Extrapolation of General Population Guidelines to Dialysis Patients: Appropriate or Inappropriate?

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- Relationship of BP with CV risk is "strong, continuous, independent, predictive and etiologically significant."

JNC 6, *Arch Intern Med*. 1997;157:2413-46.

- ***Patients with CKD are in the "highest-risk" group for CVD (Strong).*** Patients with CKD are at increased risk of CVD. Hypertension is a risk factor for CVD events in CKD. However, **there have been few controlled trials to demonstrate the efficacy of blood pressure lowering to reduce the risk of CVD in CKD**; therefore, the Work Group made recommendations for CKD based on extrapolation from evidence on the efficacy of antihypertensive therapy in the general population.

K/DOQI Clinical Practice Guidelines on Hypertension and Antihypertensive Agents in Chronic Kidney Disease

Target Blood Pressure

For Individuals With:	BP Goal:
Hypertension (no diabetes or renal disease)	**<140/90 mmHg (JNC 7)**
Diabetes Mellitus	**<130/80 mmHg (ADA, JNC 7)**
Renal Disease with proteinuria >1 gram/24 hours or diabetic kidney disease	**<135/85 mmHg <125/75 mmHg (NKF)**

Chobanian AV et al. *JAMA*. 2003;289:2560–2571.
American Diabetes Association. *Diabetes Care*. 2002;25:134–147.
National Kidney Foundation. *Am J Kidney Dis*. 2002;39(suppl 1):S1–S266.

Criteria for Extrapolation of General Population Guidelines to CKD Patients

1) The mechanism and expression of CVD in CKD should be similar to those observed in the general population. Specifically, the features of CVD, the relationship of CVD outcomes to hypertension, the mechanism of blood pressure lowering, and the responsiveness of risk factors to lifestyle modifications and pharmacological therapy should be similar in patients with CKD and the general population.
2) Therapies in patients with CKD should be as safe, or nearly so, as in the general population. In particular, there should not be additional adverse effects of a specific therapy that limits its usefulness in patients with CKD, either because of altered pharmacokinetics, drug interactions, or increased risk of toxicity to the kidney.
3) The duration of therapy required to improve CVD outcomes in the general population should not exceed the life expectancy of patients with CKD. Numerous studies of CVD in the general population have shown a benefit of interventions within 2 to 5 years, with greater and earlier benefits in patients at highest risk. Thus, it is likely that patients with CKD Stages 1-4 could benefit from more effective treatment of CVD.

Levey AS et al, NKF Task Force on CVD *Am J Kidney Dis* 32:853-906, 1998

Rationale for Extrapolation of General Population Guidelines to CKD Patients

1) The mechanism and expression of CVD in CKD should be similar to those observed in the general population. Specifically,
    1) the features of CVD,
    2) the relationship of CVD outcomes to hypertension,
    3) the mechanism of blood pressure lowering, and
    4) the responsiveness of risk factors to lifestyle modifications and pharmacological therapy should be similar in patients with CKD and the general population.

Levey AS et al, NKF Task Force on CVD *Am J Kidney Dis* 32:853-906, 1998

General population

- N=310,232,863 (July 2010 est.)
- Median age: 36.8 years
- Ethnic composition
  - White 79.96%
  - Black 12.85%
  - Hispanic 15.1%
- Expected remaining life time: 25.2 years

ESRD

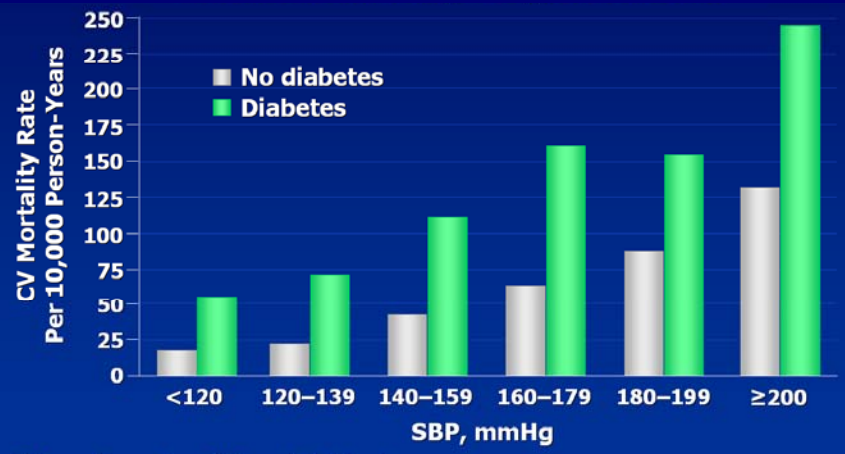
- N=368,544 (December 31, 2007)
- Median age: 59.1 years
- Ethnic composition
  - White 55.7%
  - Black 37.1%
  - Hispanic 15.6%
- Expected remaining life time: 5.9 years

https://www.cia.gov/library/publications/the-world-factbook/geos/us.html
http://www.cdc.gov/NCHS/data/nvsr/nvsr58/nvsr58_19.pdf
U S Renal Data System, USRDS 2009 Annual Data Report

	General population	CKD	p
Mean SBP (95%CI)	135.9 (135.0 to 136.9)	141.3 (139.7 to 142.9)	<0.001
Mean DBP (95%CI)	76.1 (75.4 to 76.8)	67.5 (66.1 to 68.9)	<0.001
Mean pulse pressure (95%CI)	59.8 (58.9 to 60.7)	73.8 (71.6 to 75.9)	<0.001
On antihypertensive medications (%, 95%CI)	37.2 (34.9 to 39.7)	66.4 (63.7 to 69.0)	<0.001

Platinga et al, *Hypertension* 2009;54;47-56

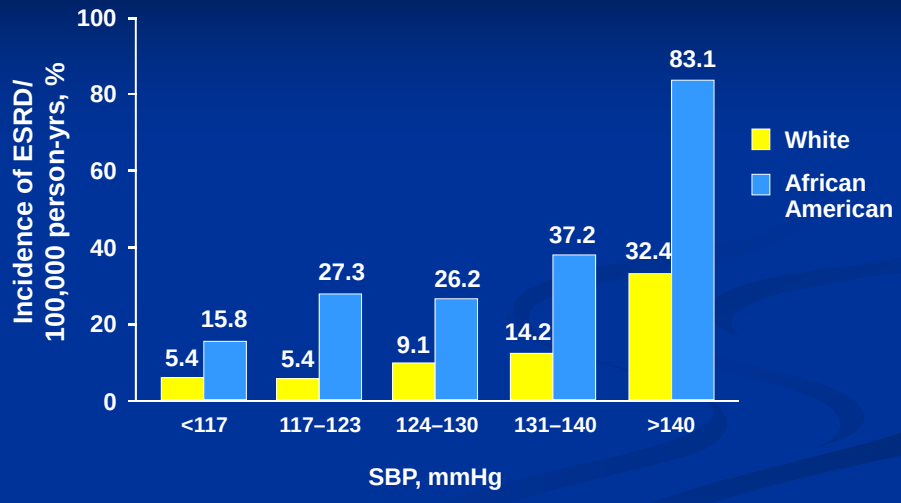
SBP and CV mortality in the general population



CV=cardiovascular; SBP=systolic blood pressure.

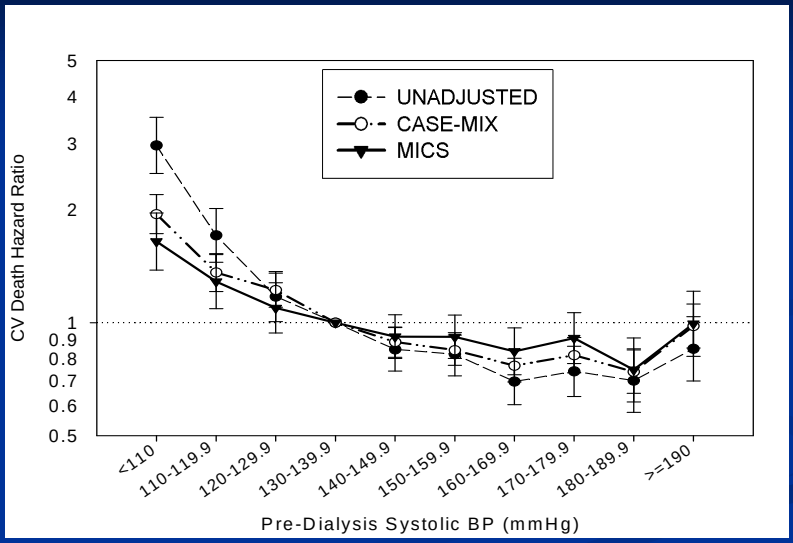
Stamler et al, *Diabetes Care* 1993;16:434-444

Incidence of ESRD by SBP: MRFIT

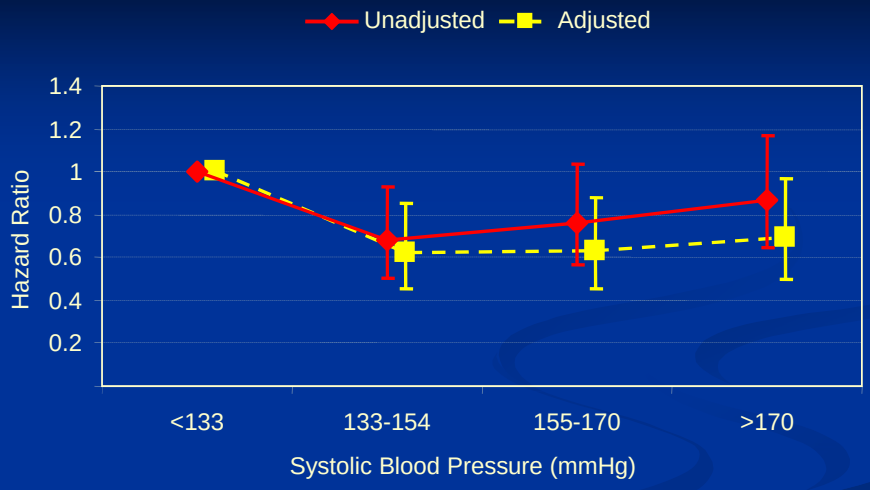


Klag MJ et al. *JAMA.* 1997;277:1293–1298.

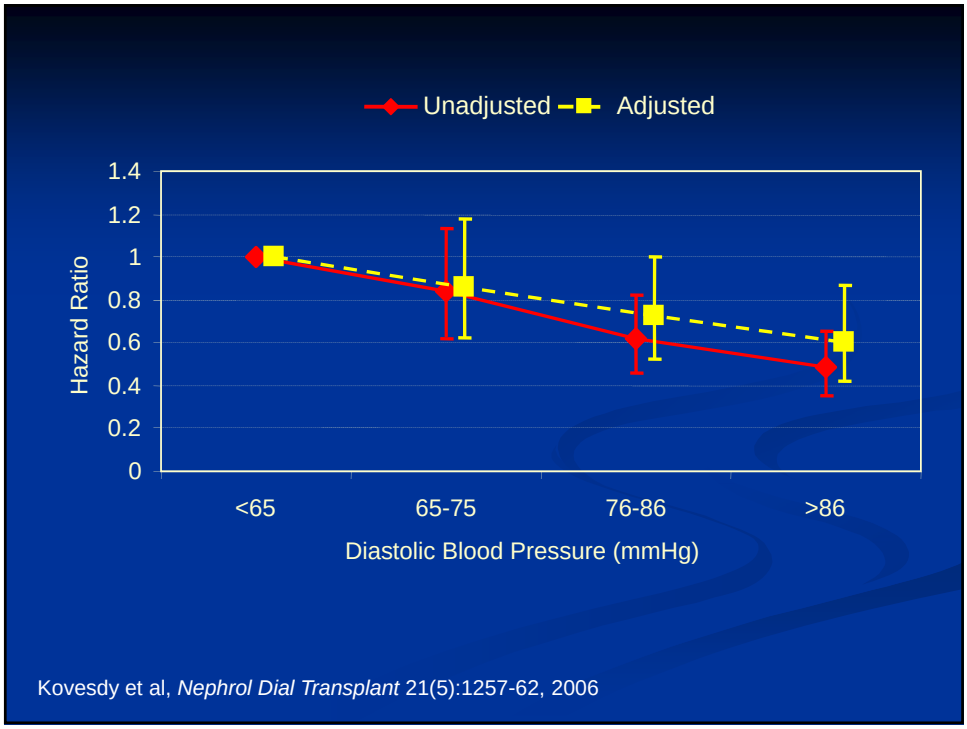
15-Month CV Death Risk in 40,933 HD Patients



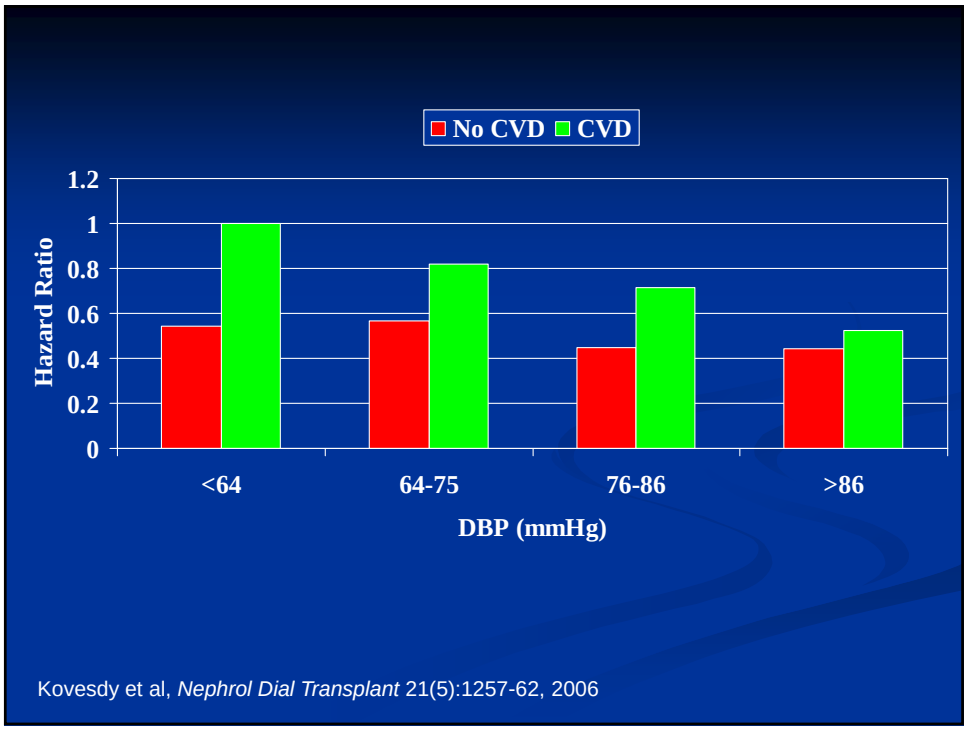
Kalantar-Zadeh et al, *Hypertension* 2005



Kovesdy et al, *Nephrol Dial Transplant* 21(5):1257-62, 2006

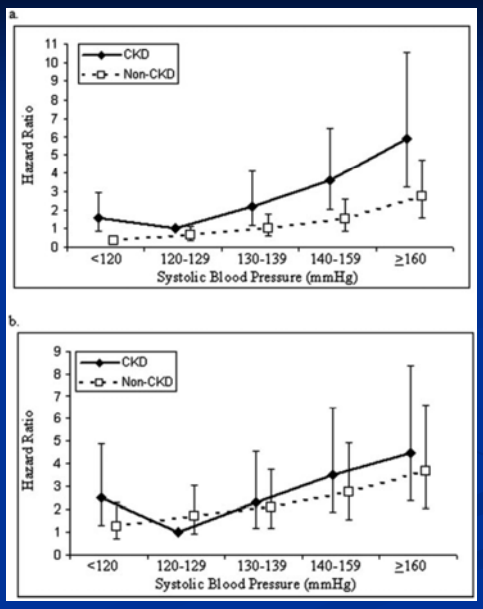


Kovesdy et al, *Nephrol Dial Transplant* 21(5):1257-62, 2006

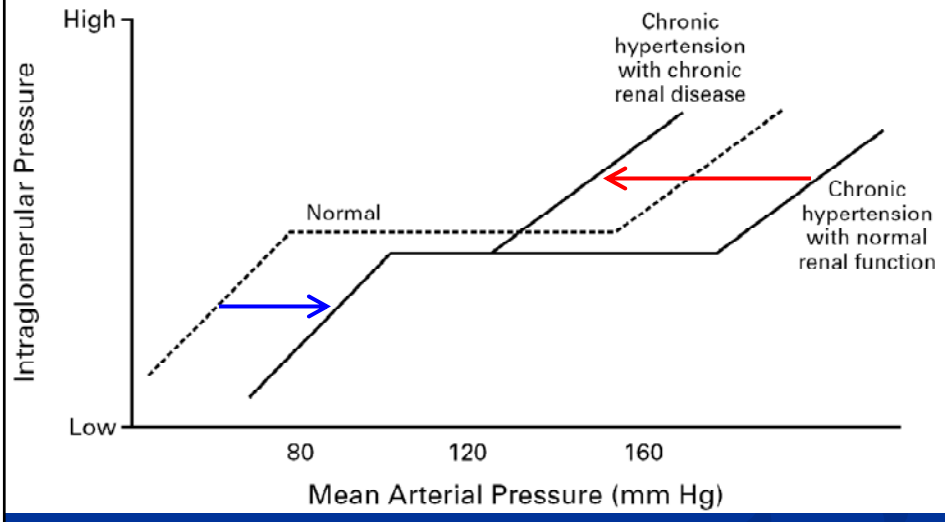


Kovesdy et al, *Nephrol Dial Transplant* 21(5):1257-62, 2006

SBP and stroke in CKD vs. non-CKD patients



Weiner et al, J Am Soc Nephrol 18: 960–966, 2007



Palmer BF, N Engl J Med 2002; 347(16):1256-1261

Changes in renal vasculature

- Afferent arteriolar endothelial dysfunction leading to impaired vasodilatation
- Hyaline arteriosclerosis
- Myointimal hyperplasia

- Result is impaired autoregulatory capacity
- Intraglomerular pressure begins to vary directly with changes in systemic pressure

Ditscherlein G, *Hypertension* 1985;7:II-29–II-32.
Bidani et al, *Hypertension* 1994;24:309-16.
Pelayo and Westcott, *J Clin Invest* 1991;88:101-5.
Hayashi et al, *J Hypertens* 1996;14:1387-401.
Palmer BF, *Am J Med Sci* 2001;321:388-400.

Table 1. Factors Increasing Susceptibility to Renal Hypoperfusion.

Failure to decrease arteriolar resistance
Structural changes in renal arterioles and small arteries
Old age
Atherosclerosis
Chronic hypertension
Chronic kidney disease
Malignant or accelerated hypertension
Reduction in vasodilatory prostaglandins
Nonsteroidal antiinflammatory drugs
Cyclooxygenase-2 inhibitors
Afferent glomerular arteriolar vasoconstriction
Sepsis
Hypercalcemia
Hepatorenal syndrome
Cyclosporine or tacrolimus
Radiocontrast agents
Failure to increase efferent arteriolar resistance
Angiotensin-converting–enzyme inhibitors
Angiotensin-receptor blockers
Renal-artery stenosis

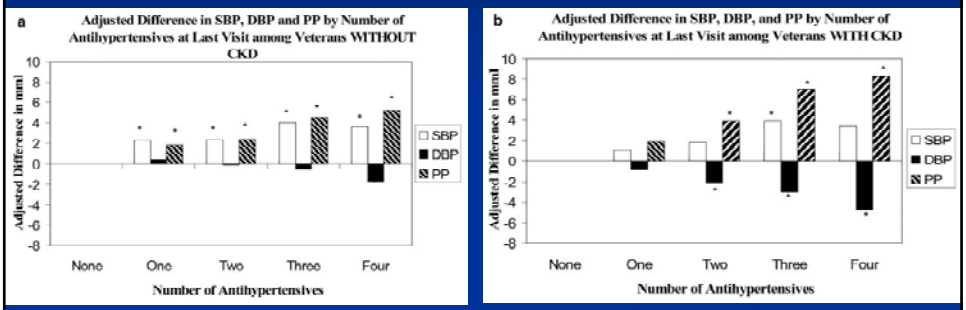
Abuelo JG, N
Engl J Med 2007;357:797-805.

Rationale for Extrapolation of General Population Guidelines to CKD patients

2) Therapies in patients with CKD should be as safe, or nearly so, as in the general population. In particular, there should not be additional adverse effects of a specific therapy that limits its usefulness in patients with CKD, either because of altered pharmacokinetics, drug interactions, or increased risk of toxicity to the kidney.

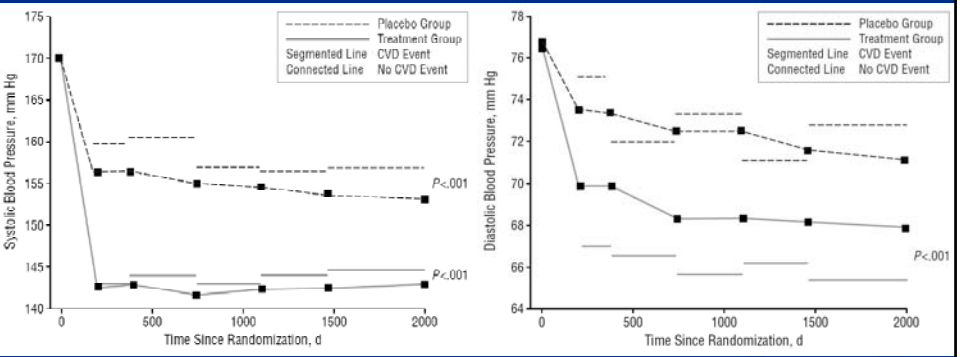
Levey AS et al, NKF Task Force on CVD *Am J Kidney Dis* 32:853-906, 1998

Antihypertensive therapy and diastolic hypotension in CKD



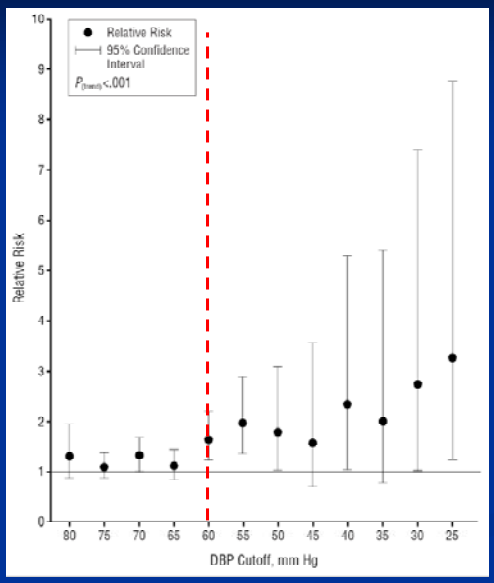
Peralta et al, *Hypertension*. 2007;50:474-480

The role of diastolic blood pressure in ISH



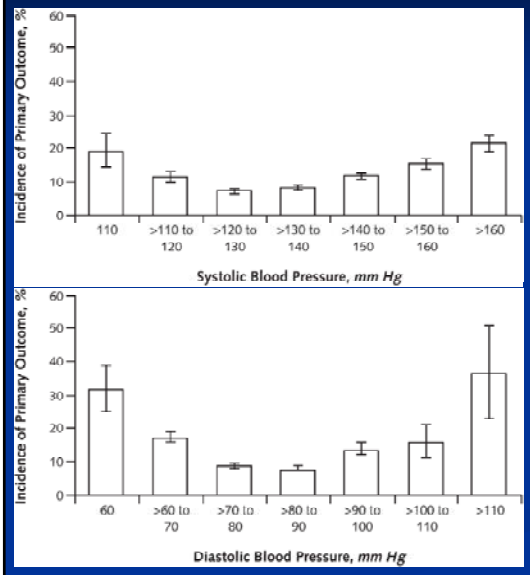
Somes et al, *Arch Intern Med. 1999;159:2004-2009*

The role of diastolic blood pressure in elderly patients with ISH



Somes et al,
Arch Intern Med. 1999;159:2004-2009

Aggressive BP lowering and outcomes in patients with hypertension and CAD



Messerli FH et al,
Ann Intern Med. 2006;144:884-893.

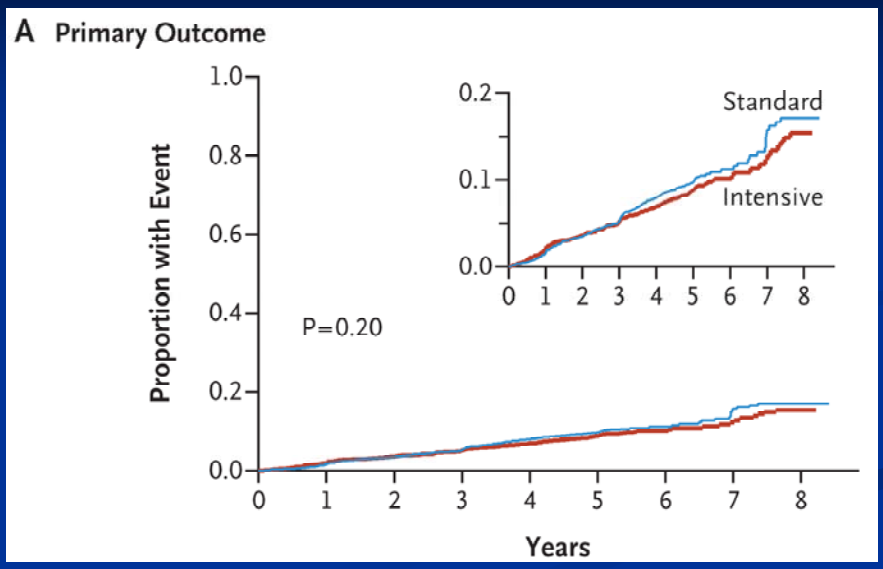
Aggressive BP lowering and outcomes in patients with hypertension and CAD

Messerli FH et al, *Ann Intern Med.* 2006;144:884-893.

Aggressive BP lowering and outcomes in patients with hypertension and CAD

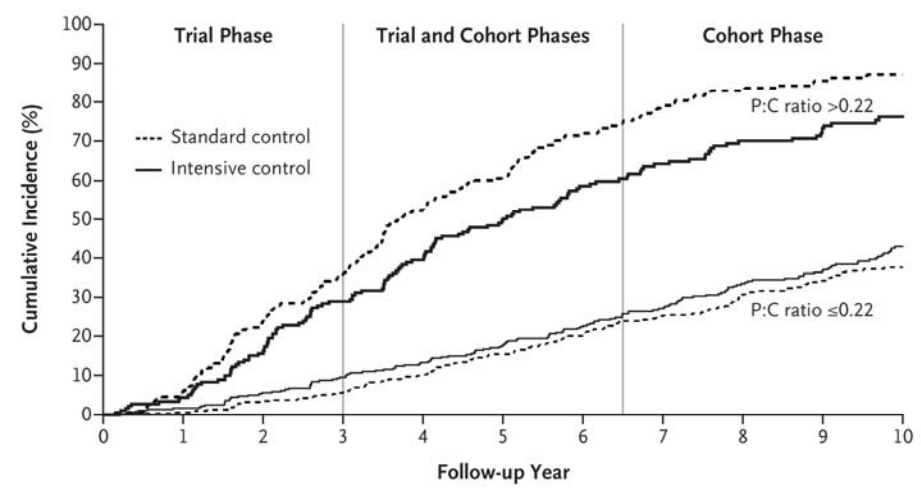
Messerli FH et al, *Ann Intern Med.* 2006;144:884-893.

Intensive BP control in Type 2 DM



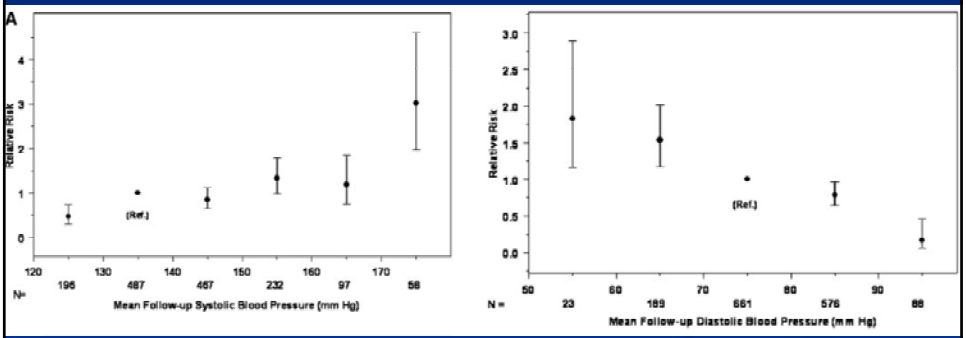
The ACCORD Study Group, N Engl J Med 2010;362:1575-85.

Intensive BP control and outcomes in CKD



Appel LJ et al, N Engl J Med 2010;363:918-29.

Cardiovascular mortality associated with achieved SBP and DBP in CKD



Berl et al, J Am Soc Nephrol 16: 2170–2179, 2005

Conclusions

- Changes in vascular biology and subsequent alterations in autoregulatory capacity make patients with CKD and ESRD more susceptible to the deleterious effects of both high and low BP.
- Epidemiologic studies support the possibility that low blood pressure, especially low diastolic blood pressure may be associated with adverse outcomes.

Conclusions

- Some clinical trials in patients with CKD and patients with characteristics similar to those found in CKD and ESRD (elderly, presence of CVD) support the idea that strict BP control may not be advantageous and that excessive decrease in BP (especially diastolic BP) may be deleterious.

Conclusions

- The applicability of the current general population guidelines for HTN control in patients with CKD and ESRD is questionable.
- The paucity of clinical trials of blood pressure control in CKD and ESRD makes it difficult to establish specific BP goals for this patient population.
- Management of HTN in CKD should be done with consideration of patient characteristics (age, comorbidities) and individual response to therapy (Opinion).