Short term Blood Pressure Variability
Does it matter in prescription?

By
Mohie Aldien Elsayed (MD)
Some cite the writing of Sushruta in the 6th BCC as being the first mention of symptoms like those of hypertension (haed pulse disease). Main treatment was often treated with bleeding and leeches. Well known individuals such as Yellow Emperor of China, Cornelius Celsus, Galen and Hipocrates advocated such treatment.

At 2600 B.C., when the ancient Chinese could only suspect hypertension by the quality of one’s pulse. At that time, a hard pulse that could not be compressed.
In 1733 Reverend Stephen Hales was first to measure BP

* Measured the height of a column of blood after cannulating the carotid artery in a horse with a brass pipe.
* The brass pipe was attached to a 12 inch glass tube.
* Tube was connected to the pipe via trachea of a goose!
The concept of essential hypertension ('hypertonie essential') was introduced in 1925 by the physiologist Otto Frank to describe elevated blood pressure for which no cause could be found. In 1928, the term malignant hypertension was coined by physicians from the Mayo Clinic to describe a syndrome of very high blood pressure, severe retinopathy and adequate kidney function which usually resulted in death within a year from strokes, heart failure or kidney failure. A prominent individual with severe hypertension was Franklin D. Roosevelt.

• Descriptions of hypertension as a disease came among others from Thomas Young in 1808 and especially Richard Bright in 1836.
• The first report of elevated blood pressure in a person without evidence of kidney disease was made by Frederick Akbar Mahomed (1849–1884).
In 1931, John Hay, Professor of Medicine at Liverpool University, wrote that:
"there is some truth in the saying that the greatest danger to a man with a high blood pressure lies in its discovery, because then some fool is certain to try and reduce it

“The treatment of hypertension itself is a difficult and almost hopeless task in the present state of knowledge, and in fact for aught we know...the hypertension may be an important compensation mechanism which should not be tampered with, even were it certain that we could control it.”

—Paul Dudley White, 1937
Charles Friedberg's 1949 classic textbook "Diseases of the Heart", stated that

“In a patient with mild benign hypertension, i.e., blood pressure <200/<100 mm Hg, there is no indication for use of hypotensive drugs. Continued observation is desirable and conservative treatment consisting of reassurance, mild sedatives, and weight reduction is indicated.”

Friedberg. Diseases of Heart, 1946
Historical Lessons on the Risks of Hypertension and the Benefits of Treatment

Hypertension Increases Morbidity and Mortality

- Normotension
- Hypertension

Treatment Decreases Morbidity and Mortality

- Placebo
- Active Treatment

The Framingham Study


The Vet. Adm. Study II

Hypertension

JNC BP Classifications: DBP

JNC II. Arch Intern Med. 1980;140:1280-1285.
JNC III. Arch Intern Med. 1984;144:1045-1057.
Hypertension

JNC BP Classifications: SBP

<table>
<thead>
<tr>
<th>SBP (mm Hg)</th>
<th>JNC I</th>
<th>JNC II</th>
<th>JNC III</th>
<th>JNC IV</th>
<th>JNC V</th>
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<tr>
<td>220</td>
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<td>Optimal</td>
<td>Optimal</td>
<td>Normal</td>
<td>Normal</td>
</tr>
</tbody>
</table>

No recommendations for SBP in JNC I or JNC II

JNC II. Arch Intern Med. 1980;140:1280-1285.
JNC III. Arch Intern Med. 1984;144:1045-1057.
physicians and scientists have been distracted from consideration of variability by giving obsession attention to mean blood pressure (MBP).

The hypertension guidelines, which insist on reduction of Mean Arterial blood pressure (MBP) per se and remove BP variability from consideration,
Blood pressure variability (BPV)

1. Short-term BPV, which is the variability of BP over minutes or hours, such as is seen on 24-hour ambulatory blood pressure measurement (ABPM).

2. Long-term BPV, such as is seen with repeated recordings over weeks or months, and which is often called visit-to-visit BPV.

The determinants of BPV remain unclear, and the underlying mechanism of BPV reduction has never been elucidated precisely in subjects with hypertension.

Medicographia. 2012;34:25-31
What is the True Blood Pressure?

- Clinic BP?
- Daytime BP?
- Dipping Pattern?
- Nighttime BP?
- 24 Hr Average BP?
- Morning Surge?
- Variability of BP?
- Home BP?
Short term BP variability Types

1) Nocturnal BP Dipping
2) Morning BP surge
3) BP variability
Definition of morning surge in BP.

(Hypertension. 2010;56:765-773.)
- mild daytime S (150 mmHg), borderline daytime D (87 mmHg),
- borderline night time S (123 mmHg) and normal night time D (68 mmHg) with a white coat effect (187 /104 mmHg).
- Normal dipping pattern.

Hypertension (73.5%)

Hypertensive dipper

severe 24-h S&D hypertension, non dipper

Abnormal awake and sleep BP 4.5%

Abnormal awake BP 0.2%

Abnormal BP 18.5%

normal BP 18.5%

Associated conditions

- Nocturnal hypertension type (Riser / non-dipper)
  - Medicated hypertension
  - Diabetes
  - Post-stroke
  - Congestive heart failure
  - Sleep apnea syndrome
  - Orthostatic hypotension

Surge type

- Increased arterial stiffness
- Impaired baroreflex
- Orthostatic hypertension

Daytime: 5:00–21:00; nighttime: 21:00–5:00.
Nocturnal BP Changes and CV Mortality: Ohasama study

(Ohkubo et al; AJH 1997; 10: 1201)
Stroke and fatal stroke incidence for four dipping types. Shaded areas indicate nonfatal stroke incidence; solid areas, fatal stroke incidence.
based on 24-h ABPM and T:P ratio values, lisinopril with or without addition of HCTZ, has a stronger antihypertensive effect and a longer duration of action than equivalent doses of enalapril in patients with essential hypertension.

Medicated hypertension

Efficacy of Atacand 16 mg versus ramipril 10 mg on systolic blood pressure by using ambulatory blood pressure measurement in essential hypertension. (the carapas study)

Changes in SBP control in the 24 hours after a missed dose of telmisartan 80 mg or valsartan 160 mg in patients with mild-to-moderate hypertension (the MICADO I and II studies). SBP, systolic blood pressure.

24-hour powerful blood pressure-lowering: is there a clinical need?


http://dx.doi.org/10.1016/j.jash.2008.03.004
Heart failure (\(\downarrow\) COP, LVEF < 40% / \(\uparrow\) Demand)

- \(\downarrow\) ABP
- \(\uparrow\) Baroreceptors
- \(\uparrow\) symp. (catecholamines)
- \(\uparrow\) Aldosterone
- \(\uparrow\) Angiotensin II
- \(\uparrow\) ADH
- \(\uparrow\) pressure overload (catecholamines)
- \(\uparrow\) vasoconstriction
- \(\uparrow\) Myocyte necrosis
- \(\downarrow\) organ perfusion
- \(\downarrow\) baroreceptor sensitivity
- \(\downarrow\) HR variability
- \(\uparrow\) Baroreceptors
- \(\downarrow\) Baroreceptors

* persistent

** Myocyte loss

** Fatigue, \(\downarrow\) exercise capacity

** Volume overload
# Recommended ACEI maintenance doses per day in heart failure

<table>
<thead>
<tr>
<th>Drug</th>
<th>Initiating dose</th>
<th>Maintenance dose</th>
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</thead>
<tbody>
<tr>
<td>Captopril</td>
<td>6.25 mg (3 × 1)</td>
<td>150 mg (50 mg × 3)</td>
</tr>
<tr>
<td>Enalapril</td>
<td>2.5 mg</td>
<td>20 mg (10 mg × 2)</td>
</tr>
<tr>
<td>Lisinopril</td>
<td>2.5 mg</td>
<td>20–30 mg (OD)</td>
</tr>
<tr>
<td>Perindopril</td>
<td>2 mg</td>
<td>4 mg (OD)</td>
</tr>
<tr>
<td>Ramipril</td>
<td>1.25–2.5 mg</td>
<td>5–10 mg (OD, 5 mg × 2)</td>
</tr>
<tr>
<td>Trandolapril</td>
<td>0.5 mg</td>
<td>2–4 mg (OD, 2 mg × 2)</td>
</tr>
</tbody>
</table>

*Journal of Clinical and Basic Cardiology 2001; 4 (Issue 4), 279-283*
<table>
<thead>
<tr>
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</tr>
</thead>
<tbody>
<tr>
<td>In hypertension, all ARBs are approved</td>
<td>Proven to reduce BP in hypertension</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>In HF; only 2 ARBs are approved (NYHA Class II-IV with LVEF ≤40%)</td>
<td>Proven to reduce HF hospitalization</td>
<td>✓</td>
<td></td>
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<tr>
<td></td>
<td>Proven to reduce CV death in HF</td>
<td>✓</td>
<td></td>
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<tr>
<td></td>
<td>Proven to add these benefits when used with an ACEI in HF</td>
<td>✓</td>
<td></td>
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<tr>
<td></td>
<td>Once-daily dosing in HF</td>
<td>✓</td>
<td></td>
<td></td>
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<td></td>
<td>(Twice /day)</td>
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</table>
Definition of morning surge in BP

**Sleep-trough surge** = Morning SBP - Lowest nighttime SBP

**Prewaking surge** = Morning SBP - Preawake SBP

**Rising BP surge** = Morning SBP on rising - SBP on supine <30 min before rising

**ME difference** = Morning SBP - Evening SBP (by home BP self-measured)

SBP, systolic BP
Fig. 2 Definition of morning hypertension using self-monitored home BP (Jichi Medical School)
The early morning BP surge, which coincides with the peak incidences of stroke and myocardial infarction, BP, blood pressure.

Gordon McInnes

24-hour powerful blood pressure-lowering: is there a clinical need?


http://dx.doi.org/10.1016/j.jash.2008.03.004
Circadian Incidence of Cardiovascular Events: Myocardial Ischemia

Comparative effect of candesartan and amlodipine, on early morning hypertension and heart rate. (The DOHSAM study)

S. Minatoguchi et al. Blood Pressure, 2013; Early Online: 1–9
Comparative effect of candesartan and amlodipine, on early morning hypertension and heart rate. (The DOHSAM study)

Changes in heart rate in the early morning and at the office.

S. Minatoguchi et al. Blood Pressure, 2013; Early Online: 1–9
Effectiveness of Candesartan on Morning Blood Pressure Control at Home

Objectives. Blood pressure measured at home is superior to office-measured blood pressure in predicting the risk of cerebro-cardiovascular mortality and morbidity. A high morning blood pressure surge is an independent risk factor of cardiovascular events. For these reasons, control of blood pressure in the morning is essential.

Methods. We surveyed self-measured morning home blood pressure levels in essential hypertensive patients who were taking angiotensin II receptor blockers, candesartan, losartan, and valsartan.

Results. The mean blood pressure in candesartan, losartan, and valsartan groups was 141.7±8.4 / 74.7±4.6mmHg, 148.2±18.2 / 78.4±5.1mmHg, and 147.2±19.0 / 77.7±9.1mmHg, respectively. Systolic pressure was significantly lower in the candesartan treatment group than in the losartan treatment group (p=0.044). Diastolic pressure was reduced by candesartan more effectively than by losartan and valsartan (p=0.019 and 0.0359).

Conclusion: We conclude that candesartan is useful to control high morning blood pressure in patients with essential hypertension.
Change of Medication to Candesartan from Valsartan is Effective for Patients with Morning Hypertension (ATOM-convert C study)-Candesartan is Effective for Morning Hypertensive Patients-

TAMAKI Shinji; NAKAMURA Yasuyuki; YOSHINO Tomohide; MATSUMOTO Yuichi; TAKAYAMA Tomoyuki; TARUTANI Yasuhiro; OKABAYASHI Tabito; KAWASHIMA Takeshi; HORIE Minoru;

we reported that patients who had taken valsartan demonstrated a particularly large morning surge, and a significant difference (p = 0.02) was observed compared to that in those taking candesartan (ATOM study).

Methods and Subjects Patients in our outpatient clinic diagnosed with morning hypertension (over 135/85mmHg), men, 14; women, 14) who were previously prescribed valsartan, and then changed to candesartan, We estimated, from home blood pressure, the differences in morning and evening blood pressure values after changing the medication.

Conclusion: It was shown that a medication change to candesartan from valsartan is effective in morning hypertensive patients.
Candesartan significantly decreased early morning hypertension more than amlodipine (D=1 year).
Effect of switching from valsartan, losartan, telmisartan and olmesartan to candesartan, on early morning hypertension and heart rate

SHINYA MINATOGUCHI, TAKUMA Aoyama, NAOKI KAWAI, MITSUNORI IWASA, MASAYUKI ODA, KEIJI KIDA, SYOJIRO KOJIMA, NAOMI GOTO, MASAHIRO GOTO, FUSAYOSHI SUGISHITA, KUNIYUKI TAKAI, RYUHEI TANAKA, KEIJI HIEI, TARO MINAGAWA, NORITAKA YAMAMOTO, IKUO WATANABE, TAKAO YASUE & HIROSHI KOBAYASHI.

Changes in systolic and diastolic blood pressure after switching from other angiotensin receptor blockers (ARBs) to candesartan.
and effect of switching from valsartan, losartan, telmisartan and olmesartan to candesartan, on early morning hypertension and heart rate

Changes in systolic and diastolic blood pressure after switching from other ARBs to candesartan.

Minatoguchi et al. Blood Pressure, 2013; Early Online: 1–9
Meta-Analysis of Effects of Antihypertensive Drug Classes on Daytime & Nighttime BP
Weiner, Rieckmann, & Pickering, 2005

• Medline search of trials in which effects of antihypertensive drugs on daytime, nighttime, and 24 hr BP were described

• 55 trials satisfied criteria, & were grouped into 3 classes: ACEI, ARBs, Beta blockers (n=10), CCBs & Diuretics (n=35), and combinations (n=10).

• Across all studies, the absolute change of daytime BP (14/8 mmHg) was significantly greater than the change of nighttime BP (12.5/4.5 mmHg, p<0.01).

• The magnitude of the difference between the daytime & nighttime changes did not differ between the groups (p>0.7).
Meta-Analysis of Effects of Antihypertensive Drug Classes on Daytime & Nighttime BP

Weiner, Rieckmann, & Pickering, 2005

Change of SBP with Treatment mmHg

- CCB-DHP
- CCB-nonDHP
- ACEI
- ARB

Night
Day
Risk factors and target organ damage associated with morning surge in BP. The corresponding reference numbers are shown as superscripts.

- Sleep disorder
- Impaired baroreceptor reflex
- Elderly

BP, blood pressure; CRP, C-reactive protein; IL-6, interleukin 6, IL-18, interleukin 18; SD, standard deviation; LV, left ventricular; IMT, intima-media thickness; NF-kB, nuclear factor kappa B; MMP-9, matrix metalloproteinase-9; SMC, smooth muscle cell; PWV, pulse wave velocity, M/L ratio, media thickness to lumen diameter ratio.

*Hypertension.* 2010;56:765-773

*Journal of Hypertension* 2006, Vol 24 (suppl 2) ;S11–S16
Relative Effects of Telmisartan (40mg), Candesartan (8mg) and Losartan (50mg) on Alleviating Arterial Stiffness in Patients with Hypertension Complicated by Diabetes Mellitus: An Evaluation Using the Cardio-Ankle Vascular Index (CAVI)

The Journal of International Medical Research 2008; 36: 1094 – 1102
Risk factors and target organ damage associated with morning surge in BP. The corresponding reference numbers are shown as superscripts.

- Sleep disorder
- Impaired baroreceptor reflex
- Elderly

**Inflammatory markers**
- CRP↑, IL-6↑, IL-18↑

**BP variability**
- Orthostatic hypertension
- SD of daytime BP↑

**Arterial disease**
- Large artery disease
  - Carotid IMT↑
  - Vulnerable plaque
  - NF-κB activation↑, MMP-9↑
  - Macrophages↑, T-lymphocytes↑
  - SMC↓, Collagen↓, Oxidative stress↑
  - Ubiquitin-proteasome system↑

**Hypertensive heart disease**
- LV hypertrophy
- LV diastolic function↓
- Myocardial ischemia
- QTc dispersion and duration↑

**Albuminuria**
- (Diabetes) 27

**Small artery disease**
- M/L ratio of resistance artery↑
- Silent cerebral infarct

BP, blood pressure; CRP, C-reactive protein; IL-6, interleukin 6; IL-18, interleukin 18; SD, standard deviation; LV, left ventricular; IMT, intima-media thickness; NF-κB, nuclear factor kappa B; MMP-9, matrix metalloproteinase-9; SMC, smooth muscle cell; PWV, pulse wave velocity; M/L ratio, media thickness to lumen diameter ratio.
Change in PAI-1 antigen levels: Differing effects of ARBs cand (16mg), Los(100mg), Irbes (300mg),

126 Patients with hypertension

Change in Tissue factor activity level: Differing effects of ARBs cand (16mg), Los(100mg), Irbes (300mg),

126 Patients with hypertension

<table>
<thead>
<tr>
<th>Drug</th>
<th>% Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
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</tr>
<tr>
<td>Losartan 100 mg</td>
<td>-10</td>
</tr>
<tr>
<td>Irbesartan 300 mg</td>
<td>-20</td>
</tr>
<tr>
<td>Candesartan 16 mg</td>
<td>-30</td>
</tr>
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</table>

P = 0.001 by ANOVA

Change in Malondialdehyde levels (antioxidant):

Differing effects of ARBs: cand (16mg), Los (100mg), Irbes (300mg),

126 Patients with hypertension

Change in monocyte chemoattractant protein-1 (pg/ml):

Differing effects of ARBs cand (16mg), Los (100mg), Irbes (300mg),

126 Patients with hypertension

Comparison of Anti-arteriosclerotic Effects of Candesartan and Valsartan in Type 2 Diabetic Patients with Hypertension —Evaluation by Flow-mediated Dilatation (FMD)

UEHARA Goro; MORI Kanako; SAKAI Takako; MORITA Yasuko; TAKEDA Hiroshi;

Objective To compare the effects of candesartan and valsartan on endothelial function assessed by measurement of flow-mediated vasodilation (FMD) in type 2 diabetes patients with hypertension.

Methods: Subjects who were receiving treatment with valsartan prior to registration were switched to candesartan 8 mg/day (VC group, n=21) whereas those who were receiving candesartan were switched to valsartan 80 mg/day (CV group, n=19) for an observation period lasting 3 months. Percent FMD, blood pressure, and HbA$_{1c}$ were examined at baseline and 3 months after starting treatment.

Results: The two groups did not differ in terms of patients' baseline clinical characteristics and laboratory data. At 3 months, there were no significant changes in blood pressure and HbA$_{1c}$ in both groups. In the VC group percent FMD significantly increased at 3 months (from 4.7% to 5.8%; p<0.001), while in the CV group it significantly decreased (from 4.7% to 4.3%; p<0.001). Moreover, percent FMD at 3 months in the VC group was significantly higher than that in the CV group (p< 0.05).

Conclusions: This study indicates that suppression of progression of endothelial dysfunction by different ARBs is not a class effect; candesartan is more effective against progression of arterial sclerosis than valsartan.

Yakuri to chiryo , 2009, vol. 37, no9, pp. 757-762 [6 page(s) (article)]
Risk factors and target organ damage associated with morning surge in BP. The corresponding reference numbers are shown as superscripts.

Hypertension. 2010;56:765-773

Journal of Hypertension 2006, Vol 24 (suppl 2) ;S11–S16
CATCH study: Design

Inclusion
- LVH [LVMI >120 g/m² in men and >100 in women]
- Untreated or uncontrolled HT (150-200/95-115 )

Randomisation:
- Candesartan 8 mg qd
- Enalapril 10 mg qd
- If target BP not reached, dose X2, HCTZ added

Echo:
- At randomisation
- 24 and 48 w.

Cuspidi et al J Hypertens 2002
CATCH study: ITT population - pre-post treatment mean changes – LVH regression

Equal BP reduction in both groups

at the end of the study 36% of patients treated with candesartan and 30% treated with enalapril showed a complete LVH regression

Cuspidi et al J Hypertens 2002

LV mass index (g / m$^2$)

- **amlodipine**
  - 13.4

- **Candesartan**
  - 22.9

\[ P = 0.023 \]
Effects of candesartan versus amlodipine on home-measured blood pressure, QT dispersion and left ventricular hypertrophy in high-risk hypertensive patients

Matsuno Y, Minatoguchi S, Fujiwara H; GIFU Substudy Group of The Case-J Trial.

The GIFU substudy of the Candesartan Antihypertensive Survival Evaluation in Japan (CASE-J) trial was conducted to compare the long-term effects of candesartan and amlodipine on office- and home-measured blood pressure (BP), QTc dispersion and left ventricular mass index (LVMI) in high-risk Japanese patients with hypertension.

We used a prospective, randomized, open-label design with blinded assessment of endpoints. Patients were assigned to candesartan-based therapy up to 12 mg/day ($n = 100$) or amlodipine-based therapy up to 10 mg/day ($n = 101$) and followed for 3 years. LVMI was assessed by echocardiography and QTc dispersion was obtained from electrocardiograms. Both candesartan and amlodipine lowered and controlled office- and home-measured BP levels with no significant between-treatment differences. In patients diagnosed with left ventricular hypertrophy (LVH) at baseline, both candesartan and amlodipine significantly regressed LVMI after 3 years. However, **candesartan** (41.7 ± 15.1 ms at baseline vs 32.9 ± 16.6 ms after 3 years, $p < 0.01$), **but not amlodipine** (41.4 ± 13.5 ms at baseline vs 41.5 ± 16.1 ms after 3 years), produced a significant reduction in QTc dispersion. Larger studies in patients treated for longer periods are needed to determine whether this candesartan effect will translate into improved prognosis in terms of cardiovascular mortality and morbidity

**CHARM-Preserved Investigator Reported CHF Hospitalizations**

*Yusuf et al Lancet 2003*

**Proportion of patients (%)**

- Placebo: 20%
- Candesartan: 15%

**Number of episodes**

- Placebo: 600
- Candesartan: 500

**HR = 15%**

**p = 0.017**

**RRR = 29%**

**p = 0.014**

*ESC Guidelines for the Diagnosis and Treatment of CHF - 2005*
ACEi in HF with Preserved EF

CHARM Preserved
CVS Death or
HF Hospitalisation


PEP-CHF
Death or
HF Hospitalisation

Cleland JGF, et al. EHJ 2006;27:2338
Risk factors and target organ damage associated with morning surge in BP. The corresponding reference numbers are shown as superscripts.

BP, blood pressure; CRP, C-reactive protein; IL-6, interleukin 6; IL-18, interleukin 18; SD, standard deviation; LV, left ventricular; IMT, intima-media thickness; NF-kB, nuclear factor kappa B; MMP-9, matrix metalloproteinase-9; SMC, smooth muscle cell; PWV, pulse wave velocity, M/L ratio, media thickness to lumen diameter ratio.

Hypertension. 2010;56:765-773

Journal of Hypertension 2006, Vol 24 (suppl 2) ;S11–S16
Effect of ARBs on proteinuria

Candesartan

Proteinuria reduction vs. placebo (%)

- 8 mg/d
- 16 mg/d
- 32 mg/d

* p < 0.05 vs. placebo;
+ p < 0.01 vs. 8 mg.

32.8%  58.9%  52.6%

Valsartan (DROP trial)

Proteinuria reduction vs. placebo (%)

- 160 mg/d
- 320 mg/d
- 640 mg/d

25%  49%  51%

* p < 0.05 vs. baseline;
+ p < 0.01 vs. 160 mg.

N=391


Rossing K et al, Diabetic care 2003.25, 150-155
# ARB nephro/CV protection trials with solid end point*

*Doubling of baseline serum creatinine, end-stage renal disease*

<table>
<thead>
<tr>
<th>Study(N)</th>
<th>ARB</th>
<th>Renal outcome *</th>
<th>CV outcomes</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>IDNT (1715)</strong> (proteinuria )</td>
<td>Irbesartan 300 mg/d vs amlodipine 10 mg</td>
<td>↓20% vs placebo, and ↓23% vs amlodipine</td>
<td>NS</td>
<td>2.6 y</td>
</tr>
<tr>
<td><strong>RENAAL (1514)</strong> (proteinuria)</td>
<td>Losartan 100 mg/d vs placebo†</td>
<td>↓16%</td>
<td>NS</td>
<td>3.4 y</td>
</tr>
<tr>
<td><strong>TRANSCEND (2207)</strong> microalbuminuria</td>
<td>Telmisartan 80 mg Vs placebo</td>
<td>↓ Progress to proteinuria . renal outcome (NS)</td>
<td>NS</td>
<td>4.5 y</td>
</tr>
<tr>
<td><strong>ORIENT (n=566)</strong> (proteinuria)</td>
<td>Olmesartan (10 -40 mg) Vs placebo</td>
<td>↓ urinary protein/creatinine , renal outcome (NS)</td>
<td>↑ CV mortality (p=0.039)</td>
<td>5 y</td>
</tr>
<tr>
<td><strong>ROADMAP (N = 4400)</strong> (Normalbuminuria)</td>
<td>Olmesartan 40 mg Vs placebo</td>
<td>↓23% develop proteinuria, renal outcome(NS),</td>
<td>↑ CV mortality (p = 0.01)</td>
<td>3.2 y</td>
</tr>
<tr>
<td><strong>CASE-J (2720)</strong> ,proteinuria /GFR &lt; 60 ml /min /1.73m2</td>
<td>Candesartan (4-12 mg) Vs amlodipine (2.5-10 mg)</td>
<td>↓ 57-87%</td>
<td>↓CV mortality at Stage 4 by 55%</td>
<td>3.2 y</td>
</tr>
<tr>
<td><strong>HIJ-CREATE (n=1012)</strong> (creatinine clearance &lt;60ml/min)</td>
<td>Candesartan based regimen Vs Non-ARB based regimen</td>
<td>Not determined</td>
<td>↓ MACE by 20%</td>
<td>4.2years</td>
</tr>
</tbody>
</table>
Thank you