β – adrenergic blockade, a renal perspective

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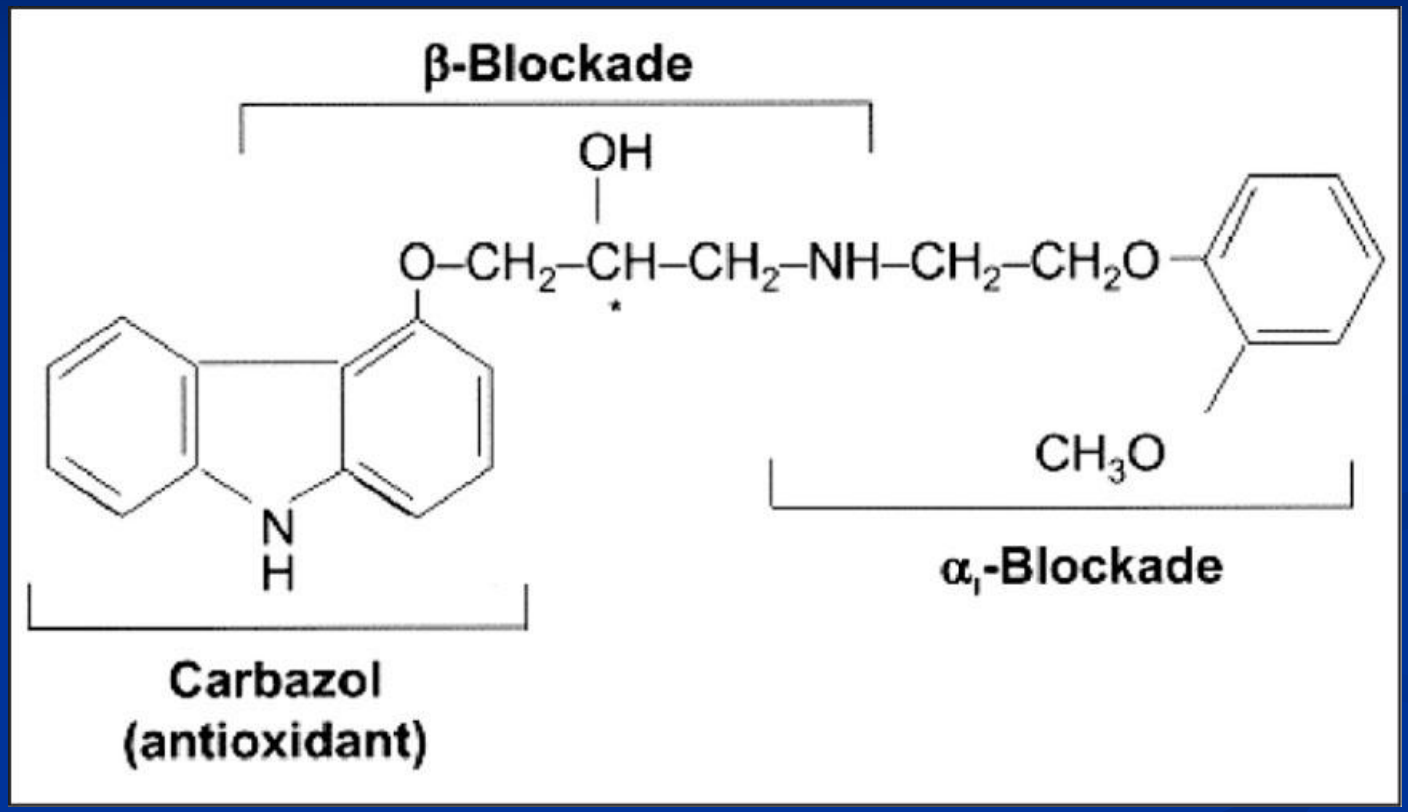
Carvedilol

- Third generation β –blocker (both β_1 and β_2)
- Possesses α_1 – adrenergic blocking properties.
- β: α blocking ratio 7:1 to 3:1
- Antioxidant
- Calcium antagonist

Structure of carvedilol



1-(9*H*-carbazol-4-yloxy)-
3-[2-(2-methoxyphenoxy)ethylamino]propan-2-ol

Carvedilol

- Improves myocardial function
- Attenuates or reverses adverse myocardial remodelling in HF
- Decreases peripheral vascular resistance (α_1 and β_2 receptors).
- Lacks intrinsic sympathomimetic activity (ISA)
- Low levels of inverse agonist activity compared to other β - blockers

Carvedilol

- Originally used for hypertension
- Improves symptoms in patients with heart failure and stable angina pectoris.
- Decreases secondary cardiac events of the MI.
- Reduces infarct size following MI and reperfusion injury.

Pharmacological effects of Carvedilol

- Direct
- Indirect:
  - Fall in IL-10
  - Fall in TNF-α
  - Fall in soluble TNF receptor levels

β – blocker use in diabetes I

- Improve outcomes more in patients with DM and history of AMI or CAD than in patients without DM.
- This is despite the fact that β – blockers elevate TG and lower HDL-C levels.

β – blocker use in diabetes II

- The positive effects of β – blockade relate to:
  - Decrease in HR and BP
  - Improved diastolic function
  - Antiarrhythmogenic effects
  - Anti-inflammatory effects
  - Shifting of the metabolism of myocardium away from FFA towards glucose utilization.
  - Turn around the total gene induction programme to reverse myocardial remodeling and improve ventricular function

Major problem with β – blockers use in diabetes

- Increased insulin resistance and worsening of glycaemic control, noted in:
  - LIFE study (Lorsataan vs atenolol)
  - COMET (Carvedilol vs Metoprolol)
  - A community - based study
- The above have shown 22 – 28% increase in new onset diabetes.

GEMINI study

- Head to head trial of Carvedilol and Metroprolol.
- Subjects and outcome:
  - Hypertensive diabetic patients receiving RAS – blocking agents

GEMINI trial

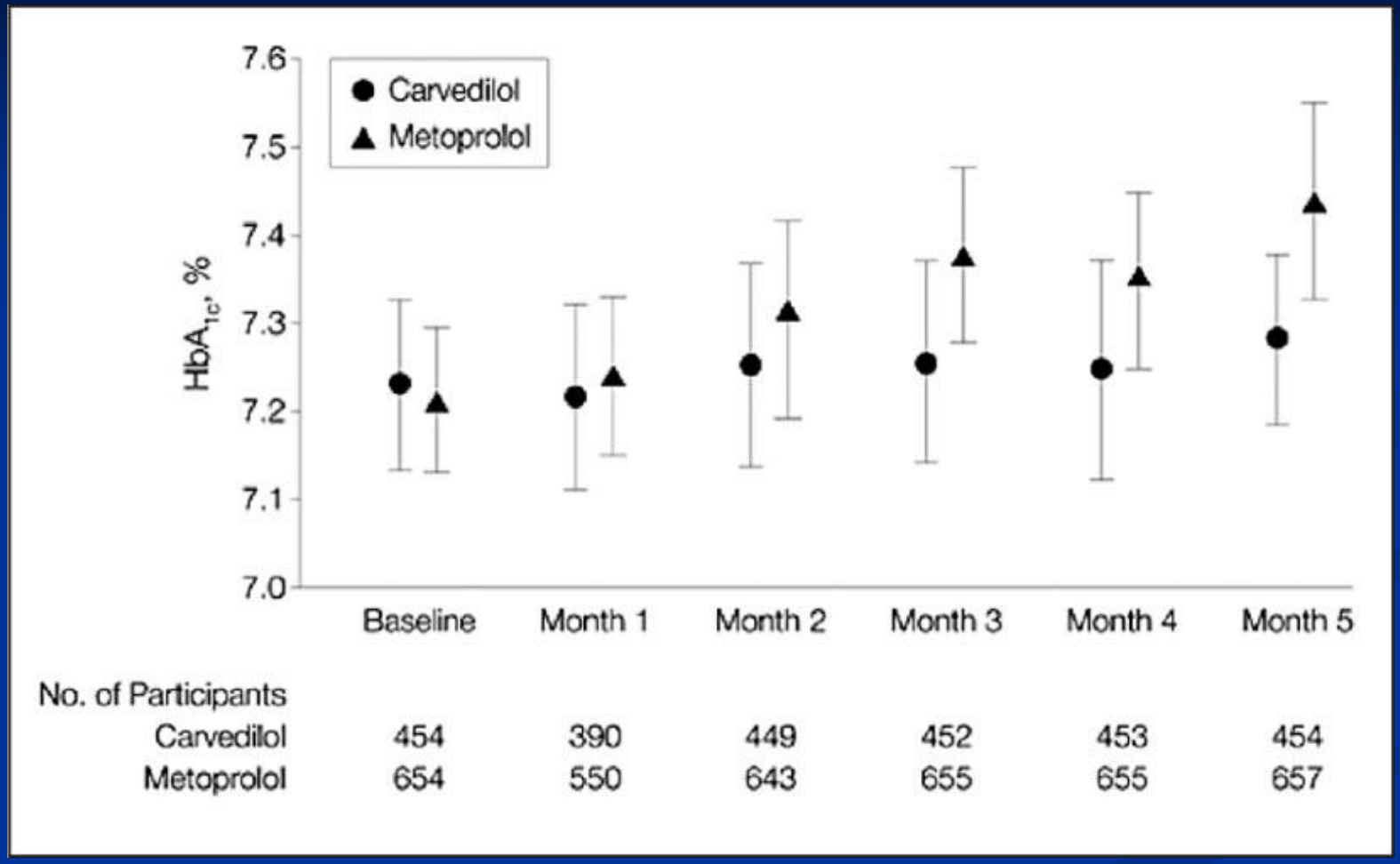


Figure 2. Glycosylated hemoglobin (HbAic) at baseline and each maintenance month by treatment in the modified intention-to-treat population. The change from baseline to maintenance Month 5 (primary outcome) was significant (mean difference [SD], 0.13% [0.05%]; 95% confidence interval, −0.22% to −0.04%; p=0.004). Error bars indicate SD from mean. Reprinted with permission from JAMA. *2004;292:2227-2236.*[23]

β – blockers in management of CKD

- High prevalence of CVD in people with CKD:
  - Hypertension
  - CAD
  - MI
  - Heart failure

CKD vs CVD

- Clear benefits of mortality obeserved for most β - blockers in clinical trials (bisoprolol I & II, carvedilol, metoprolol SR etc).
- β – blockers relatively under-used in:
  - CKD patients:
    - Agodoa et al 30%
    - USRDS 20%
  - Patients on dialysis:
    - Agodoa et al 24% dialysis patients with CAD
- Similar trend in predialysis patients.
- Reason for under - utilization: fear of adverse haemodynamic effects on renal physiology and effects on lipids and glucose levels.

Rationale for use of β – blockers in CKD

- There is sympathetic over activity in patients with CKD.
- Sympathetic overdrive has a role in:
  - Genesis of HTN
  - Complications of CVD
  - Progression of kidney disease

β – blockers vary significantly in their pharmacologic properties which determine how well they work and how tolerable they will be in patients with CKD

Pharmacological properties of β - blockers

- Lipid solubility
- Cardioselectivity
- Metabolism and excretion.
- Adjunctive properties:
  - Vasodilatory
  - Antioxidant
  - Calcium – blocking activity
- Metabolic factors:
  - Lipoproteins
  - Glycaemic control
  - Hyperkalaemia

Lipid solubility I

Lipophilic agents undergo extensive first pass hepatic metabolism with relatively very little being excreted unchanged in urine

Lipid solubility II

Hydrophilic agents are excreted primarily by the kidney and require dose adjustments in patients with ESRD.

Lipid solubility III

Hydrophilic agents agents may yield low blood levels due to poor absorption after oral administration

Cardioselectivity I

- β1 – selective blockers are cardiospecific and result in reduced CO, HR and BP

Cardioselectivity II

- β_1 – β_2 blockers antagonize the effects of catecholamine stimulation on β – adrenergic receptors in resistance vessels as well as the myocardium.
- β_2 – blockade downgrades the pro-arrhythmic effect of NE.

Cardioselectivity III

- Inhibititon of β_2 vasodilation leaves the reflex α_1- mediated vasoconstrictor response to arterial underfilling unopposed in the face of decreased BP or CO.
- The effects of β – blockade amplified by reduction in production of renin by the JGA.

Addition of α_1-inhibiting activity to β-adrenergic antagonist

- Blocks reflex vasoconstriction
- May increase blood flow to skeletal muscle there improving glucose availability and disposal.
- Both non-selective and selective β-blockers can increase insulin resistance.
- α-blocking activity if increased may improve insulin sensitivity in both diabetic and non-diabetics.

Conclusion

Addition of α_1-blocking activity to certain β–blockers may impact both diabetes and ateriosclerotic CVD by promoting better glycaemic control with less compensatory hyperinsulinaemia and fewer proatherogenic changes in serum lipids

Effect of β-blockers on lipid metabolism

- β1 selective and non-selective β-blockers:
  - Increase blood levels of TG
  - Lower levels of HDL-C
- α_1-blocking activity:
  - Lowers TG
  - Raises HDL-C

Summary of the effects of some common β-blockers

	Propranolol	Metoprolol	Atenolol	Labetalol	Carvedilol
Lipophilic	Y	Y	N	Y	Y
Nonselective (β_1/β_2)	Y	N	N	Y	Y
Cardioselective (β_1)	N	Y	Y	N	N
α_1-blockade	N	N	N	Y	Y
Insulin sensitivity	↓	↓	↓	↔	↑
Serum triglycerides	↑	↑	↑	↔	↓
Serum HDL cholesterol	↓	↓	↓	↔	↑
Hyperkalemia in ESRD	Y	N	N	Y	N
Renal effects in CKD					
RVR	↑	↓	↔	↔	↓
RBF	↓	↔	↔	↔	↑
GFR	↓	↔	↔	↔	↑

↑, increases with use of drug; ↓, decreases with use of drug; ↔,remains the same with use of drug; **CKD**, chronic kidney disease; **ESRD**,end-stage renal disease; **GFR**, glomerular filtration rate; **HDL**,high-density lipoprotein; **N**, no; **RBF**, renal blood flow; **RVR**, renalvascular resistance; **Y**, yes.

Properties of carvedilol

- Lowers blood pressure in both younger and older black and white patients
- Reduces peripheral resistance
- Does not reduce cardiac output or renal function in long-term studies
- Has a neutral effect on lipids and glucose
- Is well tolerated by most patients
- Possesses antioxidant effects in pharmacologic studies (inhibits oxygen-free radicals. This action may be important in slowing down the process of atherogenesis and protecting against brain tissue injury)

Properties of carvedilol

- Reduces morbidity and mortality in patients with congestive heart failure who are already being treated with angiotensin converting enzyme inhibitors, diuretics, and digitalis (reduces preload and afterload).
- Reduces infarct size to a significant degree in animal models and improves survival (effect not demonstrated with other b-blockers).
- Has antiproliferative effects on smooth muscle cells (in response to angiotensin II, platelet-derived growth factor, etc)

Nebivolol

- Relatively new lipophilic β_1-blocker approved for HTN.
- Devoid of Intrinsic Sympathomimetic Membarane Stabilizing Activity.
- Has NO – mediated vasodilatory effect.
- Glucose and lipid not affected.
- Not much tested clinically in other areas.

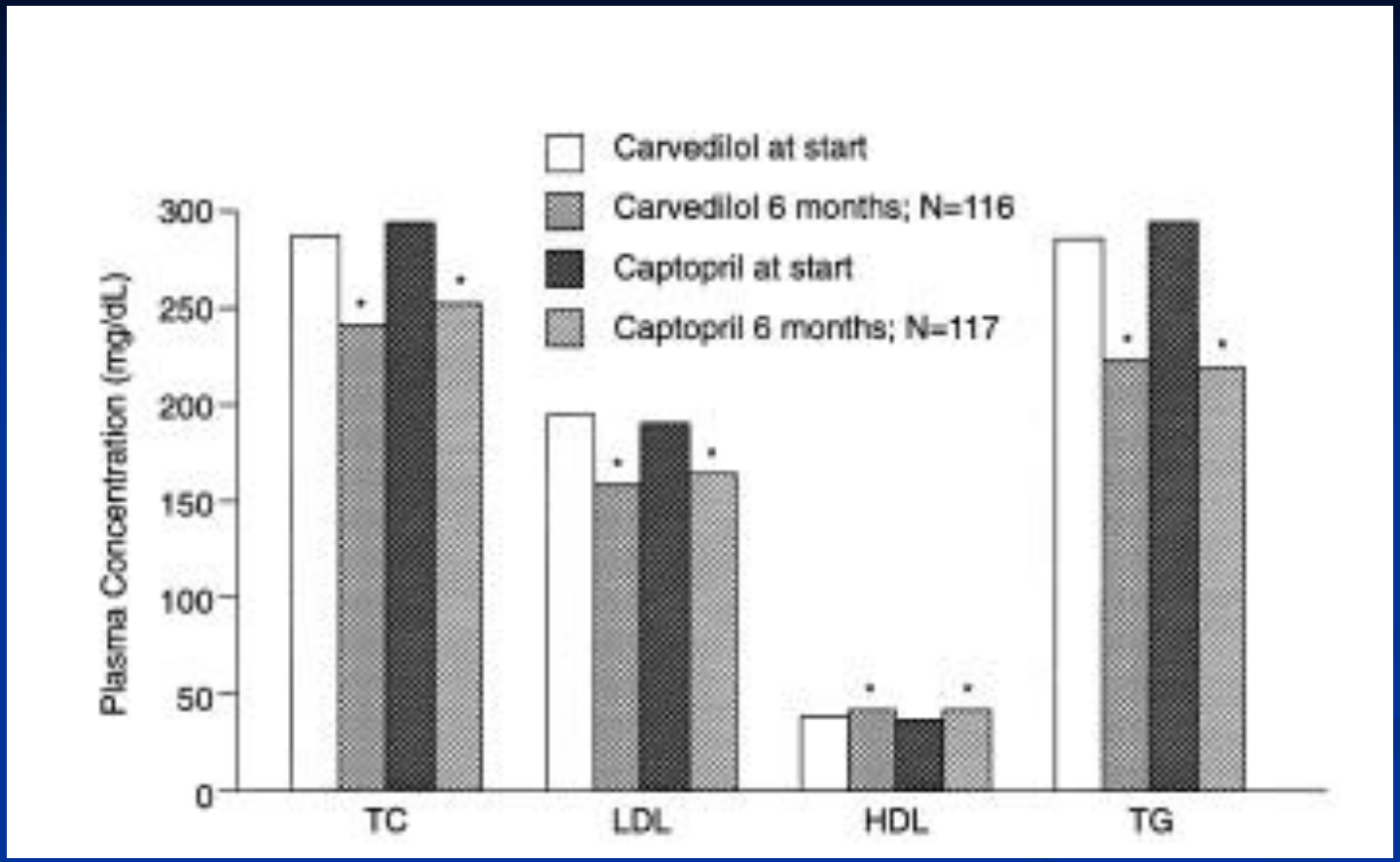


FIGURE 2. *Changes in serum lipids in a 6-month double-blind study of 220 hypertensive patients receiving either carvedilol (25 to 0 mg/day) or captopril (25 to 50 mg/day). *P , .0001 versus baseline. Start 5 end of 4-week placebo washout phase; HDL, high-density lipoprotein; LDL, low density lipoprotein; TC, total cholesterol; TG, triglyceride. Data from Hauf-Zachariou et al.8*

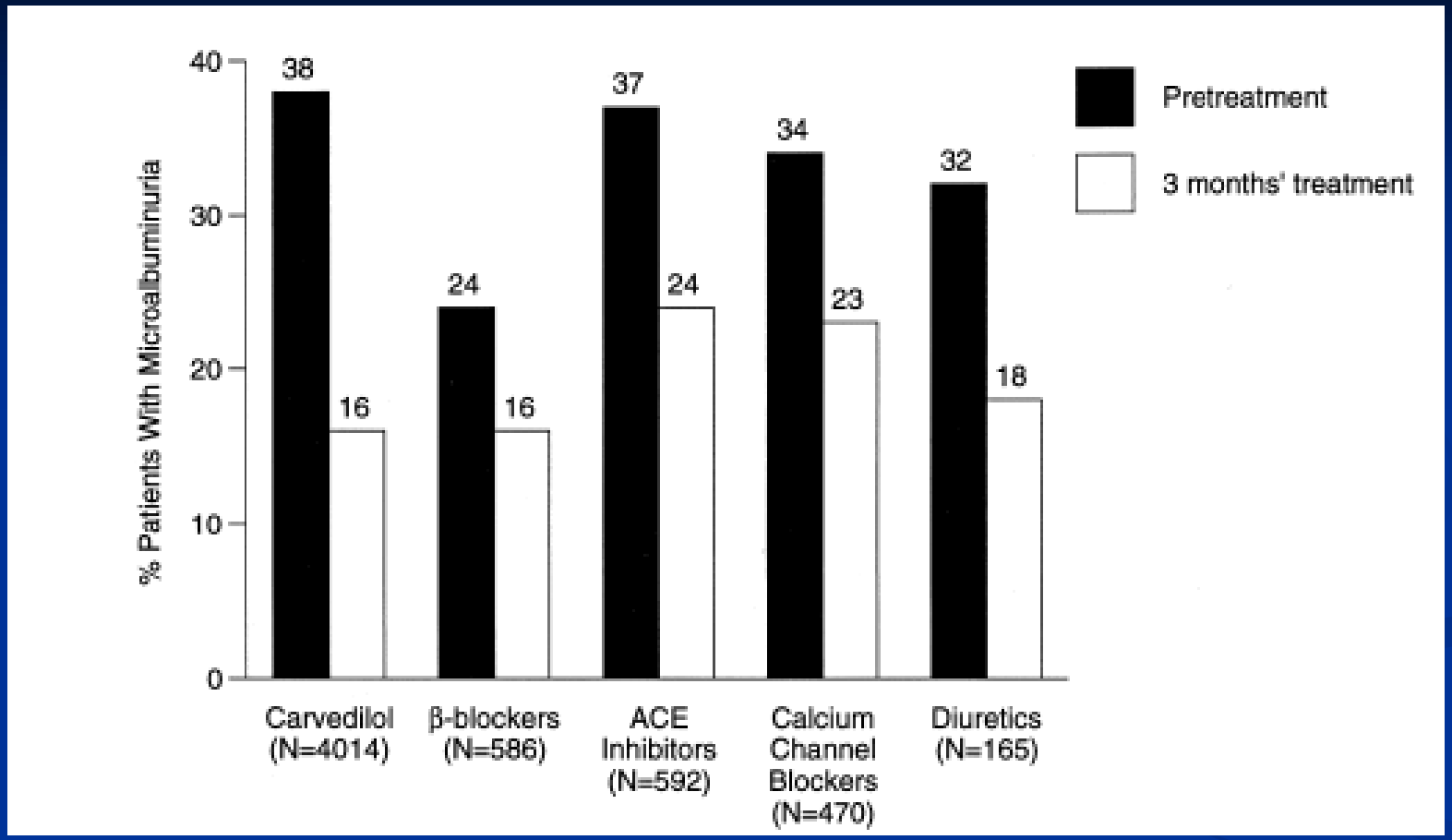


FIGURE 3. *Percentage of patients with reduction or increase in urinary albumin level with carvedilol compared to other antihypertensive agents (reproduced from Marchi and Ciriello,24 with permission.).*

THE END

- THANK YOU