



# **BP CONTROL: AIMING FOR THE OPTIMAL TARGET**

**KDIGO Clinical Practice Guideline for  
Management of Blood Pressure in  
CKD**

**EDGAR V. LERMA, MD, FACP, FASN**

**Clinical Professor of Medicine**

**University of Illinois at Chicago College of Medicine**

**Chicago, IL**

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# GENERAL OUTLINE

- Overview of KDIGO Guidelines
- Scope
- Target BP
  - Albuminuria/ Proteinuria
  - Target Population
- Agent (s) of Choice
- Summary
- Controversies

Future Perspectives



# Grading of Recommendations

Strength of recommendation	1	Strong	Quality of supporting evidence	A	High
	2	Weak or discretionary		B	Moderate
C				Low	
D	Very low				

Grade\*

Clinicians

Level 1  
'We recommend'

Most patients should receive the recommended course of action.

Level 2  
'We suggest'

Different choices will be appropriate for different patients. Each patient needs help to arrive at a management decision consistent with her or his values and preferences.



# Contributors

## Guideline Chairs

- Gavin Becker (Australia)
- David Wheeler (UK)

## Work Group **No Diabetes**

- Mark Sarnak (USA) **Chair**
- Cibele Rodrigues (Brazil)
- Hallvard Holdaas (Transplant)(Norway)

## Work Group **Diabetes**

- Charlie Tomson (UK) **Chair**
- Dick de Zeeuw (Netherlands)
- Guntram Schernthaner (Austria)
- Carmine Zoccali (Italy)

## Work Group **Diet & Lifestyle**

- Vlado Perkovic (Australia) **Chair**
- Toshiro Fujita (ISH) (Japan)
- Suzanne Oparil (JNC8) (USA)
- Susan Furth (Pediatrics) (USA)

## Evidence Review Team

- Katrin Uhlig
- Ashish Upadhyay
- Amy Earley
- Shana Haynes

## KDIGO Staff

- Michael Cheung, Tom Manley
- Sean Slifer

## KDIGO Chairs

- Kai-Uwe Eckardt (Germany)
- Bertram Kasiske (USA)



# Our Scope

- BP targets for stages 1-5 CKD
- **Not CKD 5D (dialysis)**
- Lifestyle modifications that may lower BP
- Choice of antihypertensive agents
- Diabetes and no diabetes, Transplanted, Children (<19years) and Elderly (≥65years)



# Not in scope

- CKD 5D
- How to measure BP\*
- Technical aspects of ambulatory BP monitoring or self measured BP\*
- In depth pharmacological reviews\*
- Management of of renal artery stenosis\*
- Prevention: patients with eGFR  $>60$  ml/min/1.73m<sup>2</sup> without albuminuria\*

\*refer to prior guidelines as appropriate



# Our Scope

- **BP targets** for stages 1-5 CKD
- **Not CKD 5D (dialysis)**
- **Lifestyle modifications** that may lower BP
- **Choice of antihypertensive agents**
- **Diabetes** and no diabetes, **Transplanted, Children (<19years)** and **Elderly (≥65years)**



# Populations of Interest

Adult CKD stages ND 1-5 non-diabetic

Adult CKD stages 1-5 ND diabetic

Transplant recipients

Children (<18 years)

Elderly (>65yrs)

Level of Albuminuria

(Not able to stratify by stage of CKD – because of lack of data and lack of heterogeneity of effect)





# Quality of evidence

**Highest- systematic review of RCTs**

**High- randomised controlled trials**

**Low- Observational data**

**Very low- Other evidence**

Adjusted for study quality, consistency, directness, strength, etc



# KDIGO BP Guideline: Headlines

- **Target BP = Threshold for treatment**
- Individualize treatment
- Balance risk vs. benefit
- **Graded approach** including lifestyle
- Action depends on **+/- albuminuria**
- **ACE/ARB preferred** in specific group
- Cautious approach in the **elderly**

# Lifestyle and pharmacological treatments for lowering blood pressure in CKD ND patients

- **2.1: Individualize BP targets and agents** according to age, co-existent cardiovascular disease and other co-morbidities, risk of progression of CKD, presence or absence of retinopathy (in CKD patients with diabetes) and tolerance of treatment. **(Not Graded)**
- **2.2: Inquire about postural dizziness and check for postural hypotension regularly when treating CKD patients with**
- **BP-lowering drugs. (Not Graded)**



# Lifestyle and pharmacological treatments for lowering blood pressure in CKD ND patients

- **2.3: Encourage lifestyle modification** in patients with CKD to lower BP and improve long-term cardiovascular and other outcomes:
- **2.3.1: We recommend achieving or maintaining a healthy weight (BMI 20 to 25). (1D)**
- **2.3.2: We recommend lowering salt intake to < 90 mmol (< 2 g) per day of sodium (corresponding to 5 g of sodium chloride), unless contraindicated. (1C)**

## Lifestyle and pharmacological treatments for lowering blood pressure in CKD ND patients

- **2.3.3:** We recommend undertaking an **exercise program** compatible with cardiovascular health and tolerance, aiming for **at least 30 minutes 5 times per week.** (1D)
- **2.3.4:** We suggest limiting alcohol intake to no more than two standard drinks per day for men and no more than one standard drink per day for women. (2D)

## Blood pressure management in CKD ND patients without diabetes mellitus

- **3.1:** We recommend that non-diabetic adults with CKD ND and **urine albumin excretion < 30 mg per 24 hours** (or equivalent\*) whose **office BP is consistently > 140 mm Hg systolic or > 90 mm Hg diastolic** be treated with BP-lowering drugs to maintain a BP that is consistently  $\leq 140$  mm Hg systolic and  $\leq 90$  mm Hg diastolic. **(1B)**

# Categories for Albuminuria

To allow assessment of RCTs where albuminuria or proteinuria was measured in different ways, and to enable recommendations based on these categories:

Albumin Excretion mg/day	ACR mg/mmol	PCR mg/mmol	Dipstick
<b>&lt;30</b>	<b>&lt;3</b>	<b>&lt;15</b>	<b>negative</b>
<b>30-300</b>	<b>3-30</b>	<b>15-49</b>	<b>1+</b>
<b>&gt;300</b>	<b>&gt;30</b>	<b>&gt;50</b>	<b>2-3+</b>

It is acknowledged that this brings approximations and inaccuracies depending on gender, age and other factors, but it is a pragmatic strategy.

## Blood pressure management in CKD ND patients without diabetes mellitus

- **3.2:** We suggest that **non-diabetic adults with CKD ND and urine albumin excretion of 30 to 300 mg per 24 hours (or equivalent\*)** whose **office BP is consistently > 130 mm Hg systolic or > 80 mm Hg diastolic** be treated with BP-lowering drugs to maintain a BP that is consistently  $\leq 130$  mm Hg systolic and  $\leq 80$  mm Hg diastolic. **(2D)**



## Blood pressure management in CKD ND patients without diabetes mellitus

- **3.3:** We suggest that **non-diabetic adults with CKD ND and urine albumin excretion >300 mg per 24 hours (or equivalent\*)** whose **office BP is consistently > 130 mm Hg systolic or > 80 mm Hg diastolic** be treated with BP-lowering drugs to maintain a BP that is consistently  $\leq 130$  mm Hg systolic and  $\leq 80$  mm Hg diastolic. **(2C)**

# Blood pressure management in CKD ND patients without diabetes mellitus

- **3.4:** We suggest that an **ARB or ACE-I** be used in **non-diabetic adults with CKD ND** and **urine albumin excretion of 30 to 300 mg per 24 hours** (or equivalent\*) in whom treatment with BP-lowering drugs is indicated. **(2D)**
- **3.5:** We recommend that an **ARB or ACE-I** be used in **non-diabetic adults with CKD ND** and **urine albumin excretion > 300 mg per 24 hours** (or equivalent\*) in whom treatment with BP-lowering drugs is indicated. **(1B)**

# Recommendations in CKD without diabetes mellitus

Albuminuria mg/day	BP Target mmHg	Preferred Agent
<30	<140/90 (1B)	None
30-300	<130/80 (2D)	ACEi or ARB (2D)
>300	<130/80 (2C)	ACEi or ARB (1B)

## Blood pressure management in CKD ND patients with diabetes mellitus

- **4.1:** We recommend that adults with **diabetes and CKD ND** with **urine albumin excretion < 30 mg per 24 hours** (or equivalent\*) whose **office BP is consistently >140 mm Hg systolic or > 90 mm Hg diastolic** be treated with BP-lowering drugs to maintain a BP that is consistently  $\leq 140$  mm Hg systolic and  $\leq 90$  mm Hg diastolic. **(1B)**

## Blood pressure management in CKD ND patients with diabetes mellitus

- **4.2:** We suggest that adults with **diabetes and CKD ND** with **urine albumin excretion >30 mg per 24 hours (or equivalent\*)** whose **office BP is consistently > 130 mm Hg systolic or > 80 mm Hg diastolic** be treated with BP-lowering drugs to maintain a BP that is consistently  $\leq 130$  mm Hg systolic and  $\leq 80$  mm Hg diastolic. **(2D)**

## Blood pressure management in CKD ND patients with diabetes mellitus

- **4.3:** We suggest that an **ARB** or **ACE-I** be used in adults with **diabetes** and **CKD ND** with **urine albumin excretion of 30 to 300 mg per 24 hours** (or equivalent\*). **(2D)**
- **4.4:** We recommend that an **ARB** or **ACE-I** be used in adults **with diabetes** and **CKD ND** with **urine albumin excretion > 300 mg per 24 hours** (or equivalent\*). **(1B)**

# Recommendations in CKD with diabetes mellitus

Albuminuria mg/day	BP Target mmHg	Preferred Agent
<30	<140/90 (1B)	None
30-300	<130/80 (2D)	ACEi or ARB (2D)
>300	<130/80 (2D)	ACEi or ARB (1B)

# Annals of Internal Medicine

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## Review

### Systematic Review: Blood Pressure Target in Chronic Kidney Disease and Proteinuria as an Effect Modifier

Ashish Upadhyay, MD; Amy Earley, BS; Shana M. Haynes, DHSc; and Katrin Uhlig, MD, MS

Three trials with a total of 2272 participants were included. Lower blood pressure target of <130/80 mm Hg no more beneficial than a target of <140/90 mm Hg. Participants in the low target groups had a slightly higher rate of adverse events. Lower target may be beneficial in subgroups with albuminuria.





**Prognosis of CKD by GFR  
and Albuminuria Categories:  
KDIGO 2012**

				Persistent albuminuria categories Description and range		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				<30 mg/g <3 mg/mmol	30-300 mg/g 3-30 mg/mmol	>300 mg/g >30 mg/mmol
GFR categories (ml/min/1.73m <sup>2</sup> ) Description and range	G1	Normal or high	≥90			
	G2	Mildly decreased	60-89			
	G3a	Mildly to moderately decreased	45-59			
	G3b	Moderately to severely decreased	30-44			
	G4	Severely decreased	15-29			
	G5	Kidney failure	<15			

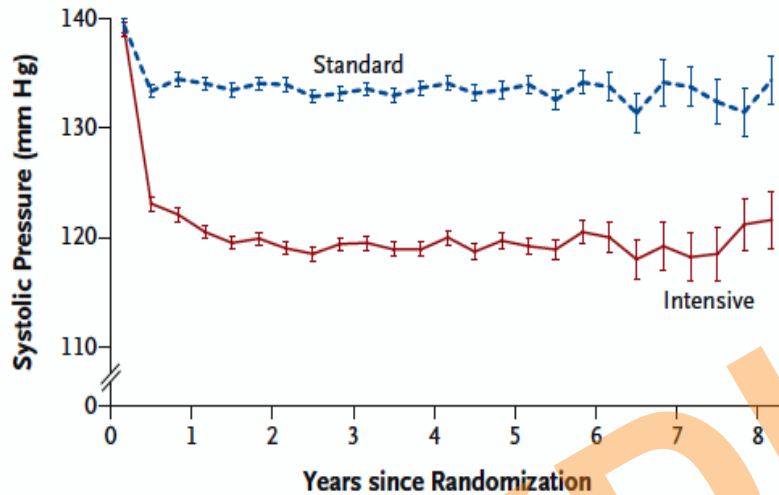
# ACCORD BP

- 4733 Type 2 DM, with vascular disease (40 yr), or risk ( $\geq 55$  yr),  $<80$  yr.
- Cr not  $>1.5$  mg/dL, proteinuria  $<1$ g/day.
- RCT SBP  $<140$ mmHg or  $<120$ mmHg
- Also RCT of control of glucose and other factors

Cushman et al NEJM 2010; 362; 1575-1585



# ACCORD



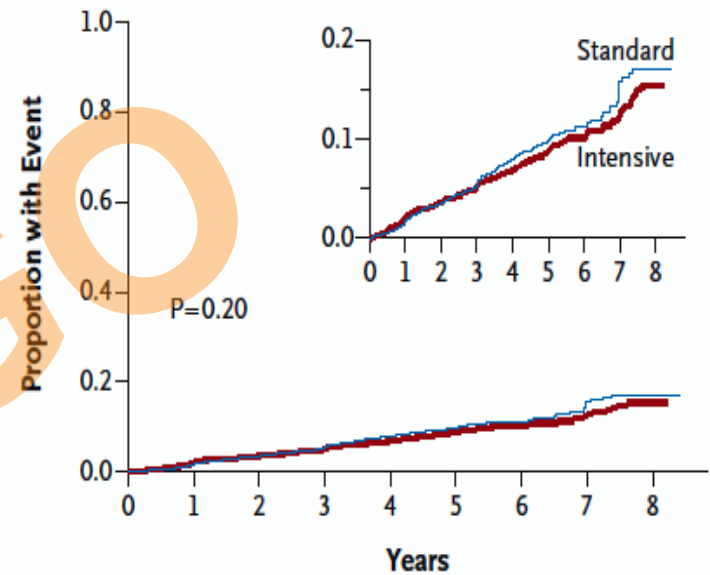
## Mean No. of Medications Prescribed

Intensive	3.2	3.4	3.4	3.5	3.5	3.5	3.4	3.4
Standard	1.9	2.1	2.1	2.2	2.2	2.3	2.3	2.3

## No. of Patients

Intensive	2174	2071	1973	1792	1150	445	156	156
Standard	2208	2136	2077	1860	1241	504	203	201

## A Primary Outcome



## No. at Risk

Intensive	2362	2273	2182	2117	1770	1080	298	175	80
Standard	2371	2274	2196	2120	1793	1127	358	195	108



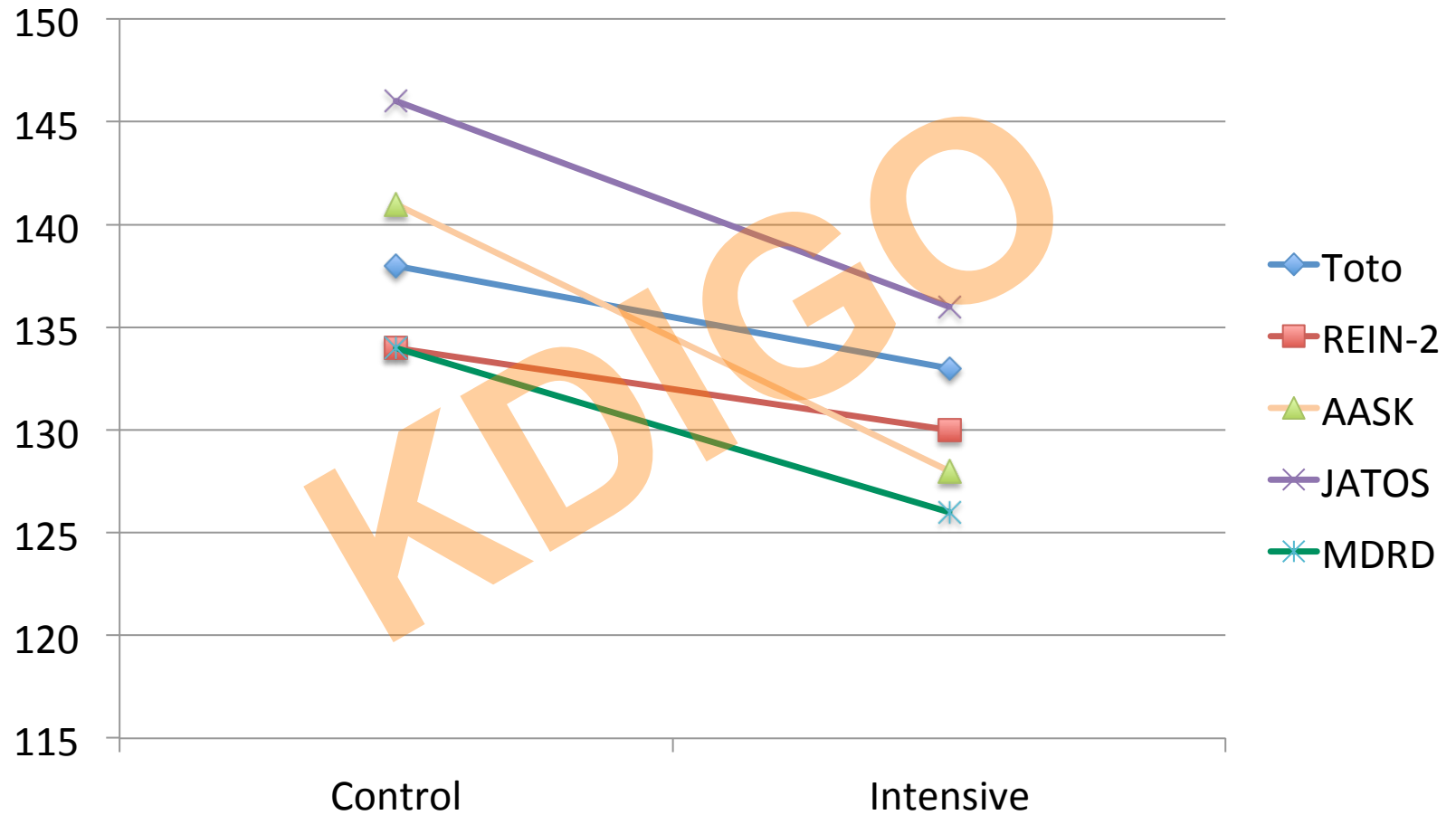
# ACCORD: Primary & Secondary Outcomes

	Intensive Events (%/yr)	Standard Events (%/yr)	HR (95% CI)	P
Primary	208 (1.87)	237 (2.09)	0.88 (0.73-1.06)	0.20
Total Mortality	150 (1.28)	144 (1.19)	1.07 (0.85-1.35)	0.55
Cardiovascular Deaths	60 (0.52)	58 (0.49)	1.06 (0.74-1.52)	0.74
Nonfatal MI	126 (1.13)	146 (1.28)	0.87 (0.68-1.10)	0.25
Nonfatal Stroke	34 (0.30)	55 (0.47)	0.63 (0.41-0.96)	0.03
Total Stroke	36 (0.32)	62 (0.53)	0.59 (0.39-0.89)	0.01

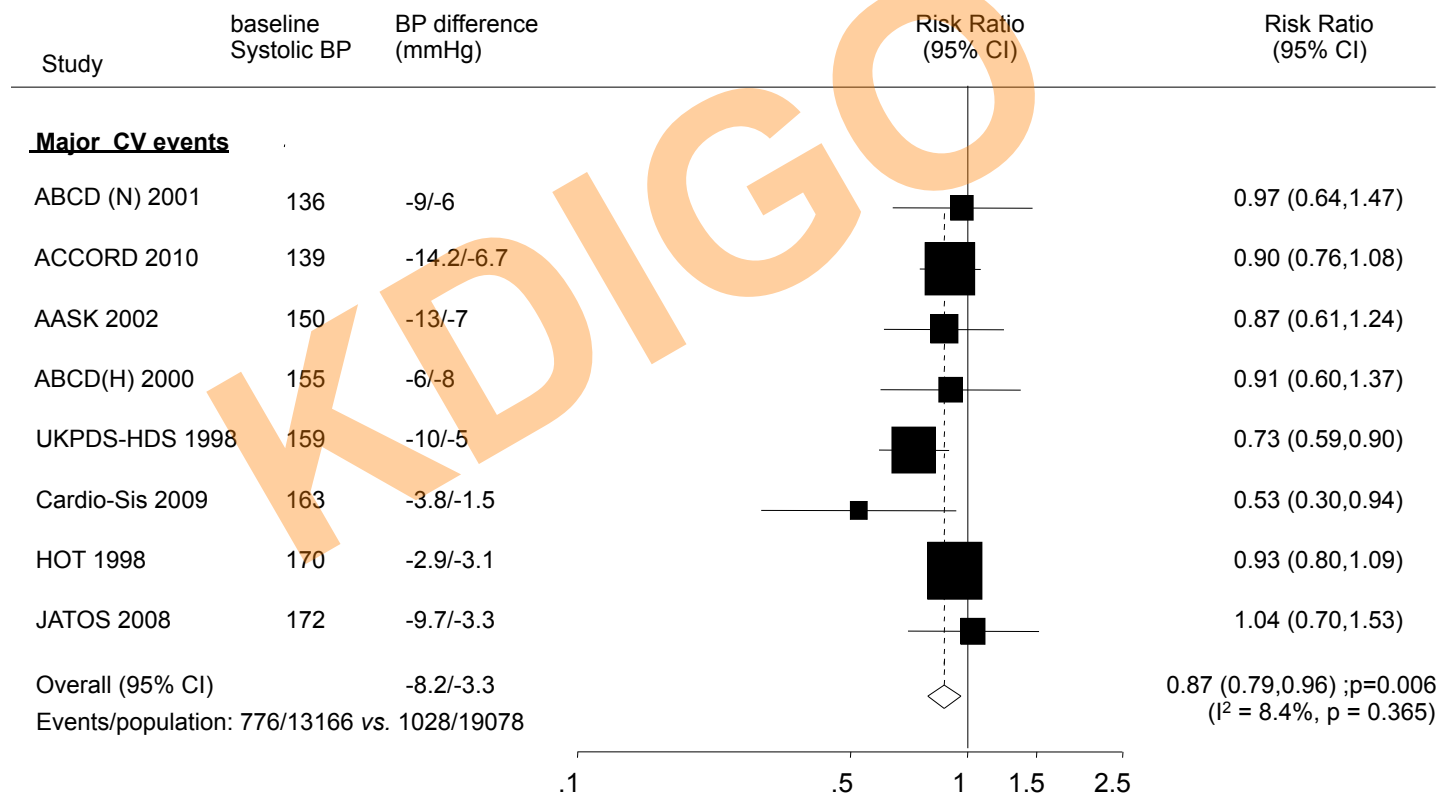
Serious adverse events attributed to medications : 3.3% vs. 1.27%  $p < 0.001$   
(mainly hypotension, hyperkalemia, arrhythmias)



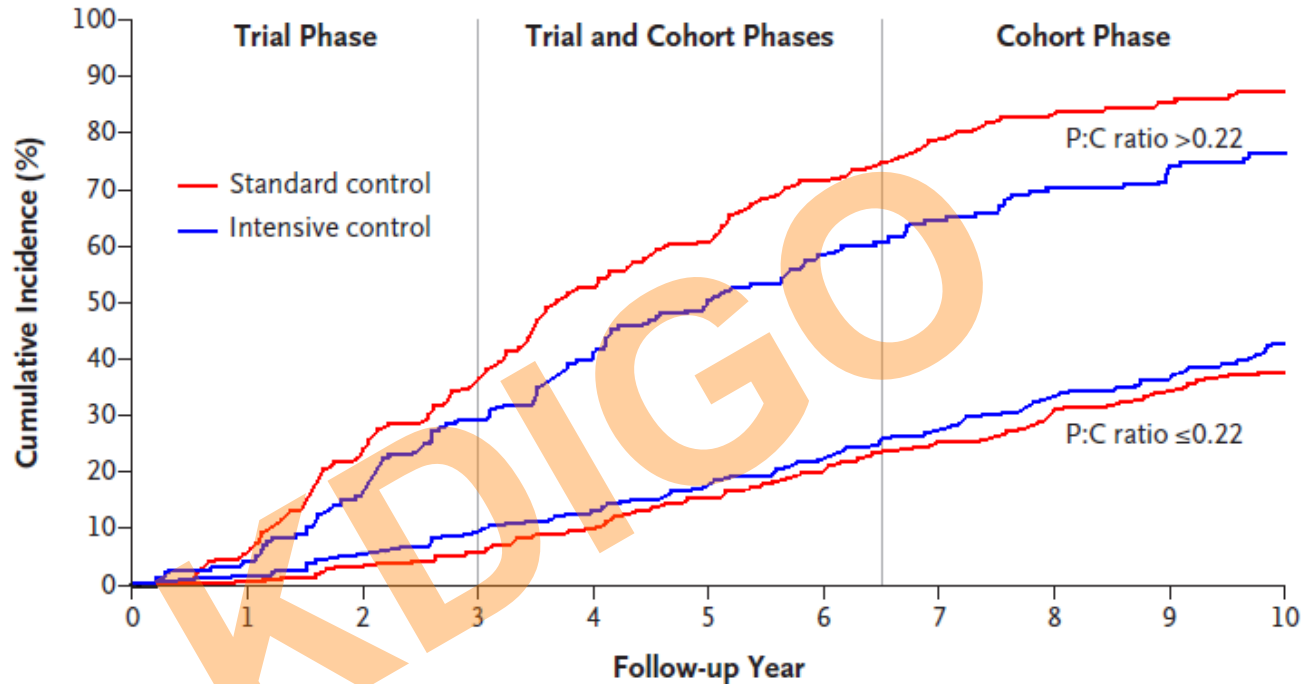
# BP differences- Intensity trials



# Intensive BP lowering and CV events



# AASK: Cumulative incidence of composite primary outcome



N=1094

## P:C Ratio >0.22

Standard control	176	165	134	113	81	66	45	32	26	22	13
Intensive control	181	172	151	128	109	87	67	56	47	40	25

## P:C Ratio ≤0.22

Standard control	376	373	362	353	332	302	267	234	214	196	128
Intensive control	357	350	335	321	306	282	254	228	206	189	128



## ESKD or death stratified by level of proteinuria: AASK

	All Patients		Urinary protein-to-creatinine ratio $\leq 0.22\text{g/g}$		Urinary protein-to-creatinine ratio $> 0.22\text{g/g}$	
	HR (95% CI)	P Value	HR (95% CI)	P Value	HR (95% CI)	P Value
<b>Trial Phase</b>	0.84 (0.66-1.07)	0.16	0.98 (0.66-1.47)	0.94	<b>0.76</b> <b>(0.56-1.04)</b>	<b>0.09</b>
<b>Cohort Phase</b>	0.86 (0.67-1.12)	0.27	1.22 (0.87-1.72)	0.25	<b>0.55</b> <b>(0.37-0.84)</b>	<b>0.005</b>
<b>Both Phases</b>	0.85 (0.71-1.02)	0.08	1.12 (0.87-1.45)	0.39	<b>0.67</b> <b>(0.52-0.87)</b>	<b>0.002</b>

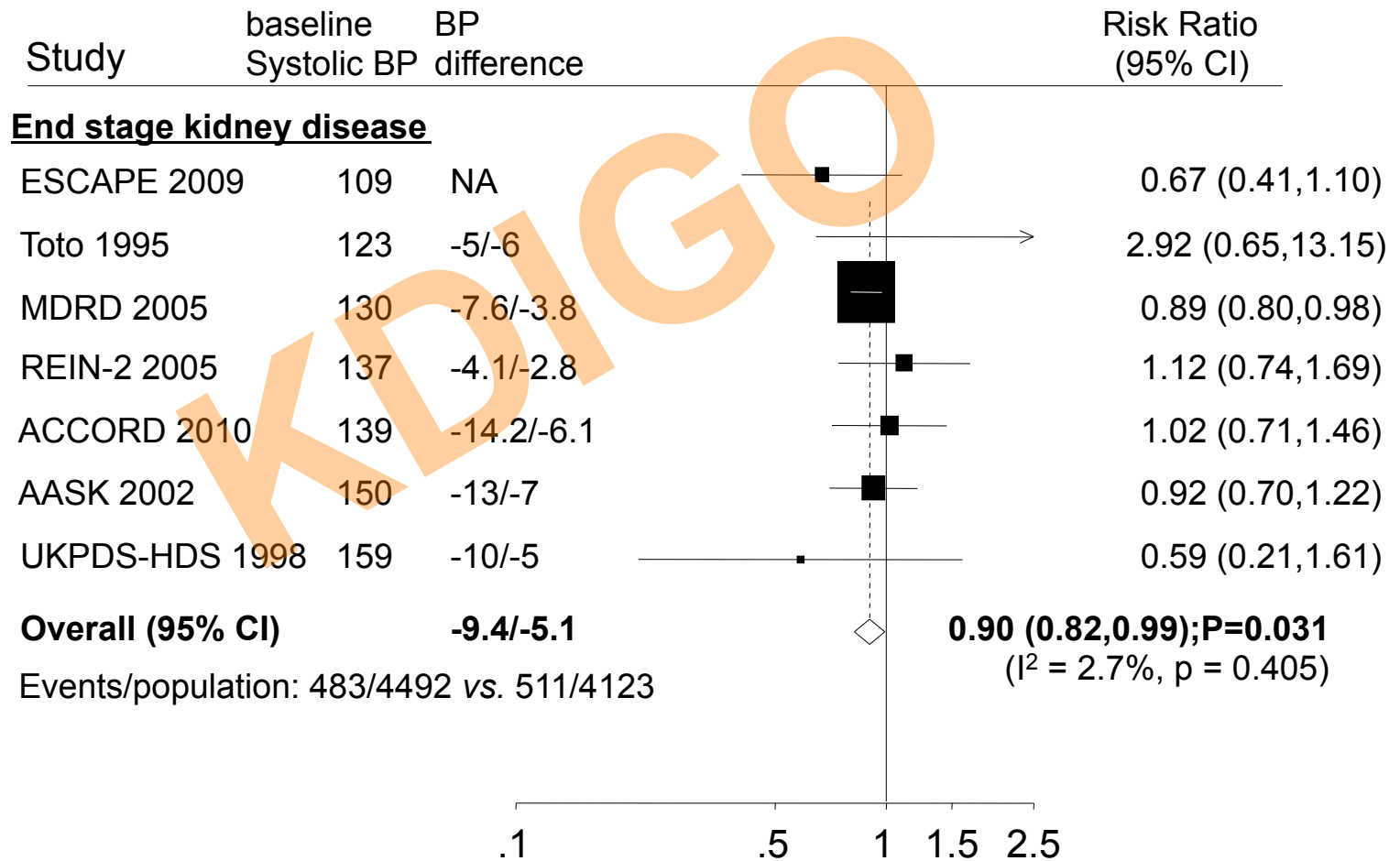
N=1094

AASK: Appel et al. *NEJM* 2010

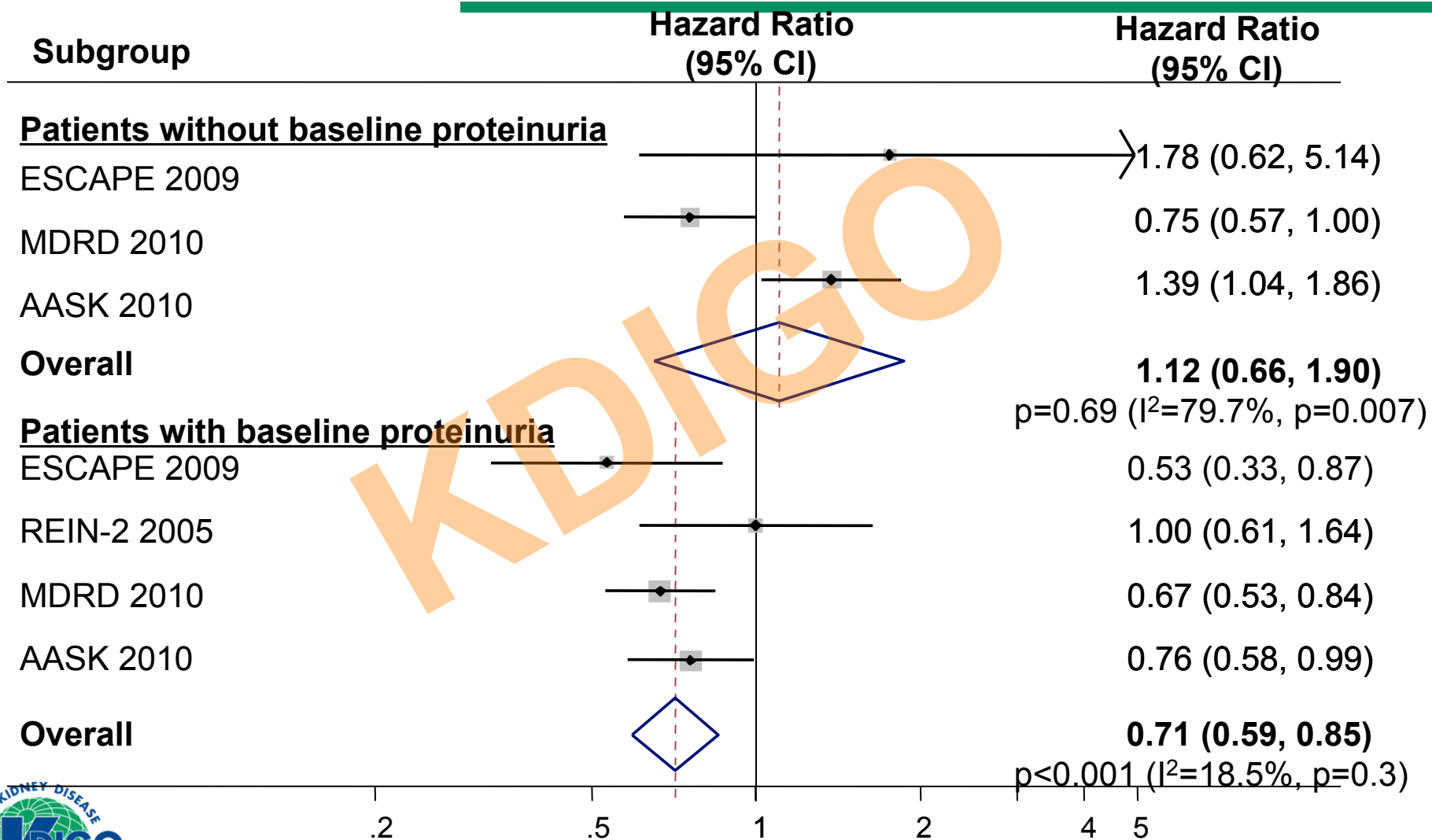




# Intensive BP lowering and ESKD

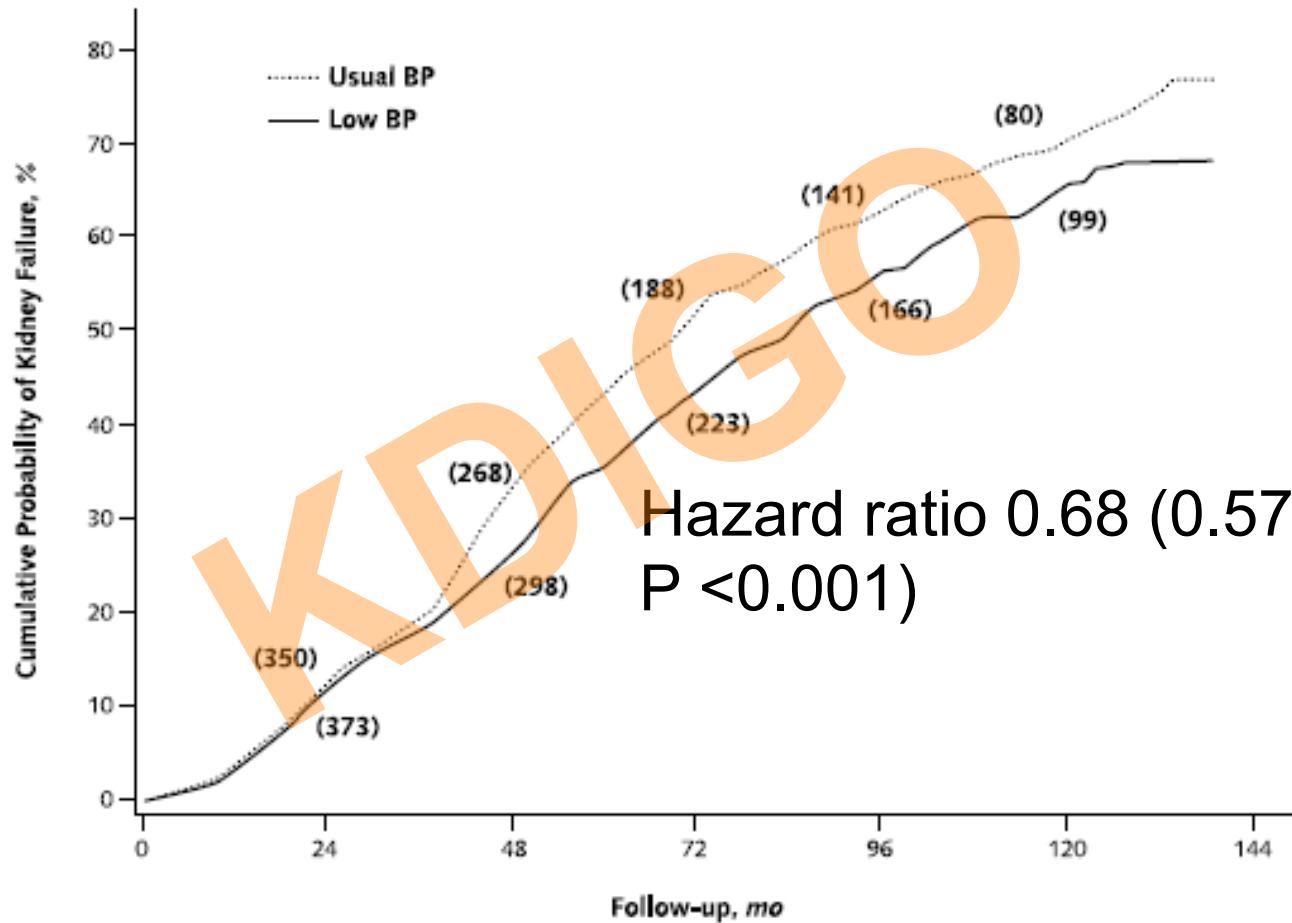


# Subgroup analysis for ESKD by baseline proteinuria (0.3g/day)

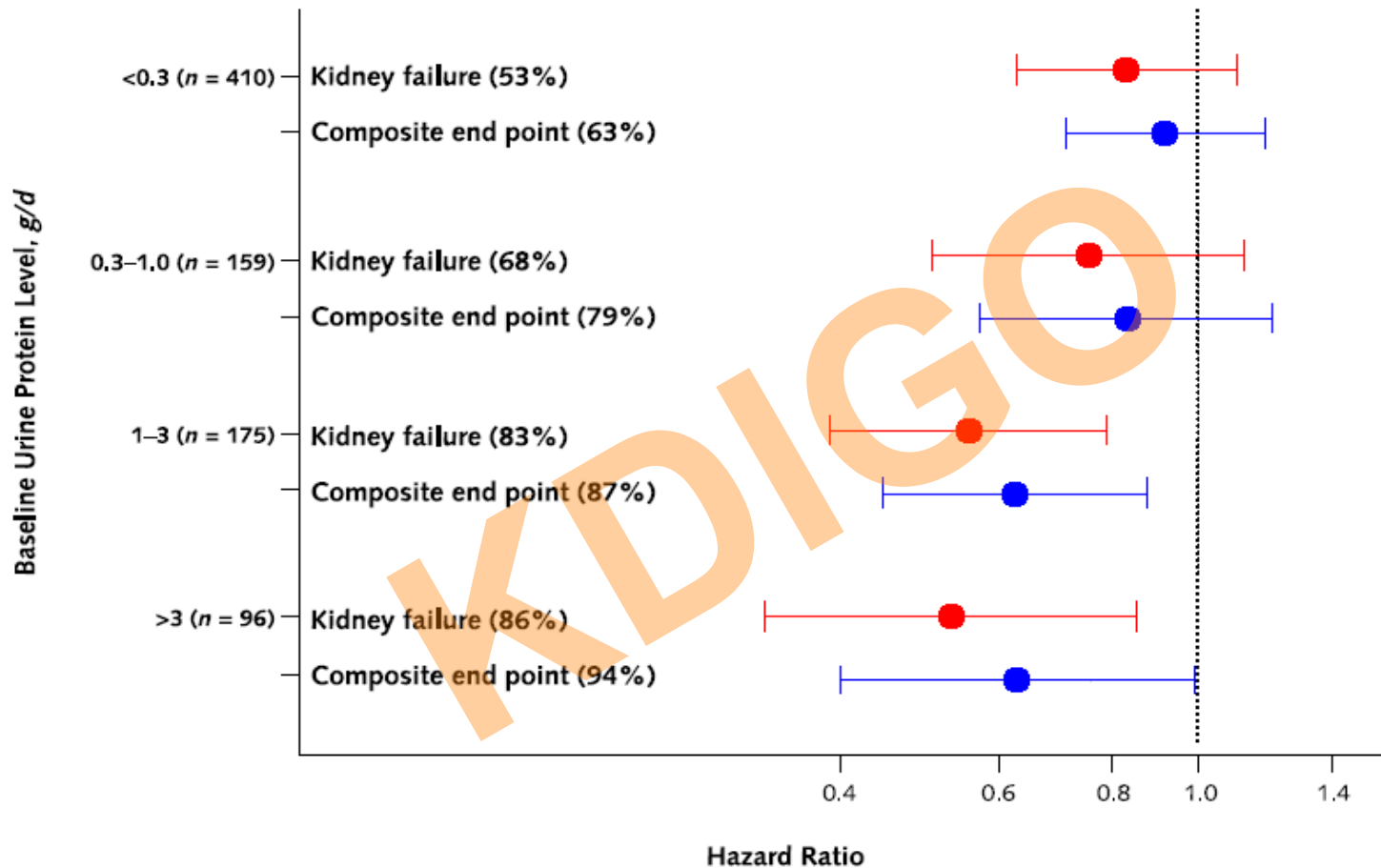


# BP and kidney failure

## MDRD long term follow up



# Adjusted hazard ratios for low BP vs. usual BP by baseline urine protein level: MDRD



P for interaction  
0.09



# Blood pressure management in kidney transplant recipients (CKD T)

- **5.1:** We suggest that **adult kidney transplant recipients** whose office BP is consistently  $> 130$  mm Hg systolic or  $> 80$  mm Hg diastolic be treated to maintain a BP that is consistently  $\leq 130$  mm Hg systolic and  $\leq 80$  mm Hg diastolic, irrespective of the level of urine albumin excretion. (2D)

# Blood pressure management in kidney transplant recipients (CKD T)

- **5.2:** In adult kidney transplant recipients, choose a BP-lowering agent after taking into account the time after transplantation, use of **calcineurin inhibitors**, presence or absence of persistent **albuminuria**, and other co-morbid conditions. **(Not Graded)**

# Blood pressure management in children with CKD ND

- **6.1:** We recommend that in children with CKD ND, BP-lowering treatment is started when BP is consistently above the 90th percentile for age, sex, and height. **(1C)**

# Blood pressure management in children with CKD ND

- **6.2:** We suggest that in **children with CKD ND** (particularly those with **proteinuria**), BP is lowered to consistently achieve systolic and diastolic readings less than or equal to the 50th percentile for age, sex, and height, unless achieving these targets is limited by signs or symptoms of hypotension. **(2D)**
- **6.3:** We suggest that an ARB or ACE-I be used in children with CKD ND in whom treatment with BP-lowering drugs is indicated, irrespective of the level of proteinuria. **(2D)**



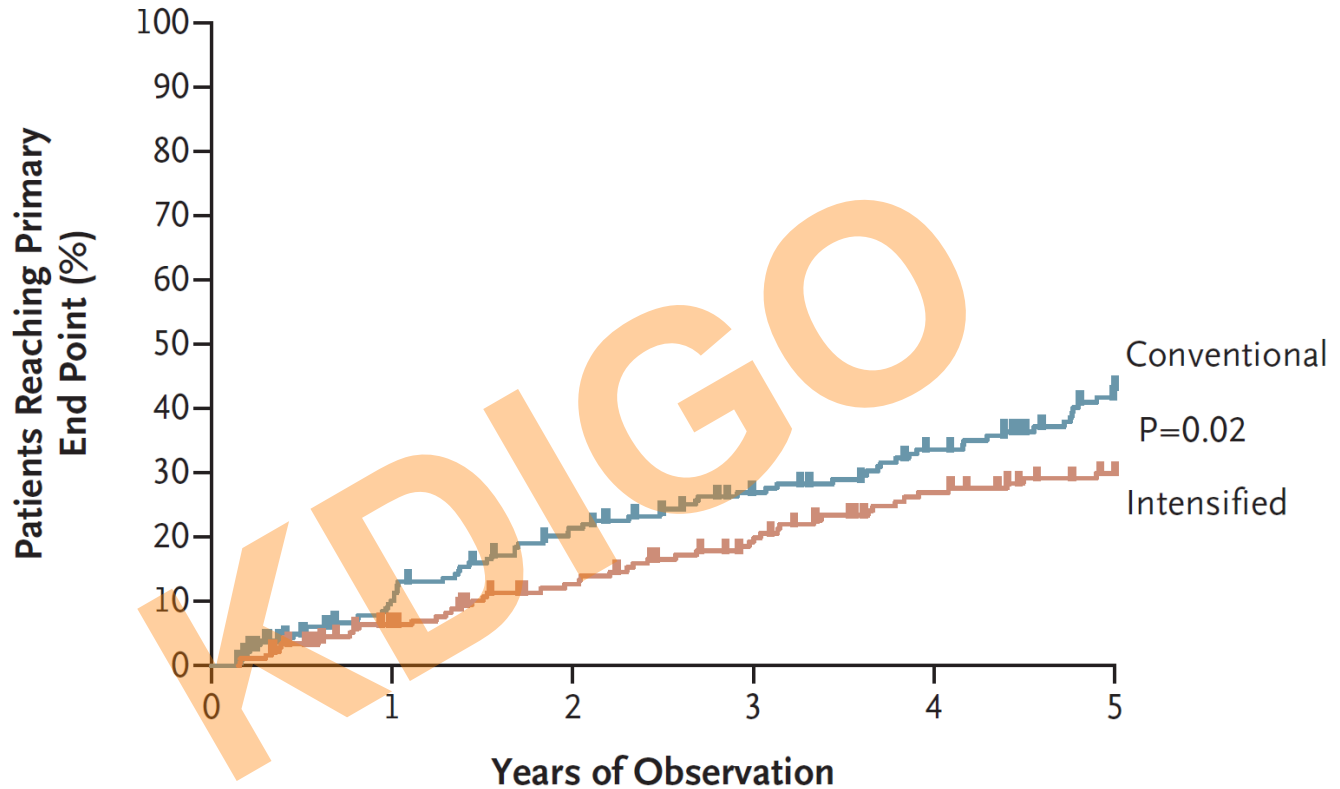
# Children – ESCAPE TRIAL

- 3-18 years, N = 385
- All on ramipril
- 24hr Ambulatory BP: 50<sup>th</sup> percentile (Intensive BP control) vs. 50-95 percentile (Conventional BP control)
- 5 year follow-up
- **Primary end points:** ESKD or 50% reduction in GFR
- **Secondary end points:** BP, GFR, Urinary protein.



# ESCAPE – primary end-point: ESKD or 50% reduction in Schwartz eGFR

All Patients



No. at Risk

Intensified

Conventional

182	167	152	142	135	126	119	110	102	97	90
190	168	154	142	131	122	112	107	97	86	75



*Kidney Disease: Improving Global Outcomes*

Wuhl NEJM 2009; 361, 1639-1650

# Blood pressure management in children with CKD ND

- **7.1:** Tailor BP treatment regimens in **elderly patients with CKD ND** by carefully considering age, co-morbidities and other therapies, with gradual escalation of treatment and close attention to adverse events related to BP treatment, including electrolyte disorders, acute deterioration in kidney function, orthostatic hypotension and drug side effects. **(Not Graded)**

# BP in Elderly

Populations studies: Age specific BP versus Vascular Mortality  
Metanalysis from 1 million adults in 61 prospective studies

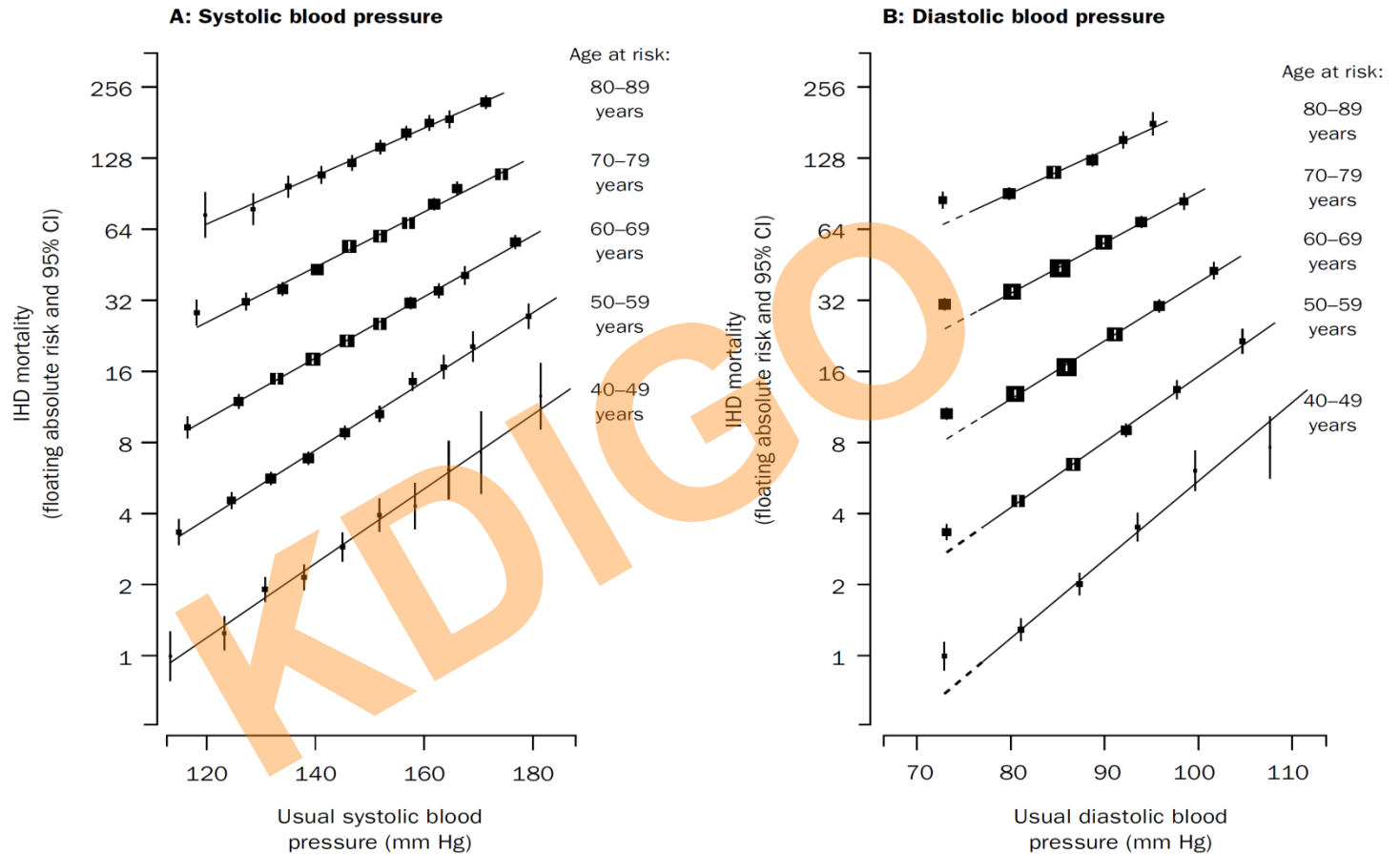
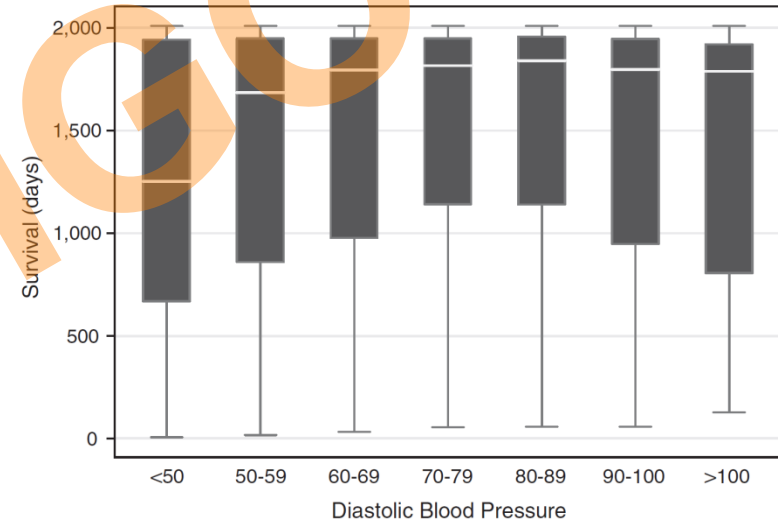
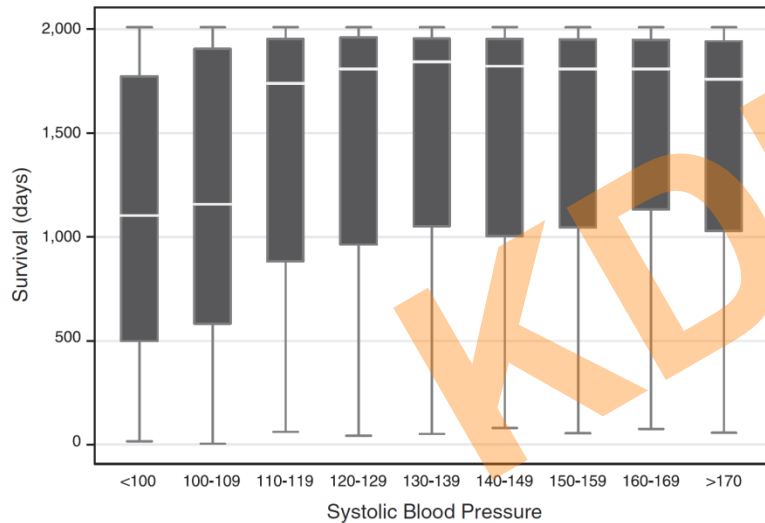
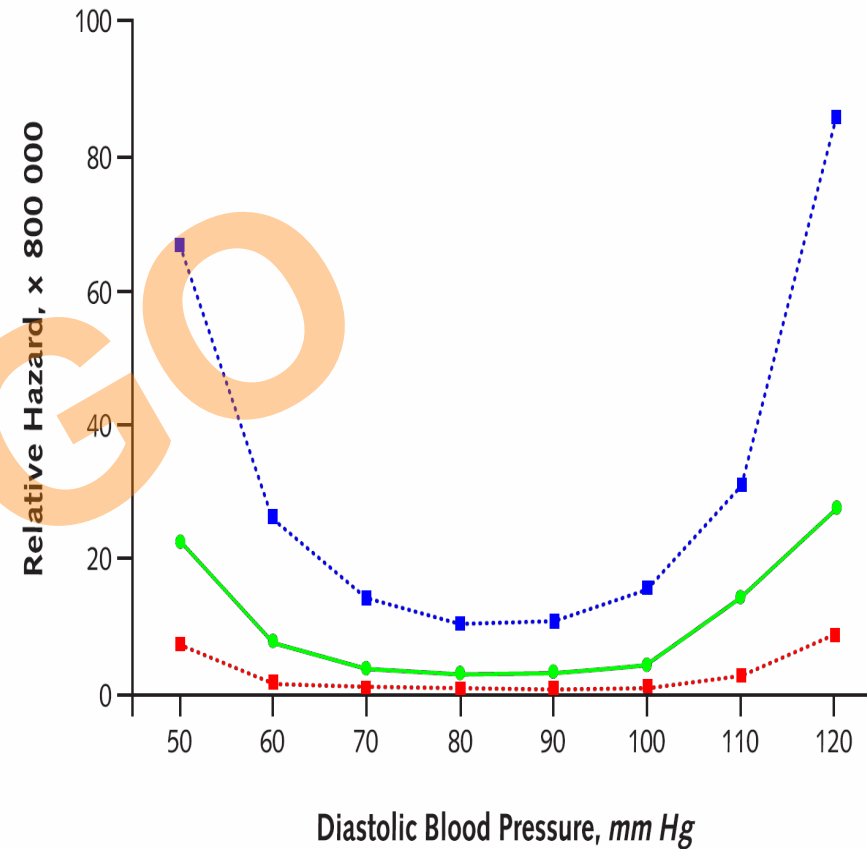
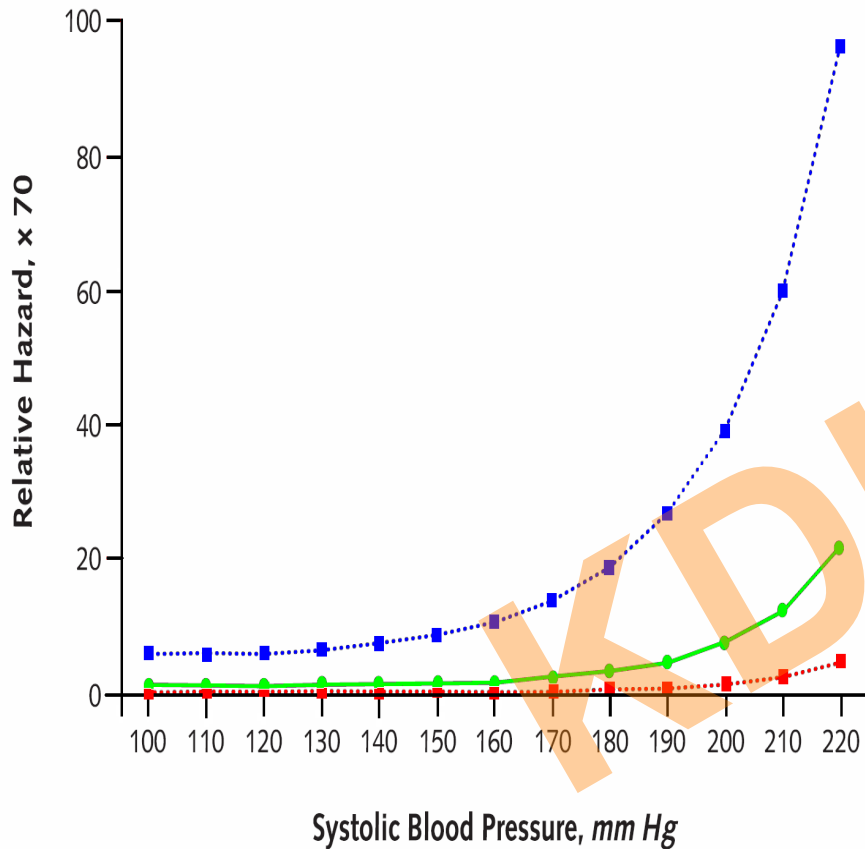


Figure 4: **Ischaemic heart disease (IHD) mortality rate in each decade of age versus usual blood pressure at the start of that decade**  
Conventions as in figure 2.

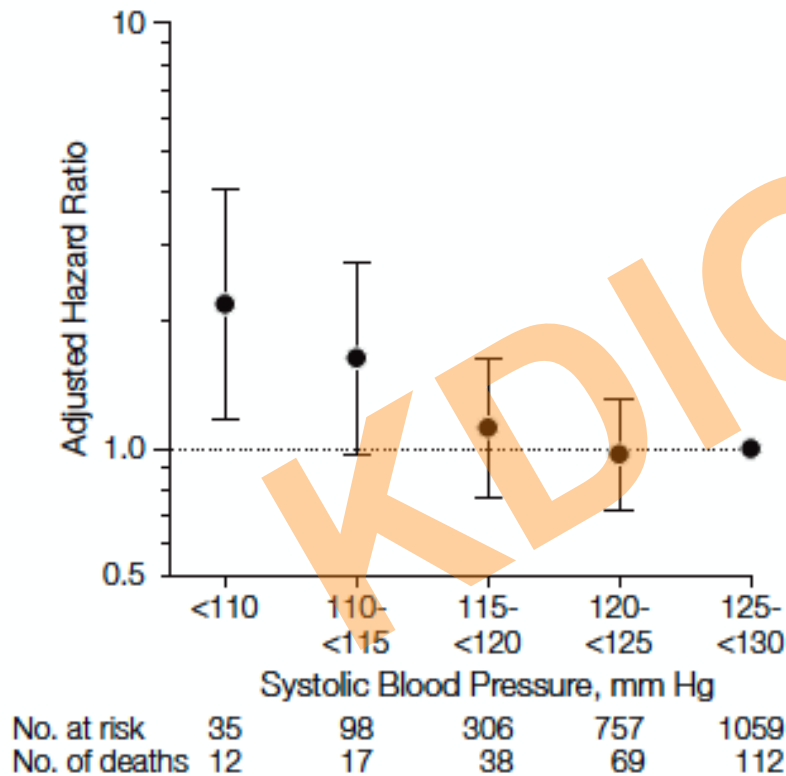
# Elderly males (>80yrs) on treatment: BP vs. Survival



# Patients with coronary artery disease and hypertension: Post hoc analysis of the INVEST Trial



# INVEST: DM2, age>50, CAD: achieved SBP and outcome

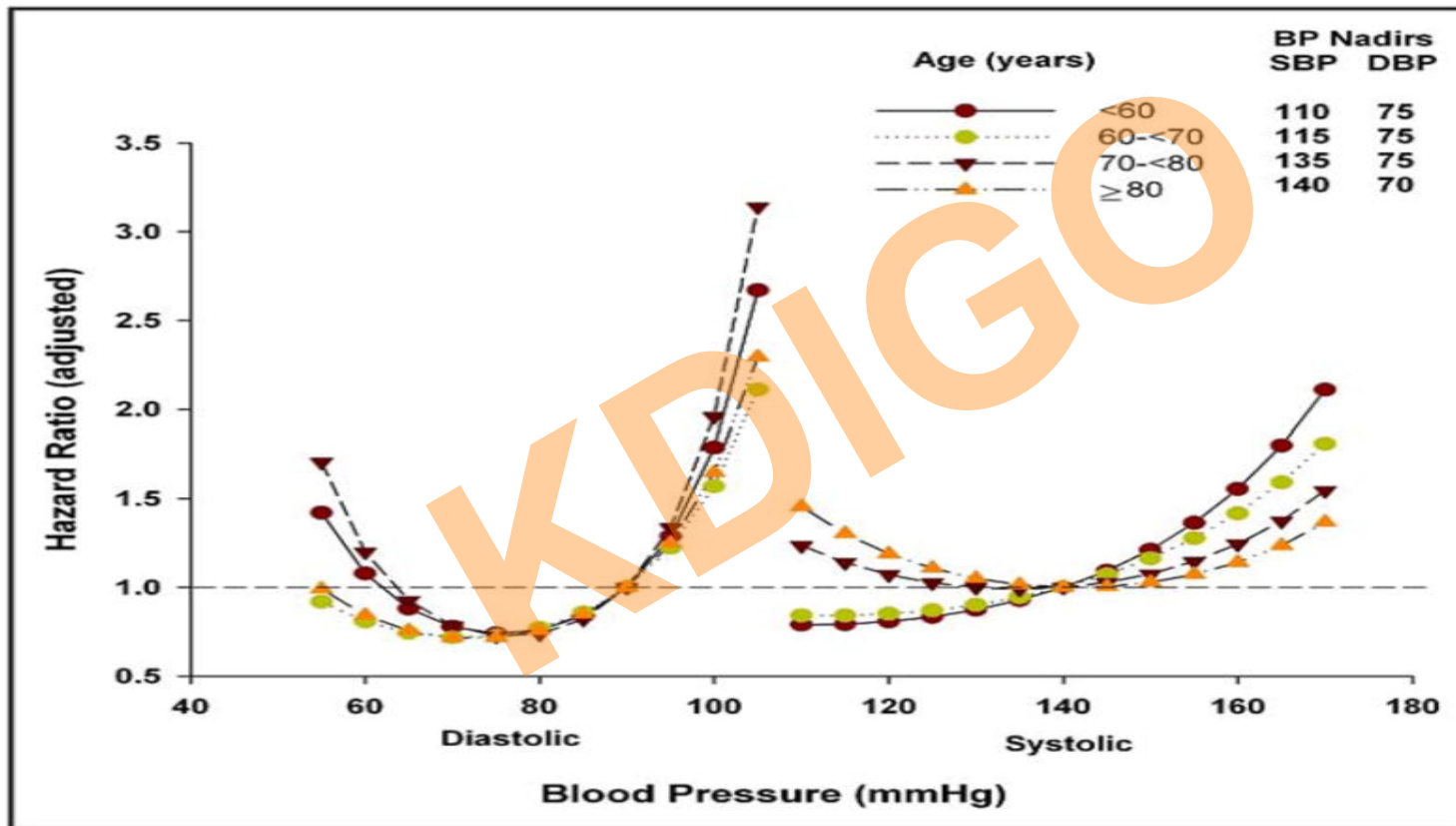


INVEST: n=22,576 with hypertension and coronary artery disease, randomised to verapamil, then trandolapril, then hydrochlorothiazide VS atenolol, then hydrochlorothiazide, then trandolapril

N=6400 diabetic participants



# INVEST – Mortality, AMI and stroke vs. BP per age decade





# The whole guideline in one slide

- Target **<140/90 mmHg** for CKD patients without albuminuria
- Lower target (**<130/80 mmHg**) if (any) albuminuria
- Consider lifestyle changes
- **ACE/ARB preferred** if ACR >30 mg/24hr (whether or not diabetes is present)
- Lower target (<130/80mmHg) in transplant recipients
- Tailor treatment depending on co-morbidities
- Take care in the elderly



# BP Target Recommendations in people with CKD (mmHg)

Albuminuria mg/day	BP Target Diabetes	BP Target No diabetes
<30 (A1, normo)	<140/90 (1B)	<140/90 (1B)
30-300 (A2, micro)	<130/80 (2D)	<130/80 (2D)
>300 (A3, macro)	<130/80 (2D)	<130/80 (2C)

# Recommendations in CKD without diabetes mellitus

Albuminuria mg/day	BP Target mmHg	Preferred Agent
<30	<140/90 (1B)	None
30-300	<130/80 (2D)	ACEi or ARB (2D)
>300	<130/80 (2C)	ACEi or ARB (1B)

# Recommendations in CKD with diabetes mellitus

Albuminuria mg/day	BP Target mmHg	Preferred Agent
<30	<140/90 (1B)	None
30-300	<130/80 (2D)	ACEi or ARB (2D)
>300	<130/80 (2D)	ACEi or ARB (1B)

# BP Guidelines: Headlines

## BP targets

- **Non-albuminuric CKD**
  - Target BP: **consistently  $\leq 140/90$  mmHg**
- **Albuminuric and transplant CKD**
  - Target BP: **consistently  $\leq 130/80$  mmHg**

## Drugs

- **Non-albuminuric and transplant CKD**
  - Choice of agent **depends on co-morbidities, other drugs etc**
- **Albuminuric CKD**
  - First agent: **ARB / ACEI preferred**



# Controversies

- 8.1 How should blood pressure be measured?
- 8.2 Is there evidence for a lower limit BP target level?
- 8.3 Should albuminuria reduction be a target for treatment with antihypertensive therapies?
- 8.4 Should we maximise blockade of the renin-angiotensin system (aldosterone antagonists, direct renin inhibitors)?
- 8.5 Should ACE and ARB be discontinued in stage 5 CKD because they compromise residual kidney function?
- 8.6 Should ethnicity, race and genes influence treatment?

# Future perspectives

- Renal data from ACCORD
- **SPRINT trial**
- Need more studies
  - BP lowering in normotensive
  - Target vs non-target approach



Thank You

Diolch Kiitos Sheun umesc Kasih Mamnoon Todah Shnorhakalutun Shokriya Ngnyabonga Dze kuje Dze kuje Shokrun Spaas Mul Ači Xie Gamsahapnida Dekuju/Dekujeme Hvala Ngiyabonga Cam Dze kuje Shokrun Spaas Mul Ači Xie Dank Waad Kop Salamat Merci Gra or al Dhanyavaad Dhanyavaad Xie Dakujem Daw Waad Kop Salamat Merci Gra or al Dhanyavaad Dhanyavaad Xie krap Dhanyavaadalau Takk Te°eküür Dekuju/Dekujeme Hvala Ngiyabonga Cam Dze kuje Shokrun Spaas Mul Ači Xie Dankie Dankie Kruthagnathalu Faleminderit Arigatou Dhonnobaad Gra or al Dhanyavaad Dhanyavaad Xie Tack Grazzi raibh Gracias Nandree Blagodariya Gomapsupnida Fyrir Terima Danke Euxaristo Kun Shukriya Shukriya Or ederim Hain Dhan daa