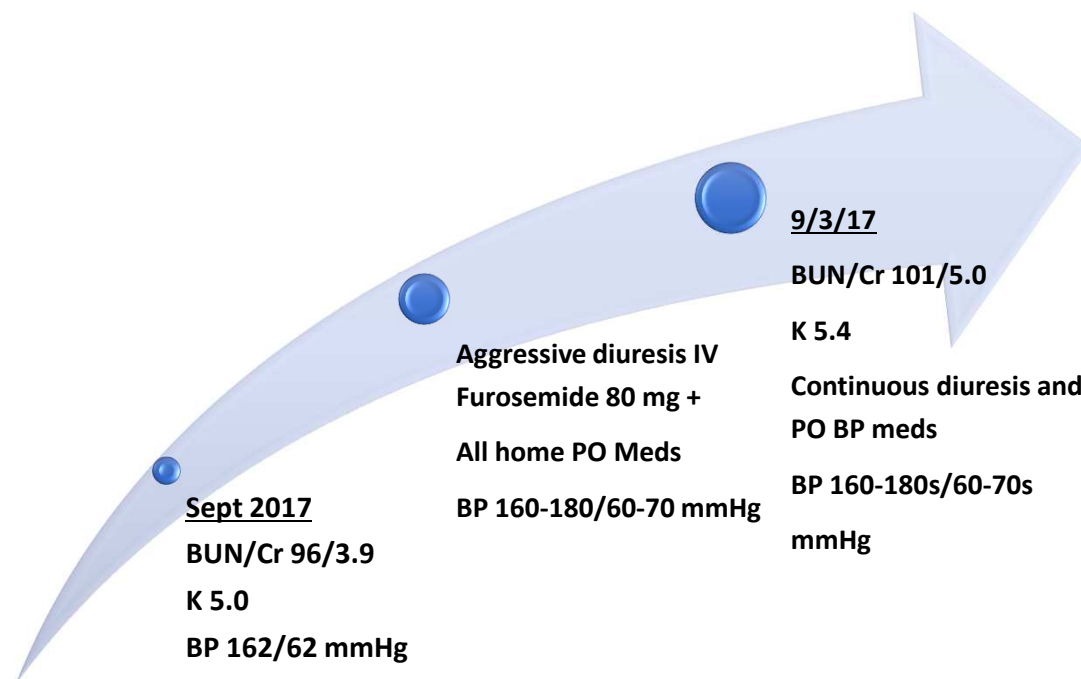
Case History

- 83 y/o woman with a history of difficult to control hypertension despite a 6 – medication regimen!
- Hospital admissions for TIA, hypertensive urgency and AKI with various providers
- History of Heart Failure with preserved ejection fraction (EF of 60%)
- History of longstanding osteoarthritis of the knees and hips with chronic pain
- CKD Stage IIIB (eGFR – 23.9 ml/min/1.73m²)
 - o Baseline Serum Cr ~2.0



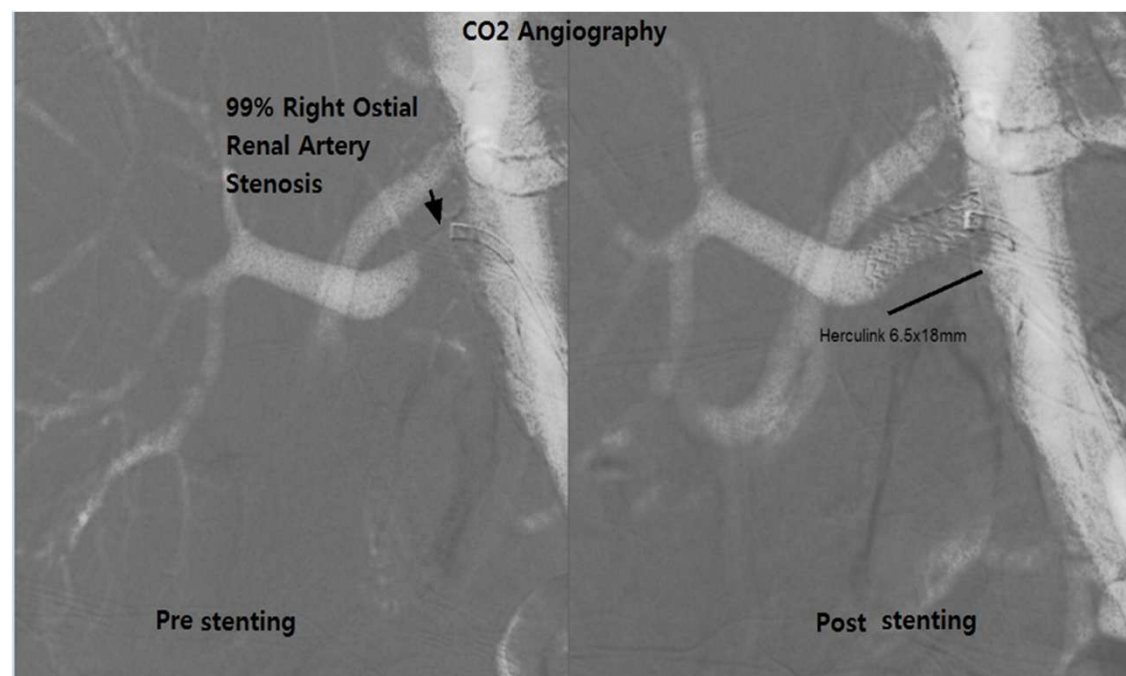


Hospitalization due to progression of CKD



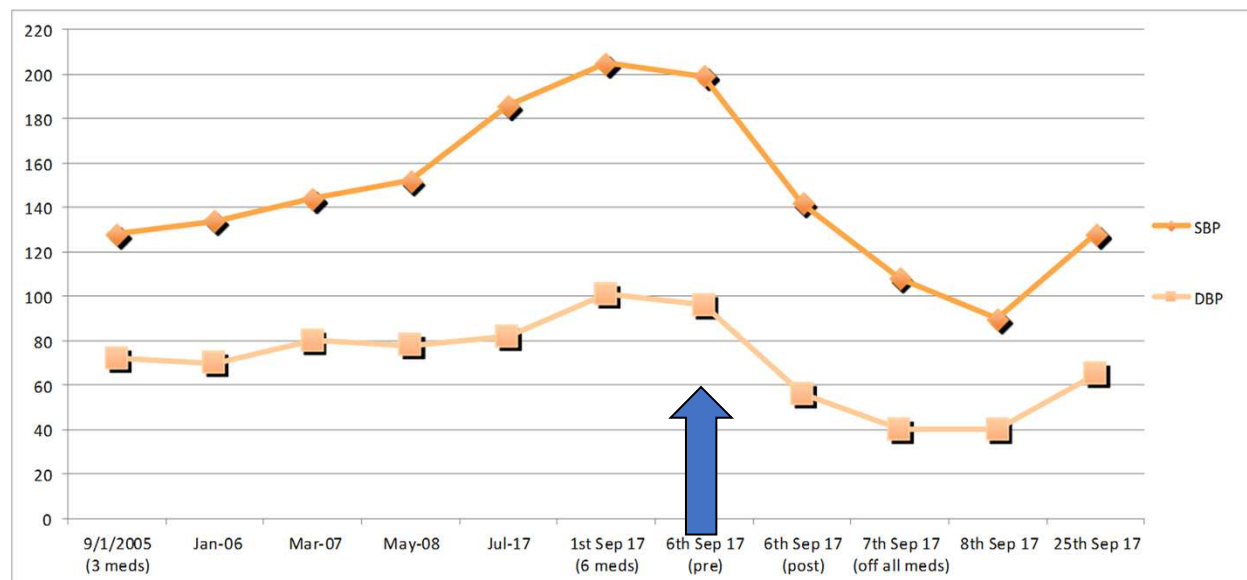


Selective Right Renal Angiogram before and after Percutaneous Intervention





Blood Pressures Following Renal Revascularization





Kidney Function Following Revascularization

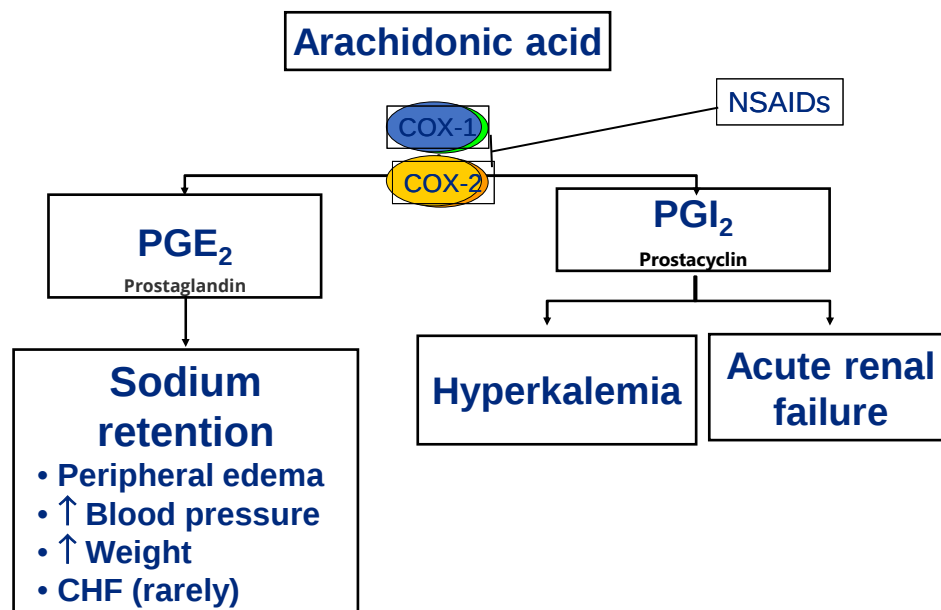
DATE	Events	BUN (mg/dl)	Creatinine (mg/dl)	eGFR (ml/min/1.73m ²)
Feb 2007		34	1.1	51.8
	INFINITY TRIAL*			
Aug 2017	Resumed OTC Naproxen	69	2.1	23.9
1st Sept 17	ARB dosed once	94	3.9	
2 nd Sept 17		96	4.6	
3 rd Sept 17		101	5.0	
6th Sept 17	Angioplasty	91	3.5	
7 th Sept 17		61	2.1	
8 th Sept 17		40	1.6	
25 th Sept 17		29	1.2	45.5

* White WB et al. Circulation 2019; 140: 1626-1635.





Potential Effects of NSAIDs on Cardiorenal Physiology

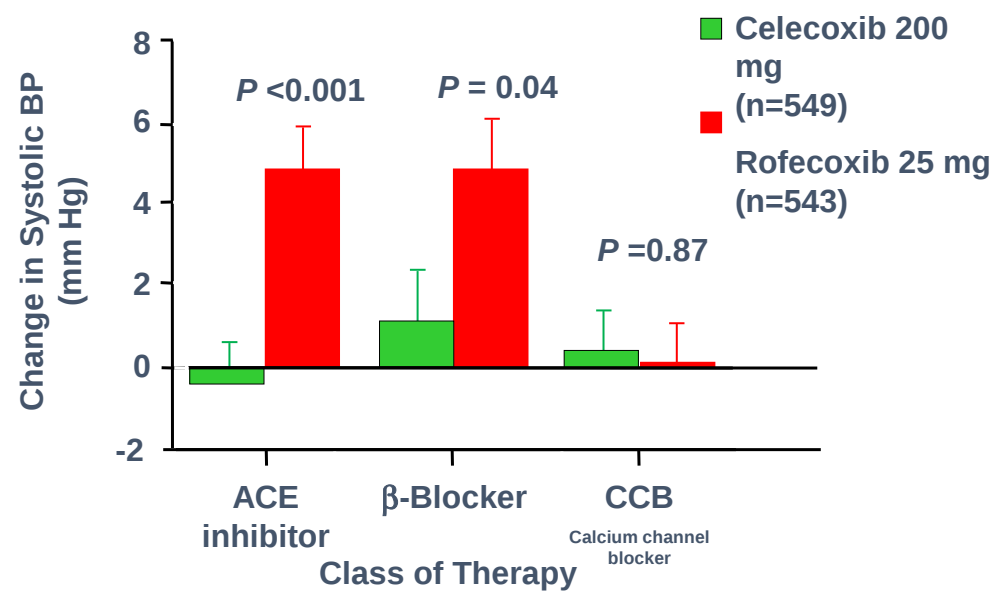


Brater DC. Am J Med. 1999;107:65S.





Effects of COX-2 Selective Inhibitors on Systolic BP in Treated Hypertensives (n = 1092)

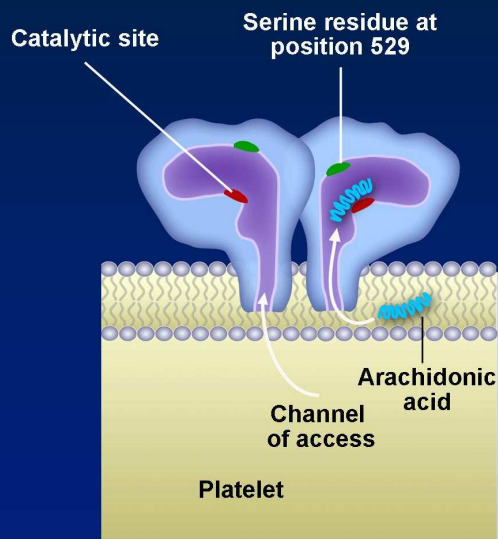


Whelton A, White WB. Am J Cardiol. 2002;90:959-963.

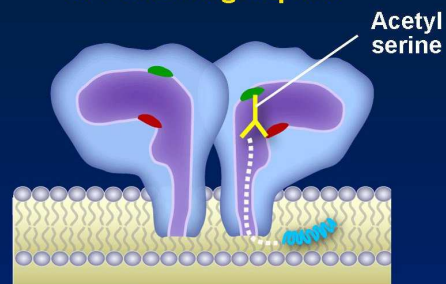


The Effect of Aspirin Alone and of Ibuprofen Plus Aspirin on Platelet Cyclooxygenase-1

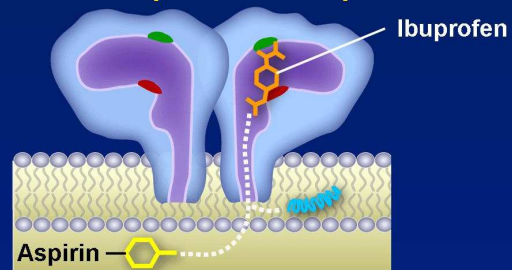
A. Platelet cyclooxygenase-1



B. Following aspirin



C. With ibuprofen and aspirin



* ns-NSAID in this model was ibuprofen
Adapted with permission from Catella-Lawson F, et al. *N Engl J Med.* 2001;345(25):1809-1817.

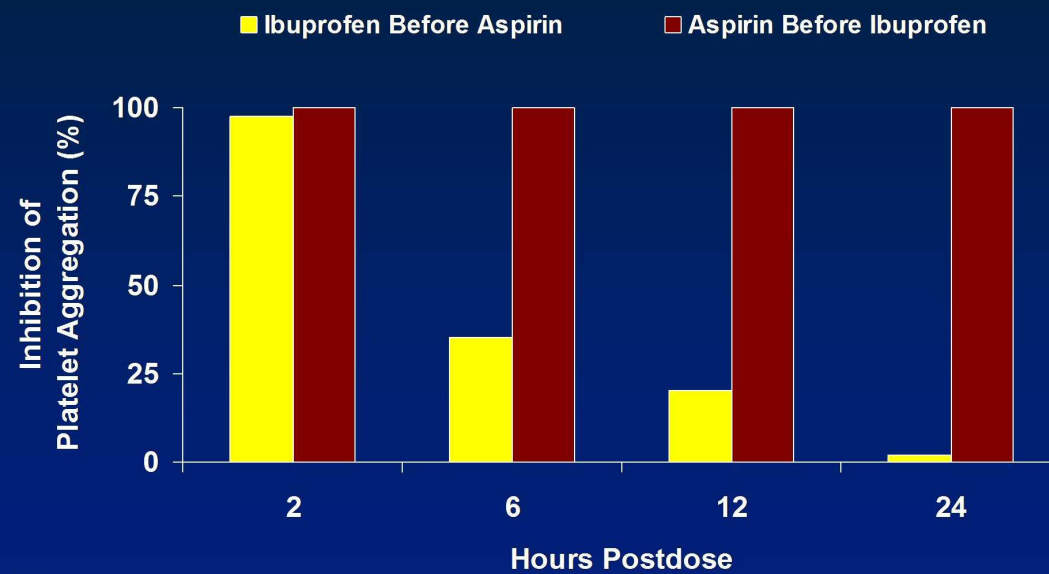
34

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Catella-Lawson et al, 2001

Effect of Ibuprofen on Aspirin's Inhibition of Platelet Aggregation



$P < .001$.

*Ibuprofen, 400 mg; aspirin, 81 mg.

Adapted with permission from Catella-Lawson F, et al. *N Engl J Med*. 2001;345(25):1809-1817.

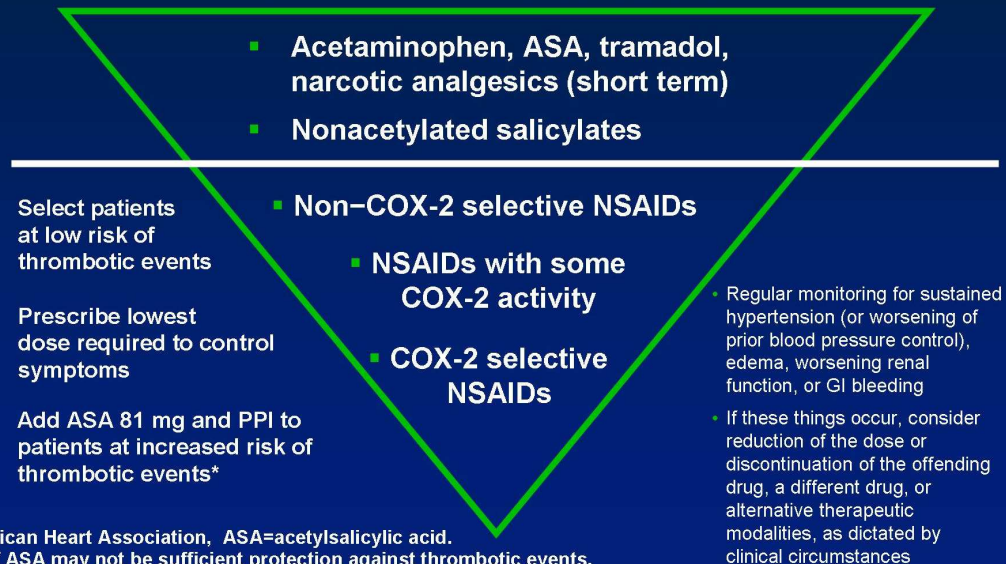
35

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American Heart Association: AHA Science Advisory: March 2007

Stepped Care Approach to Pharmacologic Therapy for Musculoskeletal Symptoms With Known CV Disease or Risk Factors for Ischemic Heart Disease



AHA=American Heart Association, ASA=acetylsalicylic acid.
Addition of ASA may not be sufficient protection against thrombotic events.
Adapted with permission from Antman EM, et al. *Circulation*. 2007;115(12):1634-1642.



Considerations from the Rheumatology Community

- The rheumatologist has to weigh the desirable and undesirable effects of NSAIDs and decide what is best for their individual patient.
- The bottom line: There must be a balance in the benefit-risk ratio, the patient must be informed, and physicians must be knowledgeable.
- Sufficient treatment options are of critical importance in the management of pain and arthritis.

Ullman. Rheumatologist 2007; 1(6): 16-17.





Thank You.
