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The effect of treatment based on a diuretic (indapamide) ± ACE inhibitor (perindopril) on fractures in the Hypertension in the Very Elderly Trial (HYVET)

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Abstract

Background: fractures may have serious implications in an elderly individual, and fracture prevention may include a careful choice of medications.
Design: the Hypertension in the Very Elderly Trial (HYVET) was a double-blind placebo-controlled trial of a thiazide-like diuretic (indapamide 1.5 mg SR) with the optional addition of the angiotensin-converting enzyme (ACE) inhibitor (perindopril 2–4 mg). Fracture was a secondary end point of the trial.
Setting: HYVET recruited participants from Eastern and Western Europe, China, Australasia, and Tunisia.
Subjects: all participants were ≥80 years of age and hypertensive.
Methods: participants were randomised to receive a thiazide-like diuretic (indapamide 1.5 mg SR) ± ACE inhibitor (perindopril 2–4 mg) or matching placebos. Incident fractures were validated and analysed based on time to first fracture.
Results: there were 3,845 participants in HYVET and a total 102 reported fractures (42 in the active and 60 in the placebo group). When taking only validated first fractures, 90 were included in the analyses (38 in the active and 52 in the placebo group). Cox proportional hazard regression, adjusted for key baseline risk factors, resulted in a point estimate of 0.58 (95% CI 0.33–1.00, $P=0.0498$).
Conclusions: despite the lowering of blood pressure, treatment with a thiazide-like diuretic and an ACE inhibitor does not increase and may decrease fracture rate.

Keywords: *fractures, bone, aged, antihypertensive agents, elderly*

Introduction

A fracture can be a devastating occurrence in a very elderly individual and may result in a loss of independence. This can affect both the short- and long-term ability to carry out activities of daily living and the ability to live independently in a way that would not be seen in younger adults [1–3]. Such consequences may impact upon the quality of life and psychosocial well-being of the very elderly person, upon their immediate relatives or carers, and upon society with increased costs of additional support and care [4, 5]. A fall is the most likely cause of a fracture, and there is much work based around the prevention of falls [2, 6–9]. However, if we accept that some falls will occur, it is useful to consider whether it is possible to reduce the risk of fracture in other ways. One possibility is via the use of thiazide diuretics, which have been shown to increase passive reabsorption of calcium in the proximal renal tubules and to be associated with lower rates of calcium excretion [10, 11]. This has also been shown in the 'thiazide-like' diuretics such as indapamide [12–17], and it has been suggested that the use of such drugs could preserve bone mineral density (BMD) and potentially decrease the risk of fracture [18–23].

The Hypertension in the Very Elderly Trial (HYVET) was a double-blind placebo-controlled trial designed to examine the relative risks and benefits associated with the treatment of hypertension in those aged 80 and over. The treatment was with a thiazide-like diuretic indapamide sustained release 1.5 mg ± an ACE inhibitor perindopril 2–4 mg with a primary end point of stroke. Since fracture risk is of particular consideration in the very elderly, a secondary end point of this trial was incident fracture. The trial was stopped prematurely in 2007 having shown significant benefit in favour of treatment for stroke, total mortality, cardiovascular events and heart failure, and the main results have been reported elsewhere [24]. The use of both a thiazide-like diuretic and an ACE inhibitor in a very elderly population using a double-blind placebo-controlled design provides an opportunity to examine any effect that the trial treatment may have had on fracture risk.

Methods

The HYVET recruited patients aged 80 and over. In order to enter the trial, the participants were required to have a sitting systolic blood pressure of ≥160 mmHg, a diastolic pressure of <110 mmHg and a standing systolic pressure of ≥140 mmHg. A requirement for a minimum diastolic pressure of 90 mmHg was removed during the trial, and a protocol amendment was approved by all ethics and regulatory bodies. The participants were recruited from 192 centres, based in hospital and general practice settings, in Eastern and Western Europe, China, Australasia, and Tunisia. The full details of the protocol for the main trial and for the Fracture substudy have been published elsewhere [25, 26]. In brief, patients were randomised to receive indapamide sustained release (SR) 1.5 mg or matching placebo to which could be added perindopril 2–4 mg or matching placebos to achieve a goal blood pressure of less than 150/80 mmHg. Participants entered the trial after a 2-month placebo run-in phase, and were followed up at least every 3 months after randomisation during the first year and every 6 months thereafter. Serious adverse events (SAE) were routinely collected using the standard definition of an SAE, and supporting documentation was requested including any available X-ray reports for SAEs that included fractures. Since not all fractures would necessarily be classified as SAEs, at each trial visit, investigators were also asked to report whether the participant had suffered from a fracture since the previous visit and, if so, to provide supporting documentation. Each fracture, and all relevant details, was reviewed by an expert member of the trial end point committee who was blind to treatment allocation. The incident fractures were classified in three categories: definite, probable and insufficient evidence to show that a fracture had occurred. Definite and probable fractures were considered to be validated and were analysed.

Cox proportional hazard regression models were used to determine the effect of treatment upon time to first fracture and adjusted for the impact of potential baseline risk factors for fracture.

All analyses were performed on an intention-to-treat basis and completed using SAS software version 9.1. The trial is registered with ClinicalTrials.gov number NCT00122811.

This work (the HYVET) was funded by grants from the British Heart Foundation and Servier International. The trial was co-ordinated by the Department of Care of the Elderly, Imperial College London. Imperial College was the sponsor of the trial. The analysis, interpretation of the data, generation of the manuscript and decision to submit for publication were carried out independently of the funding bodies, and the primary author had full access to all of the data and final responsibility for the decision to submit for publication.

Results

A total of 3,845 participants were randomised into HYVET, and the mean follow-up was 2.1 years. (Please see Figure 1 in the supplementary data showing the flow of participants through the trial. Supplementary data are available in *Age and Ageing* online.)

There were a total of 104 fractures reported (see Table 1); of which, 61 were classified as definite (fracture), 40 as probable and 3 as having insufficient evidence. Two participants had three fractures, and a further seven had two. For the purposes of these analyses, only the first reported fracture was used. This gave 90 definite/probable fractures for analysis (53 definite and 37 probable).

The treatment groups were well matched at baseline, and were similar for age, blood pressure, and other cardiovascular and sociodemographic characteristics (Table 2). By 2 years, 73.8% of participants had been titrated up to receive the additional perindopril.

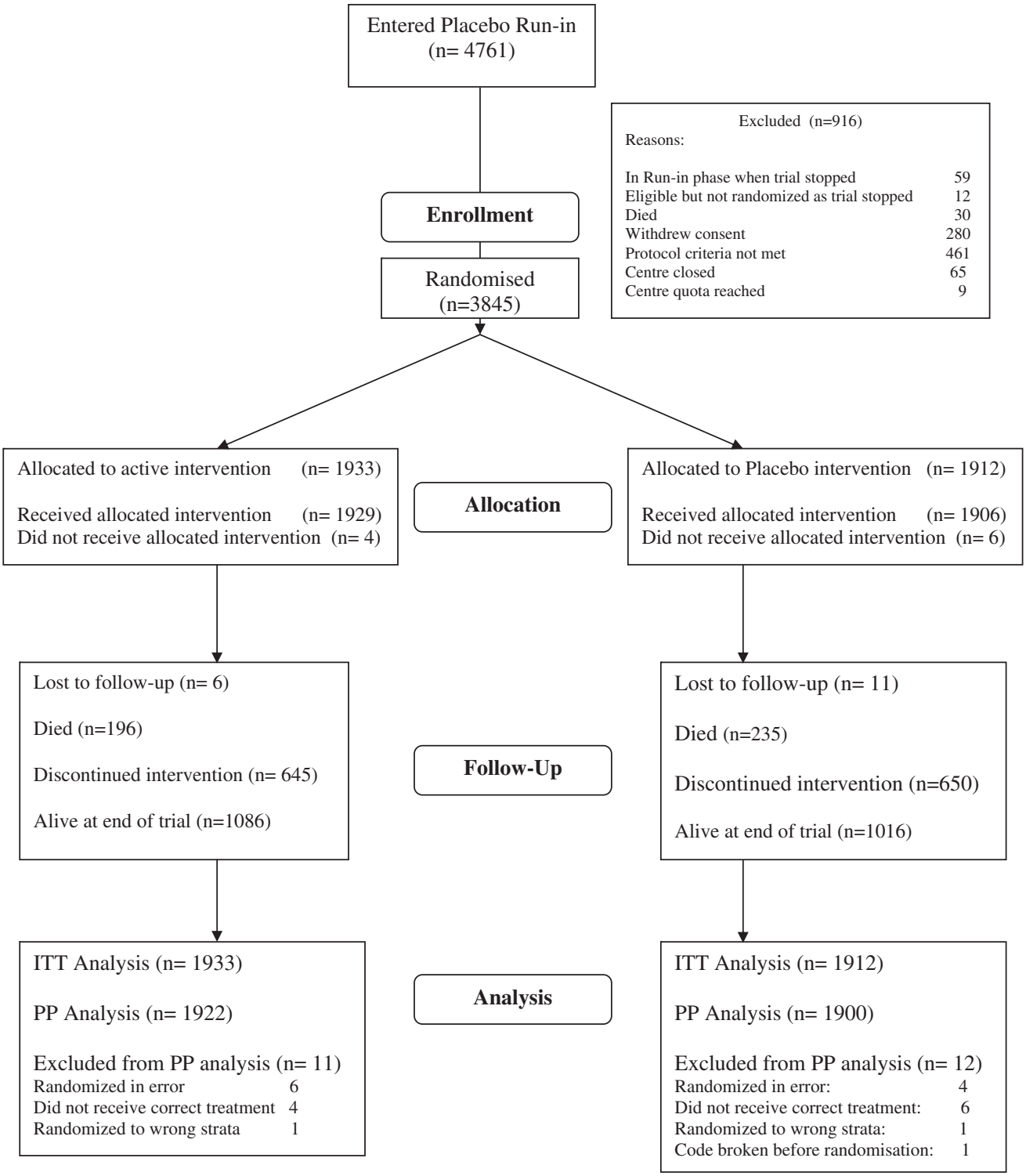

Figure 1. Flow diagram of participants in the Hypertension in the Very Elderly Trial.

Table 3 shows the baseline characteristics of patients who did and did not suffer from a fracture. The patients who suffered from a fracture were more likely to be female ($P=0.003$) and older ($P=0.015$). For each additional year of age, fracture risk increased by 7%, and women were twice as likely to suffer from a fracture compared with men.

There were 1,933 participants in the active (antihypertensive) treatment arm and 1,912 in the placebo arm. The corresponding numbers for the first occurring fractures were 38 in the active arm and 52 in placebo. If all fractures are included, this results in 41 validated (out of 42 reported) in the active group, and 58 validated (out of 60 reported) in the placebo group.

Table 1. Site of reported fractures

Fracture type	Validation			
	Number reported	Definite fracture	Probable fracture	Insufficient evidence
Ribs, sternum and thoracic spine	5	2	0	3
Lumbar spine and pelvis	8	6	2	0
Shoulder and upper arm	9	8	1	0
Forearm	13	7	6	0
Wrist and hand	11	4	7	0
Femur	55	33	22	0
Lower leg including ankle	3	1	2	0

One individual may suffer from multiple fractures on the same date.

Table 2. Baseline characteristics by group

		Active treatment (indapamide SR 1.5 mg±perindopril 2–4 mg) n = 1,933	Placebo n = 1,912
Age, years (SD)		83.6 (3.2)	83.5 (3.1)
Percent female (%)		60.7 (n = 1174)	60.3 (n = 1152)
Previous fracture (%)		10.1 (n = 196)	7.9 (n = 151)
Mean sitting systolic blood pressure (mmHg) at entry (SD)		173.0 (8.4)	173.0 (8.6)
Orthostatic hypotension (defined as a fall of 20 mmHg in systolic or 10 mmHg in diastolic blood pressure)		7.9 (n = 152)	8.8 (n = 169)
Smoker (%)		6.4 (n = 123)	6.6 (n = 127)
Consumes alcohol (%)		18.3 (n=353)	17.2 (n=328)
Mean number of non-cardiovascular co-morbidities (SD)		1.8 (1.6)	1.7 (1.5)
Mean number of medications (SD)		0.7 (1.1)	0.7 (1.1)
Number taking beta blockers prior to trial entry (%)		7.4 (n = 144)	6.6 (n = 120)
Living alone (%)		22.7 (n=439)	21.0 (n=402)
Education (%)	None	26.6 (n=515)	26.9 (n=515)
	Primary	28.5 (n=551)	28.9 (n=552)
	Secondary	29.1 (n=562)	28.2 (n=540)
	Higher	12.7 (n = 246)	12.7 (n = 243)
	Further	3.1 (n=59)	3.2 (n=62)
Median Mini-Mental State Exam (baseline)		26	26
Mean Mini-Mental State Exam (baseline)		25.3 (3.9)	25.3 (3.8)

When the treatment groups were compared using a Cox proportional hazard regression model, the group receiving antihypertensive treatment tended to be favoured with a hazard ratio (HR) of 0.69 [95% confidence interval (CI) of 0.46–1.05, P=0.086]. (Please see Figure 2 in the supplementary data showing the cumulative hazard of fracture over time for the two treatment groups. Supplementary data are available in *Age and Ageing* online.) Adjusting for the baseline factors that were indicated as potentially impacting on subsequent fracture, (age, gender and previous use of beta blockers) resulted in HR of 0.58 (95% CI 0.33–1.00, P= 0.0498) in favour of active treatment. Rerunning the analyses including all reported fractures, regardless of whether they were validated or not, resulted in an unadjusted HR of 0.69 (95% CI 0.45–1.03, P=0.071) and an adjusted HR of 0.54 (95% CI 0.32–0.94, P=0.028). The proportional hazard assumptions were not violated. The mean time to fracture in the placebo group was 515.12 days with a standard deviation (SD) of 443.8 days and a range from 21 to 2,177 days. For the actively treated group, the corresponding mean was 742.8 days (SD 508.8) and range 57–2,188 days.

When the previous treatment with antihypertensives, i.e. treatment before entry into the HYVET, was examined by class, only beta blockers were found to have a relationship with incident fracture with an adjusted HR of 2.05 (1.03–4.08, P=0.042).

It has been suggested that certain types of concomitant medication may impact upon risk of fracture [20]. In HYVET, benzodiazepines, antipsychotics, antidepressants, corticosteroids, antiepileptics, hormone replacement therapies, statins, calcium, fluoride or vitamin D supplementations were not used by a large number of participants (all were less than 1% of the population), and so were not included in the analysis.

Discussion

In the HYVET, the assessment of validated fractures in the placebo group as compared with the actively treated group resulted in a non-significant reduction in hazard of incident fracture of 31% with active treatment (indapamide SR± perindopril). With adjustment for baseline factors, this was just significant with a 42% reduction in hazard. Including all fractures (validated and non-validated) produced similar, although more statistically significant, results.

Further analyses showed that risk of incident fracture was significantly increased with older age and female gender. Conversely, the risk of incident fracture was not significantly associated with number of co-morbidities, smoking, alcohol consumption or low cognitive function at baseline. Previously, it has been shown that use of beta blockers may be associated with a reduced risk of fractures in middle-aged and older subjects [27]. It is not clear whether our findings support this in the elderly. Although those taking beta blockers prior to trial entry had a higher risk of subsequent fracture, it is not clear whether this was the result of stopping the use of beta blocker (as required to enter the trial), their prior use had prompted a higher risk, or those who entered the trial and stopped beta blockers were a selected group, although the allocation to trial treatment group was of course random. In addition, HYVET did not recruit those who required an ongoing treatment with beta blockers for heart failure.

Table 3. Relationships between baseline risk factors and incident fracture

	Participants without incident fracture (% or mean ± SD) n=3,755	Participants with incident fracture (% or mean ± SD) n=90	Univariate	
			Hazard ratio (HR)	95% CI
Age (years)	83.5 ± 3.2	84.3 ± 3.4	1.07	1.01–1.13
Gender (% female)	60.1	76.7	2.08	1.28–3.40
Glucose (mmol/l)	5.4 ± 1.5	5.3 ± 1.1	0.98	0.85–1.14
Previous fracture	8.4	13.3	1.60	0.87–2.93
Previous cardiovascular disease	11.7	14.4	1.39	0.77–2.50
Orthostatic hypotension	8.4 ± 9.0	6.7	0.80	0.35–1.84
Centrally acting drugs prior to trial entry	14.6	18.9	1.48	0.74–2.94
ACE inhibitors prior to trial entry	41.7	39.0	0.80	0.47–1.35
Diuretics prior to trial entry	32.9	27.3	0.73	0.40–1.32
Beta blockers prior to trial entry	10.9	18.5	1.97	0.99–3.93
Calcium channel blockers prior to trial entry	36.9	38.6	1.07	0.63–1.82
Other antihypertensives prior to trial entry	16.5	16.7	1.32	0.64–2.72
Co-morbidities	1.7 ± 1.6	1.9 ± 1.5	1.04	0.91–1.18
Smoking	6.0	5.6	1.15	0.47–2.83
Consuming alcohol	17.8	13.3	0.59	0.33–1.09
Baseline Mini-Mental State Exam	25.3 ± 2.9	25.3 ± 4.0	0.99	0.94–1.05
Self-reported dizziness	79.6	81.0	1.10	0.82–1.46

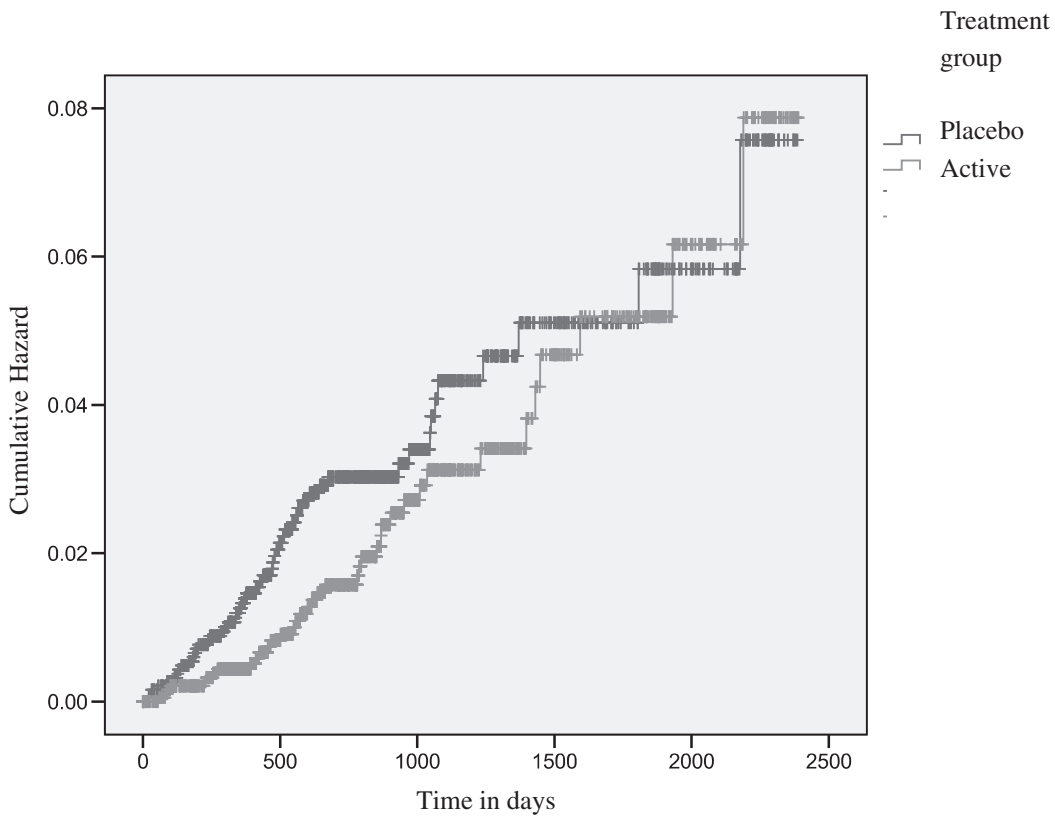

Figure 2. A graph showing cumulative hazard of fracture over time for the two treatment groups (active and placebo).

The HYVET was terminated early due to an unexpected and statistically significant reduction in mortality in the actively treated group at the time of the second interim analysis. The early stopping prevented the collection of additional fracture end points in a prolonged double-blind setting. This reduced power, and may have or may have not contributed to the lack of a strongly statistically significant finding for validated fracture end points.

There are many studies that have reported in this area with varying results; however, two meta-analyses, one in 1995 and one systematic review and meta-analysis in 2006, were in agreement and found that thiazide diuretics were associated with reduced fracture risk. The former reported a summary odds ratio (OR) of 0.82 (95% CI 0.62–1.08), and the later one a statistically significant summary relative risk (RR) of 0.86 (95% CI 0.81–0.92) [22, 23]. This would support the hypothesis that the use of thiazide diuretics reduces fracture risk with the most recent meta-analysis including 25 studies. This meta-analysis also found a reduction in risk with the use of beta-blockers (RR 0.86, 95% CI 0.70–0.98) (eight studies) and reported one study of ACE inhibitor use that also showed a reduction (RR 0.81, 95% CI 0.73–0.89) [22]. Wiens *et al.* found only one study assessing calcium channel blocker use, two using alpha blockers (all non-significant), and no studies assessing the use of angiotensin receptor blockers and fracture risk [22].

By 2 years, the majority of the HYVET participants were taking both a thiazide-like diuretic (indapamide SR 1.5 mg) and an ACE inhibitor (perindopril 2–4 mg). Our findings showing a just significant reduction in fracture risk with the actively treated group largely fit with previous studies including the two meta-analyses, which suggested a reduction in fracture associated with diuretic use, and one study showing reduction with ACE inhibitor use [22, 23]. In addition, other studies observed that fractures occur more frequently in women and in older subjects [4, 28].

The reason for the lack of effect from number of co-morbidities, smoking, alcohol consumption and low cognitive function at baseline is not clear. It could be that these factors do not influence fracture rate in this population. This could be particularly true for the HYVET population as these probably represent the more healthy elderly. In HYVET, patients could not be recruited if they needed nursing care or had a diagnosis of dementia. Moreover, those at risk from, for example alcohol consumption, may have been more healthy in general and consumed only modest quantities of alcohol.

Possible limitations of this study include this recruitment of the healthier elderly. In addition, the designated trial visits were at 6-month intervals after the first year which may have meant that some non-serious fractures were not reported to the investigators by the patients. Detailed data on falls were also not collected. Due to the healthcare systems in each country where HYVET was run, the investigators may have had difficulties in collecting all information relating to fractures. Moreover, no attempt was made to routinely identify fractures of the spine, for example, vertebral collapse. Patient adherence to trial treatment is also a possible problem in all such studies. Nevertheless, HYVET was a double-blind, randomised, placebo-controlled study, and therefore followed the recognised gold standard in terms of testing the effects of a drug treatment. Furthermore, the significant reductions in stroke and mortality associated with active treatment would seem to indicate that the patients were taking a sufficient trial medication [24]. Other strengths of HYVET include the population recruited, as this is representative of a rapidly growing part of the population globally in developed and developing countries. In addition to this, although the trial visits were 6 months apart, the designated trial coordinating office provided training and met with every investigator annually, reinforcing the need to collect fracture data (and all other data), and many investigators saw the participants more frequently than every 6 months. Specific forms were also used to collect fracture information, and the investigators were asked to provide hospital and X-ray reports, all of which were used for validation purposes.

In summary, the treatment used in HYVET may have achieved a 31% reduction in hazard of incident fractures. When adjusted for baseline factors, this just reached significance. We consider that this finding may have clinical importance. Older individuals and females were statistically significantly more likely to suffer from a fracture. The HYVET population was representative of the more healthy elderly which is a fast growing sector globally.

Key points

- Antihypertensive treatment in the hypertensive very elderly was not associated with an increase in fracture rate.
- Antihypertensive treatment based on a diuretic and ACE inhibitor was associated with a just significant decrease in fracture rates when adjusted for baseline risk factors.
- The population is ageing, and antihypertensive treatment has been shown to be beneficial in very elderly hypertensives; these data reinforce this message.

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Conflicts of interest

Imperial College received funding from the British Heart Foundation and Servier International to run the trial, and support salary and consultancy costs for staff including C.B., N.B., R.P. and L.B. Honoraria for speaking at symposia have also been received by C.B., N.B. and R.P.

Author's contributions

R.P. was the deputy co-ordinator for the HYVET trial and wrote the manuscript.
N.B. was the co-ordinator for the HYVET trial and commented on the manuscript.

L.B. was the HYVET trial endpoint and pharmacovigilance co-ordinator and carried out the statistical analysis for the manuscript.
M.-C.d.V. was the member of the HYVET end point committee responsible for validating the fractures and commented on the manuscript.
L.L. was the HYVET country co-ordinator for China and commented on the manuscript.
J.D. was a member of the HYVET end point committee and commented on the manuscript.
C.S. was a member of the HYVET steering committee and commented on the manuscript.
B.G.-E. was a member of the HYVET steering committee and commented on the manuscript.
A.F. was the co-principal investigator of HYVET and commented on the manuscript.
C.B. was the principal investigator of HYVET and commented on the manuscript.

Sponsor's role

HYVET was funded by grants from the British Heart Foundation and the Institute de Recherches Internationales Servier. Imperial College was the sponsor and co-ordinator of the trial. The funding bodies had no influence on design, methods, recruitment, data collection, analysis or preparation of the paper.
The HYVET trial is registered with ClinicalTrials.gov number NCT00122811 http://clinicaltrials.gov/.
The committee members and investigators for HYVET were as follows: **Co-ordinating Centre:** C.B. (lead investigator), A.F. (co-investigator), N.B. (trial coordinator), R.P. (deputy trial coordinator), HYVET coordinating team at Imperial College London (1999–2008);

HYVET Committees: Steering Committee: T. McCormack, J. Potter, B.G. Extremera, P. Sever, F. Forette, D. Dumitrascu, C. Swift, J. Tuomilehto, J. Coope (retired in 2001), C. Nachev (deceased); Data Monitoring Committee: J. Staessen, L. Thijs, R. Clarke, K. Narkiewicz; End Points Committee: C. Davidson (retired in 2003), J. Duggan, G. Leonetti, N. Gainsborough, M.C. De Vernejoul, J. Wang, V. Stoyanovsky; Dementia Validation Committee: J. Tuomilehto, R. Clarke, A. Waldman, I. Walton, C. Ritchie; Ethics Committee: R. Fagard, J. Grimley Evans, B. Williams;

Investigators: (*National Co-ordinators)

Australia—R. Warne* and I. Puddey*, M. Woodward, R. Penhall, C. Inderjeeth, S. Roger, R. Scholes, C. Johnson; ***Belgium***—H. Celis*, G. Adriaens, W. Onsea, K. Cornelli, D. Vantroyen, P. Cleen, P. de Voogt; ***Bulgaria***—C. Nachev* (deceased) (national coordinator from 1998 to 2005), V. Stoyanovsky* (national coordinator after 2005), P. Solakov, R. Prokopova, E. Mantova, D. Smilkova, S. Mantov, K. Yankulova, R. Kermova, D. Popov, V. Sirakova, V. Gergova, D. Kamenova, F. Grigorov, T. Vassileva, R. Alahverdian, M. Tzekova; A. Postadjian, M. Geneva, V. Mincheva, T. Petrusheva A. Toncheva, I. Gruev, V. Tsanova; ***China***—L. Liu*, H. Ge, S. Wang, J. Wang, W. Zhang, S. Jin, L. Ge, Y.F. Lu, S. Ma, L. Shen, J. Guo, Z. Lv (deceased), R. Huang, X. Li, B. Guo, G. E. Yuan, T. Zhang, L. Zhang, J. Feng, Z. He, J. Wang, L. Deng, L. Liu, Q. Yuan, F. Zhang, H. Li, D. Wang, K. Yang, M. Sun, H. Liu, X. Yan, F. Ren, J. Tang, M. Zhao, X. Luo, H. Zhou, H. Sang, Jie Wang, L. Yan, Zhixing Wang, J. Zhang, Chengzhi Wang; ***Finland***—R. Antikainen*, T. Strandberg, T. Konttila, A. Hynninen, M. Jääskivi, J. Airas, T. Jääskeläinen, J. Tuomilehto, H. Litmanen, T. Karhi, H. Yliharsila; ***France***—F. Forette*, J. Doucet, J. Belmin, A. Benetos, G. Berrut, T. Boge, M. Bonnefoy, A. Carre, N. Charasz, J. Covillard, T. Dantoine, M. Escande, Y. Frances, R. Joire, C. Jeandel, S. Legrain, A. Lion, M. Maillet-Vioud, J.P Escaillas, S. Meaume, P. Pfitzenmeyer, F. Puisieux, Quercy, O. Rodat, J. Soubeyrand, B. de Wazieres, H. Hindennach, L. Lugassy, J. Rossi, M. Martel, J.-M. Paladel, C. Ravier, A. Visconti, J.P. Gallet, D. Zygouritsas, D. Charles, F. Flamand, G. Grandmottet, M. Grandmottetegermann, C. Gevrey, P.L. Mesnier, G. Robert, C. Besset-Prat, A. Brousse, P. Lafont, J. Morelli, P. Vernede, A. Volkmann, X. Bodin, B. Destrube, R. Eoche, A. Boye, F. Seropian, P. Gernigon, D. Meker, J. Thomere, Y. Thual, F. Volny, E. Grassart, M. Herent, D. Lejay, J.-P. Lopez, B. Mannessier, G. Pruvost, J.-C. Urbina; ***Ireland***—J. Duggan*; ***New Zealand***—C. Anderson*, S. Lillis, J. Gommans; ***Poland***—T. Grodzicki*, Z. Chodorowski, Z. Gaciong; ***Romania***—D. Dumitrascu*, M. Comsa, V. Sandru, G. Prada, M. Dunca-Moisin, D. Jianu, D. Jinga-Lazar, V. Enachescu, C. Zaharia; ***Russia***—Y. Nikitin*, A. Kirichenko, L. Olbinskaya, A. Martynov, V. Zadionchenko, V. Moiseev, G. Storohzakov, S. Nedogoda, R.S. Karpov, O. Barbarash, G. Efremushkin, V. Kostenko, M. Boyarkin, S. Churina, T. Tyurina, M. Ballyuzek, L. Ermoshkina, A. Timofeev, S. Yakusheva, N. Shilkina, V. Barbarich, L.Latunceva, S. Burakova, T. Ripp, S. Pekarsky, V. Mordovin; ***Tunisia***—A. Belhani*, E. Boughzela, S. Soraya, B. Youssef-Zouari, A.B. Khalfallah, M.H. Houman, A.K. Abida; ***United Kingdom***—C. Rajkumar*, M.Wilkins, N.D. Pandita-Gunawardena, J. Potter, E. Ekpo, M. Price, N. de Kare-Silver, A. Starczewski, S. Chandran, N. Nasar, M. Datta-Chaudhuri, T. McCormack, N. Majmudar, A. Gordon, L. Brawn, T. Solanki, F. Dockery, R. Schiff.

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Supplementary data

Supplementary data mentioned in the text is available to subscribers in *Age and Ageing* online.

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