Hypertension and Diabetes

Mohammad Taghi Najafi M.D.
Associate Professor of Nephrology TUMS
Who dedicates his life to Diagnose and Treat High Blood Pressure
May 2024

Problem Case :
DM management and Hypertension Management ?

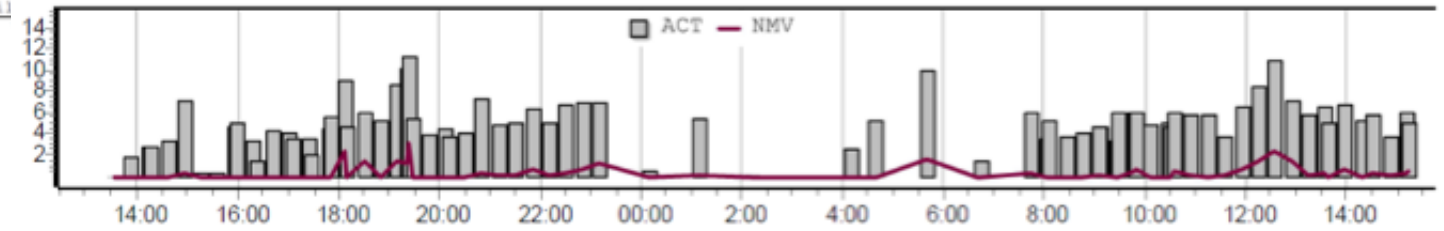
- A 57 Years Old Man referred to our clinic with High Blood Pressure and Diabetes and Proximal weakness
- BP=184/97. PR= 75
- PMH: HTN 12y / DM 12y / CAG: nl 2 weeks ago / Hypokalemia in last admission 2w ago.
- FH: DM and HTN and CVD in Father and Mother and Three Sisters and Brother
- His brother passed away 3 month ago (MI)
- Drug: Empa 10mg/d . ASA 80/d . Exforge 160/5 mg BD. Prazocin 1mg TDS. Carvedilol 6.25mg BD. Kcit 10mg BD.
- Lab: Cr:1.2/ Urea: 32/ Uric acid: 4.5 / Na: 140 / K:3.3 /FBS:136 / A1C:7
- Renin: <0.1
- Kidney color dopler and Adrenal SONO was Normal.
- ECHo: ef=55% and Moderate LVH
- PWV: Vascular Age: 62y / 10.6m/s

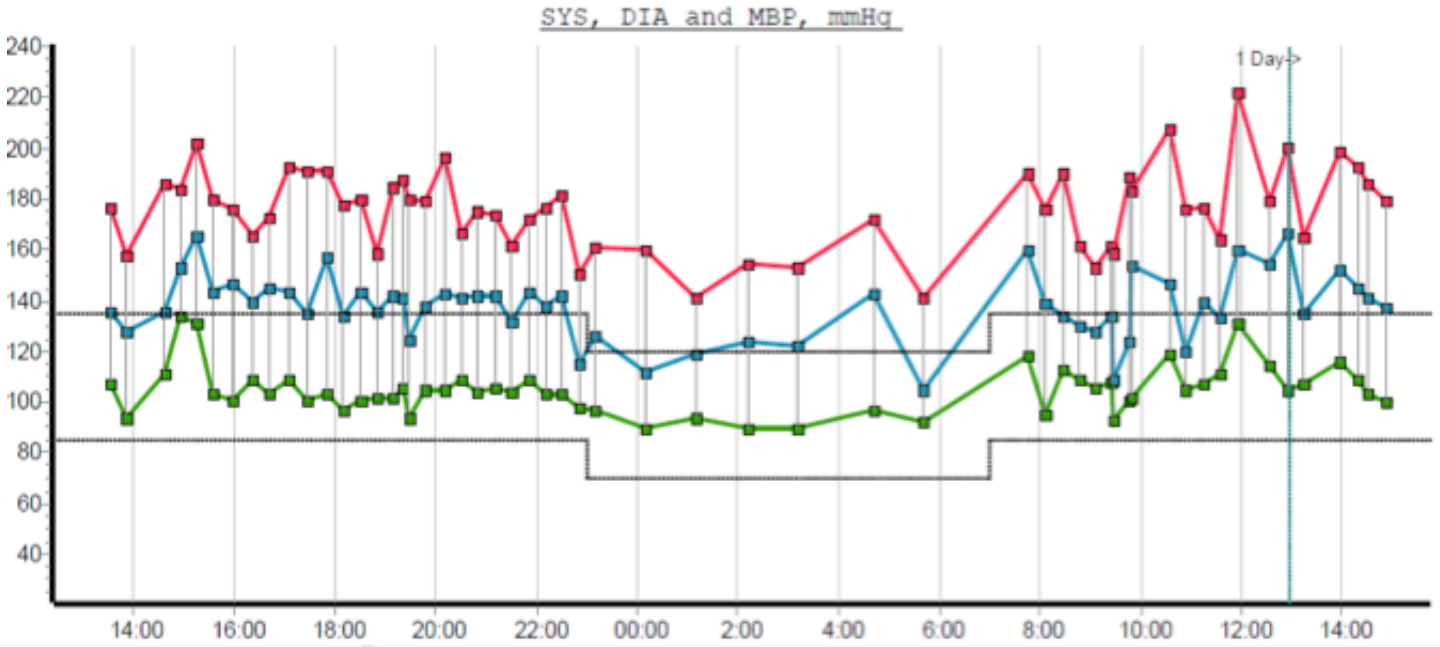
Daytime (07:00 - 23:00). Number of readings: 49

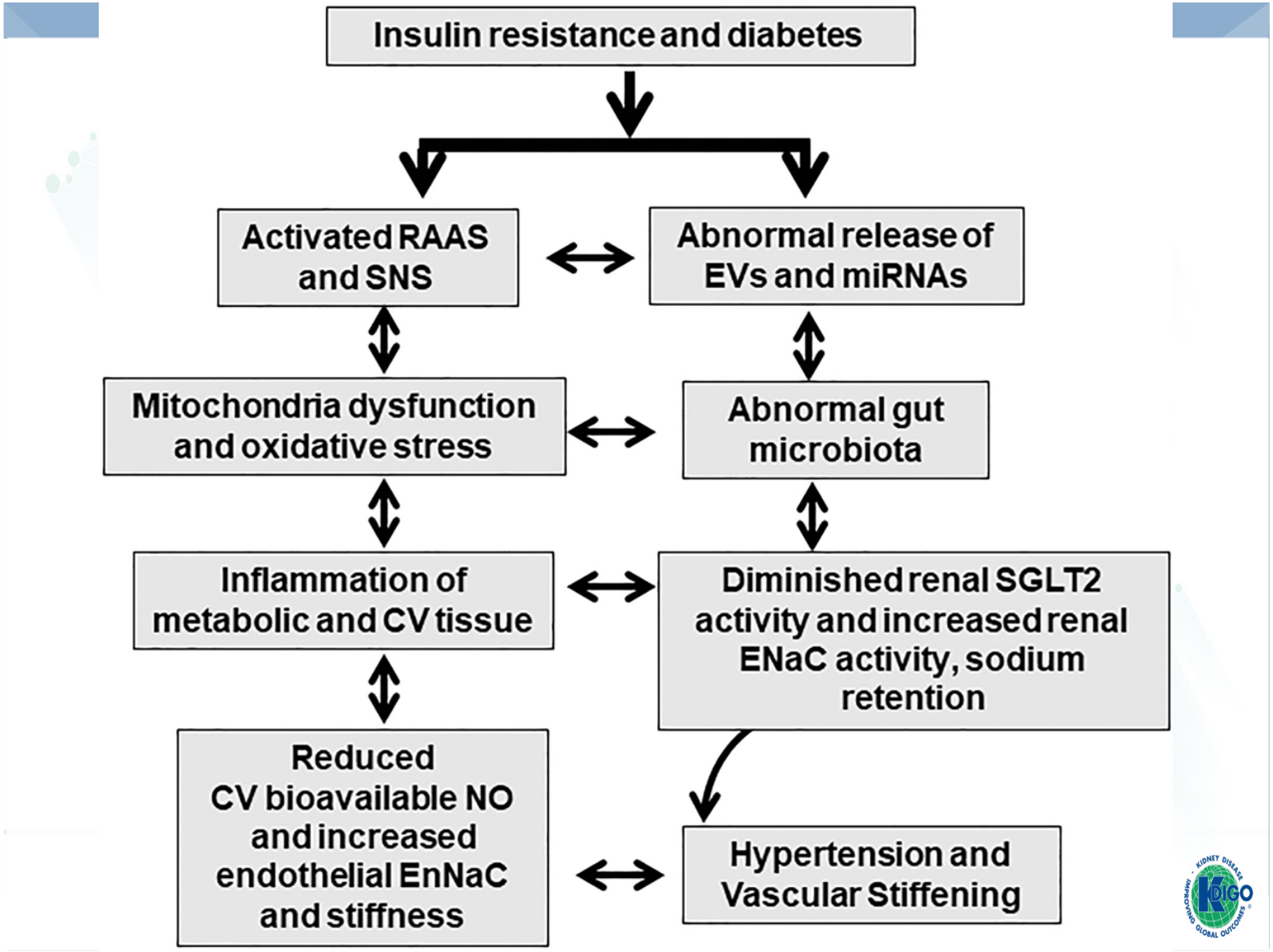
Average SYS	180 mmHg	above normal (>=135)
Average DIA	107 mmHg	above normal (>=85)
Time index SYS	100 %	High (>=30%)
Time index DIA	100 %	High (>=30%)
Variability SYS	15 mmHg	High (>=15)
Variability DIA	9 mmHg	Norm (<14)

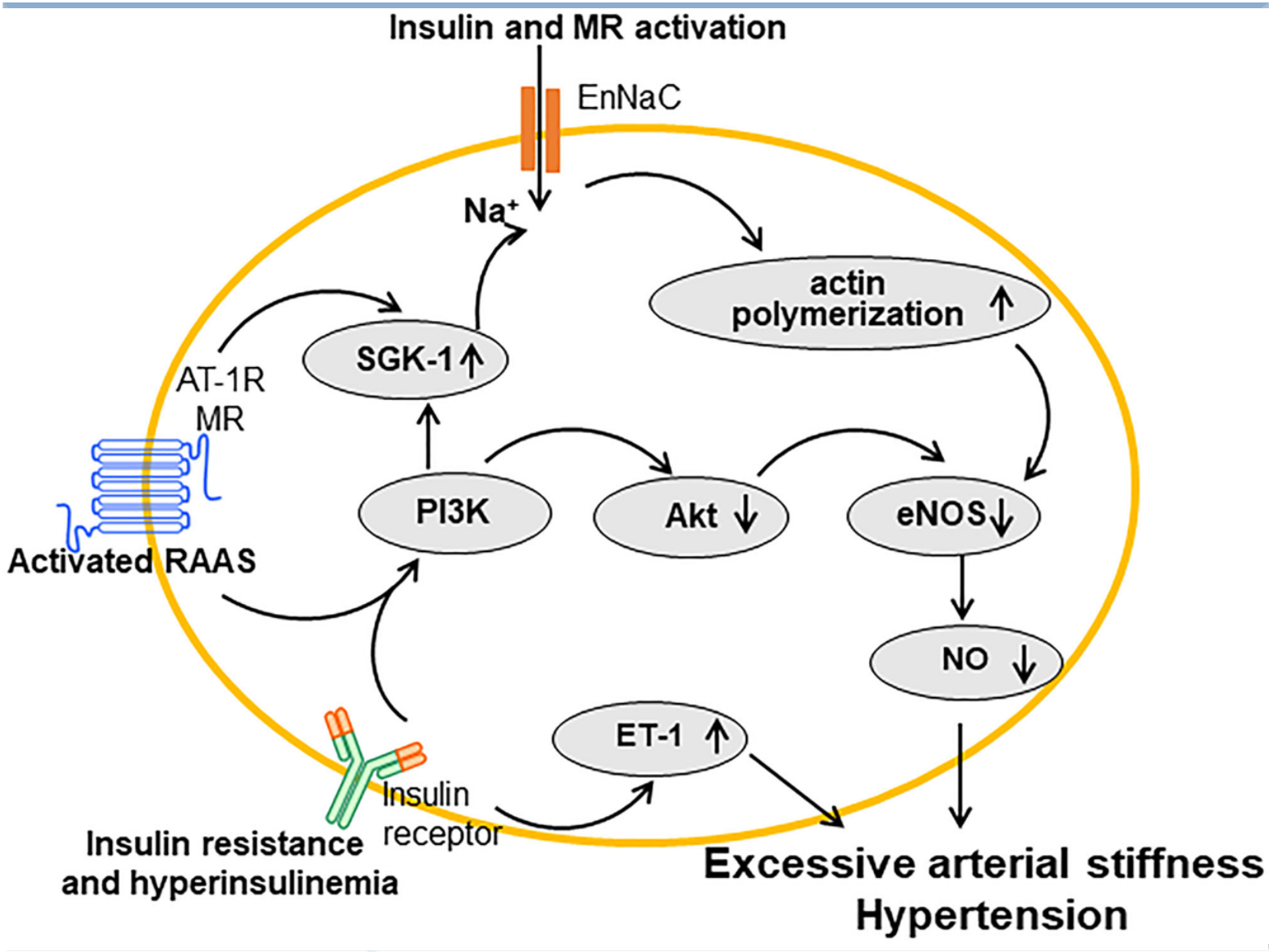
Nighttime (23:01 - 06:59). Number of readings: 7

Average SYS	155 mmHg	above normal (>=120)
Average DIA	93 mmHg	above normal (>=70)
Time index SYS	100 %	High (>=30%)
Time index DIA	100 %	High (>=30%)
Variabil[illegible] SYS	[illegible] mmHg	[illegible]
Variabil		






Insulin resistance and diabetes
Activated RAAS and SNS
Abnormal release of EVs and miRNAs
Mitochondria dysfunction and oxidative stress
Abnormal gut microbiota
Inflammation of metabolic and CV tissue
Diminished renal SGLT2 activity and increased renal ENaC activity, sodium retention
Reduced CV bioavailable NO and increased endothelial EnNaC and stiffness
Hypertension and Vascular Stiffening


Insulin and MR activation
EnNaC
Na+
actin polymerization ↑
SGK-1↑
AT-1R
MR
Activated RAAS
PI3K
Akt ↓
eNOS↓
NO ↓
ET-1 ↑
Insulin receptor
Insulin resistance and hyperinsulinemia
Excessive arterial stiffness
Hypertension

2023 ESH Guidelines for the management of arterial hypertension

The Task Force for the management of arterial hypertension of the European Society of Hypertension

Endorsed by the European Renal Association (ERA) and the International Society of Hypertension (ISH)

Problem Size

- In white Europeans, 10–30% of people with type 1 diabetes and 60–80% of those with newly diagnosed type 2 diabetes have hypertension
- It has also been recognized that, in diabetes, hypertension usually exhibits characteristics that differ from those of nondiabetic hypertensive patients.
- The most frequent characteristics are
  - a greater SBP elevation, a wider pulse pressure,
  - a higher BP variability,
  - a nondipping pattern,
  - salt-sensitivity,
  - a trend to hyperkalemia and orthostatic hypotension, particularly as the duration of the diabetes increases
  - in patients with type 2 diabetes, the prevalence of MH is much higher than in the general population

Hypertension Treatment strategies in diabetes

Recommendations and statements	CoR	LoE
BP should be monitored to detect hypertension in all patients with diabetes, because it is a frequent comorbidity associated with an increase CV risk and risk for kidney events.	I	A
Non-dipping or elevated night-time BP are frequent in type 2 diabetes and should be monitored by ABPM or HBPM.	I	B
Antihypertensive treatment in type 2 diabetes is recommended to protect against macrovascular and microvascular complications.	I	A
Immediate lifestyle interventions and antihypertensive drug treatment are recommended for people with type 2 diabetes when office SBP is ≥ 140 mmHg and DBP is ≥ 90 mmHg.	I	A

Hypertension Treatment strategies in diabetes

Drug treatment strategies in patients with type 2 diabetes should be the same as for patients without diabetes but the primary aim is to lower BP below <130/80 mmHg	I	A
BP control is difficult in diabetes and combination treatment is almost always necessary.	I	B
SGLT2is are recommended to reduce cardiac and kidney events in type 2 diabetes. These agents have a BP lowering effect.	I	A
The non-steroidal MRA finerenone can be used, because of its nephroprotective and cardioprotective properties in patients with diabetic CKD and moderate to severe albuminuria. Finerenone has a BP lowering effect.	I	A
There are only limited data on the potential benefits of combining SGLT2is and finerenone.	II	C

HypertensionTreatment strategies in patients with kidney disease

Recommendations and statements	CoR	LoE
BP should be monitored at all stages of CKD, because hypertension is the second most important risk factor for end-stage kidney disease (ESKD).	I	A
Non-dipping or elevated night-time BP are frequent in CKD patients and should be monitored by ABPM or HBPM.	I	B
In both diabetic and non-diabetic CKD with hypertension, BP-lowering treatment slows the decline of kidney function and reduces the risk of ESKD and CV outcomes.	I	A
Immediate lifestyle interventions and antihypertensive drug treatment are recommended in most patients with CKD independently of the CKD stage if SBP≥ 140mmHg or DBP ≥90mmHg.	I	C

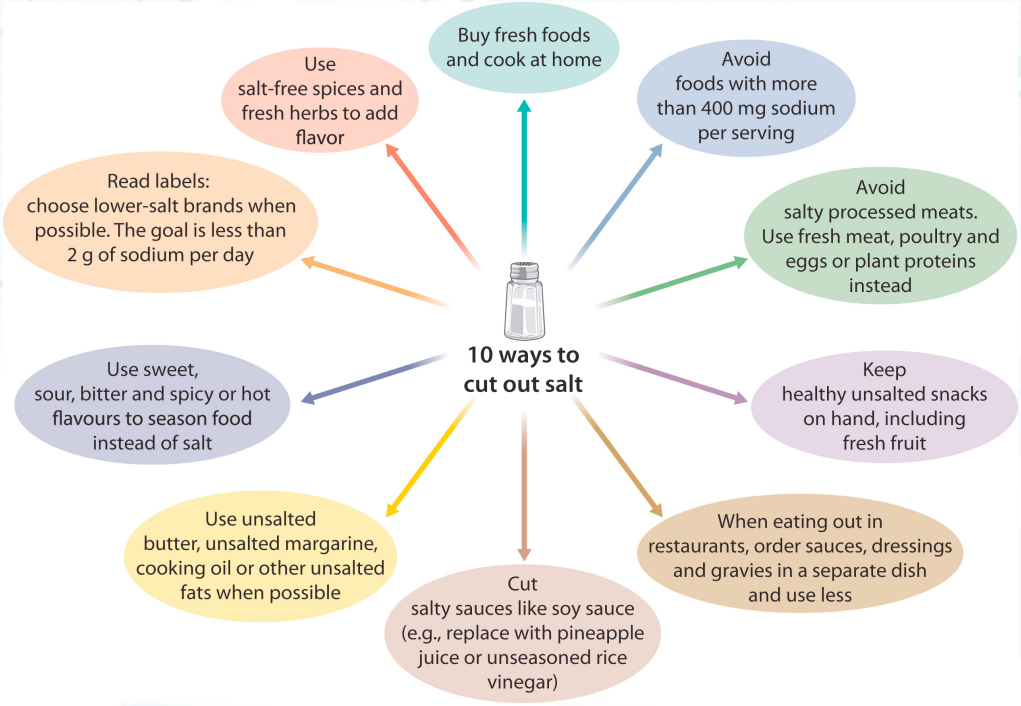
Hypertension Treatment strategies in diabetes

In all patients with CKD the primary goal is to lower office BP to <140 mmHg systolic and <90 mmHg diastolic.	I	A
In most CKD patients (young patients, patients with an albumin/creatinine ratio ≥ 300 mg/g, high CV risk patients) office BP should be lowered to <130/80 mmHg if tolerated.	II	B
In kidney transplant patients with hypertension, office BP should be lowered to <130 mmHg systolic and <80 mmHg diastolic.	II	B
In patients with CKD regardless of the presence of albuminuria, BP should not be lowered below 120/70 mmHg.	III	C
An ACEi or an ARB, titrated to the maximum tolerated doses is recommended for patients with CKD and moderate (UACR 30 to 300 mg/g) or severe (UACR > 300 mg/g) albuminuria.	I	A

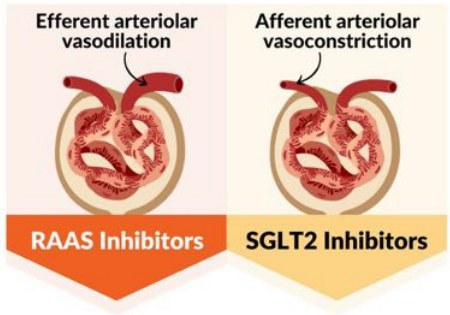
Hypertension Treatment strategies in diabetes

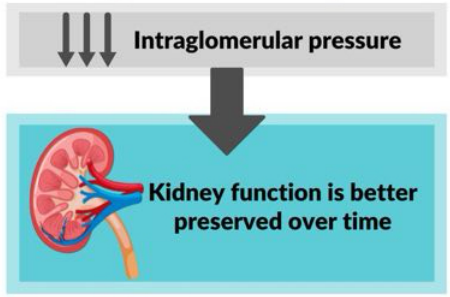
Dual combination of an ACEi with an ARB is not recommended.	III	A
BP control is difficult in CKD and resistant hypertension is very frequent. Therefore combination treatment is almost always recommended.	I	B
SGLT-2 inhibitors are recommended for patients with diabetic and non-diabetic nephropathies CKD if eGFR is at least 20 or 25 ml/min/1.73².[a]	I	A
The non-steroidal MRA finerenone is recomended in patients with CKD and albuminuria associated with type 2 diabetes mellitus if eGFR is at least 25 ml/min/1.73² and serrum potassium <5.0 mmo/L.	I	A
In CKD patients with hyperkalemia a potassium binder can be used to maintain normal or near normal serum potassium levels (<5.5 mmol/L) in order to allow optimal treatment with a RAS-blocker or a MRA to continue.	II	B

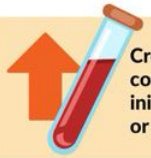
FIGURE 19. TEN WAYS TO CUT OUT SALT



One Small Dip in eGFR, One Big Leap for Kidney Protection

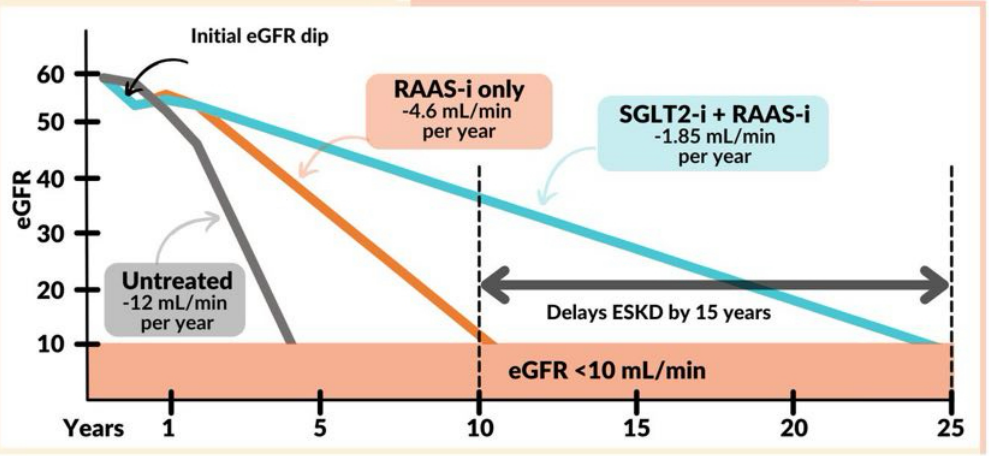






Creatinine and cystatin-C commonly rise during initiation of RAAS inhibitors or SGLT2 inhibitors

RAAS-i only	SGLT-i + RAAS-i
Faster eGFR decline	Slower GFR decline
ESKD in 10 years	ESKD in 25 years



Conclusion: Both RAAS inhibitors & SGLT2 inhibitors reduce intraglomerular pressure. This reduces pressure within the glomerulus and kidney function is better preserved over time, as shown in numerous trials. Indices of glomerular filtration rise when initiating these drugs. It is important to be aware that these drugs are expected to reduce glomerular filtration rate (GFR): it is a sign that they are protecting the kidney.

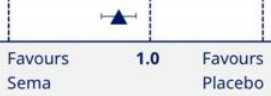
Reference: Meraz-Munoz et al. *eGFR decline after SGLT2 inhibitor initiation: the tortoise and the hare reimagined*. 2021 10.34067/KID.0001172021

Visual Abstract by Carlo Trinidad, MD @hellokidneyMD

Sema 1.0 mg demonstrates 24% reduction in the risk of kidney disease-related events in people with type 2 diabetes and CKD

The FLOW trial evaluated semaglutide in people with T2D and CKD

Composite renal event		HR [95% CI]
Sema 1.0mg/Placebo		0.76 [0.66; 0.88]



The combined primary endpoint[1] included five components measuring the progression of CKD and the risk of kidney and CV mortality

Both CKD and cardiovascular components of the primary endpoint contributed to risk reduction

In the trial, semaglutide 1.0 mg appeared to have **a safe and well-tolerated profile** in line with previous semaglutide 1.0 mg trials

Testing hierarchy of primary and secondary confirmatory endpoints

1. Superiority of semaglutide 1.0 mg vs placebo confirmed for time from randomisation to first composite kidney event
2. Superiority of semaglutide 1.0 mg vs placebo confirmed for annual rate of change in eGFR
3. Superiority of semaglutide 1.0 mg vs placebo confirmed for time from randomisation to first MACE
4. Superiority of semaglutide 1.0 mg vs placebo confirmed for time from randomisation to all-cause death

[1]Composite primary endpoint: Onset of persistent ≥ 50% reduction in eGFR, onset of persistent eGFR (CKD-EPI) < 15 mL/min/1.73 m2, initiation of chronic kidney replacement therapy (dialysis or kidney transplantation), death from kidney disease or death from cardiovascular disease
CKD: Chronic kidney disease; CI: Confidence interval; CV: Cardiovascular; eGFR: estimated glomerular filtration rate; HR: Hazard ratio; MACE: Major adverse cardiovascular event; Sema: Semaglutide; T2D: Type 2 diabetes
Note: Treatment policy estimand shown for primary endpoint

Journal of
Clinical Medicine

MDPI

Editorial

Diabetes Mellitus and Diabetic Kidney Disease: The Future Is Already Here

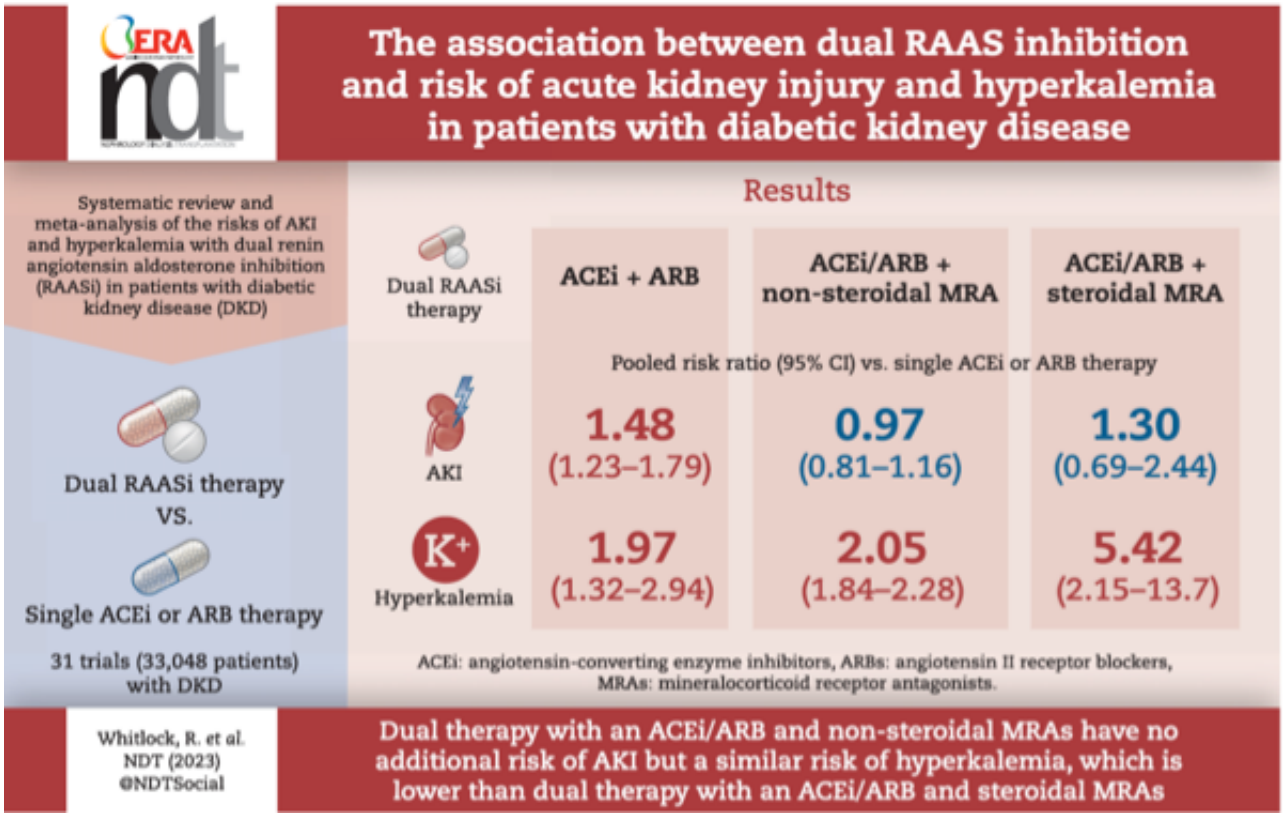
(1) **The Angiotensin-Converting-Enzyme (ACE) inhibitors and Angiotensin II Receptor Blockers** (AIIRBs), RAAS inhibitors are maintained as the first step of treatment for DM patients with hypertension and/or albuminuria or proteinuria.

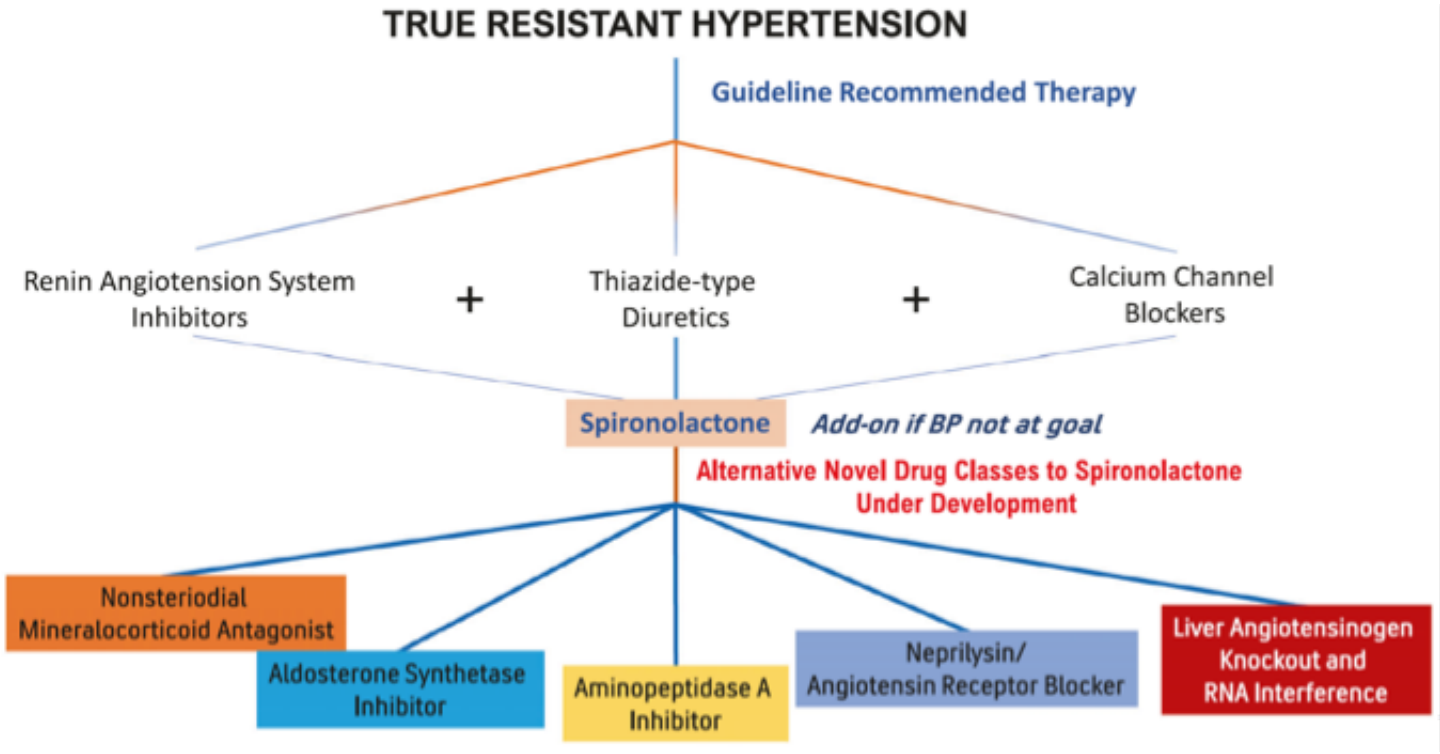
(2) **Sodium-glucose-transporter 2 (SGLT2) inhibitors.** Their discovery led to the introduction of these drugs to the usual hypoglycaemic therapy for adequate control in subjects with DM. They also offer a safe nephro and CV protection profile.

(3) **Glucagon-like peptide-1 receptor agonists (GLP-1RAs)**. This is a class of incretin drugs that can improve CV and renal events in DKD.

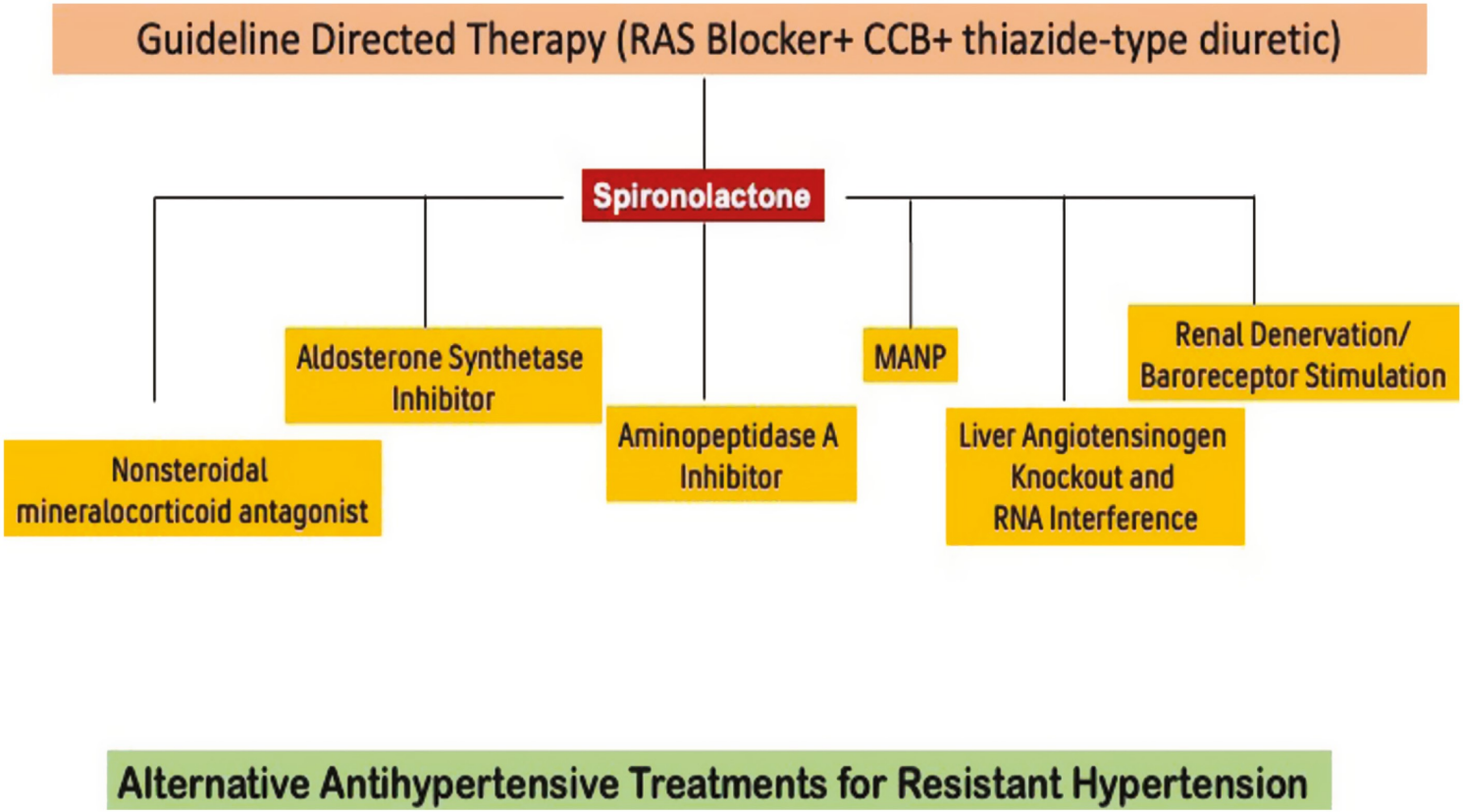
(4) **Antagonists of Endothelin-1 (ET-1s).** Some, but not all studies on ET-1s have proved their ability to reduce albuminuria and proteinuria.

(5) **The Mineralocorticoid Receptor (MCR) antagonist, finerenone**. Very recently, finerenone was used in a RCT as an antifibrotic agent.


The association between dual RAAS inhibition and risk of acute kidney injury and hyperkalemia in patients with diabetic kidney disease
Systematic review and meta-analysis of the risks of AKI and hyperkalemia with dual renin angiotensin aldosterone inhibition (RAASi) in patients with diabetic kidney disease (DKD)
Dual RAASi therapy
VS.
Single ACEi or ARB therapy
31 trials (33,048 patients) with DKD
Results
Dual RAASi therapy
ACEi + ARB
ACEi/ARB + non-steroidal MRA
ACEi/ARB + steroidal MRA
Pooled risk ratio (95% CI) vs. single ACEi or ARB therapy
AKI
1.48 (1.23–1.79)
0.97 (0.81–1.16)
1.30 (0.69–2.44)
Hyperkalemia
1.97 (1.32–2.94)
2.05 (1.84–2.28)
5.42 (2.15–13.7)
ACEi: angiotensin-converting enzyme inhibitors, ARBs: angiotensin II receptor blockers, MRAs: mineralocorticoid receptor antagonists.
Whitlock, R. et al. NDT (2023) @NDTSocial
Dual therapy with an ACEi/ARB and non-steroidal MRAs have no additional risk of AKI but a similar risk of hyperkalemia, which is lower than dual therapy with an ACEi/ARB and steroidal MRAs


TRUE RESISTANT HYPERTENSION
Guideline Recommended Therapy
Renin Angiotension System Inhibitors
+
Thiazide-type Diuretics
+
Calcium Channel Blockers
Spironolactone
Add-on if BP not at goal
Alternative Novel Drug Classes to Spironolactone Under Development
Nonsteriodial Mineralocorticoid Antagonist
Aldosterone Synthetase Inhibitor
Aminopeptidase A Inhibitor
Neprilysin/ Angiotensin Receptor Blocker
Liver Angiotensinogen Knockout and RNA Interference

Graphical Abstract



Am J Hypertens, Volume 36, Issue 2, February 2023, Pages 73–81, https://doi.org/10.1093/ajh/hpac111

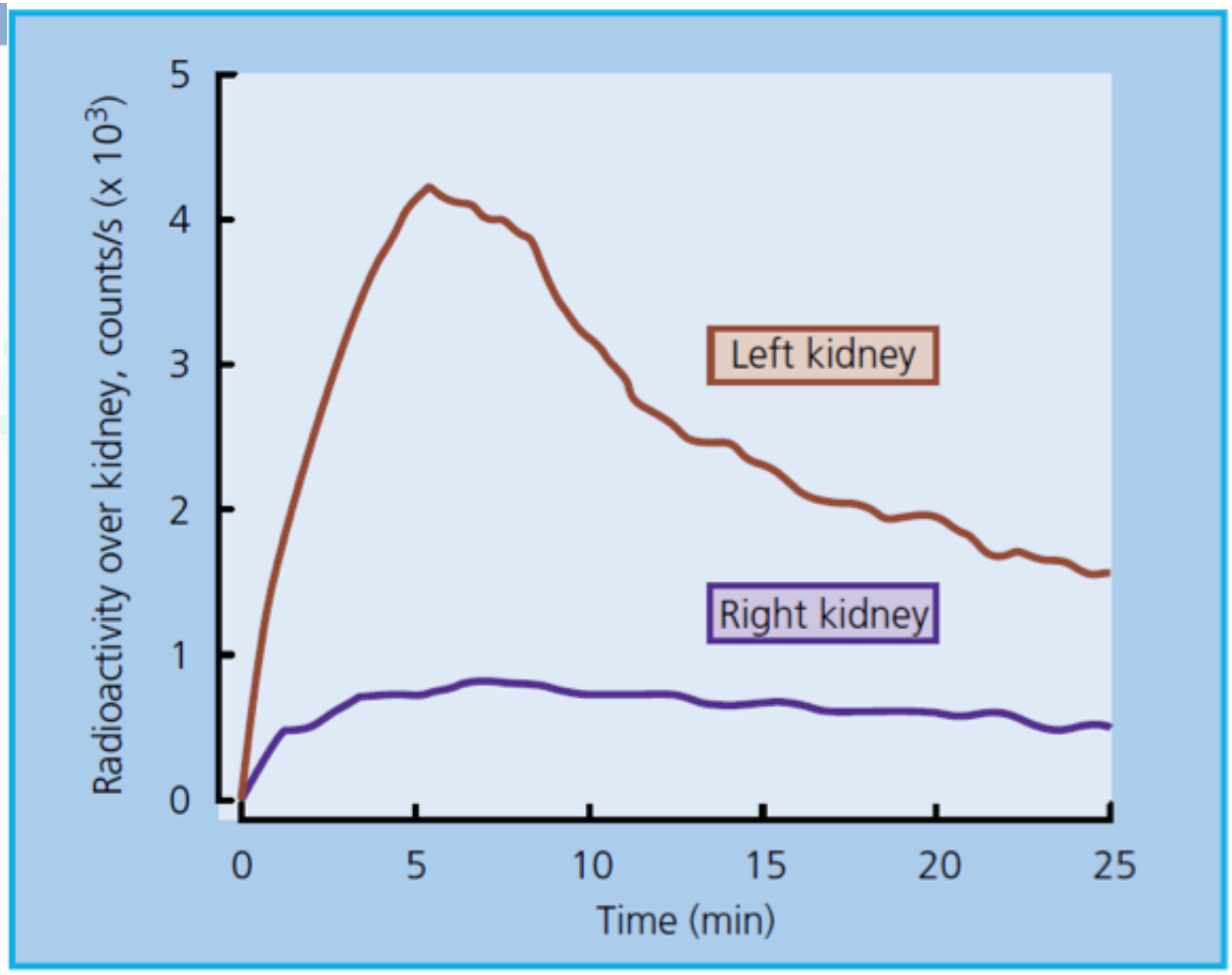


Figure 47.6 Renal artery stenosis affecting the right kidney in a person with diabetes and hypertension. Uptake of the isotope on this side is markedly reduced and delayed.

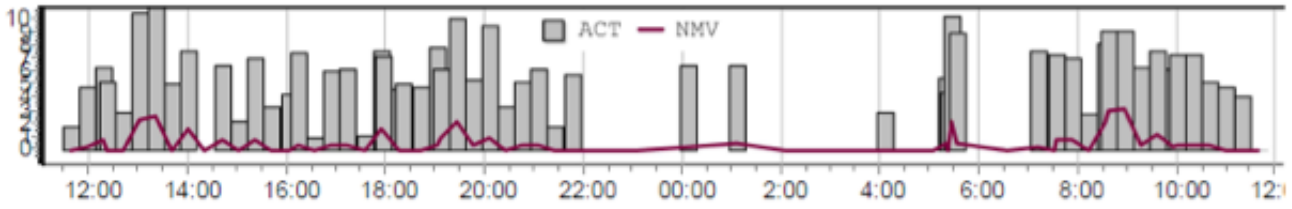
Daytime (07:00 - 23:00). Number of readings: 36

Average SYS	127 mmHg	Norm (101..134)
Average DIA	84 mmHg	Norm (61..84)
Time index SYS	25 %	Possibly high (15% ... 30%)
Time index DIA	36 %	High (>=30%)
Variability SYS	14 mmHg	Norm (<15)
Variability DIA	9 mmHg	Norm (<14)

Nighttime (23:01 - 06:59). Number of readings: 8

Average SYS	125 mmHg	above normal (>=120)
Average DIA	84 mmHg	above normal (>=70)
Time index SYS	87 %	High (>=30%)
Time index DIA	97 %	High (>=30%)
Variability SYS	10 mmHg	Norm (<15)
Variability DIA	10 mmHg	Norm (<12)

Activity parameters



SYS, DIA and MBP, mmHg