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Centre universitaire
de médecine générale
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Vignette C

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Vignette clinique

- Patiente de 68 ans, retraitée
- HTA systolodiastolique sous trithérapie de longue date
- Valeurs tensionnelles souvent élevées le soir
- Consultation de contrôle annuel
  - Adaptation de la posologie
  - Adaptation de l’horaire : soir à la place du matin ?
- Que répondez-vous?

Contexte

- Selon la littérature, facteurs d'ECV → variation de TA, HTA nocturne, poussées matinales
- Effet incertain de l'horaire d'administration d'un traitement antihypertenseur, matinale ou vespérale
- Limitations méthodologiques des études existantes

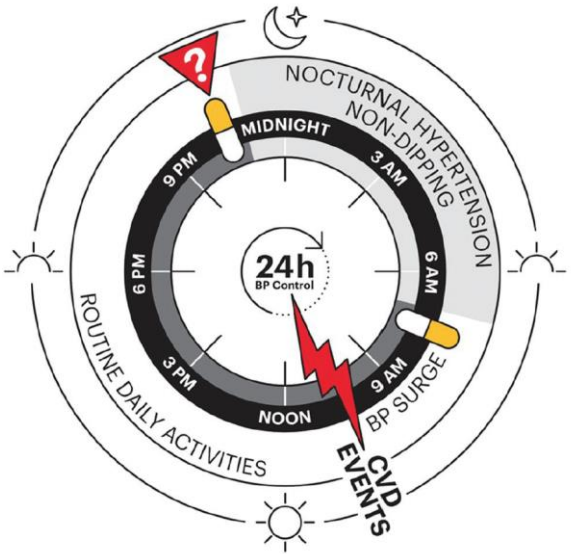
Hypertension

Morning Surge in Blood Pressure and Cardiovascular Risk

Evidence and Perspectives

Kazuomi Kario

Originally published 11 Oct 2010 | https://doi.org/10.1161/HYPERTENSIONAHA.110.157149 | Hypertension. 2010;56:765–773



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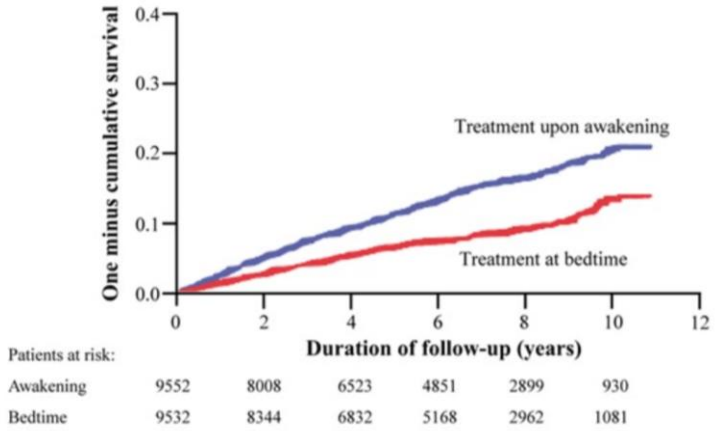
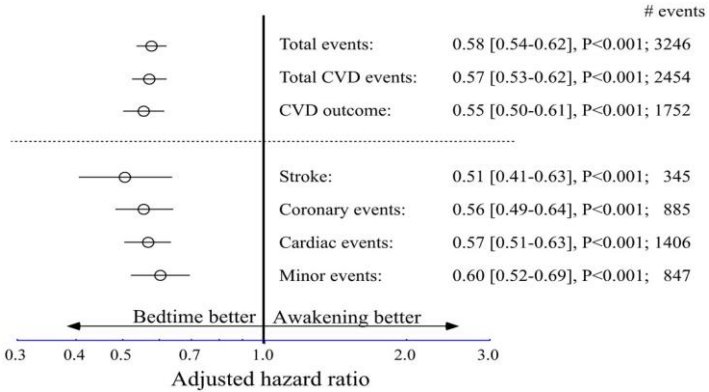
Stergiou G, Brunström M, MacDonald T, et al. Bedtime dosing of antihypertensive medications: systematic review and consensus statement: International Society of Hypertension position paper endorsed by World Hypertension League and European Society of Hypertension. J Hypertens. 2022;40(10):1847-1858. doi:10.1097/HJH.0000000000003240

Contexte

- 2 études prospectives randomisées contrôlées :
  - MAPEC → RR ajusté 0.33, IC95% 0.19–0.55
  - Hygia Chronotherapy → HR ajusté 0.55, IC95% 0.50–0.61
- ↓ ECV tt coucher vs matinal





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Hermida RC, Crespo JJ, Domínguez-Sardiña M, et al. Bedtime hypertension treatment improves cardiovascular risk reduction: the Hygia Chronotherapy Trial. Eur Heart J. 2020;41(48):4565-4576. doi:10.1093/eurheartj/ehz754

Cardiovascular outcomes in adults with hypertension with evening versus morning dosing of usual antihypertensives in the UK (TIME study): a prospective, randomised, open-label, blinded-endpoint clinical trial

*Isla S Mackenzie, Amy Rogers, Neil R Poulter, Bryan Williams, Morris J Brown, David J Webb, Ian Ford, David A Rorie, Greg Guthrie, J W Kerr Grieve, Filippo Pigazzani, Peter M Rothwell, Robin Young, Alex McConnachie, Allan D Struthers, Chim C Lang, Thomas M MacDonald, on behalf of the TIME Study Group**

TIME study: ***T**reatment **i**n **M**orning vs **E**vening*

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Méthodologie

Patients	21’104 patient.e.s, > 18 ans 42.5% femmes âge moyen 65.1 90.5% caucasien.e.s
Intervention	Traitement anti-HTA au coucher (20h00 - 24h00)
Control	Traitement anti-HTA matinal (06h00 - 10h00)
Outcome	Issue primaire → composite de décès d’origine vasculaire ou d’hospitalisations pour un IM ou un AVC non-fatal Issues secondaires → hospitalisation pour IM non-fatal ou AVC, glaucome, décès vasculaire et mortalité toute cause confondue...
Timeline	2011 - 2021 Suivi médian 5.2 ans
Study Design	Etude britannique prospective, pragmatique, randomisée 1:1, décentralisée, open-label (ouverte à toutes et à tous)

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	Evening dosing group (n=10 503)	Morning dosing group (n=10 601)
Age, years	65·0 (9·3)	65·2 (9·2)
Sex		
Male	6041 (57·5%)	6095 (57·5%)
Female	4462 (42·5%)	4506 (42·5%)
Place of residence		
England	9243 (88·0%)	9289 (87·6%)
Scotland	873 (8·3%)	943 (8·9%)
Wales	384 (3·7%)	366 (3·5%)
Northern Ireland	3 (<0·1%)	3 (<0·1%)
Ethnicity		
White	9476 (90·2%)	9625 (90·8%)
Black, African, Caribbean, or Black British	45 (0·4%)	53 (0·5%)
Asian or Asian British	74 (0·7%)	81 (0·8%)
Mixed or multiple	34 (0·3%)	52 (0·5%)
Other	12 (0·1%)	15 (0·1%)
Not reported	862 (8·2%)	775 (7·3%)
Smoking history		
Never	6066 (57·8%)	6012 (56·7%)
Former	3944 (37·6%)	4063 (38·3%)
Current	428 (4·1%)	457 (4·3%)
Missing	65 (0·6%)	69 (0·7%)

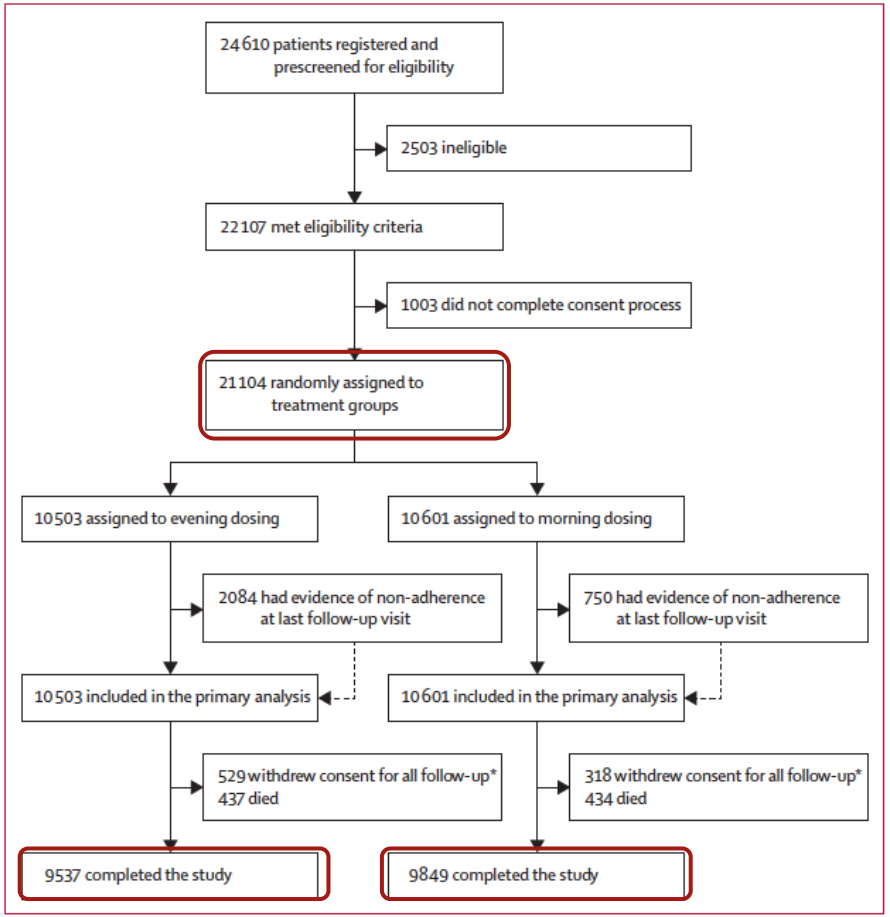

Figure 1: **Study profile**
*Reasons for withdrawal of consent to follow-up are listed in the appendix (p 4); participants who withdrew consent for all follow-up were included in the time-to-event analysis up to the point of withdrawal.

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Résultats

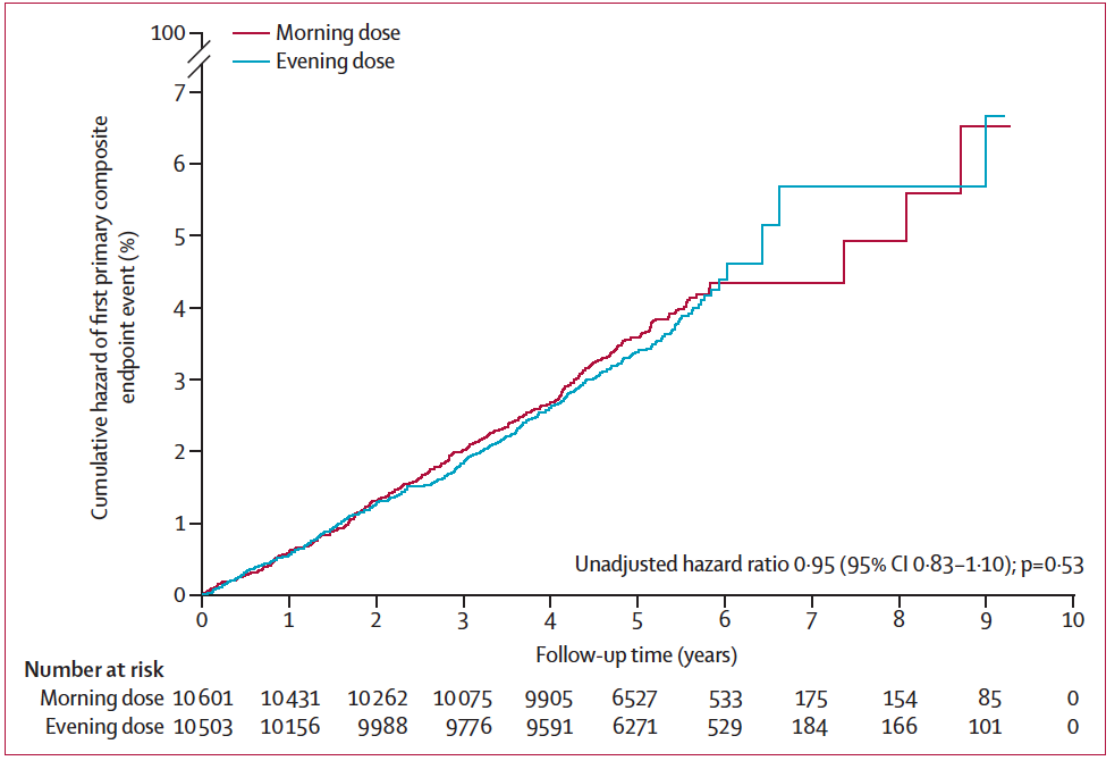

Figure 2: **Cumulative hazard of the first primary composite endpoint event, accounting for the competing risk of deaths not included in the endpoint (intention-to-treat population; n=21 104)**
The primary composite endpoint was vascular death or hospitalisation for non-fatal myocardial infarction or non-fatal stroke.

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Résultats

	Evening dosing group (n=10 503)		Morning dosing group (n=10 601)		Hazard ratio (95% CI)	p value
	Participants, n (%)	Rate per 100 patient-years (95% CI)	Participants, n (%)	Rate per 100 patient-years (95% CI)		
Primary composite endpoint	362 (3·4%)	0·69 (0·62–0·76)	390 (3·7%)	0·72 (0·65–0·79)	0·95 (0·83–1·10)	0·53
Secondary cardiovascular and mortality endpoints						
Hospitalisation for non-fatal myocardial infarction	134 (1·3%)	0·25 (0·21–0·30)	150 (1·4%)	0·27 (0·23–0·32)	0·92 (0·73–1·16)	0·48
Hospitalisation for non-fatal stroke	129 (1·2%)	0·24 (0·20–0·29)	143 (1·3%)	0·26 (0·22–0·31)	0·93 (0·73–1·18)	0·54
Vascular death	115 (1·1%)	0·22 (0·18–0·26)	108 (1·0%)	0·20 (0·16–0·24)	1·10 (0·84–1·43)	0·49
All-cause death	437 (4·2%)	0·82 (0·74–0·90)	434 (4·1%)	0·79 (0·72–0·87)	1·04 (0·91–1·18)	0·59
Hospitalisation or death from congestive heart failure	76 (0·7%)	0·14 (0·11–0·18)	99 (0·9%)	0·18 (0·15–0·22)	0·79 (0·59–1·07)	0·12

Table 2: **Primary composite outcome and secondary cardiovascular and mortality outcomes (intention-to-treat population; n=21 104)**

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Résultats

	Evening dosing group (n=9574)*	Morning dosing group (n=10 054)*	Between-group difference (95% CI)†
Dizziness or light-headedness	3511 (36·7%)	4007 (39·9%)	−3·2% (−4·6 to −1·8)
Excessive visits to the toilet during the day or night	3825 (40·0%)	3660 (36·4%)	3·6% (2·2 to 4·9)
Sleep problems	4017 (42·0%)	4125 (41·0%)	0·9% (−0·5 to 2·3)
Upset stomach or indigestion	2639 (27·6%)	3050 (30·3%)	−2·8% (−4·1 to −1·5)
Diarrhoea	1803 (18·8%)	2170 (21·6%)	−2·8% (−3·9 to −1·6)
Feeling generally less well	3079 (32·2%)	3311 (32·9%)	−0·8% (−2·1 to 0·6)
Muscle aches	3724 (38·9%)	4352 (43·3%)	−4·4% (−5·8 to −3·0)
Other (not specified)	2970 (31·0%)	2686 (26·7%)	4·3% (3·0 to 5·6)

Numbers reported are the number of participants who indicated that they had experienced each prespecified symptom. *Number of participants who submitted at least one completed study follow-up form. †Difference in percentage: evening dosing group minus morning dosing group.

Table 3: **Prespecified adverse events (symptoms) in safety analysis population (n=19 628)**

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Conclusions de l’étude

- Pas de différence significative entre les deux groupes concernant l’issue primaire et les issues secondaires
- Les effets de l’administration d’un traitement antihypertenseur le soir ne semblent pas être différents de ceux d’un traitement matinal concernant les évènements cardiovasculaires majeurs (HR 0.95, IC 95% 0.83 – 1.10, p=0.53)
- Les auteurs proposent que les patients prennent leur traitement habituel au moment qui minimise leurs effets secondaires

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Forces et faiblesses

Forces :

- Bonne validité externe
- Methodologie robuste
- 2011 – 2021, suivi médian 5.2 ans

Faiblesses :

- Risque de biais, étude open-label
- Biais de rappel (*recall bias*) et de participation
- Adhésion

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Implications pour la pratique

- Selon l’étude, le moment de prise d’un tt anti-HTA ne semble pas avoir une importance significative sur le plan cardiovasculaire

- Choix personnalisé à partager avec le patient

- Profil d’effets indésirables à tenir en compte au choix