Update on Blood Pressure Management Goals in CKD

A Moving Target?

Lisa Zhu, BScPhm, ACPR, PharmD
Clinical Pharmacist, Sunnybrook Health Sciences Centre

Disclosure Statement

- No actual or potential Conflict of Interest in relation to this presentation

Objectives

By the end of the session you will be able to:

- Summarize the current recommended blood pressure targets relevant for managing CKD patients
- Discuss the evidence & controversy for BP targets in:
  - Non-diabetic CKD patients
  - Diabetic patients
  - Very elderly patients (≥80 years)

Targets for non-diabetic CKD Patients

Clinical Vignette

72 female with stage 4 CKD (eGFR 22mL/min)

- PMHx: HTN
- Prior clinic visit BP 161/95 mmHg, currently 154/81 mmHg
- Urinary protein 1.18g/24 hours, ACR 86.4 mg/mmol

What is the optimal blood pressure target for non-diabetic CKD patients?

Targets for non-diabetic CKD Patients

PAST to PRESENT

KDOQI Guidelines
Target <130/80 mmHg
Consider lower target if urinary protein >0.5-1g/day

KDIGO Guidelines
Target ≤140/90
If urine albumin excretion 30-300mg/day
Target ≤130/80

1999 — 2004 — 2006 — 2012

CHEP
Target 130/80 mmHg
If urinary protein >1g/day target <125/74

CHEP
Target <130/80 mmHg
Removed lower target of <125/75 for proteinuric patients

CHEP
Target increased to <140/90 mmHg

CMAJ 1999;161(12 Suppl); www.kidney.org
www.hypertension.ca; www.kdigo.org

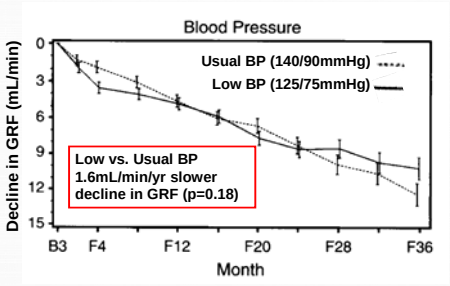
Targets for non-diabetic CKD Patients

CURRENT GUIDELINES

CHEP 2013	KDIGO 2012
• Target blood pressure is <140/90 mm Hg (Grade B)	• Target ≤140/90mmHg (1B) • If urine albumin excretion of >30 mg/24 hours (or equivalent*) target ≤130/80 (2D)

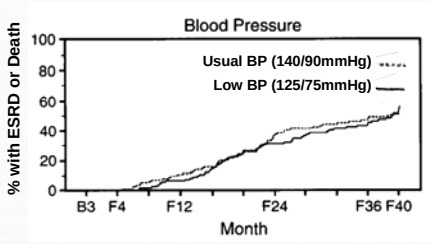
www.hypertension.ca; www.kdigo.org

Modification of Diet in Renal Disease



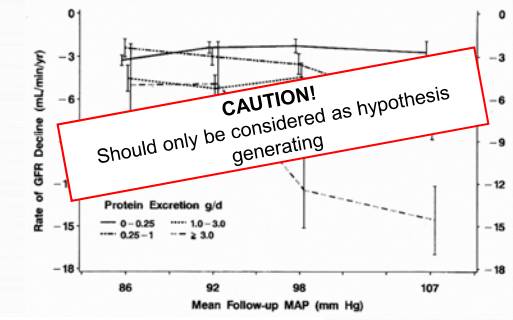
NEJM 1994;330-877-84

Modification of Diet in Renal Disease



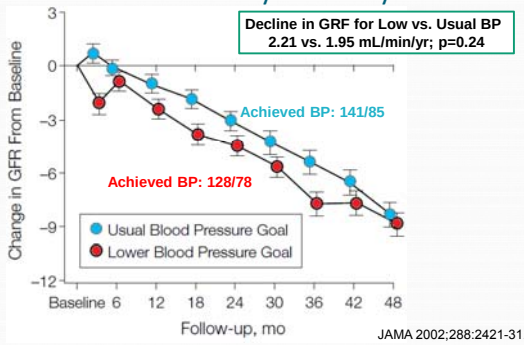
NEJM 1994;330-877-84

MDRD Post-Hoc Analysis



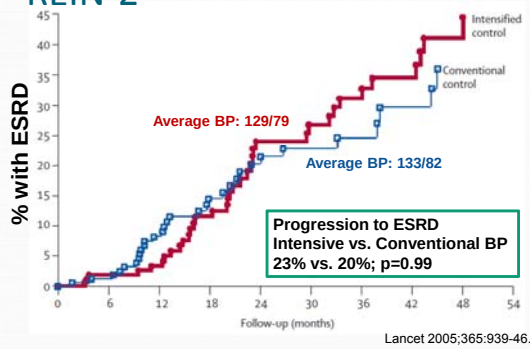
Ann Intern Med 1995;123:754-62.

African American Study of Kidney Disease



JAMA 2002;288:2421-31.

REIN-2



Lancet 2005;365:939-46.

Summary of Trials

	MDRD	AASK	REIN-2
n	840	1094	338
CKD stage	3-5	3	3-4
Target BP	125/75 vs. 140/90	125/75 vs. 140/90	130/80 vs. DBP <90
1º endpoint	Rate of change in GFR	Rate of change in GFR Composite ↓GFR, ESRD or death	ESRD
Kidney failure	HR 0.76 (CI 0.52 to 1.1) P=0.15	Risk reduction, 6% (CI -29% to 31%); p=0.72	23% vs. 20% P=0.99
GRF decline/yr (mL/min)	1.6 less in low target group; p=0.18	0.26 less in low target group; p=0.25	0.22 vs. 0.24; p=0.62
Mortality %	2 (tight) vs. 1; p=ND	2 (tight) vs. 2; p=ND	2 (tight) vs. 1; p=ND
CVD events	RR 1.03 (CI 0.59 to 1.79)	2% vs. 3%; p=ND	--

Ann Intern Med. 2011;154:541-48.

Targets for non-diabetic CKD Patients

Back to the Case…

72 female with stage 4 CKD & proteinuria

What is the optimal blood pressure target? <140/90

Summary of Current Evidence:

- Lower BP targets (i.e. <130/80) do **not** provide greater benefits compared to targeting <140/90
- In patients with proteinuria, evidence of benefit with lower BP targets (<125/75) is low quality (post-hoc or observational data)
- Participants in lower BP target groups required more antihypertensive medications & had slightly higher rates of adverse effects

Ann Intern Med. 2011;154:541-48.

Targets for Patients with Diabetes

Clinical Vignette

64 male with stage 4 CKD (eGFR 19mL/min)

- PMHx: Type II Diabetes, HTN, CAD
- Prior clinic visit BP 145/95 mmHg, currently 143/92 mmHg

What is the optimal blood pressure target for patients with diabetes?

Targets for Patients with Diabetes *CURRENT GUIDELINES*

American Diabetes Association 2013[1]	KDIGO 2012 *(Diabetes with CKD)*	2013 CHEP[2] & Canadian Diabetes Association[3]
• Target for many people with diabetes and HTN should be <140mmHg (CHANGED) • Lower SBP <130 may be appropriate for certain individuals, such as younger patients, if it can be achieved without undue treatment burden	• If urine albumin excretion <30 mg per 24hrs target ≤140/90 (1B) • If urine albumin excretion >30mg per 24hrs target ≤130/80 (2D)	• Target SBP < 130mmHg (Grade C) and DBP < 80mmHg (Grade A). (UNCHANGED)

1. Diabetes Care. 2013;36:S1-S110; 2. CHEP 2013; 3. Can J Diabetes 2013;37(suppl 1):S1-S212.

Diastolic BP Target –HOT Trial

Effects of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension: principal results of the Hypertension Optimal Treatment (HOT) randomised trial

*Lennart Hansson, Alberto Zanchetti, S George Carruthers, Björn Dahlöf, Dag Elmfeldt, Stevo Julius, Joël Ménard, Karl Heinz Rahn, Hans Wedel, Sten Westerling for the HOT Study Group**

STUDY DESIGN
Multi-centre, randomized study; Average follow-up: 3.8 years
PATIENT POPULATION
19, 193 patients aged 50-80 years with HTN and DBP 100-115 mmHg (n=1501 DM patients)
INTERVENTION
Randomized to one of 3 DBP targets: ≤90mmHg, ≤85mmHg or ≤80mmHg

Lancet 1998;351:1755-62.

HOT Trial Results – Diabetes Subgroup

Event	Number of events	Events/ 1000 patient-years	p for trend	Comparison	Relative risk (95% CI)
Major cardiovascular events					
≤90 mm Hg	45	24·4		90 *vs* 85	1·32 (0·84–2·06)
≤85 mm Hg	34	18·6		85 *vs* 80	1·56 (0·91–2·67)
≤80 mm Hg	22	11·9	0·005	90 *vs* 80	2·06 (1·24–3·44)
Major cardiovascular events, including silent myocardial infarction					
≤90 mm Hg	48	26·2		90 *vs* 85	1·13 (0·75–1·71)
≤85 mm Hg	42	23·3		85 *vs* 80	1·42 (0·89–2·26)
≤80 mm Hg	30	16·4	0·045	90 *vs* 80	1·60 (1·02–2·53)
All myocardial infarction					
≤90 mm Hg	14	7·5		90 *vs* 85	1·75 (0·73–4·17)
≤85 mm Hg	8	4·3		85 *vs* 80	1·14 (0·41–3·15)
≤80 mm Hg	7	3·7	0·11	90 *vs* 80	2·01 (0·81–4·97)
All myocardial infarction, including silent cases					
≤90 mm Hg	18	9·7		90 *vs* 85	1·12 (0·57–2·19)
≤85 mm Hg	16	8·7		85 *vs* 80	1·07 (0·53–2·16)
≤80 mm Hg	15	8·1	0·61	90 *vs* 80	1·20 (0·60–2·38)

HOT Trial Results – Diabetes Subgroup

Event	Number of events	Events/ 1000 patient-years	p for trend	Comparison	Relative risk (95% CI)
All stroke					
≤90 mm Hg	17	9·1		90 *vs* 85	1·30 (0·63–2·67)
≤85 mm Hg	13	7·0		85 *vs* 80	1·10 (0·50–2·40)
≤80 mm Hg	12	6·4	0·34	90 *vs* 80	1·43 (0·68–2·99)
Cardiovascular mortality					
≤90 mm Hg	21	11·1		90 *vs* 85	0·99 (0·54–1·82)
≤85 mm Hg	21	11·2		85 *vs* 80	3·0 (1·29–7·13)
≤80 mm Hg	7	3·7	0·016	90 *vs* 80	3·0 (1·28–7·08)
Total mortality					
≤90 mm Hg	30	15·9		90 *vs* 85	1·03 (0·62–1·71)
≤85 mm Hg	29	15·5		85 *vs* 80	1·72 (0·95–3·14)
≤80 mm Hg	17	9·0	0·068	90 *vs* 80	1·77 (0·98–3·21)

- Significant reductions in major CVD events and CVD mortality for patients with target DBP ≤80 vs. ≤90

Systolic BP Target

- Lack of direct evidence from studies for SBP target
- Target of <130 mmHg **not** from RCTs
- Observational studies suggest lower SBP is better
- CHEP guideline recommendation for SBP grade C

ACCORD BP

NEJM 2010;362:1575-85.

STUDY DESIGN
Multi-centre, randomized unblinded study Average follow-up: 4.7 years
PATIENT POPULATION
4733 patients with DM2 age ≥ 40y with CVD
INTERVENTION
Randomized to intensive vs. control: SBP <120mmHg vs. <140mmHg
ENDPOINTS
1° composite: Non-fatal MI, non-fatal stroke or death from CVD

ACCORD BP Results

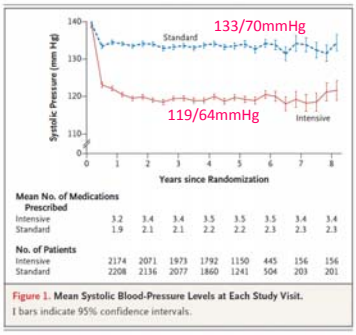


Figure 1. Mean Systolic Blood-Pressure Levels at Each Study Visit. I bars indicate 95% confidence intervals.

NEJM 2010;362:1575-85.

ACCORD BP Results

Table 3. Primary and Secondary Outcomes.

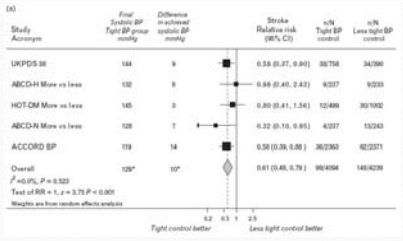
Outcome	Intensive Therapy (N=2363) no. of events	%/yr	Standard Therapy (N=2371) no. of events	%/yr	Hazard Ratio (95% CI)	P Value
Primary outcome*	208	1.87	237	2.09	0.88 (0.73–1.06)	0.20
Prespecified secondary outcomes						
Nonfatal myocardial infarction	126	1.13	146	1.28	0.87 (0.68–1.10)	0.25
Stroke						
Any	36	0.32	62	0.53	0.59 (0.39–0.89)	0.01
Nonfatal	34	0.30	55	0.47	0.63 (0.41–0.96)	0.03
Death						
From any cause	150	1.28	144	1.19	1.07 (0.85–1.35)	0.55
From cardiovascular cause	60	0.52	58	0.49	1.06 (0.74–1.52)	0.74
Primary outcome plus revascularization or nonfatal heart failure	521	5.10	551	5.31	0.95 (0.84–1.07)	0.40
Major coronary disease event†	253	2.31	270	2.41	0.94 (0.79–1.12)	0.50
Fatal or nonfatal heart failure	83	0.73	90	0.78	0.94 (0.70–1.26)	0.67

- Serious adverse events (i.e. syncope, hyperkalemia): 3.3% vs. 1.3%; p=0.001

NEJM 2010;362:1575-85.

Reboldi et al. Meta-Analysis

- 31 trials of anti-HTN vs. placebo with DM patients
- Results for stroke in studies comparing different BP goals:



NEJM 2010;362:1575-85.

Reboldi et al. Meta-Analysis

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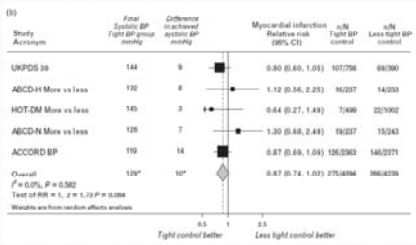


NEJM 2010;362:1575-85.

Bangalore et al. Meta-Analysis

STUDIES
• 13 RCTs enrolling DM2 patients (N=37,736) with follow-up ≥1 year • Achieved intensive SBP ≤135 mmHg vs. achieved ≤140 mmHg
OUTCOME MEASURES
Micro & macro vascular outcomes

- Intensive BP control was associated with:
  - 10% reduction in all-cause mortality (OR 0.9; CI 0.83-0.98)
  - 17% reduction in stroke (OR 0.83; CI:0.73-0.95)
  - 20% ↑ in serious adverse effects (OR 1.2; CI: 1.08 -1.32)
  - No difference in:
    - CVD mortality, myocardial infarction, heart failure

Circulation 2011;123:2799-2810.

Targets for Patients with Diabetes

Back to the Case…

64 male with DM2 & stage 4 CKD (eGFR 19mL/min)

What is the optimal blood pressure target? <130/80

Summary of Current Evidence:

- Significant reductions in major CVD events and CVD mortality for patients with target DBP ≤80 vs. ≤90
- Intensive SBP control **not** shown to reduce major CVD events or CVD mortality
- Intensive SBP control is a trade-off between ↓ risk of stroke vs. potential ↑ in adverse effects (hypotension, syncope, bradycardia)

Targets for Very Elderly Patients

Clinical Vignette

86 male with stage 4 CKD (eGFR 27mL/min)

- PMHx: DM2, HTN
- Sitting BP 145/95mmHg, standing BP 127/85 mmHg with some transient postural dizziness

What is the optimal blood pressure target for very elderly patients?

Targets for Very Elderly (≥80 yrs)

CHEP 2013 Recommendation: the very elderly

III. Choice of Therapy for Adults With Hypertension without Compelling Indications for Specific Agents	New Recommendation for 2013
A) Recommendations for Individuals with Isolated Systolic Hypertension	**ADD:** **In the very elderly (age 80 years and older), the target for systolic BP should be < 150 mmHg (Grade C).**

Antihypertensive drugs in very old people: a subgroup meta-analysis of randomised controlled trials

OBJECTIVE	
Determine if treatment with antihypertensive drugs is beneficial in patients > 80 years	
STUDIES	
7 trials of antihypertensive therapy vs. placebo including patients >80 years (n=1670); average follow-up of 3.5 yrs	
OUTCOME MEASURES	
1^0 endpoint: fatal or non-fatal stroke (*not including TIA)	2^0 endpoints: all cause mortality, CVD death, fatal & non-fatal coronary and CVD events and HF

Lancet 1999;353:793-6.

Results

- Fatal & non-fatal stroke:
  - Relative risk 0.66 (95% CI 0.48-0.92); p=0.014
- Reduction in CVD events and heart failure
- No difference in coronary events
- No difference in CVD death or total mortality
- Trend toward increased total mortality
  - 6% relative excess of death from all causes

Conflicting findings:

- reductions in non-fatal events but potential increase in fatal events

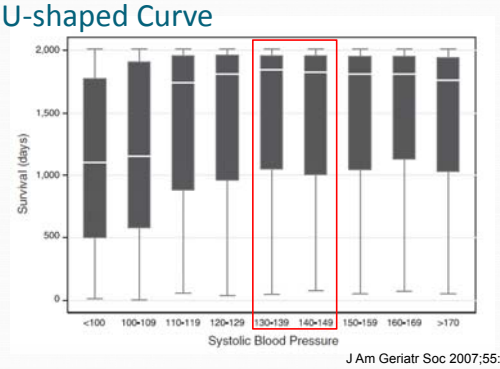
Lancet 1999;353:793-6.

Oates et al.

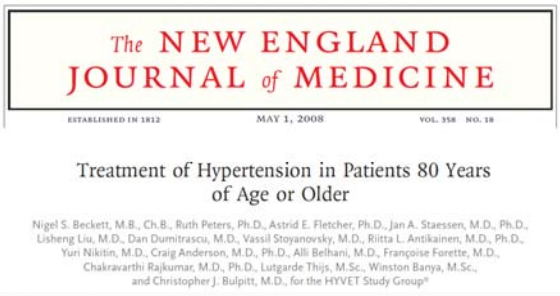
OBJECTIVE
To determine the relationship between BP and all-cause mortality in patients ≥80 yrs
STUDY DESIGN
Retrospective cohort study of 10 Veterans Affairs centers
PATIENT POPULATION
N= 4071 ambulatory patients ≥80 years with HTN
ANALYSIS
Cox regression model

J Am Geriatr Soc 2007;55:383-8.

U-shaped Curve



J Am Geriatr Soc 2007;55:383-8.


The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MAY 1, 2008 VOL. 358 NO. 18

Treatment of Hypertension in Patients 80 Years of Age or Older

Nigel S. Beckett, M.B., Ch.B., Ruth Peters, Ph.D., Astrid E. Fletcher, Ph.D., Jan A. Staessen, M.D., Ph.D., Lisheng Liu, M.D., Dan Dumitrascu, M.D., Vassil Stoyanovsky, M.D., Riitta L. Antikainen, M.D., Ph.D., Yuri Nikitin, M.D., Craig Anderson, M.D., Ph.D., Alli Belhani, M.D., Françoise Forette, M.D., Chakravarthi Rajkumar, M.D., Ph.D., Lutgarde Thijs, M.Sc., Winston Banya, M.Sc., and Christopher J. Bulpitt, M.D., for the HYVET Study Group*

NEJM 2008;358:1887-98

HYVET

STUDY DESIGN	
Multi-centre, RCT, DB study; ITT analysis Median follow-up: 1.8yrs (terminated early at 2nd interim analysis)	
PATIENT POPULATION	
Men & Women ≥80yrs with persistent HTN with SBP ≥160mmHg (N=3845) Exclusions: secondary HTN, hemorrhagic stroke in prior 6 mths, HF, Scr >150umol/L	
TREATMENT	
Indapamide SR 1.5mg vs. placebo +/- perindopril or placebo to achieve a BP target of 150/80 mmHg	
OUTCOME MEASURES	
1^0 endpoint: fatal or non-fatal stroke *not including TIA	2^0 endpoints: all cause mortality, CVD death, death from stroke, death from cardiac causes

NEJM 2008;358(18):1887-98.

Sitting BP 15/6.1mmgHg lower in active treatment group

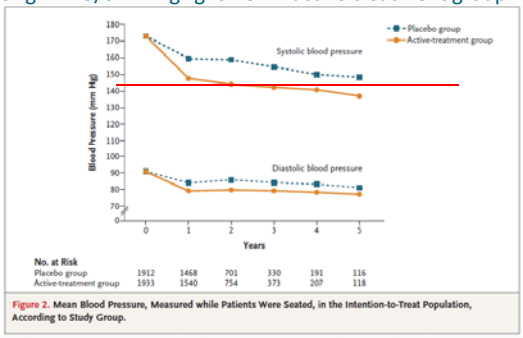


Figure 2. Mean Blood Pressure, Measured while Patients Were Seated, in the Intention-to-Treat Population, According to Study Group.

N EJM. 2008;358(18):1887-98.

Table 2. Main Fatal and Nonfatal End Points in the Intention-to-Treat Population.

End Point	Rate per 1000 Patient-Yr (No. of Events)		Unadjusted Hazard Ratio (95% CI)	P Value
	Active	Placebo		
	no. (%)			
Stroke				
Fatal or nonfatal	12.4 (51)	17.7 (69)	0.70 (0.49–1.01)	0.06
Death from stroke	6.5 (27)	10.7 (42)	0.61 (0.38–0.99)	0.046
Death				
From any cause	47.2 (196)	59.6 (235)	0.79 (0.65–0.95)	0.02
From noncardiovascular or unknown causes	23.4 (97)	28.9 (114)	0.81 (0.62–1.06)	0.12
From cardiovascular cause	23.9 (99)	30.7 (121)	0.77 (0.60–1.01)	0.06
From cardiac cause*	6.0 (25)	8.4 (33)	0.71 (0.42–1.19)	0.19
From heart failure	1.5 (6)	3.0 (12)	0.48 (0.18–1.28)	0.14
Fatal or nonfatal				
Any myocardial infarction	2.2 (9)	3.1 (12)	0.72 (0.30–1.70)	0.45
Any heart failure	5.3 (22)	14.8 (57)	0.36 (0.22–0.58)	<0.001
Any cardiovascular event†	33.7 (138)	50.6 (193)	0.66 (0.53–0.82)	<0.001

NEJM. 2008;358(18):1887-98.

ACCF/AHA 2011 Consensus Document Hypertension in the Elderly

- BP goal of <140/90 mm Hg for very elderly based on expert opinion **not** evidence from clinical trials
- Ideal BP for patients ≥80 years ± comorbid conditions has not been established
- SBP < 140 mm Hg reasonable for most patients ≤79 years
- SBP 140 to 145 mm Hg is acceptable, if tolerated for those ≥80 years
- ↓DBP <65 to 70 mm Hg may increase the risk of cardiovascular events thus keep DBP >65 mm Hg
- Treatment may be withheld in frail patients, those medically unstable or who are approaching ≥ 90 years

J Am Coll Cardiol. 2011;57(20):2037-2114

Targets for Very Elderly Patients

Back to the Case…

86 male with DM2 & stage 4 CKD (eGFR 27mL/min)

What is the optimal blood pressure target? SBP <150

Summary of Current Evidence:

- Previous evidence found conflicting findings of ↓ in non-fatal events with potential ↑ in fatal events
- Epidemiologic evidence suggests U-shaped curve with lower BP targets associated with lower rates of survival
- Exact BP target remains uncertain & based on expert opinion
- HYVET suggests in healthy very elderly patients targeting SBP <150mmHg provides reductions in all cause mortality & CVD events

Summary of Canadian BP Targets

Patient Population	BP Target
Non-diabetic CKD	<140/90
Diabetes	<130/80
Very elderly (≥80)	SBP <150

- **CKD patients:**
  - Lower BP target (125/75 to 130/80) **not** more beneficial than target of <140/90 but associated with ↑ need for medications and risk of side effects
- **Patients with DM:**
  - Intensive BP control is a trade-off between ↓ risk of stroke vs. potential ↑ in adverse effects (hypotension, syncope, bradycardia)
- **Very elderly:**
  - Lower BP targets associated with reduced survival
  - Exact target remains uncertain & based on expert opinion
  - HYVET: targeting SBP <150mmHg provides ↓ in mortality & CVD events

Questions