Retinal arteriolar narrowing and HT

What comes first?

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Debate

Key points to be made

- ABPM is the state-of-the-art method to measure BP (ESH, NICE, CHEP,…)
- The paradigm that retinal arterial narrowing, as index of peripheral arterial resistance, precedes HT mainly originated from 3 retrospective population studies (concurrent *vs.* past BP as correlates of retinal vessel diameter) and 7 prospective population studies (retinal imaging → HT).
  The diagnosis of HT relied on error-prone in-office BP measurement (single reading or the average of only two).
  - NT included masked HT, a high-risk condition;
  - HT included white-coat HT, a low-risk condition.
- Retinal arterial narrowing does not precede, but trails HT. The proposed paradigm can be explained by the limitations of in-office BP measurement.

Debate

Outline of presentation

- HT drives cerebrovascular complications (retina < brain);
- Review of the evidence from population studies:
  - Retrospective (3);
  - Prospective (7);
- ABPM as tool for risk stratification:
  - White-coat HT;
  - Masked HT;
- FLEMENGHO data.

BP is the predominant risk factor for stroke

The retinal microcirculation mirrors the brain

GBD

Conclusions of this section

- The GBD 2012 confirmed the overriding role of HT as the predominant modifiable CV risk factor, in particular for stroke. High BP causes 9.4 million deaths every year—more than half of the estimated 17 million deaths per year attributable to CV disease

  Murray CJL et al. Lancet 2012;380:2063-6

- The retina is an extension of the brain. The proposal that retinal arteriolar narrowing would precede HT is counterintuitive.

Review of the literature

Retrospective and “so-called” prospective studies

REVIEW

Does arteriolar narrowing reflect current or previous BP?

Three retrospective population studies addressed the question whether arterial narrowing occurs in response to *current BP*, or whether it relates to *previous BP*, irrespective of current BP, thereby reflecting persistent arteriolar damage.

- **Atherosclerosis Risk in Community (ARIC) study**
  (*AJE 1999;*150:263-70);
- **Cardiovascular Health Study (CHS)**
  (*Br J Ophtalmol 2002;*86:1007-13);
- **Blue Mountains Eye Study (BMES)**
  (*J Hypertens. 2004;* 22:1543-49).

REVIEW

Conclusion of the retrospective population studies

- Continuous analyses of ARIC, CHS, BMES, demonstrated that "*key*" retinal microvascular traits were closer correlated with concurrent than past BP.

- AV nicking in ARIC and generalised arteriolar narrowing ($<P_{20}$) in CHS were the only of 8 or 4 traits associated with <u>both</u> past and concurrent BP.

REVIEW

Retinal arteriolar narrowing precedes HT!

Seven prospective population studies proposed the hypothesis.

- **Beaver Dam Eye Study (BDES)** (*BMJ;* 2 June 2004);
- **Atherosclerosis Risk in Communities Study (ARIC)** (*Ann Intern Med 2004;*140:248-55);
- **Blue Mountains Eye Study (BMES1)** (*Hypertension 2004;*44:442-7);
- **Rotterdam Study (RS)** (*Hypertension 2006;*47:189-94);
- **Bleu Mountains Eye Study (BMES2)** (*AJE 2008;*168:80-8);
- **Multi-Ethnic Study of Atherosclerosis (MESA)** (J *Hypertens 2009;27*:2386-93);
- **Funagata Study (FS)** (*Microcirculation 2010;*17:94-102).

Tien Yin Wong authored all studies with the exception of the RS.

REVIEW BP measurement

- BP was a single “in-office” reading in BMES and Funagata, or the average of two readings in BDES, ARIC, Rotterdam, and MESA;
- BP was measured, using the error-prone auscultatory approach (without any report on quality assurance, quality control, or number or digit preference*) or with an oscillometric method in MESA.
- The Hawskley random zero sphygmomanometer (BDES, ARIC, Rotterdam) and the oscillometric Dinamap PRO-100 (MESA) did not pass validation.

Lancet 1990; 336:1465-8 // Hypertension 1993;21:632-7 // AJH 2006;19:353-60

* Kuznetsova T, et al. *BPM 2002;*7:215-24–520.

REVIEW Results of prospective studies

Continuous analyses

Maximally adjusted ORs, expressing the HT risk per 1-SD increment in CRAE (MESA, Funagata), AVR (BDES), or both (Rotterdam, BMES), ranged:

- from 1.10 (1.10-1.20) to 1.53 (1.08-2.18) for *CRAE*;
- from 1.10 (1.00-1.20) to 1.31 (1.18-1.45) for *AVR*.

Top *vs.* bottom quantile

Maximally adjusted ORs across thirds (Funagata), fourths (BDES, Rotterdam, MESA) or fifths (ARIC, BMES) ranged:

- from 1.47 (1.01-2.14) to 2.15 (1.58-2.93) for *CRAE*;
- from 1.50 (1.20-2.00) to 2.00 (1.30-3.00) for *AVR*.

CRAE, central retinal arteriolar equivalent; AVR, arteriole-to-venule ratio.

REVIEW Conclusions of this section

- Far reaching conclusions based on poor BP measurement.
- The insight that out-of-the-office BP monitoring is required to characterise an individual's BP was not yet available at the time the reviewed prospective population studies were designed, but it was available at the time of their publication.
- None of the reviewed studies reported on the quality of the in-office (conventional) BP phenotype.*

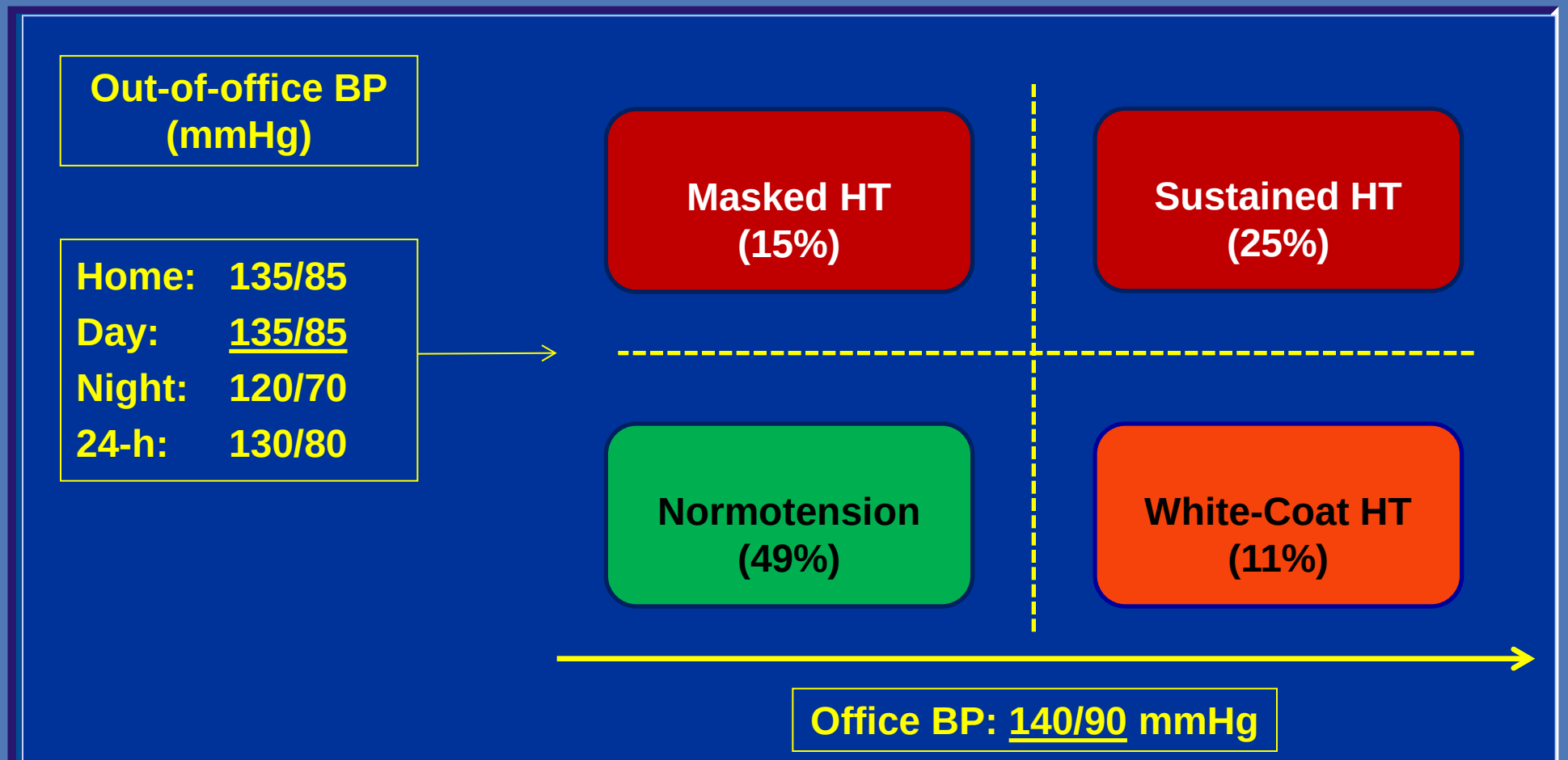
* Kuznetsova T, et al. *BPM 2002;*7:215-24–520.

Ambulatory BP monitoring

State-of-the-art method recommended by ESH, NICE, CHEP,…

Methods

Cross-classification

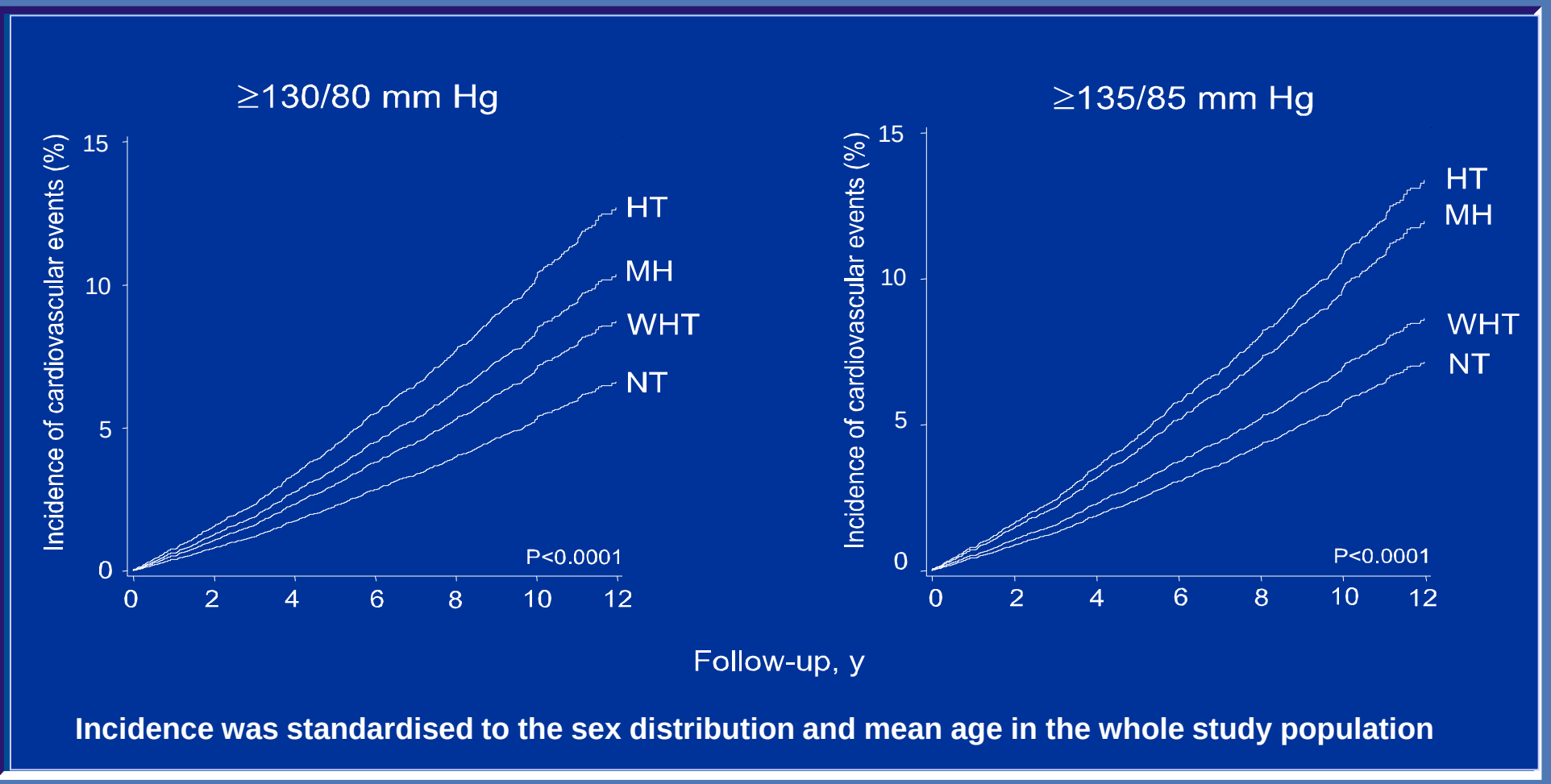


IDACO Populations

3 continents
12 countries
12,854 subjects

IDACO

Incidence of CV events according to the cross classification of conventional and daytime BP

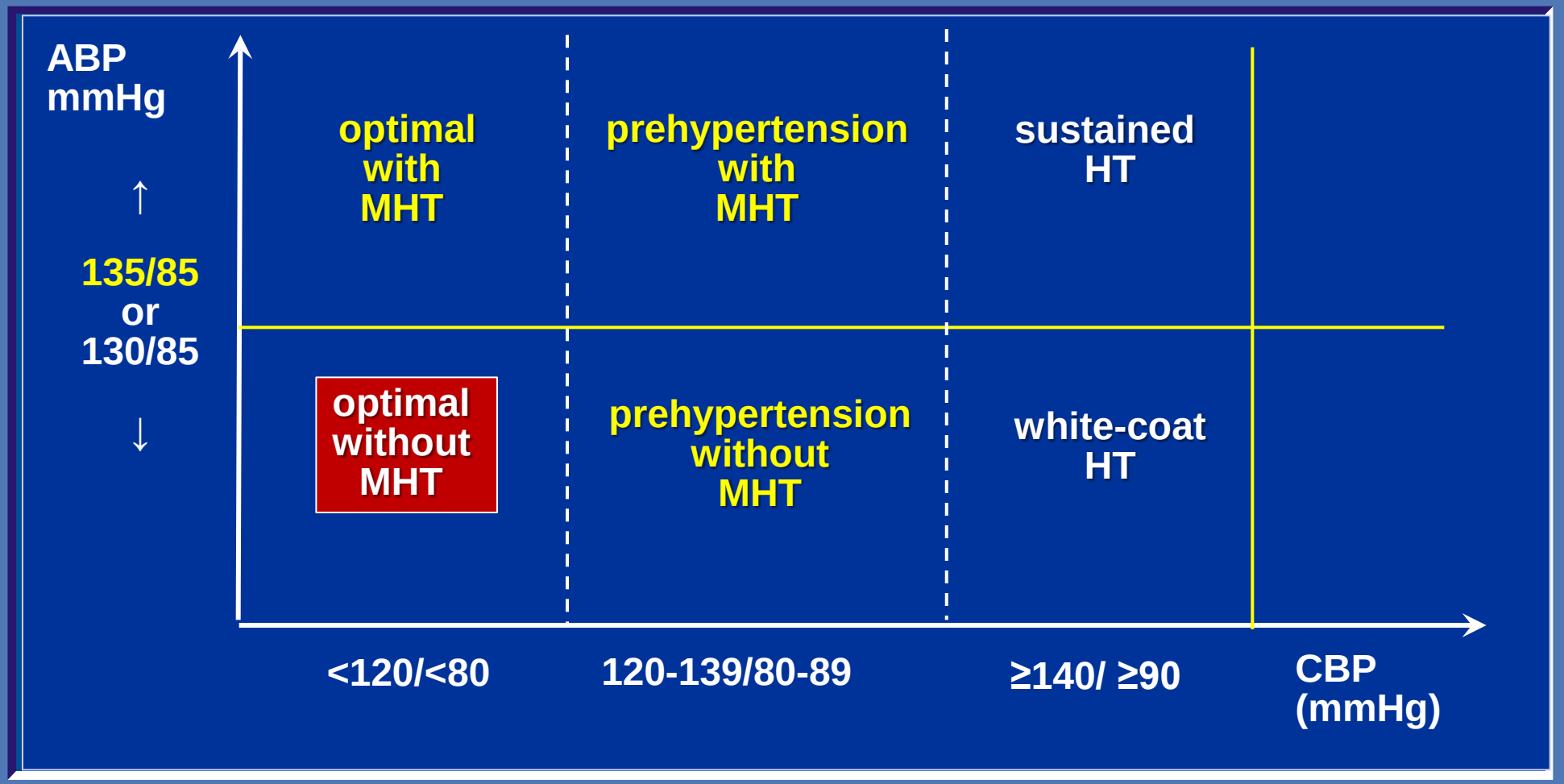


Incidence was standardised to the sex distribution and mean age in the whole study population

Hansen TW et al. *J Hypertens 2007*;25:1554-64

IDACO

Masked HT *vs.* true normotension

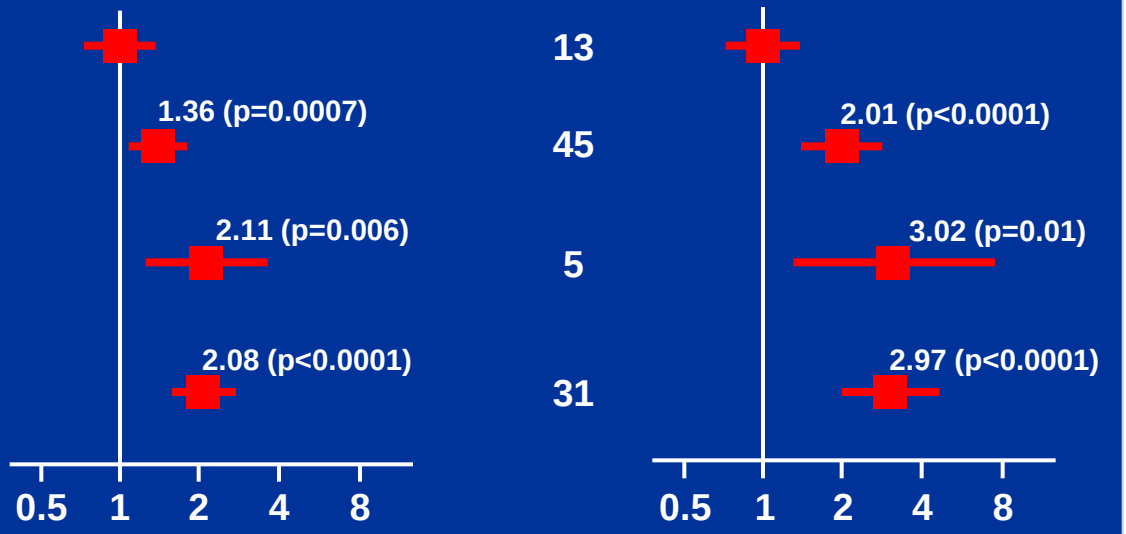


Asayama K et al, PLOS Medicine 2014; doi:10.1371/journal.pmed.1001591.t001

IDACO

HRs (*vs.* NT) associated with daytime masked HT

	No. of subjects	No. of events (CV events)	No. of events (Stroke)
NT	2441	63	13
Pre-HT	2776	129	45
NT with masked HT	198	14	5
Pre-HT with masked HT	900	90	31



Daytime BP ≥135/≥85 mmHg

Brguljan Hitij J et al. *Am J Hypertens 2014*; 27: 956-65

IDACO Conclusions of this section

- CV risk gradually increases from normotension over WCH to MH and sustained HT.
- Over a prolonged period of follow-up, the risk of WCH remains significantly less than that of sustained HT.
- The risk associated with MH almost equals that of sustained HT.

Hansen TW et al. *J Hypertens 2007*; 25: 1554-64 // Brguljan Hitij J et al. *Am J Hypertens 2014*; 27: 956-65

FLEMENGHO data

ABP predicts retinal arteriolar narrowing better than current BP

FLEMENGHO

Objective

To assess in continuous and categorical analyses to what extent conventional BP and daytime ABP “at baseline” predict narrowing of the retinal microvasculature at “follow-up”.

Wei FF, et al. *Hypertension 2016;*68:511–20.

FLEMENGHO

Study population

FLEMENGHO: Flemish study on Environment, Genes and Health Outcomes

- Random selection of families from the general population;
- Recruitment from 1985 until 2004;
- In-office BP (average of five consecutive readings and daytime ABP measured within 7 days at baseline (1989-2008);
- Retinal imaging at FU (2008–2015), post-processed using IVAN software (median FU, 10.5 y).

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Wei FF, et al. *Hypertension 2016;*68:511–20.

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Characteristics (continuous)

Characteristics	Baseline	FU
Age, y	38.2	49.3*
BMI, kg/m^2	24.7	26.4*
Conventional BP		
SBP/DBP, mmHg	121/75	129*/82*
Daytime BP		
SBP/DBP, mmHg	123/76	
TCHOL, mmol/L	5.10	4.95*
BSUG, mmol/L	5.05	4.78*

* p≤0.05 for Δ baseline *vs.* FU.

Wei FF, et al. *Hypertension 2016;*68:511–20.

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Characteristics (categorical)

Characteristics, %	Baseline	Follow-Up
CSMK	21.2	15.8*
CALC	27.1	40.9*
Overweight	32.6	39.0*
Obesity	10.0	18.6*
DM	1.0	3.3*
HT	12.1	29.6*
AHT	8.4	22.2*

* p≤0.05 for Δ baseline *vs.* FU.

Wei FF, et al. *Hypertension 2016;*68:511–20.

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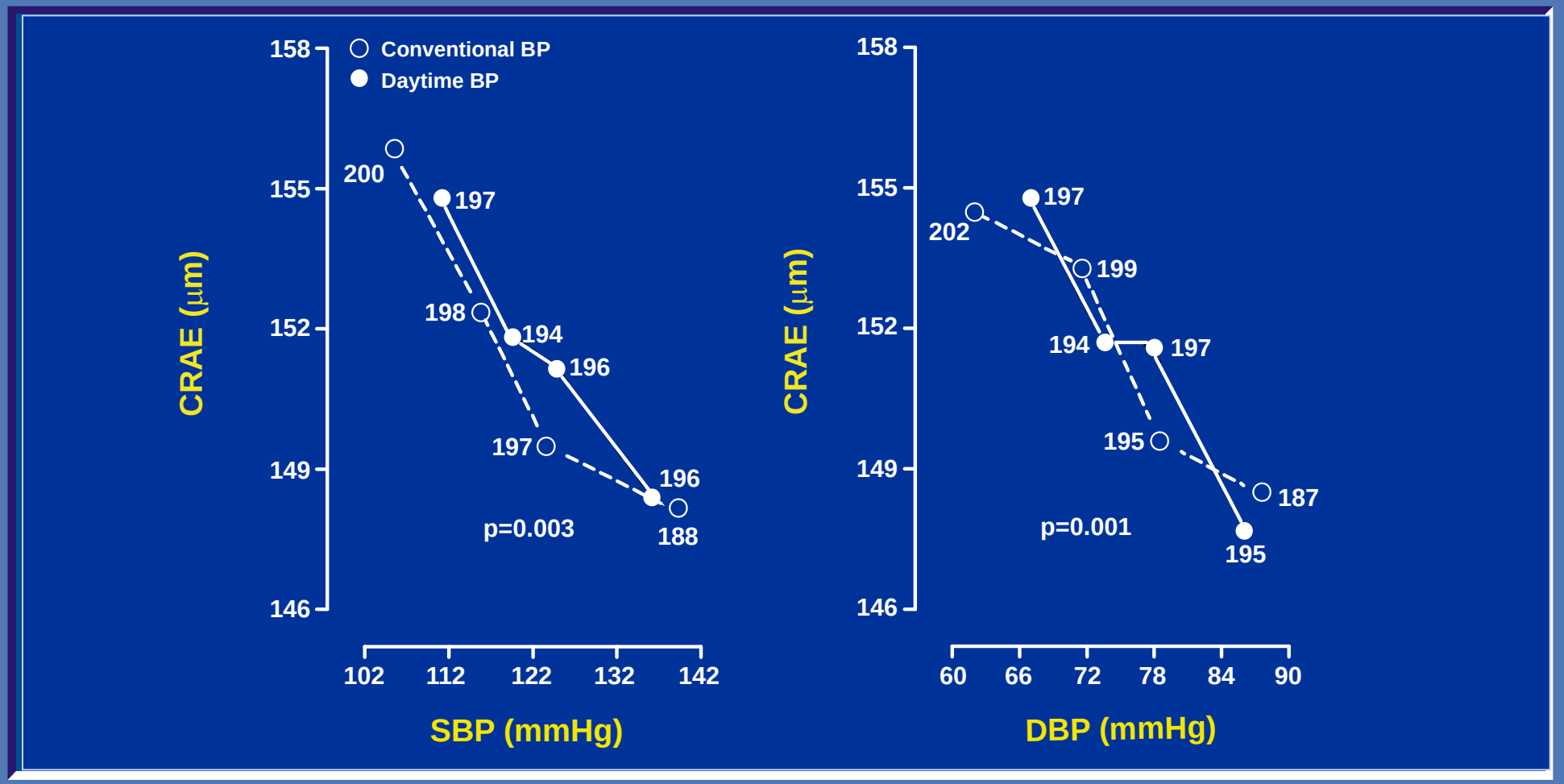
Associations of CRAE with OBP and daytime ABP



Wei FF, et al. *Hypertension 2016*;68:511–20.

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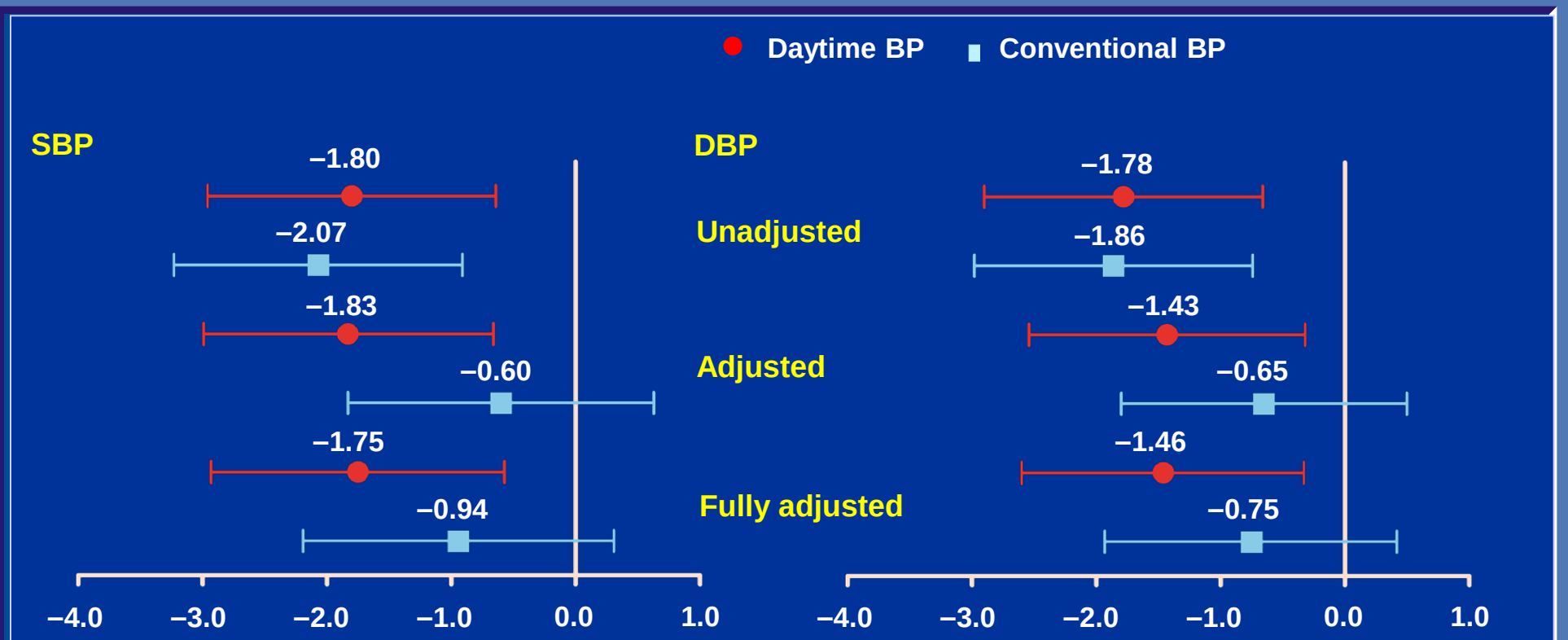
CRAE in relation to OBP *and* daytime ABP



Effect sizes (95% CI) express ΔCRAE associated with 1-SD increase in OBP and ABP. Adjusted models account for sex, age, and CSMK. Fully adjusted models additionally include BMI, TCHOL, BSUG, and CALC at baseline, FU duration, and 3 indicator variables coding for starting or stopping AHT from baseline to FU or remaining on AHT.

Wei FF, et al. *Hypertension 2016;*68:511–20.

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Baseline characteristics by BP status (continuous)

Characteristics	NT (608)	WCHT (42)	MHT (80)	SHT (53)
Age, y	36.1	47.2‡	41.1*	50.4‡
BMI, kg/m^2	24.2	26.2†	26.0	26.3
Conventional SBP/DBP, mmHg	116/72	140‡/90‡	125‡/77‡	148‡/91‡
Daytime SBP/DBP, mmHg	119/74	123‡/77†	136‡/85‡	142‡/90‡
TCHOL, mmol/L	4.98	5.46†	5.37	5.81*
BSUG, mmol/L	5.00	5.05	5.28	5.30

Δ with the left adjacent group: * p≤0.05; † p≤0.01, ‡ p≤0.001.

Wei FF, et al. *Hypertension 2016;*68:511–20.

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Retinal arteriolar narrowing by HT category

Traits	NT	WCHT	MHT	SHT
Unadjusted				
CRAE, μm	152.7‡	150.5*	147.5	145.0
AVR, units	0.70*	0.68	0.68	0.67
Adjusted				
CRAE, μm	152.2*	153.1	148.3	148.2
AVR, units	0.70*	0.68	0.68	0.67
Fully adjusted				
CRAE, μm	152.2*	152.8*	148.6	147.6
AVR, units	0.70†	0.68	0.68	0.67

Δ with sustained HT: * p≤0.05; † p≤0.01, ‡ p≤0.001.

Wei FF, et al. *Hypertension 2016;*68:511–20.

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Baseline daytime BP *vs.* concurrent BP

	Model 1		Model 2	
	Baseline ABP	Concurrent OBP	Baseline ABP	Concurrent OBP
SBP				
CRAE, µm	–2.30‡	–3.10‡	–1.61†	–2.60†
AVR, units	–0.011‡	–0.014‡	–0.009‡	–0.011†
DBP				
CRAE, µm	–1.79‡	–2.74‡	–1.04*	–2.40‡
AVR, units	–0.012‡	–0.017‡	–0.007*	–0.014‡

Model 1 includes a single type of BP measurement. Model 2 includes both types of BP measurement.
All estimates account for family cluster, sex, age, BMI, TCHOL, BSUG and CALC at FU, for FU duration, and for 3 indicator variables coding for starting, stopping or continuing AHT from baseline to FU.
Significance of the effect sizes: * p≤0.05; † p≤0.01, and ‡ p≤0.001.

Wei FF, et al. *Hypertension 2016;*68:511–20.

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Conclusions of this section

- CRAE at FU correlated with baseline BP, irrespective of the type of measurement.
- In the presence of daytime BP, baseline OBP did not predict retinal arteriolar narrowing at FU. Baseline ABP still predicted retinal arteriolar narrowing at FU over and beyond the concurrent OBP.
- MHT was associated with same degree of retinal arteriolar narrowing as SHT, whereas retinal diameters were similar in NT and WCHT.

Wei FF, et al. *Hypertension 2016;*68:511–20.

Debate

Take home message

Retinal arterial narrowing does not precede, but trails HT.

The proposed paradigm can be fully explained by the limitations of in-office BP measurement.