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Detecting Risks Of Postural Hypotension (DROP): derivation and validation of a prediction score for primary care

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Abstract

Objectives

Falls are a common problem in older people. Postural hypotension contributes to falls but is often asymptomatic. In the absence of symptoms, postural hypotension is only infrequently checked for in clinical practice. We undertook this study to derive, validate and explore the prospective associations of a prediction tool to identify people likely to have unrecognised postural hypotension.

Design and setting

Cross-sectional and prospective multivariable cohort analysis.

Participants

1317 participants of the InCHIANTI study, a population based cohort representative of the older Italian population.

Primary outcome measures

Predictive value of score to suggest presence of postural hypotension,

Methods

Subjects were randomised 1:1 to derivation or validation cohorts. Within the derivation cohort univariable associations for candidate predictors of postural hypotension were tested. Variables with P<0.1 entered multivariable linear regression models. Factors retaining multivariable significance were incorporated into unweighted and weighted DROP scores. These scores were tested in the validation cohort against prediction of postural hypotension, cognitive decline and mortality over nine years' follow up.

Results

Postural hypotension was present in 203 (15.4%) of participants. Factors predicting postural hypotension were: digoxin use, Parkinson's disease, hypertension, stroke or cardiovascular disease, and an inter-arm systolic blood pressure difference. Area under the curve was consistent at 0.65 for all models, with significant odds ratios (OR) of 1.8 to 2.4 per unit increase in score for predicting postural hypotension. For a DROP score ≥1, five cases need to be tested to identify one with postural hypotension.

Increasing DROP scores predicted mortality (OR 1.8 to 2.8 per unit rise) and increasing rates of decline of Mini Mental State Examination score (ANOVA p<0.001) over 9 years of follow up.

Conclusions

The DROP score provides a simple method to identify people likely to have postural hypotension, and increased risks to health, who require further evaluation.

(296 words)

Strengths and limitations of this study

- This study, to derive and validate a score ("DROP score") predicting the presence of postural hypotension, was undertaken using data from a well-established cohort representative of a free living older population in Italy. Comprehensive recording of baseline variables by the InCHIANTI investigators allowed a large number of previously reported risk markers for PH to be tested in the analyses.

- The study was undertaken according to TRIPOD guidelines and randomised splitting of the cohort allowed internal validation of the findings to be undertaken.

- The findings confirmed that a simple risk marker based score can predict who may benefit from testing for postural hypotension. Sensitivity, specificity and area under the curve results were modest; the study requires replication in a larger cohort before implementation of the DROP score can be recommended in practice.

- Guidelines advise testing for postural hypotension in the elderly and those with diabetes. Neither of these risk markers appeared significant in the current analyses. Refinement of the scoring system within a larger cohort more representative of the older UK population is planned to explore this further.

Introduction

Falls are a major cause of morbidity and mortality in older people; 35% of people older than 65 and 50% of people older than 80 fall at least once a year.[1 2] Falls are the leading cause of disability and the leading cause of death from injury among people over 75 in the UK, and cost the NHS around £2.3 billion per year.[3] Postural or orthostatic hypotension is a major risk factor for falls,[4 5] and is independently associated with increased mortality rates.[6-8] Postural hypotension has also been associated with dementia and cognitive impairment, and may have more subtle adverse effects on wellbeing and cognition.[9]

Postural hypotension is commonly defined as a fall of either ≥20mmHg in systolic blood pressure or ≥10mmHg in diastolic blood pressure, from sitting or lying, within three minutes of standing up.[10] Reported prevalences of postural hypotension vary widely, and are sensitive to both care setting, occurring in over half of patients admitted to care of the elderly,[11-13] and to the presence of co-morbidity. General adult population prevalence appears to be around 7%,[14 15] rising to 11 to 15% in persons 65 years old and older,[16-18] and 19% in those aged over 80 or older.[15] Prevalence is reported to be higher in the presence of hypertension,[19-23] stroke,[24 25] myocardial infarction,[25 26] and diabetes.[22 27]

Guidelines vary in recommendations for the detection of postural hypotension. The National Institute for Health and Care Excellence (NICE) recommends testing in the presence of symptoms whist the European Society for Hypertension also recommends testing in the elderly and in the presence of diabetes.[1 28] Unfortunately most individuals with postural hypotension are asymptomatic,[7] and we have found that, in practice, postural hypotension is seldom looked for in patients who do not report postural symptoms.[29] Anecdotally, testing is not undertaken due to time constraints; screening for postural hypotension is not supported in the literature, being regarded as lacking an evidence base, and primary care workloads are rising.[30 31] Risks of hospitalisation, nursing home admission or mortality can already be predicted by the electronic frailty index (eFI), a score derived from existing information in primary care computer records, and incorporated into many general practice computing systems. However the association of eFI with, and its ability to predict, postural hypotension (which itself is poorly tested for and recorded in primary care) is unclear,[32] and comparable frailty indices have not been found to be predictive of postural hypotension.[33] To address this gap in care we hypothesised that a simple prediction score, based on easily recognised risk markers, might help clinicians identify those most likely to have postural hypotension thereby allowing a targeted implementation of sitting and standing blood pressure measurement in the absence of symptoms. We therefore undertook the current analysis, in a well-documented cohort known to be representative of an older population living in the community. Aims were to explore the feasibility of deriving and internally validating a prediction score, to assess its value and its prospective associations.

Methods

The study was conducted and reported in accordance with the TRIPOD statement.[34] We studied participants from the InCHIANTI study; a cohort study designed to explore declining mobility in later life. The Italian National Research Council on Aging ethical committee approved the InCHIANTI study protocol, and the current analysis proposals were approved by the investigating committee of the InCHIANTI study.

The InCHIANTI study methods have been described in detail elsewhere.[35] In brief, 1270 participants aged 65 years or more were randomly selected from the population registries of two villages: Greve

in Chianti, and Antella in Bagno a Ripoli. Additional people were randomly selected from these sites to complete recruitment of at least 30 men and 30 women for each age decile from age 20 to 29 upwards. Extensive baseline interviews and examinations were conducted at recruitment, between September 1998 and March 2000, and follow up data were obtained after three, six and nine years. blood pressure was initially measured supine, sequentially in both arms, to identify the higher reading arm, then a further two measurements were made on the higher reading arm. Subjects then stood and blood pressure was measured once after 1 minute and once more after 3 minutes standing. All measurements were obtained by research assistants using a standard mercury sphygmomanometer.

Baseline blood pressure was calculated as the mean of the second and third supine blood pressure readings.[36] Postural changes in blood pressure from lying to standing were calculated by subtraction of this mean from the standing blood pressure. Postural hypotension was considered to exist where there was as a reduction in blood pressure on standing of ≥20mmHg systolic or ≥10mmHg diastolic after 1 or after 3 minutes.[10] Hypertension was defined as use of antihypertensive drugs and/or a documented history of hypertension at recruitment.

For this analysis, participants were randomly allocated in a 1:1 ratio using a split-sample method,[37] stratified for gender and study site, to either a *derivation* or a *validation* group by a statistician (FW) blinded to postural hypotension status and medical history. A literature review was undertaken to identify potential risk markers for consideration in the analyses (appendix). These were mapped to variables available in the InCHIANTI dataset (table 1), which were then tested in the derivation cohort for univariable associations with postural hypotension, using t-tests or χ^2 tests as appropriate to the data. Variables signalling potential univariable associations (defined as $p<0.1$) were included in multivariable model analyses using an automated backward stepwise regression method.[38] We also included age (explored both continuously and as a dichotomous variable with cut-offs of 60, 65 and 70 years) and gender in all multivariable models. Prospective associations of postural hypotension with survival up to 9 years of follow-up were tested using Kaplan-Meier plots and Cox proportional hazard ratios. Cognitive decline was defined as a reduction in Mini Mental State Examination score (MMSE score) of 5 points or more from baseline, and rate of cognitive decline was defined as change in MMSE scores averaged per year of follow up.

Risk markers that retained significance in the multivariable models were used to derive both weighted and unweighted scores (DROP scores); weighted scores were derived by the addition of the multivariable Log (n) odds ratio (OR) for each marker present, whereas the unweighted model allocated one point for each risk marker present. Scores were tested in the validation cohort for ability to predict postural hypotension using ROC analysis, to predict future mortality using Cox proportional hazard ratios, and cognitive decline over nine years using ANOVA. All analyses were undertaken using IBM SPSS Statistics v24.0.0.2.

Results

Data for standing blood pressure existed for 1317 of the 1453 participants (91%) and they formed the cohort for this study. The derivation cohort (n=649) and validation cohort (n=668) were well matched for all important characteristics and putative risk markers (table 2); overall postural hypotension was present for 203 (15.4%) of participants at recruitment. Mean age of participants was 68.3 (standard deviation 15.5).

For the derivation cohort postural hypotension was associated, over 9 years of follow-up, with increased all-cause mortality (Hazard Ratio (HR) 1.9; 95% confidence interval (95%CI) 1.4 to 2.7), cardiovascular mortality (HR 2.1; 95%CI 1.2 to 3.4), and non-cardiovascular mortality (HR 2.0; 95%CI 1.3 to 3.0). Results of univariable testing are summarised in table 3. Using a cut off value of p<0.1 the following candidate predictors were entered into multivariable models: age (continuous, or dichotomous for age 60 or 70 cut offs), MMSE score, digoxin use, presence of hypertension, any cardiovascular disease (composite of history of myocardial infarction, angina pectoris or congestive heart failure), stroke, Parkinson's disease, hospital admission within the last year, WHO disability level, any disability in activities of daily living, systolic inter-arm difference (continuous or using ≥10mmHg cut off).

Backward stepwise regression analysis produced consistent findings with any permutation of discrete and continuous variables for age (which was not retained in any model) or for inter-arm difference (model 1 and model 2; table 4). Consequently, a dichotomous cut off for inter-arm difference of ≥10mmHg was selected for simplicity, and retained with five other factors to derive weighted (using log OR) and unweighted (score 1 for each factor present; possible range 0 to 6) *DROP* scores. The scores were tested in the validation cohort. Since inter-arm difference is not routinely measured a third model excluding inter-arm difference (model 3, table 4) was also used to derive DROP scores without this term (possible range 0 to 5).

All versions of the DROP score were found to predict postural hypotension in the validation cohort with similar areas under the curve of 0.65 but a trend to higher odds of postural hypotension with the exclusion of inter-arm difference from the model (Figure 1, table 5). Sensitivities and specificities of the unweighted DROP score without the inter-arm difference term were 76%, 16%, 5% and 53%, 91%, 99% respectively for cut-offs of ≥1, ≥2 and ≥3, although only 15 participants attained a DROP score of 3 and only one a score of 4. This equated to a number needed to test in order to detect one case of postural hypotension of 5, 5 and 2 for DROP scores of 1, 2 and 3 respectively. For the weighted DROP score without inter-arm difference a cut off value of 0.6 or more had a sensitivity of 74% and specificity of 55% for detection of postural hypotension. A similar pattern was seen for the DROP models including inter-arm difference; for an unweighted DROP score of 1 or more sensitivity and specificity for postural hypotension were 81% and 46% respectively predicting detection of one case of postural hypotension for every five tested. For the weighted score, a cut off value of 0.26 had a sensitivity of 81% and a specificity of 46% for detection of postural hypotension.

DROP scores were predictive of mortality over nine years of follow-up, with increasing ORs according to DROP score with adjustment for age (Figure 2). Classification by unweighted DROP scores was also predictive of declines in MMSE after nine years (Figure 3).

Discussion

Main findings

This analysis has confirmed that it is feasible, in a community living cohort of predominantly older people, to derive a score based on easily recognised risk markers, that can help to identify older persons that are likely to have postural hypotension and require further clinical evaluation. The score, consisting of six risk markers: use of digoxin, presence of Parkinson's disease, hypertension, cardiovascular disease, stroke, and a difference in systolic blood pressure between arms ≥10mmHg, performs similarly with or without weighting, therefore a simple additive score is preferred. Performance is also similar when the inter-arm term is omitted, further simplifying its application.

In this population, postural hypotension is associated with a doubling of risk of death over nine years of follow-up. The DROP score also predicts increasing future mortality from any cause and is associated with greater decline in Mini Mental State Examination scores.

Strengths and weaknesses

The cohort was chosen as representative of a free-living elderly population and the 15.4% prevalence of postural hypotension is consistent with figures ranging from 11 to 15% in other general elderly (over 65) populations.[16-18] Comprehensive recording of baseline variables allowed a large number of previously reported risk factors for postural hypotension to be tested. Since this was undertaken as a feasibility study no formal sample size calculation was undertaken, however there were sufficient events to support the multivariable analyses performed.[38] Although the relatively low numbers attaining DROP scores higher than 2 did lead to imprecision around the predictive values of those higher levels of scores. Re-analysis and external validation in a larger sized cohort could overcome this limitation. Blood pressures were measured supine and standing for this study whereas in practice sitting and standing measurements are commonly recommended.[36] These are less sensitive but more practical in primary care,[39] however a score derived in supine to standing cases of postural hypotension cannot be assumed to perform similarly in the sitting to standing setting. Therefore, we regard this analysis as a feasibility study that supports the concept of a simple pragmatic prediction score to aid daily practice, in need of refinement through larger scale analyses, and exploration in cohorts with sit to stand measurements.

Relevance to literature

Postural hypotension has previously been reported as a significant independent predictor of four year all-cause mortality in the Honolulu Heart programme.[6] It also predicted mortality in the Malmo Heart study,[8] but not in the Helsinki ageing study.[40] Frailty was associated with a higher prevalence of postural hypotension in the TILDA study, and adjustment for frailty may influence associations with mortality.[41 42] However no measures of frailty remained predictive of postural hypotension on inclusion in the current multivariable analyses, and a frailty index predicted postural *symptoms* but not postural hypotension within TILDA.[33]

Prevalence of postural hypotension rises with age.[15] Although those with postural hypotension in this study were on average five years older age was not a significant independent predictor of postural hypotension in our models. This may have been in part due to the skewed nature of the age profile in InCHIANTI, although sensitivity analyses excluding those under 65 made no difference (not reported). Prevalence of postural hypotension is elevated in association with a history of stroke or TIA,[43-45] cardiovascular disease,[24-26] diabetes,[22 27] or hypertension, which itself affects over 60% of the over 65 age group.[46] Thus the significant factors in our models were all age related conditions which seems the likely explanation for loss of age itself as an independent predictor due to collinearity. Parkinson's disease was the strongest predictor of postural hypotension in our analyses although, affecting only 1.1% of participants, it was also the least common factor. Postural hypotension has previously been reported to have prevalence approaching 50% in some groups of Parkinson's sufferers,[47 48] although only a third of those with postural hypotension report symptoms.[49]

The association of postural hypotension with presence of an inter-arm difference is, to our knowledge, a novel finding. We have previously associated inter-arm difference with white coat effects, which can confound detection of postural hypotension.[50 51] Arterial stiffness is a postulated cause of inter-arm difference,[52] and is also associated with postural hypotension;[53 54] thus inter-arm difference as a proxy measure of arterial stiffness might account for the observed association.

Although postural hypotension is associated with diabetes, and with other complications such as neuropathy, retinopathy and proteinuria,[55] there was no univariable association in this study. Prevalence of postural hypotension in diabetes is associated with complications and duration of disease;[56 57] in this cohort diabetes was present in only 6% of participants, whereas recent data suggest that 25% of adults over the age of 65 in the US have it.[58] Therefore a validation of our models in other larger representative populations is needed.

Postural hypotension has been associated with mild cognitive impariement.[59 60] and reduced cognitive performance.[61] Postural hypotension did not predict cognitive decline in a two year prospective study of older Finns,[62] but is predictive over longer follow up.[63] In the current analysis postural hypotension per se was not predictive of cognitive decline over nine years of follow up but the DROP score was. This seems plausible given that it includes a number of risk markers known to be associated with cognitive decline.

Relevance to clinical practice

Testing sitting (or lying) and standing blood pressure takes time and training. The skills of nurses measuring postural hypotension are variable when compared with guidelines;[64] incorrect arm positioning can underestimate postural hypotension,[65] and the alerting reaction can over-estimate it.[66] Early and accurate detection of postural hypotension is a pre-requisite to intervening with medication withdrawal to reduce postural blood pressure drops and their associated risks including falls. Currently symptoms appear to be the main trigger for testing.[29] This should continue, however, a tool to identify which *asymptomatic* patients to test may help to target additional testing to those most likely to benefit. A DROP score of one or more appears to have such potential, and may support proposals that individuals at elevated risk of postural hypotension should be tested.[67]

The strongly cardiovascular composition of the DROP score means that patients will commonly be taking antihypertensive drugs. Potential adverse effects of withdrawing antihypertensive medication to ameliorate postural hypotension are unclear, and medication withdrawal may concern clinicians, carers and patients. Risk of falls rises incrementally with each added orthostatic drug.[68] Prevalence of postural hypotension in hypertension is related to use of cardiovascular drugs (antihypertensive agents, vasodilators, diuretics),[69 70] alpha blockers,[71] and the number of antihypertensive drugs used,[72 73] and is associated with resistant or uncontrolled hypertension.[74 75] Successful treatment of blood pressure in the elderly is in fact associated with lower prevalence of postural hypotension,[76 77] but withdrawal of antihypertensive therapy improves postural hypotension.[78 79]

We retained Parkinson's disease in our models due to the strength of the association with postural hypotension, however, on clinical grounds, testing for postural hypotension would be better regarded as integral to any review in Parkinson's disease, given the high prevalence of postural hypotension in this condition.[49]

We sought to develop a pragmatic score to support busy clinicians, faced with a rising workload and increasingly multimorbid caseload.[31] Although measurement of blood pressure in both arms has become more frequent over time it is not part of a routine review.[29 80] Therefore we derived a DROP score omitting inter-arm difference, which performed with similar sensitivity and specificity. For the same reasons, we prefer the unweighted score as a practical aide memoire to recognition of the risk of postural hypotension.

Further research

This study has examined the feasibility of identifying whom should be tested with sitting and standing blood pressure measurements to detect asymptomatic postural hypotension. It seems that

a simple pragmatic scoring system can support this. We need to refine and externally validate this approach in larger samples more representative of UK primary care. Further work is needed to examine the feasibility and implications of medication review and antihypertensive withdrawal based on detection of postural hypotension in primary care.

Conclusion

We have described the derivation and validation of a score predicting the presence of postural hypotension. Initial testing suggests this approach to be feasible, and has identified the potential utility of the score in predicting mortality and cognitive decline over a nine year period of follow up. Further validation of the score in larger cohorts of individuals is warranted.

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Authors' contributions

CEC conceived and undertook this analysis. DT contributed to the analysis. FW contributed to the analysis and offered statistical advice and support. DL offered advice on analysis and interpretation of cognitive impairment indices. LF supported the study on behalf of the InCHIANTI investigators. JLC supervised study conduct. CEC drafted the manuscript, all authors revised and edited the manuscript and all authors have read, reviewed, and approved the final manuscript.

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Competing interests statement

All authors assert that they have no competing interests to declare

Data sharing statement

The InCHIANTI datasets are available on application with a research proposal to the InCHIANTI investigators at http://inchiantistudy.net/wp/

Previous dissemination

Interim reports on this work have been presented at annual scientific meetings of the European Society for Hypertension, Paris 2016 (Clark C, Thomas D, Warren F et al. Predicting postural hypotension, falls, and cognitive impairment: the InCHIANTI study. *J Hypertens* 2016; 34, e-Supplement 2: e32, September 2016) and the British and Irish Hypertension Society, Dublin, 2016 (Clark C, Thomas D, Mejzner N, et al. Can we predict who should be tested for postural hypotension? Derivation and validation of a prediction tool. *Journal of Human Hypertension* 2016;30 doi: doi:10.1038/jhh.2016.60)

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Figure 1. Prevalence of postural hypotension vs DROP Score.

Figure 2. Kaplan Meier survival plot for DROP scores over 9 years follow up

Figure 3. Mean change in Mini Mental State Examination score over nine years per DROP score

Group	Risk marker included in analysis
Demographics	age
	gender
Medical History	hypertension
	heart failure
	myocardial infarction
	angina
	stroke
	diabetes
	Parkinson's disease
	cancer
	dementia
Examination	Mini Mental State Examination
Medications	antiarrhythmics
	antidepressants
	antipsychotics
	anxiolytics
	anticholinesterase inhibitors
Frailty	hospital admission, fall, or weight loss in last 12 months
	WHO physical disability level
	ADL disability score

Table 1. Risk markers included in univariable analysis

	Derivation Cohort	Validation Cohort	p
N	**649**	**668**	
	Mean (SD) or N/%	**Mean (SD) or N/%**	**t/ χ^2**
age	68.5 (15.7)	68.2 (15.3)	0.77
BMI	27.2 (4.3)	27.1 (4.0)	0.59
Supine SBP (higher arm)#	145.9 (21.3)	146.3 (21.6)	0.76
Supine DBP (higher arm)#	82.9 (8.8)	83.1 (9.5)	0.59
Standing SBP 1 min	140.4 (21.0)	141.2 (21.3)	0.51
Standing DBP 1 min	83.0 (8.9)	83.6 (9.4)	0.25
Standing SBP 3 min	141.4 (20.9)	141.9 (20.9)	0.66
Standing DBP 3 min	82.7 (9.0)	83.0 (9.4)	0.60
Female	368 (56.7)	358 (53.6)	0.27
Site (Greve vs Bagno a Ripoli)	320 vs 329	327 vs 341	0.91
Deceased @ 9 years	199 (30.7)	203 (30.4)	0.95
Systolic drop ≥20mmHg 1min	56 (8.6)	45 (6.7)	0.21
Diastolic drop ≥10mmHg 1min	41 (6.3)	40 (6.0)	0.82
Systolic drop ≥20mmHg 3 min	47 (7.2)	42 (6.3)	0.51
Diastolic drop ≥10mmHg 3min	46 (7.1)	48 (7.2)	1.00
Postural Hypotension present*	107 (16.5)	96 (14.4)	0.32
Systolic inter-arm difference ≥10mmHg	121 (18.8)	121 (18.1)	0.83
Previous stroke	44 (6.8)	45 (6.7)	1.00
Pre-existing diabetes	80 (12.3)	76 (11.4)	0.61
Pre-existing hypertension	279 (43.0)	292 (43.7)	0.82
Pre-existing CV disease	63 (9.7)	50 (7.5)	0.17
Pre-existing dementia	38 (5.9)	27 (4.0)	0.16
Pre-existing Parkinson's disease	9 (1.4)	6 (0.9)	0.45
Fall in preceding 12 months	143 (22.0)	130 (19.5)	0.28

#mean of 2nd and 3rd readings

*defined as a drop of ≥20mmHg systolic or ≥10mmHg diastolic within 3 minutes of standing

Table 2. Baseline characteristics of derivation and validation cohorts

Variable (n (%) unless otherwise stated)	PH absent (n=542)	PH present (n=107)	p value
Age (mean, SD)	67.7 (15.8)	72.2 (14.6)	0.005
Age over 60	438 (81)	96 (90)	0.027
Age over 65	421 (78)	90 (84)	0.160
Age over 70	302 (56)	73 (68)	0.018
MMSE score (mean, SD)	25.3 (4.9)	24.1 (5.1)	0.031
Female gender	301 (55.5)	67 (62.6)	0.200
Digoxin	27	14	0.004
Antiarrhythmics, class I and III	10	4	0.264
Psycholeptics: typical antipsychotics	8	4	0.119
Psycholeptics: atypical antipsychotics	6	1	1.000
Psycholeptics: anxiolytics	103	18	0.684
Psychoanaleptics: antidepressants	22	5	0.791
Drugs for dementia	5	0	1.000
Hypertension	217	62	0.001
Congestive heart failure	22	10	0.028
Myocardial infarction	23	6	0.607
Angina	21	7	0.421
Any CV disease	45	18	0.011
Stroke	28	16	0.001
Diabetes	64	16	0.420
Parkinson's disease	4	5	0.008
Any cancer	30 (5.5)	8 (7.5)	0.497
Dementia	29	9	0.257
MMSE score 22 to 26	150	27	0.637
hospital admission in past year	54	18	0.044
Weight loss ≥10lbs in past year	22	7	0.301
Any fall in past year	115	28	0.254
Any ADL disability	100 (18.5)	28 (26.2)	0.083
WHO disability level >1	66 (12.2)	24 (22.6)	0.045
Systolic inter-arm difference (mean, SD) mmHg	2.0 (4.1)	4.7 (5.9)	<0.001
Systolic inter-arm BP difference ≥10mmHg	81 (14.9)	40 (37.4)	<0.001
Systolic inter-arm BP difference ≥ 15mmHg	10 (1.8)	6 (5.6)	0.007

Table 3. Univariable associations of risk markers with postural hypotension in derivation cohort

Variable	Odds Ratio	95% Confidence Interval
Model 1		
Parkinson's disease	4.7	1.2 to 19.2
Previous stroke	2.2	1.1 to 4.5
Taking digoxin	2.2	1.0 to 4.7
Previous cardiac disease	1.9	1.0 to 3.6
Hypertension	1.7	1.1 to 2.6
Systolic inter-arm difference (continuous per mmHg)	1.1	1.1 to 1.2
Model 2		
Parkinson's disease	5.0	1.2 to 19.9
Previous stroke	2.2	1.1 to 4.4
Taking digoxin	2.4	1.1 to 5.1
Previous cardiac disease	1.9	1.0 to 2.6
Hypertension	1.7	1.1 to 5.1
Systolic inter-arm difference ≥10mmHg	3.3	2.0 to 5.3
Model 3		
Parkinson's disease	5.3	1.4 to 20.4
Previous stroke	2.4	1.2 to 4.8
Taking digoxin	2.0	0.9 to 4.3
Previous cardiac disease	1.8	0.9 to 3.4
Hypertension	1.9	1.3 to 3.0

Table 4. Multivariable prediction models for postural hypotension

	Including inter-arm difference		Excluding inter-arm difference	
	Weighted	**Unweighted**	**Weighted**	**Unweighted**
Prediction of PH per unit increase of DROP score OR (95%CI)	1.9 (1.4 to 2.5)	1.8 (1.4 to 2.3)	2.4 (1.6 to 3.4)	2.0 (1.5 to 2.6)
Area under ROC curve (95%CI)	0.65 (0.59 to 0.70)	0.65 (0.60 to 0.71)	0.65 (0.59 to 0.71)	0.65 (0.59 to 0.70)
Mortality risk per unit score OR (95%CI)	1.9 (1.6 to 2.2)	1.8 (1.5 to 2.1)	2.8 (2.2 to 3.4)	2.1 (1.8 to 2.5)
Change in MMSE score over study (ANOVA)	N/A	P=0.004	N/A	P<0.001
Annual change in MMSE score (ANOVA)	N/A	P<0.001	N/A	P<0.001

Table 5. DROP score associations with postural hypotension, mortality and cognitive decline

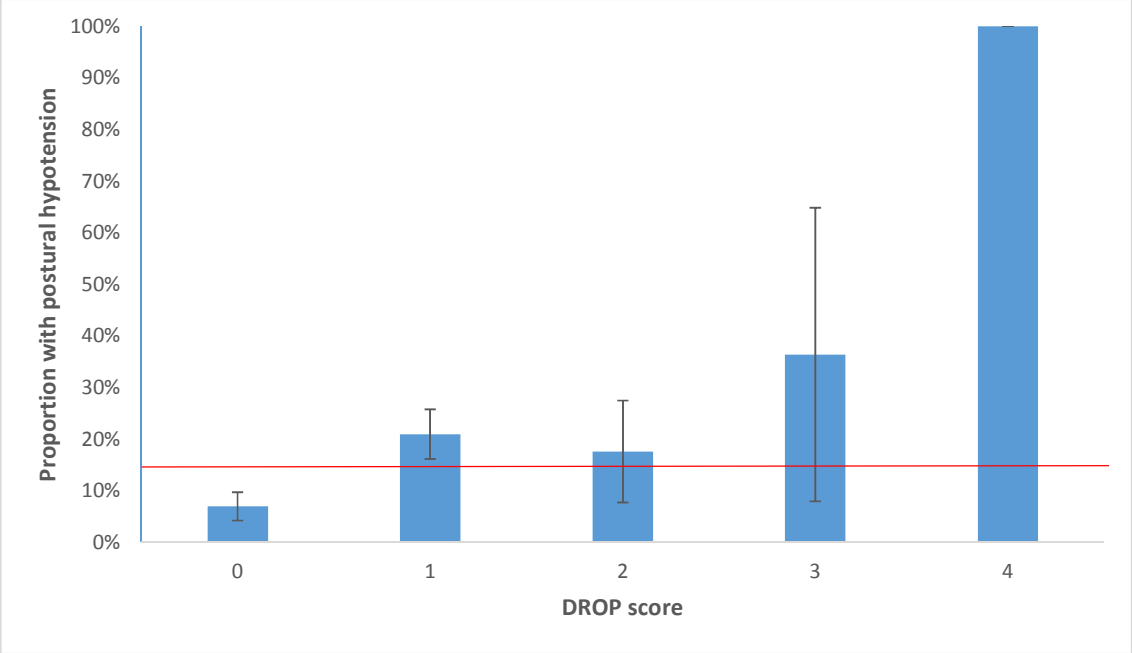

Figure 1. Prevalence of postural hypotension vs unweighted DROP Score without inter-arm difference term.

(Population prevalence indicated by horizontal line)

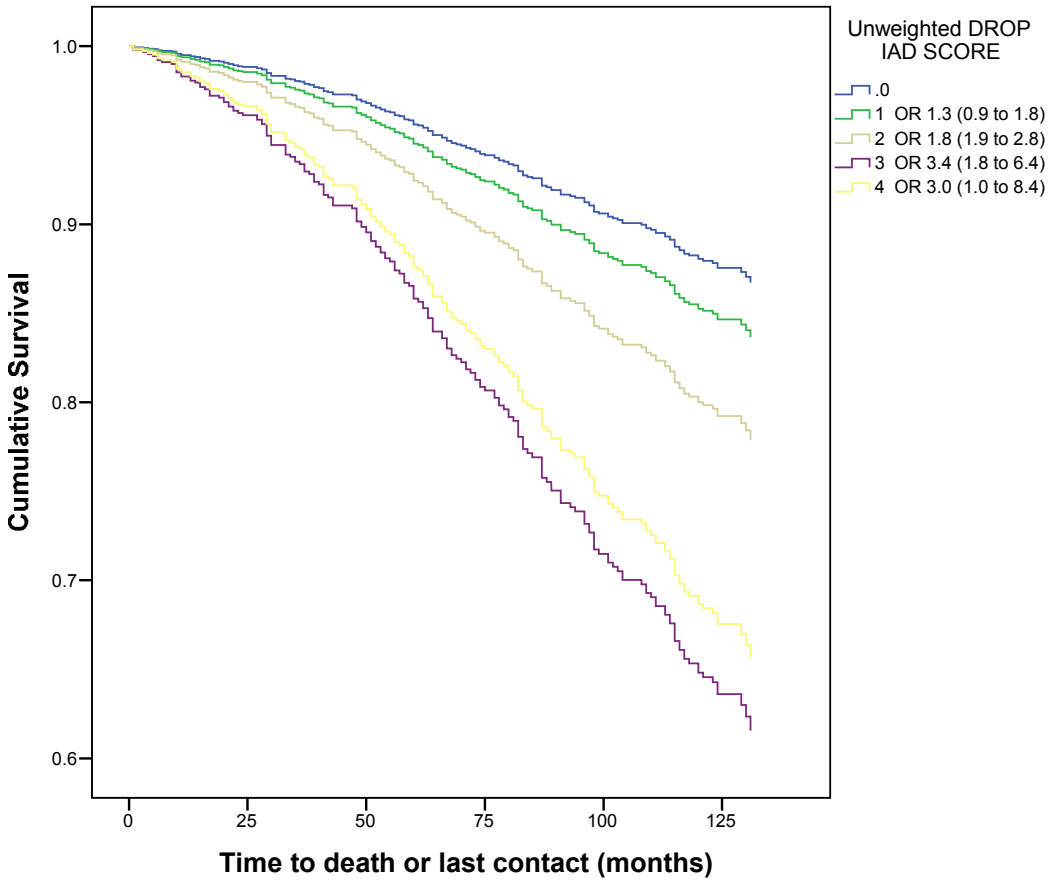

Figure 2. Kaplan Meier survival plot for DROP scores over 9 years follow up

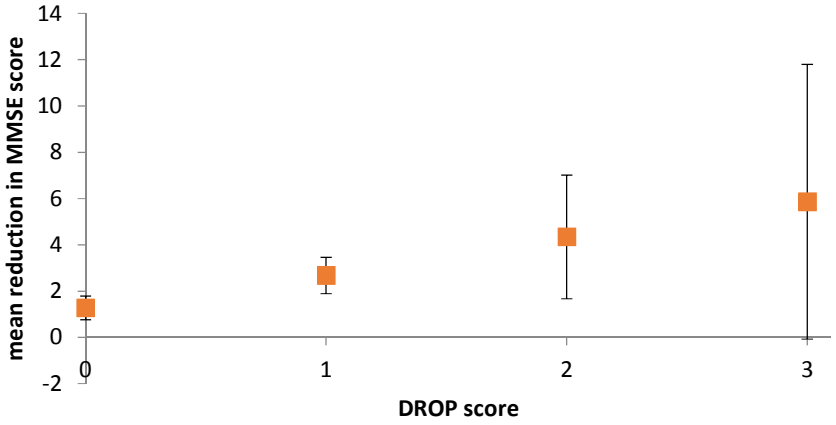

Figure 3. Mean change in Mini Mental State Examination score over nine years per DROP score

Appendix: Literature search for factors associated with postural hypotension

Demographics:	Increasing age[1-9]
	Female gender[10]
	Nursing home residence[11-15]
Medical History:	Hypertension[7-10 16-20] and uncontrolled hypertension[6 21 22]
	Diabetes and diabetic complications[17 23-28]
	Chronic Kidney Disease[10 29 30]
	Stroke[31-36]
	Ischaemic heart disease[36 37]
	Heart failure[38 39]
	Parkinson's disease[40-42]
	Cognitive impairment[43-50]
	Depression[51]
Medications:	Antiarrhythmic drugs[11]
	Antihypertensives[4 9-11 52-55] (negative association with ACE inhibitors)[10]
	Psychotropic agents (antipsychotics, sedatives, antidepressants)[23 53 56]
	Anticholinesterase inhibitors[50]
Biochemical:	Vitamin D deficiency (conflicting evidence)[1 23 57 58]
Frailty:[59 60]	Falls[61]
	Get up and go test[11]
	Reduced calf mass index[54 62]
	Activity of Daily Living disability score[1 11]
	Cumulative illness Rating Scale for Geriatrics score[23]
Environmental:	Seasons – prevalence higher in summer and in heatwaves[63 64]
	Time of day – higher in mornings[65-68]

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Start: 20150325 Conference End: 20150329 Conference Publication: (var pagings) 2015;65(4):April.

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Medline and Embase Search Strategy

Date of search 20th October 2015

	Searches	Results
1	postural hypotension.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, nm, kf, px, rx, an, ui]	3109
2	orthostatic hypotension.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, nm, kf, px, rx, an, ui]	22694
3	1 or 2	21615
4	prevalence.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, nm, kf, px, rx, an, ui]	1202953
5	3 and 4	1678
6	limit 5 to humans	1565
7	limit 6 to aged <65+ years> [Limit not valid in Ovid MEDLINE(R),Ovid MEDLINE(R) In-Process; records were retained]	661
8	remove duplicates from 7	470

TRIPOD Checklist: Prediction Model Development and Validation

Section/Topic	Item		Checklist Item	Page
Title and abstract				
Title	1	D;V	Identify the study as developing and/or validating a multivariable prediction model, the target population, and the outcome to be predicted.	1
Abstract	2	D;V	Provide a summary of objectives, study design, setting, participants, sample size, predictors, outcome, statistical analysis, results, and conclusions.	3
Introduction				
Background and objectives	3a	D;V	Explain the medical context (including whether diagnostic or prognostic) and rationale for developing or validating the multivariable prediction model, including references to existing models.	4
	3b	D;V	Specify the objectives, including whether the study describes the development or validation of the model or both.	4
Methods				
Source of data	4a	D;V	Describe the study design or source of data (e.g., randomized trial, cohort, or registry data), separately for the development and validation data sets, if applicable.	4
	4b	D;V	Specify the key study dates, including start of accrual; end of accrual; and, if applicable, end of follow-up.	4
Participants	5a	D;V	Specify key elements of the study setting (e.g., primary care, secondary care, general population) including number and location of centres.	4
	5b	D;V	Describe eligibility criteria for participants.	4
	5c	D;V	Give details of treatments received, if relevant.	N/A
Outcome	6a	D;V	Clearly define the outcome that is predicted by the prediction model, including how and when assessed.	5
	6b	D;V	Report any actions to blind assessment of the outcome to be predicted.	5
Predictors	7a	D;V	Clearly define all predictors used in developing or validating the multivariable prediction model, including how and when they were measured.	5 & table 1
	7b	D;V	Report any actions to blind assessment of predictors for the outcome and other predictors.	5
Sample size	8	D;V	Explain how the study size was arrived at.	6
Missing data	9	D;V	Describe how missing data were handled (e.g., complete-case analysis, single imputation, multiple imputation) with details of any imputation method.	N/A
Statistical analysis methods	10a	D	Describe how predictors were handled in the analyses.	5
	10b	D	Specify type of model, all model-building procedures (including any predictor selection), and method for internal validation.	5
	10c	V	For validation, describe how the predictions were calculated.	5
	10d	D;V	Specify all measures used to assess model performance and, if relevant, to compare multiple models.	5
	10e	V	Describe any model updating (e.g., recalibration) arising from the validation, if done.	N/A
Risk groups	11	D;V	Provide details on how risk groups were created, if done.	N/A
Development vs. validation	12	V	For validation, identify any differences from the development data in setting, eligibility criteria, outcome, and predictors.	None table 2
Results				
Participants	13a	D;V	Describe the flow of participants through the study, including the number of participants with and without the outcome and, if applicable, a summary of the follow-up time. A diagram may be helpful.	5
	13b	D;V	Describe the characteristics of the participants (basic demographics, clinical features, available predictors), including the number of participants with missing data for predictors and outcome.	table 2
	13c	V	For validation, show a comparison with the development data of the distribution of important variables (demographics, predictors and outcome).	table 2
Model development	14a	D	Specify the number of participants and outcome events in each analysis.	5
	14b	D	If done, report the unadjusted association between each candidate predictor and outcome.	table 3
Model specification	15a	D	Present the full prediction model to allow predictions for individuals (i.e., all regression coefficients, and model intercept or baseline survival at a given time point).	table 4
	15b	D	Explain how to the use the prediction model.	6
Model performance	16	D;V	Report performance measures (with CIs) for the prediction model.	6 table 5
Model-updating	17	V	If done, report the results from any model updating (i.e., model specification, model performance).	6
Discussion				
Limitations	18	D;V	Discuss any limitations of the study (such as nonrepresentative sample, few events per predictor, missing data).	6-7
Interpretation	19a	V	For validation, discuss the results with reference to performance in the development data, and any other validation data.	6-7
	19b	D;V	Give an overall interpretation of the results, considering objectives, limitations, results from similar studies, and other relevant evidence.	6-7
Implications	20	D;V	Discuss the potential clinical use of the model and implications for future research.	8
Other information				
Supplementary information	21	D;V	Provide information about the availability of supplementary resources, such as study protocol, Web calculator, and data sets.	N/A
Funding	22	D;V	Give the source of funding and the role of the funders for the present study.	14

TRIPOD Checklist: Prediction Model Development and Validation

*Items relevant only to the development of a prediction model are denoted by D, items relating solely to a validation of a prediction model are denoted by V, and items relating to both are denoted D;V. We recommend using the TRIPOD Checklist in conjunction with the TRIPOD Explanation and Elaboration document.

BMJ Open

Detecting Risks Of Postural Hypotension (DROP): derivation and validation of a prediction score for primary care

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Detecting Risks Of Postural Hypotension (DROP): derivation and validation of a prediction score for primary care

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Appendices: 1

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Abstract

Objectives

Falls are a common problem in older people. Postural hypotension contributes to falls but is often asymptomatic. In the absence of symptoms, postural hypotension is only infrequently checked for in clinical practice. We undertook this study to derive, validate and explore the prospective associations of a prediction tool to identify people likely to have unrecognised postural hypotension.

Design and setting

Cross-sectional and prospective multivariable cohort analysis.

Participants

1317 participants of the InCHIANTI study, a population based cohort representative of the older Italian population.

Primary outcome measures

Predictive value of score to suggest presence of postural hypotension,

Methods

Subjects were randomised 1:1 to derivation or validation cohorts. Within the derivation cohort univariable associations for candidate predictors of postural hypotension were tested. Variables with P<0.1 entered multivariable linear regression models. Factors retaining multivariable significance were incorporated into unweighted and weighted DROP scores. These scores were tested in the validation cohort against prediction of postural hypotension, cognitive decline and mortality over nine years' follow up.

Results

Postural hypotension was present in 203 (15.4%) of participants. Factors predicting postural hypotension were: digoxin use, Parkinson's disease, hypertension, stroke or cardiovascular disease, and an inter-arm systolic blood pressure difference. Area under the curve was consistent at 0.65 for all models, with significant odds ratios (OR) of 1.8 to 2.4 per unit increase in score for predicting postural hypotension. For a DROP score ≥1, five cases need to be tested to identify one with postural hypotension.

Increasing DROP scores predicted mortality (OR 1.8 to 2.8 per unit rise) and increasing rates of decline of Mini Mental State Examination score (ANOVA p<0.001) over 9 years of follow up.

Conclusions

The DROP score provides a simple method to identify people likely to have postural hypotension, and increased risks to health, who require further evaluation.

(296 words)

Strengths and limitations of this study

- This study used data from a well-established cohort representative of an older population in Italy, to derive and validate a score ("DROP score") to predict the presence of postural hypotension.
- Comprehensive recording of baseline variables at recruitment by the InCHIANTI investigators allowed a large number of previously reported risk markers for postural hypotension to be tested in the analyses.
- The study was undertaken according to TRIPOD guidelines and randomised splitting of the cohort allowed internal validation of the findings to be undertaken.
- We chose the consensus definition of postural hypotension as our outcome measure since we sought to predict this, rather than study postural symptoms, which should in any event trigger testing for postural hypotension.
- The population studied did not include residential or nursing home residents; refinement of the scoring system within larger cohorts more representative of primary care populations is required to confirm the potential of the DROP score in practice.

Introduction

Falls are a major cause of morbidity and mortality in older people; 35% of people older than 65 and 50% of people older than 80 fall at least once a year.[1 2] Falls are the leading cause of disability and the leading cause of death from injury among people over 75 in the UK, and cost the NHS around £2.3 billion per year.[3] Postural or orthostatic hypotension is a major risk factor for falls,[4 5] and is independently associated with increased mortality rates.[6-8] Postural hypotension has also been associated with dementia and cognitive impairment, and may have more subtle adverse effects on wellbeing and cognition.[9]

Postural hypotension is commonly defined as a fall of either ≥20mmHg in systolic blood pressure or ≥10mmHg in diastolic blood pressure, from sitting or lying, within three minutes of standing up.[10] Reported prevalences of postural hypotension vary widely, and are sensitive to both care setting, occurring in over half of patients admitted to care of the elderly,[11-13] and to the presence of co-morbidity. General adult population prevalence appears to be around 7%,[14 15] rising to 11 to 15% in persons 65 years old and older,[16-18] and 19% in those aged over 80 or older.[15] Prevalence is reported to be higher in the presence of hypertension,[19-23] stroke,[24 25] myocardial infarction,[25 26] and diabetes.[22 27]

Guidelines vary in recommendations for the detection of postural hypotension. The National Institute for Health and Care Excellence (NICE) recommends testing in the presence of symptoms whist the European Society for Hypertension also recommends testing in the elderly and in the presence of diabetes.[1 28] Unfortunately most individuals with postural hypotension are asymptomatic,[7] and we have found that, in practice, postural hypotension is seldom looked for in patients who do not report postural symptoms.[29] Anecdotally, testing is not undertaken due to time constraints; screening for postural hypotension is not supported in the literature, being regarded as lacking an evidence base, and primary care workloads are rising.[30 31] Risks of hospitalisation, nursing home admission or mortality can already be predicted by the electronic frailty index (eFI), a score derived from existing information in primary care computer records, and incorporated into many general practice computing systems. However the association of eFI with, and its ability to predict, postural hypotension (which itself is poorly tested for and recorded in primary care) is unclear,[32] and comparable frailty indices have not been found to be predictive of postural hypotension.[33] To address this gap in care we hypothesised that a simple prediction score, based on easily recognised risk markers, might help clinicians identify those most likely to have postural hypotension thereby allowing a targeted implementation of sitting and standing blood pressure measurement in the absence of symptoms. We therefore undertook the current analysis, in a well-documented cohort known to be representative of an older population living in the community. Aims were to explore the feasibility of deriving and internally validating a prediction score, to assess its value and its prospective associations.

Methods

The study was conducted and reported in accordance with the TRIPOD statement.[34] We studied participants from the InCHIANTI study; a cohort study designed to explore declining mobility in later life. The Italian National Research Council on Aging ethical committee approved the InCHIANTI study protocol, and the current analysis proposals were approved by the investigating committee of the InCHIANTI study.

The InCHIANTI study methods have been described in detail elsewhere.[35] In brief, 1270 participants aged 65 years or more were randomly selected from the population registries of two villages: Greve

in Chianti, and Antella in Bagno a Ripoli. Additional people were randomly selected from these sites to complete recruitment of at least 30 men and 30 women for each age decile from age 20 to 29 upwards. Extensive baseline interviews and examinations were conducted at recruitment, between September 1998 and March 2000, and follow up data were obtained after three, six and nine years. Blood pressure was initially measured supine, sequentially in both arms, to identify the higher reading arm, then a further two measurements were made on the higher reading arm. Subjects then stood and blood pressure was measured once after 1 minute and once more after 3 minutes standing. All measurements were obtained by research assistants using a standard mercury sphygmomanometer. Written informed consent was obtained from all participants at recruitment to the InCHIANTI study.

Baseline blood pressure was calculated as the mean of the second and third supine blood pressure readings.[36] Postural changes in blood pressure from lying to standing were calculated by subtraction of this mean from the standing blood pressure. Postural hypotension was considered to exist where there was as a reduction in blood pressure on standing of ≥20mmHg systolic or ≥10mmHg diastolic after 1 or after 3 minutes.[10] Hypertension was defined as use of antihypertensive drugs and/or a documented history of hypertension at recruitment.

For this analysis, participants were randomly allocated in a 1:1 ratio using a split-sample method,[37] stratified for gender and study site, to either a *derivation* or a *validation* group by a statistician (FW) blinded to postural hypotension status and medical history. A literature review was undertaken to identify potential risk markers for consideration in the analyses (appendix). These were mapped to variables available in the InCHIANTI dataset (table 1), which were then tested in the derivation cohort for univariable associations with postural hypotension, using t-tests or χ^2 tests as appropriate to the data. Variables signalling potential univariable associations (defined as $p<0.1$) were included in multivariable model analyses using an automated backward stepwise regression method.[38] We also included age (explored both continuously and as a dichotomous variable with cut-offs of 60, 65 and 70 years) and gender in all multivariable models. Prospective associations of postural hypotension with survival up to 9 years of follow-up were tested using Kaplan-Meier plots and Cox proportional hazard ratios. Cognitive decline was defined as a reduction in Mini Mental State Examination score (MMSE score) of 5 points or more from baseline, and rate of cognitive decline was defined as change in MMSE scores averaged per year of follow up.

Risk markers that retained significance in the multivariable models were used to derive both weighted and unweighted scores (DROP scores); weighted scores were derived by the addition of the multivariable Log (n) odds ratio (OR) for each marker present, whereas the unweighted model allocated one point for each risk marker present. Scores were tested in the validation cohort for ability to predict postural hypotension using ROC analysis, to predict future mortality using Cox proportional hazard ratios, and cognitive decline over nine years using ANOVA. All analyses were undertaken using IBM SPSS Statistics v24.0.0.2.

Results

Data for standing blood pressure existed for 1317 of the 1453 participants (91%) and they formed the cohort for this study. The derivation cohort (n=649) and validation cohort (n=668) were well matched for all important characteristics and putative risk markers (table 2); overall postural

hypotension was present for 203 (15.4%) of participants at recruitment. Mean age of participants was 68.3 (standard deviation 15.5).

For the derivation cohort postural hypotension was associated, over 9 years of follow-up, with increased all-cause mortality (Hazard Ratio (HR) 1.9; 95% confidence interval (95%CI) 1.4 to 2.7), cardiovascular mortality (HR 2.1; 95%CI 1.2 to 3.4), and non-cardiovascular mortality (HR 2.0; 95%CI 1.3 to 3.0). Results of univariable testing are summarised in table 3. Using a cut off value of $p<0.1$ the following candidate predictors were entered into multivariable models: age (continuous, or dichotomous for age 60 or 70 cut offs), MMSE score, angiotensin 2 antagonist, diuretic and digoxin use, presence of hypertension, any cardiovascular disease (composite of history of myocardial infarction, angina pectoris or congestive heart failure), stroke, Parkinson's disease, hospital admission within the last year, WHO disability level, any disability in activities of daily living, systolic inter-arm difference (continuous or using ≥10mmHg cut off).

Terms for systolic and diastolic blood pressure were entered into the multivariable model in a sensitivity analysis. Apart from finding that systolic blood pressure replaced the term for presence of hypertension, model outputs were unchanged. Therefore we adopted the latter for consistency with our aim to derive a pragmatic score.

Backward stepwise regression analysis produced consistent findings with any permutation of discrete and continuous variables for age (which was not retained in any model) or for inter-arm difference (model 1 and model 2; table 4). Consequently, a dichotomous cut off for inter-arm difference of ≥10mmHg was selected for simplicity, and retained with five other factors (use of digoxin, Parkinson's disease, previous stroke, previous cardiac disease and diagnosis of hypertension) to derive weighted (using log OR) and unweighted (score 1 for each factor present; possible range 0 to 6) *DROP* scores. The scores were tested in the validation cohort. Since inter-arm difference is not routinely measured a third model excluding inter-arm difference (model 3, table 4) was also used to derive DROP scores without this term (possible range 0 to 5).

All versions of the DROP score were found to predict postural hypotension in the validation cohort with similar areas under the curve of 0.65 but a trend to higher odds of postural hypotension with the exclusion of inter-arm difference from the model (Figure 1, table 5). Sensitivities and specificities of the unweighted DROP score without the inter-arm difference term were 76%, 16%, 5% and 53%, 91%, 99% respectively for cut-offs of ≥1, ≥2 and ≥3, although only 15 participants attained a DROP score of 3 and only one a score of 4. This equated to a number needed to test in order to detect one case of postural hypotension of 5, 5 and 2 for DROP scores of 1, 2 and 3 respectively. For the weighted DROP score without inter-arm difference a cut off value of 0.6 or more had a sensitivity of 74% and specificity of 55% for detection of postural hypotension. A similar pattern was seen for the DROP models including inter-arm difference; for an unweighted DROP score of 1 or more sensitivity and specificity for postural hypotension were 81% and 46% respectively predicting detection of one case of postural hypotension for every five tested. For the weighted score, a cut off value of 0.26 had a sensitivity of 81% and a specificity of 46% for detection of postural hypotension.

DROP scores were predictive of mortality over nine years of follow-up, with increasing ORs according to DROP score with adjustment for age (Figure 2). Data on MMSE were available for 529/668 (79%) of the validation cohort; classification by unweighted DROP scores was also predictive of decline in MMSE after nine years (Figure 3).

Discussion

Main findings

This analysis has confirmed that it is feasible, in a community living cohort of predominantly older people, to derive a score based on easily recognised risk markers that can help to identify older persons that are likely to have postural hypotension and require further clinical evaluation. The score, consisting of six risk markers: use of digoxin, presence of Parkinson's disease, hypertension, cardiovascular disease, stroke, and a difference in systolic blood pressure between arms ≥10mmHg, performs similarly with or without weighting, therefore a simple additive score is preferred. Performance is also similar when the inter-arm term is omitted, further simplifying its application.

In this population, postural hypotension is associated with a doubling of risk of death over nine years of follow-up. The DROP score also predicts increasing future mortality from any cause and is associated with greater decline in Mini Mental State Examination scores.

Strengths and weaknesses

The cohort was chosen as representative of a free-living elderly population and the 15.4% prevalence of postural hypotension is consistent with figures ranging from 11 to 15% in other general elderly (over 65) populations.[16-18] Comprehensive recording of baseline variables allowed a large number of previously reported risk factors for postural hypotension to be tested. Since this was undertaken as a feasibility study no formal sample size calculation was undertaken, however there were sufficient events to support the multivariable analyses performed.[38] Although the relatively low numbers attaining DROP scores higher than 2 did lead to imprecision around the predictive values of those higher levels of scores. Re-analysis and external validation in a larger sized cohort could overcome this limitation. Blood pressures were measured supine and standing for this study whereas in practice sitting and standing measurements are commonly recommended.[36] These are less sensitive but more practical in primary care,[39] however a score derived in supine to standing cases of postural hypotension cannot be assumed to perform similarly in the sitting to standing setting. Therefore, we regard this analysis as a feasibility study that supports the concept of a simple pragmatic prediction score to aid daily practice, in need of refinement through larger scale analyses, and exploration in cohorts with sit to stand measurements.

Relevance to literature

Postural hypotension has previously been reported as a significant independent predictor of four year all-cause mortality in the Honolulu Heart programme.[6] It also predicted mortality in the Malmo Heart study,[8] but not in the Helsinki ageing study.[40] Frailty was associated with a higher prevalence of postural hypotension in the TILDA study, and adjustment for frailty may influence associations with mortality.[41 42] However no measures of frailty remained predictive of postural hypotension on inclusion in the current multivariable analyses, and a frailty index predicted postural *symptoms* but not postural hypotension within TILDA.[33]

Prevalence of postural hypotension rises with age.[15] Although those with postural hypotension in this study were on average five years older age was not a significant independent predictor of postural hypotension in our models. This may have been in part due to the skewed nature of the age profile in InCHIANTI, although sensitivity analyses excluding those under 65 made no difference (not reported). Prevalence of postural hypotension is elevated in association with a history of stroke or TIA,[43-45] cardiovascular disease,[24-26] diabetes,[22 27] or hypertension, which itself affects over 60% of the over 65 age group.[46] Thus the significant factors in our models were all age related conditions which

seems the likely explanation for loss of age itself as an independent predictor due to collinearity. Parkinson's disease was the strongest predictor of postural hypotension in our analyses although, affecting only 1.1% of participants, it was also the least common factor. Postural hypotension has previously been reported to have prevalence approaching 50% in some groups of Parkinson's sufferers,[47 48] although only a third of those with postural hypotension report symptoms.[49]

The association of postural hypotension with presence of an inter-arm difference is, to our knowledge, a novel finding. We have previously associated inter-arm difference with white coat effects, which can confound detection of postural hypotension.[50 51] Arterial stiffness is a postulated cause of inter-arm difference,[52] and is also associated with postural hypotension;[53 54] thus inter-arm difference as a proxy measure of arterial stiffness might account for the observed association. Hypotension on ambulatory monitoring and elevated pulse-wave velocity are both associated with cognitive decline, lending further support to the association of inter-arm difference, arterial stiffness, and postural hypotension.[55]

Although postural hypotension is associated with diabetes, and with other complications such as neuropathy, retinopathy and proteinuria,[56] there was no univariable association in this study. Prevalence of postural hypotension in diabetes is associated with complications and duration of disease;[57 58] in this cohort diabetes was present in only 6% of participants, whereas recent data suggest that 25% of adults over the age of 65 in the US have it.[59] Therefore a validation of our models in other larger representative populations is needed.

Postural hypotension has been associated with mild cognitive impariement.[60 61] and reduced cognitive performance.[62] Postural hypotension did not predict cognitive decline in a 2 year prospective study of older Finns,[63] but is predictive over longer follow up.[64] In the current analysis postural hypotension per se was not predictive of cognitive decline over nine years of follow up but the DROP score was. This seems plausible given that it includes a number of risk markers known to be associated with cognitive decline.

Relevance to clinical practice

Testing sitting (or lying) and standing blood pressure takes time and training. The skills of nurses measuring postural hypotension are variable when compared with guidelines;[65] incorrect arm positioning can underestimate postural hypotension,[66] and the alerting reaction can over-estimate it.[67] Early and accurate detection of postural hypotension is a pre-requisite to intervening with medication withdrawal to reduce postural blood pressure drops and their associated risks including falls. Currently symptoms appear to be the main trigger for testing.[29] This should continue, however, a tool to identify which *asymptomatic* patients to test may help to target additional testing to those most likely to benefit. A DROP score of one or more appears to have such potential, and may support proposals that individuals at elevated risk of postural hypotension should be tested.[68]

The strongly cardiovascular composition of the DROP score means that patients will commonly be taking antihypertensive drugs. Potential adverse effects of withdrawing antihypertensive medication to ameliorate postural hypotension are unclear, and medication withdrawal may concern clinicians, carers and patients. Risk of falls rises incrementally with each added orthostatic drug.[69] Prevalence of postural hypotension in hypertension is related to use of cardiovascular drugs (antihypertensive agents, vasodilators, diuretics),[70 71] alpha blockers,[72] and the number of antihypertensive drugs used,[73 74] and is associated with resistant or uncontrolled hypertension.[75 76] Successful treatment of blood pressure in the elderly is in fact associated with lower prevalence of postural hypotension,[77 78] but withdrawal of antihypertensive therapy improves postural hypotension.[79 80]

We retained Parkinson's disease in our models due to the strength of the association with postural hypotension, however, on clinical grounds, testing for postural hypotension would be better regarded as integral to any review in Parkinson's disease, given the high prevalence of postural hypotension in this condition.[49]

We sought to develop a pragmatic score to support busy clinicians, faced with a rising workload and increasingly multimorbid caseload.[31] Although measurement of blood pressure in both arms has become more frequent over time it is not part of a routine review.[29 81] Therefore we derived a DROP score omitting inter-arm difference, which performed with similar sensitivity and specificity. For the same reasons, we prefer the unweighted score as a practical aide memoire to recognition of the risk of postural hypotension.

Further research

This study has examined the feasibility of identifying whom should be tested with sitting and standing blood pressure measurements to detect asymptomatic postural hypotension. It seems that a simple pragmatic scoring system can support this. We need to refine and externally validate this approach in larger samples more representative of UK primary care. Further work is needed to examine the feasibility and implications of medication review and antihypertensive withdrawal based on detection of postural hypotension in primary care.

Conclusion

We have described the derivation and validation of a score predicting the presence of postural hypotension. Initial testing suggests this approach to be feasible, and has identified the potential utility of the score in predicting mortality and cognitive decline over a nine year period of follow up. Further validation of the score in larger cohorts of individuals is warranted.

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Authors' contributions

CEC conceived and undertook this analysis. DT contributed to the analysis. FW contributed to the analysis and offered statistical advice and support. DL offered advice on analysis and interpretation of cognitive impairment indices. LF supported the study on behalf of the InCHIANTI investigators. JLC supervised study conduct. CEC drafted the manuscript, all authors revised and edited the manuscript and all authors have read, reviewed, and approved the final manuscript.

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Competing interests statement

All authors assert that they have no competing interests to declare

Previous dissemination

Interim reports on this work have been presented at annual scientific meetings of the European Society for Hypertension, Paris 2016 (Clark C, Thomas D, Warren F et al. Predicting postural hypotension, falls, and cognitive impairment: the InCHIANTI study. *J Hypertens* 2016; 34, e-Supplement 2: e32, September 2016) and the British and Irish Hypertension Society, Dublin, 2016 (Clark C, Thomas D, Mejzner N, et al. Can we predict who should be tested for postural hypotension? Derivation and validation of a prediction tool. *Journal of Human Hypertension* 2016;30 doi: doi:10.1038/jhh.2016.60)

Data sharing statement

The InCHIANTI datasets are available on application with a research proposal to the InCHIANTI investigators at http://inchiantistudy.net/wp/

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Group	Risk marker included in analysis
Demographics	age
	gender
Medical History	hypertension
	heart failure
	myocardial infarction
	angina
	stroke
	diabetes
	Parkinson's disease
	cancer
	dementia
Examination	Mini Mental State Examination
Medications	antihypertensives
	antiarrhythmics
	antidepressants
	antipsychotics
	anxiolytics
	anticholinesterase inhibitors
Frailty	hospital admission, fall, or weight loss in last 12 months
	WHO physical disability level
	ADL disability score

Table 1. Risk markers included in univariable analysis

	Derivation Cohort	Validation Cohort	p
N	**649**	**668**	
	Mean (SD) or N/%	**Mean (SD) or N/%**	**t/ χ^2**
age	68.5 (15.7)	68.2 (15.3)	0.77
BMI	27.2 (4.3)	27.1 (4.0)	0.59
Supine SBP (higher arm)#	145.9 (21.3)	146.3 (21.6)	0.76
Supine DBP (higher arm)#	82.9 (8.8)	83.1 (9.5)	0.59
Standing SBP 1 min	140.4 (21.0)	141.2 (21.3)	0.51
Standing DBP 1 min	83.0 (8.9)	83.6 (9.4)	0.25
Standing SBP 3 min	141.4 (20.9)	141.9 (20.9)	0.66
Standing DBP 3 min	82.7 (9.0)	83.0 (9.4)	0.60
Female	368 (56.7)	358 (53.6)	0.27
Site (Greve vs Bagno a Ripoli)	320 vs 329	327 vs 341	0.91
Deceased @ 9 years	199 (30.7)	203 (30.4)	0.95
Systolic drop ≥20mmHg 1min	56 (8.6)	45 (6.7)	0.21
Diastolic drop ≥10mmHg 1min	41 (6.3)	40 (6.0)	0.82
Systolic drop ≥20mmHg 3 min	47 (7.2)	42 (6.3)	0.51
Diastolic drop ≥10mmHg 3min	46 (7.1)	48 (7.2)	1.00
Postural Hypotension present*	107 (16.5)	96 (14.4)	0.32
Systolic inter-arm difference ≥10mmHg	121 (18.8)	121 (18.1)	0.83
Previous stroke	44 (6.8)	45 (6.7)	1.00
Pre-existing diabetes	80 (12.3)	76 (11.4)	0.61
Pre-existing hypertension	279 (43.0)	292 (43.7)	0.82
Pre-existing CV disease	63 (9.7)	50 (7.5)	0.17
Pre-existing dementia	38 (5.9)	27 (4.0)	0.16
Pre-existing Parkinson's disease	9 (1.4)	6 (0.9)	0.45
Fall in preceding 12 months	143 (22.0)	130 (19.5)	0.28

#mean of 2nd and 3rd readings

*defined as a drop of ≥20mmHg systolic or ≥10mmHg diastolic within 3 minutes of standing

Table 2. Baseline characteristics of derivation and validation cohorts

Variable (n (%) unless otherwise stated)	PH absent (n=542)	PH present (n=107)	p value
Age (mean, SD)	67.7 (15.8)	72.2 (14.6)	0.005
Age over 60	438 (81)	96 (90)	0.027
Age over 65	421 (78)	90 (84)	0.160
Age over 70	302 (56)	73 (68)	0.018
MMSE score (mean, SD)	25.3 (4.9)	24.1 (5.1)	0.031
Female gender	301 (55.5)	67 (62.6)	0.200
Angiotensin converting enzyme inhibitors	103 (19)	23 (22)	0.552
Angiotensin-2 antagonists	6 (1)	4 (4)	0.066
Calcium channel blockers	62 (11)	15 (14)	0.451
Diuretics	48 (9)	17 (16)	0.027
Beta-blockers	20 (4)	4 (4)	0.981
alpha-blockers	11 (2)	1 (1)	0.442
aldosterone antagonists	2 (0.4)	0 (0)	0.529
Digoxin	27 (5)	14 (13)	0.004
Antiarrhythmics, class I and III	10 (2)	4 (4)	0.264
Psycholeptics: typical antipsychotics	8 (1)	4 (4)	0.119
Psycholeptics: atypical antipsychotics	6 (1)	1 (1)	1.000
Psycholeptics: anxiolytics	103 (19)	18 (17)	0.684
Psychoanaleptics: antidepressants	22 (4)	5 (5)	0.791
Drugs for dementia	5 (1)	0 (0)	1.000
Hypertension	217 (40)	62 (58)	0.001
Congestive heart failure	22 (4)	10 (9)	0.028
Myocardial infarction	23 (4)	6 (6)	0.607
Angina	21 (4)	7 (6)	0.421
Any CV disease	45 (8)	18 (17)	0.011
Stroke	28 (5)	16 (15)	0.001
Diabetes	64 (12)	16 (15)	0.420
Parkinson's disease	4 (1)	5 (5)	0.008
Any cancer	30 (6)	8 (8)	0.497
Dementia	29 (5)	9 (8)	0.257
MMSE score 22 to 26	150 (28)	27 (25)	0.637
hospital admission in past year	54 (10)	18 (17)	0.044
Weight loss ≥10lbs in past year	22 (4)	7 (6)	0.301
Any fall in past year	115 (21)	28 (26)	0.254
Any ADL disability	100 (19)	28 (26)	0.083
WHO disability level >1	66 (12)	24 (23)	0.045
Systolic blood pressure (mean, SD) mmHg	144.3 (20.1)	153.7 (25.3)	<0.001
Diastolic blood pressure (mean, SD) mmHg	82.2 (8.8)	86.2 (8.1)	<0.001

Systolic inter-arm difference (mean, SD) mmHg	2.0 (4.1)	4.7 (5.9)	<0.001
Systolic inter-arm BP difference ≥10mmHg	81 (15)	40 (37)	<0.001
Systolic inter-arm BP difference ≥ 15mmHg	10 (2)	6 (6)	0.007

p values derived from t-tests for continuous data, or Pearson chi-square for categorical data; Fisher's exact test reported where expected cell count <5

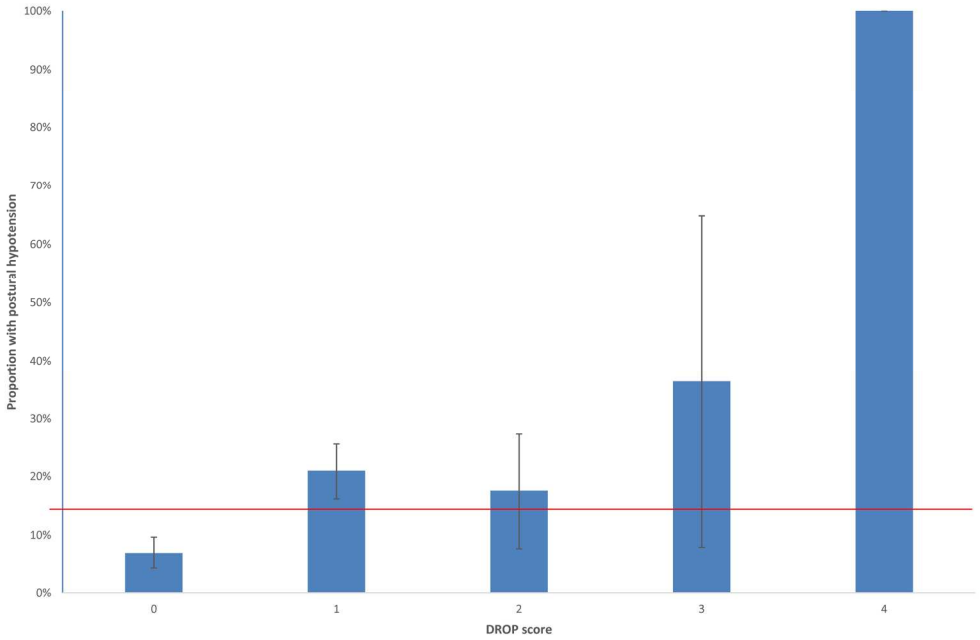
Table 3. Univariable associations of risk markers with postural hypotension in derivation cohort

Variable	Odds Ratio	95% Confidence Interval
Model 1		
Parkinson's disease	4.7	1.2 to 19.2
Previous stroke	2.2	1.1 to 4.5
Taking digoxin	2.2	1.0 to 4.7
Previous cardiac disease	1.9	1.0 to 3.6
Hypertension	1.7	1.1 to 2.6
Systolic inter-arm difference (continuous per mmHg)	1.1	1.1 to 1.2
Model 2		
Parkinson's disease	5.0	1.2 to 19.9
Previous stroke	2.2	1.1 to 4.4
Taking digoxin	2.4	1.1 to 5.1
Previous cardiac disease	1.9	1.0 to 2.6
Hypertension	1.7	1.1 to 5.1
Systolic inter-arm difference ≥10mmHg	3.3	2.0 to 5.3
Model 3		
Parkinson's disease	5.3	1.4 to 20.4
Previous stroke	2.4	1.2 to 4.8
Taking digoxin	2.0	0.9 to 4.3
Previous cardiac disease	1.8	0.9 to 3.4
Hypertension	1.9	1.3 to 3.0

Table 4. Multivariable prediction models for postural hypotension

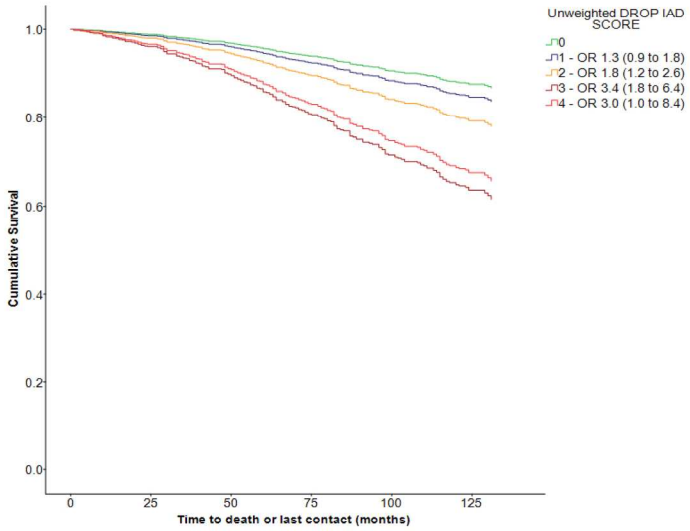
	Including inter-arm difference		Excluding inter-arm difference	
	Weighted	**Unweighted**	**Weighted**	**Unweighted**
Prediction of PH per unit increase of DROP score OR (95%CI)	1.9 (1.4 to 2.5)	1.8 (1.4 to 2.3)	2.4 (1.6 to 3.4)	2.0 (1.5 to 2.6)
Area under ROC curve (95%CI)	0.65 (0.59 to 0.70)	0.65 (0.60 to 0.71)	0.65 (0.59 to 0.71)	0.65 (0.59 to 0.70)
Mortality risk per unit score OR (95%CI)	1.9 (1.6 to 2.2)	1.8 (1.5 to 2.1)	2.8 (2.2 to 3.4)	2.1 (1.8 to 2.5)
Change in MMSE score over study (ANOVA)	N/A	P=0.004	N/A	P<0.001
Annual change in MMSE score (ANOVA)	N/A	P<0.001	N/A	P<0.001

Table 5. DROP score associations with postural hypotension, mortality and cognitive decline



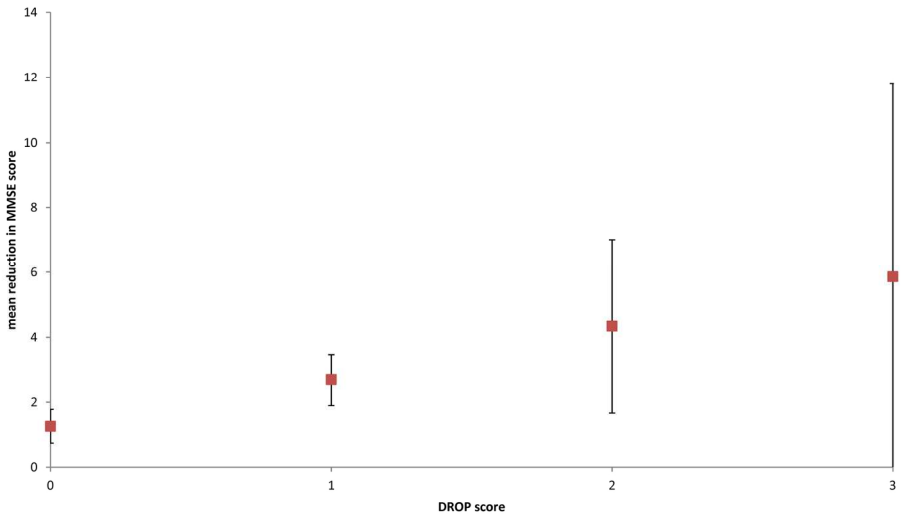
Prevalence of postural hypotension vs unweighted DROP Score without inter-arm difference term (Population prevalence indicated by horizontal line)

167x108mm (300 x 300 DPI)



Kaplan Meier survival plot for DROP scores over 9 years follow up

209x148mm (300 x 300 DPI)



Mean change in Mini Mental State Examination score over nine years per DROP score

165x108mm (300 x 300 DPI)

Appendix: Literature search for factors associated with postural hypotension

Demographics:	Increasing age[1-9]
	Female gender[10]
	Nursing home residence[11-15]
Medical History:	Hypertension[7-10 16-20] and uncontrolled hypertension[6 21 22]
	Diabetes and diabetic complications[17 23-28]
	Chronic Kidney Disease[10 29 30]
	Stroke[31-36]
	Ischaemic heart disease[36 37]
	Heart failure[38 39]
	Parkinson's disease[40-42]
	Cognitive impairment[43-50]
	Depression[51]
Medications:	Antiarrhythmic drugs[11]
	Antihypertensives[4 9-11 52-55] (negative association with ACE inhibitors)[10]
	Psychotropic agents (antipsychotics, sedatives, antidepressants)[23 53 56]
	Anticholinesterase inhibitors[50]
Biochemical:	Vitamin D deficiency (conflicting evidence)[1 23 57 58]
Frailty:[59 60]	Falls[61]
	Get up and go test[11]
	Reduced calf mass index[54 62]
	Activity of Daily Living disability score[1 11]
	Cumulative illness Rating Scale for Geriatrics score[23]
Environmental:	Seasons – prevalence higher in summer and in heatwaves[63 64]
	Time of day – higher in mornings[65-68]

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Medline and Embase Search Strategy

Date of search 20th October 2015

	Searches	Results
1	postural hypotension.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, nm, kf, px, rx, an, ui]	3109
2	orthostatic hypotension.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, nm, kf, px, rx, an, ui]	22694
3	1 or 2	21615
4	prevalence.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, nm, kf, px, rx, an, ui]	1202953
5	3 and 4	1678
6	limit 5 to humans	1565
7	limit 6 to aged <65+ years> [Limit not valid in Ovid MEDLINE(R),Ovid MEDLINE(R) In-Process; records were retained]	661
8	remove duplicates from 7	470

TRIPOD

TRIPOD Checklist: Prediction Model Development and Validation

Section/Topic	Item		Checklist Item	Page
Title and abstract				
Title	1	D;V	Identify the study as developing and/or validating a multivariable prediction model, the target population, and the outcome to be predicted.	1
Abstract	2	D;V	Provide a summary of objectives, study design, setting, participants, sample size, predictors, outcome, statistical analysis, results, and conclusions.	3
Introduction				
Background and objectives	3a	D;V	Explain the medical context (including whether diagnostic or prognostic) and rationale for developing or validating the multivariable prediction model, including references to existing models.	4
	3b	D;V	Specify the objectives, including whether the study describes the development or validation of the model or both.	4
Methods				
Source of data	4a	D;V	Describe the study design or source of data (e.g., randomized trial, cohort, or registry data), separately for the development and validation data sets, if applicable.	4
	4b	D;V	Specify the key study dates, including start of accrual; end of accrual; and, if applicable, end of follow-up.	4
Participants	5a	D;V	Specify key elements of the study setting (e.g., primary care, secondary care, general population) including number and location of centres.	4
	5b	D;V	Describe eligibility criteria for participants.	4
	5c	D;V	Give details of treatments received, if relevant.	N/A
Outcome	6a	D;V	Clearly define the outcome that is predicted by the prediction model, including how and when assessed.	5
	6b	D;V	Report any actions to blind assessment of the outcome to be predicted.	5
Predictors	7a	D;V	Clearly define all predictors used in developing or validating the multivariable prediction model, including how and when they were measured.	5 & table 1
	7b	D;V	Report any actions to blind assessment of predictors for the outcome and other predictors.	5
Sample size	8	D;V	Explain how the study size was arrived at.	6
Missing data	9	D;V	Describe how missing data were handled (e.g., complete-case analysis, single imputation, multiple imputation) with details of any imputation method.	N/A
Statistical analysis methods	10a	D	Describe how predictors were handled in the analyses.	5
	10b	D	Specify type of model, all model-building procedures (including any predictor selection), and method for internal validation.	5
	10c	V	For validation, describe how the predictions were calculated.	5
	10d	D;V	Specify all measures used to assess model performance and, if relevant, to compare multiple models.	5
	10e	V	Describe any model updating (e.g., recalibration) arising from the validation, if done.	N/A
Risk groups	11	D;V	Provide details on how risk groups were created, if done.	N/A
Development vs. validation	12	V	For validation, identify any differences from the development data in setting, eligibility criteria, outcome, and predictors.	None table 2
Results				
Participants	13a	D;V	Describe the flow of participants through the study, including the number of participants with and without the outcome and, if applicable, a summary of the follow-up time. A diagram may be helpful.	5
	13b	D;V	Describe the characteristics of the participants (basic demographics, clinical features, available predictors), including the number of participants with missing data for predictors and outcome.	table 2
	13c	V	For validation, show a comparison with the development data of the distribution of important variables (demographics, predictors and outcome).	table 2
Model development	14a	D	Specify the number of participants and outcome events in each analysis.	5
	14b	D	If done, report the unadjusted association between each candidate predictor and outcome.	table 3
Model specification	15a	D	Present the full prediction model to allow predictions for individuals (i.e., all regression coefficients, and model intercept or baseline survival at a given time point).	table 4
	15b	D	Explain how to the use the prediction model.	6
Model performance	16	D;V	Report performance measures (with CIs) for the prediction model.	6 table 5
Model-updating	17	V	If done, report the results from any model updating (i.e., model specification, model performance).	6
Discussion				
Limitations	18	D;V	Discuss any limitations of the study (such as nonrepresentative sample, few events per predictor, missing data).	6-7
Interpretation	19a	V	For validation, discuss the results with reference to performance in the development data, and any other validation data.	6-7
	19b	D;V	Give an overall interpretation of the results, considering objectives, limitations, results from similar studies, and other relevant evidence.	6-7
Implications	20	D;V	Discuss the potential clinical use of the model and implications for future research.	8
Other information				
Supplementary information	21	D;V	Provide information about the availability of supplementary resources, such as study protocol, Web calculator, and data sets.	N/A
Funding	22	D;V	Give the source of funding and the role of the funders for the present study.	14

TRIPOD Checklist: Prediction Model Development and Validation

*Items relevant only to the development of a prediction model are denoted by D, items relating solely to a validation of a prediction model are denoted by V, and items relating to both are denoted D;V. We recommend using the TRIPOD Checklist in conjunction with the TRIPOD Explanation and Elaboration document.

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Detecting Risks Of Postural Hypotension (DROP): derivation and validation of a prediction score for primary care

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Detecting Risks Of Postural Hypotension (DROP): derivation and validation of a prediction score for primary care

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Abstract

Objectives

Falls are a common problem in older people. Postural hypotension contributes to falls but is often asymptomatic. In the absence of symptoms, postural hypotension is only infrequently checked for in clinical practice. We undertook this study to derive, validate and explore the prospective associations of a prediction tool to identify people likely to have unrecognised postural hypotension.

Design and setting

Cross-sectional and prospective multivariable cohort analysis.

Participants

1317 participants of the InCHIANTI study, a population based cohort representative of the older Italian population.

Primary outcome measures

Predictive value of score to suggest presence of postural hypotension,

Methods

Subjects were randomised 1:1 to derivation or validation cohorts. Within the derivation cohort univariable associations for candidate predictors of postural hypotension were tested. Variables with P<0.1 entered multivariable linear regression models. Factors retaining multivariable significance were incorporated into unweighted and weighted DROP scores. These scores were tested in the validation cohort against prediction of postural hypotension, cognitive decline and mortality over nine years' follow up.

Results

Postural hypotension was present in 203 (15.4%) of participants. Factors predicting postural hypotension were: digoxin use, Parkinson's disease, hypertension, stroke or cardiovascular disease, and an inter-arm systolic blood pressure difference. Area under the curve was consistent at 0.65 for all models, with significant odds ratios (OR) of 1.8 to 2.4 per unit increase in score for predicting postural hypotension. For a DROP score ≥1, five cases need to be tested to identify one with postural hypotension.

Increasing DROP scores predicted mortality (OR 1.8 to 2.8 per unit rise) and increasing rates of decline of Mini Mental State Examination score (ANOVA p<0.001) over 9 years of follow up.

Conclusions

The DROP score provides a simple method to identify people likely to have postural hypotension, and increased risks to health, who require further evaluation.

(296 words)

Strengths and limitations of this study

- This study used data from a well-established cohort representative of an older population in Italy, to derive and validate a score ("DROP score") to predict the presence of postural hypotension.
- Comprehensive recording of baseline variables at recruitment by the InCHIANTI investigators allowed a large number of previously reported risk markers for postural hypotension to be tested in the analyses.
- The study was undertaken according to TRIPOD guidelines and randomised splitting of the cohort allowed internal validation of the findings to be undertaken.
- We chose the consensus definition of postural hypotension as our outcome measure since we sought to predict this, rather than study postural symptoms. Specific postural symptoms were not recorded during recruitment to the InCHIANTI study, and their presence should in any event trigger testing for postural hypotension.
- The population studied did not include residential or nursing home residents; refinement of the scoring system within larger cohorts more representative of primary care populations is required to confirm the potential of the DROP score in practice.

Introduction

Falls are a major cause of morbidity and mortality in older people; 35% of people older than 65 and 50% of people older than 80 fall at least once a year.[1 2] Falls are the leading cause of disability and the leading cause of death from injury among people over 75 in the UK, and cost the NHS around £2.3 billion per year.[3] Postural or orthostatic hypotension is a major risk factor for falls,[4 5] and is independently associated with increased mortality rates.[6-8] Postural hypotension has also been associated with dementia and cognitive impairment, and may have more subtle adverse effects on wellbeing and cognition.[9]

Postural hypotension is commonly defined as a fall of either ≥20mmHg in systolic blood pressure or ≥10mmHg in diastolic blood pressure, from sitting or lying, within three minutes of standing up.[10] Reported prevalences of postural hypotension vary widely, and are sensitive to both care setting, occurring in over half of patients admitted to care of the elderly,[11-13] and to the presence of co-morbidity. General adult population prevalence appears to be around 7%,[14 15] rising to 11 to 15% in persons 65 years old and older,[16-18] and 19% in those aged over 80 or older.[15] Prevalence is reported to be higher in the presence of hypertension,[19-23] stroke,[24 25] myocardial infarction,[25 26] and diabetes.[22 27]

Guidelines vary in recommendations for the detection of postural hypotension. The National Institute for Health and Care Excellence (NICE) recommends testing in the presence of symptoms whist the European Society for Hypertension also recommends testing in the elderly and in the presence of diabetes.[1 28] Unfortunately most individuals with postural hypotension are asymptomatic,[7] and we have found that, in practice, postural hypotension is seldom looked for in patients who do not report postural symptoms.[29] Anecdotally, testing is not undertaken due to time constraints; screening for postural hypotension is not supported in the literature, being regarded as lacking an evidence base, and primary care workloads are rising.[30 31] Risks of hospitalisation, nursing home admission or mortality can already be predicted by the electronic frailty index (eFI), a score derived from existing information in primary care computer records, and incorporated into many general practice computing systems. However the association of eFI with, and its ability to predict, postural hypotension (which itself is poorly tested for and recorded in primary care) is unclear,[32] and comparable frailty indices have not been found to be predictive of postural hypotension.[33] To address this gap in care we hypothesised that a simple prediction score, based on easily recognised risk markers, might help clinicians identify those most likely to have postural hypotension thereby allowing a targeted implementation of sitting and standing blood pressure measurement in the absence of symptoms. We therefore undertook the current analysis, in a well-documented cohort known to be representative of an older population living in the community. Aims were to explore the feasibility of deriving and internally validating a prediction score, to assess its value and its prospective associations.

Methods

The study was conducted and reported in accordance with the TRIPOD statement.[34] We studied participants from the InCHIANTI study; a cohort study designed to explore declining mobility in later life. The Italian National Research Council on Aging ethical committee approved the InCHIANTI study protocol, and the current analysis proposals were approved by the investigating committee of the InCHIANTI study.

The InCHIANTI study methods have been described in detail elsewhere.[35] In brief, 1270 participants aged 65 years or more were randomly selected from the population registries of two villages: Greve

in Chianti, and Antella in Bagno a Ripoli. Additional people were randomly selected from these sites to complete recruitment of at least 30 men and 30 women for each age decile from age 20 to 29 upwards. Extensive baseline interviews and examinations were conducted at recruitment, between September 1998 and March 2000, and follow up data were obtained after three, six and nine years. Blood pressure was initially measured supine, sequentially in both arms, to identify the higher reading arm, then a further two measurements were made on the higher reading arm. Subjects then stood and blood pressure was measured once after 1 minute and once more after 3 minutes standing. All measurements were obtained by research assistants using a standard mercury sphygmomanometer. Written informed consent was obtained from all participants at recruitment to the InCHIANTI study.

Baseline blood pressure was calculated as the mean of the second and third supine blood pressure readings.[36] Postural changes in blood pressure from lying to standing were calculated by subtraction of this mean from the standing blood pressure. Postural hypotension was considered to exist where there was as a reduction in blood pressure on standing of ≥20mmHg systolic or ≥10mmHg diastolic after 1 or after 3 minutes.[10] Hypertension was defined as use of antihypertensive drugs and/or a documented history of hypertension at recruitment.

For this analysis, participants were randomly allocated in a 1:1 ratio using a split-sample method,[37] stratified for gender and study site, to either a *derivation* or a *validation* group by a statistician (FW) blinded to postural hypotension status and medical history. A literature review was undertaken to identify potential risk markers for consideration in the analyses (appendix). These were mapped to variables available in the InCHIANTI dataset (table 1), which were then tested in the derivation cohort for univariable associations with postural hypotension, using t-tests or χ^2 tests as appropriate to the data. Variables signalling potential univariable associations (defined as $p<0.1$) were included in multivariable model analyses using an automated backward stepwise regression method.[38] We also included age (explored both continuously and as a dichotomous variable with cut-offs of 60, 65 and 70 years) and gender in all multivariable models. Prospective associations of postural hypotension with survival up to 9 years of follow-up were tested using Kaplan-Meier plots and Cox proportional hazard ratios. Cognitive decline was defined as a reduction in Mini Mental State Examination score (MMSE score) of 5 points or more from baseline, and rate of cognitive decline was defined as change in MMSE scores averaged per year of follow up.

Risk markers that retained significance in the multivariable models were used to derive both weighted and unweighted scores (DROP scores); weighted scores were derived by the addition of the multivariable Log (n) odds ratio (OR) for each marker present, whereas the unweighted model allocated one point for each risk marker present. Scores were tested in the validation cohort for ability to predict postural hypotension using ROC analysis, to predict future mortality using Cox proportional hazard ratios, and cognitive decline over nine years using ANOVA. All analyses were undertaken using IBM SPSS Statistics v24.0.0.2.

Results

Data for standing blood pressure existed for 1317 of the 1453 participants (91%) and they formed the cohort for this study. The derivation cohort (n=649) and validation cohort (n=668) were well matched for all important characteristics and putative risk markers (table 2); overall postural

hypotension was present for 203 (15.4%) of participants at recruitment. Mean age of participants was 68.3 (standard deviation 15.5).

For the derivation cohort postural hypotension was associated, over 9 years of follow-up, with increased all-cause mortality (Hazard Ratio (HR) 1.9; 95% confidence interval (95%CI) 1.4 to 2.7), cardiovascular mortality (HR 2.1; 95%CI 1.2 to 3.4), and non-cardiovascular mortality (HR 2.0; 95%CI 1.3 to 3.0). Results of univariable testing are summarised in table 3. Using a cut off value of p<0.1 the following candidate predictors were entered into multivariable models: age (continuous, or dichotomous for age 60 or 70 cut offs), MMSE score, angiotensin 2 antagonist, diuretic and digoxin use, presence of hypertension, any cardiovascular disease (composite of history of myocardial infarction, angina pectoris or congestive heart failure), stroke, Parkinson's disease, hospital admission within the last year, WHO disability level, any disability in activities of daily living, systolic inter-arm difference (continuous or using ≥10mmHg cut off).

Terms for systolic and diastolic blood pressure were entered into the multivariable model in a sensitivity analysis. Apart from finding that systolic blood pressure replaced the term for presence of hypertension, model outputs were unchanged. Therefore we adopted the latter for consistency with our aim to derive a pragmatic score.

Backward stepwise regression analysis produced consistent findings with any permutation of discrete and continuous variables for age (which was not retained in any model) or for inter-arm difference (model 1 and model 2; table 4). Consequently, a dichotomous cut off for inter-arm difference of ≥10mmHg was selected for simplicity, and retained with five other factors (use of digoxin, Parkinson's disease, previous stroke, previous cardiac disease and diagnosis of hypertension) to derive weighted (using log OR) and unweighted (score 1 for each factor present; possible range 0 to 6) *DROP* scores. The scores were tested in the validation cohort. Since inter-arm difference is not routinely measured a third model excluding inter-arm difference (model 3, table 4) was also used to derive DROP scores without this term (possible range 0 to 5).

All versions of the DROP score were found to predict postural hypotension in the validation cohort with similar areas under the curve of 0.65 but a trend to higher odds of postural hypotension with the exclusion of inter-arm difference from the model (Figure 1, table 5). Sensitivities and specificities of the unweighted DROP score without the inter-arm difference term were 76%, 16%, 5% and 53%, 91%, 99% respectively for cut-offs of ≥1, ≥2 and ≥3, although only 15 participants attained a DROP score of 3 and only one a score of 4. This equated to a number needed to test in order to detect one case of postural hypotension of 5, 5 and 2 for DROP scores of 1, 2 and 3 respectively. For the weighted DROP score without inter-arm difference a cut off value of 0.6 or more had a sensitivity of 74% and specificity of 55% for detection of postural hypotension. A similar pattern was seen for the DROP models including inter-arm difference; for an unweighted DROP score of 1 or more sensitivity and specificity for postural hypotension were 81% and 46% respectively predicting detection of one case of postural hypotension for every five tested. For the weighted score, a cut off value of 0.26 had a sensitivity of 81% and a specificity of 46% for detection of postural hypotension.

DROP scores were predictive of mortality over nine years of follow-up, with increasing ORs according to DROP score with adjustment for age (Figure 2). Data on MMSE were available for 529/668 (79%) of the validation cohort; classification by unweighted DROP scores was also predictive of decline in MMSE after nine years (Figure 3). DROP scores were not predictive of future falls; however increasing DROP scores were associated with rising prevalence of falls in the year prior to recruitment (chi^2 for trend p<0.001).

Discussion

Main findings

This analysis has confirmed that it is feasible, in a community living cohort of predominantly older people, to derive a score based on easily recognised risk markers that can help to identify older persons that are likely to have postural hypotension and require further clinical evaluation. The score, consisting of six risk markers: use of digoxin, presence of Parkinson's disease, hypertension, cardiovascular disease, stroke, and a difference in systolic blood pressure between arms ≥10mmHg, performs similarly with or without weighting, therefore a simple additive score is preferred. Performance is also similar when the inter-arm term is omitted, further simplifying its application.

In this population, postural hypotension is associated with a doubling of risk of death over nine years of follow-up. The DROP score also predicts increasing future mortality from any cause and is associated with greater decline in Mini Mental State Examination scores.

Strengths and weaknesses

The cohort was chosen as representative of a free-living elderly population and the 15.4% prevalence of postural hypotension is consistent with figures ranging from 11 to 15% in other general elderly (over 65) populations.[16-18] Comprehensive recording of baseline variables allowed a large number of previously reported risk factors for postural hypotension to be tested. Since this was undertaken as a feasibility study no formal sample size calculation was undertaken, however there were sufficient events to support the multivariable analyses performed.[38] Although the relatively low numbers attaining DROP scores higher than 2 did lead to imprecision around the predictive values of those higher levels of scores. Re-analysis and external validation in a larger sized cohort could overcome this limitation. Blood pressures were measured supine and standing for this study whereas in practice sitting and standing measurements are commonly recommended.[36] These are less sensitive but more practical in primary care,[39] however a score derived in supine to standing cases of postural hypotension cannot be assumed to perform similarly in the sitting to standing setting. Therefore, we regard this analysis as a feasibility study that supports the concept of a simple pragmatic prediction score to aid daily practice, in need of refinement through larger scale analyses, and exploration in cohorts with sit to stand measurements. Although the DROP score was associated with fall prevalence we did not have data on specific posture induced symptoms, so were unable to examine the relationship of the DROP score with postural symptoms. The presence of symptoms, however, should trigger testing for postural hypotension in any event.[1 29]

Relevance to literature

Postural hypotension has previously been reported as a significant independent predictor of four year all-cause mortality in the Honolulu Heart programme.[6] It also predicted mortality in the Malmo Heart study,[8] but not in the Helsinki ageing study.[40] Frailty was associated with a higher prevalence of postural hypotension in the TILDA study, and adjustment for frailty may influence associations with mortality.[41 42] However no measures of frailty remained predictive of postural hypotension on inclusion in the current multivariable analyses, and a frailty index predicted postural *symptoms* but not postural hypotension within TILDA.[33]

Prevalence of postural hypotension rises with age.[15] Although those with postural hypotension in this study were on average five years older age was not a significant independent predictor of postural hypotension in our models. This may have been in part due to the skewed nature of the age profile in InCHIANTI, although sensitivity analyses excluding those under 65 made no difference (not

reported). Prevalence of postural hypotension is elevated in association with a history of stroke or TIA,[43-45] cardiovascular disease,[24-26] diabetes,[22 27] or hypertension, which itself affects over 60% of the over 65 age group.[46] Thus the significant factors in our models were all age related conditions which seems the likely explanation for loss of age itself as an independent predictor due to collinearity. Parkinson's disease was the strongest predictor of postural hypotension in our analyses although, affecting only 1.1% of participants, it was also the least common factor. Postural hypotension has previously been reported to have prevalence approaching 50% in some groups of Parkinson's sufferers,[47 48] although only a third of those with postural hypotension report symptoms.[49]

The association of postural hypotension with presence of an inter-arm difference is, to our knowledge, a novel finding. We have previously associated inter-arm difference with white coat effects, which can confound detection of postural hypotension.[50 51] Arterial stiffness is a postulated cause of inter-arm difference,[52] and is also associated with postural hypotension;[53 54] thus inter-arm difference as a proxy measure of arterial stiffness might account for the observed association. Hypotension on ambulatory monitoring and elevated pulse-wave velocity are both associated with cognitive decline, lending further support to the association of inter-arm difference, arterial stiffness, and postural hypotension.[55]

Although postural hypotension is associated with diabetes, and with other complications such as neuropathy, retinopathy and proteinuria,[56] there was no univariable association in this study. Prevalence of postural hypotension in diabetes is associated with complications and duration of disease;[57 58] in this cohort diabetes was present in only 6% of participants, whereas recent data suggest that 25% of adults over the age of 65 in the US have it.[59] Therefore a validation of our models in other larger representative populations is needed.

Postural hypotension has been associated with mild cognitive impariement.[60 61] and reduced cognitive performance.[62] Postural hypotension did not predict cognitive decline in a 2 year prospective study of older Finns,[63] but is predictive over longer follow up.[64] In the current analysis postural hypotension per se was not predictive of cognitive decline over nine years of follow up but the DROP score was. This seems plausible given that it includes a number of risk markers known to be associated with cognitive decline.

Relevance to clinical practice

Testing sitting (or lying) and standing blood pressure takes time and training. The skills of nurses measuring postural hypotension are variable when compared with guidelines;[65] incorrect arm positioning can underestimate postural hypotension,[66] and the alerting reaction can over-estimate it.[67] Early and accurate detection of postural hypotension is a pre-requisite to intervening with medication withdrawal to reduce postural blood pressure drops and their associated risks including falls. Currently symptoms appear to be the main trigger for testing.[29] This should continue, however, a tool to identify which *asymptomatic* patients to test may help to target additional testing to those most likely to benefit. A DROP score of one or more appears to have such potential, and may support proposals that individuals at elevated risk of postural hypotension should be tested.[68]

The strongly cardiovascular composition of the DROP score means that patients will commonly be taking antihypertensive drugs. Potential adverse effects of withdrawing antihypertensive medication to ameliorate postural hypotension are unclear, and medication withdrawal may concern clinicians, carers and patients. Risk of falls rises incrementally with each added orthostatic drug.[69] Prevalence of postural hypotension in hypertension is related to use of cardiovascular drugs (antihypertensive

agents, vasodilators, diuretics),[70 71] alpha blockers,[72] and the number of antihypertensive drugs used,[73 74] and is associated with resistant or uncontrolled hypertension.[75 76] Successful treatment of blood pressure in the elderly is in fact associated with lower prevalence of postural hypotension,[77 78] but withdrawal of antihypertensive therapy improves postural hypotension.[79 80]

We retained Parkinson's disease in our models due to the strength of the association with postural hypotension, however, on clinical grounds, testing for postural hypotension would be better regarded as integral to any review in Parkinson's disease, given the high prevalence of postural hypotension in this condition.[49]

We sought to develop a pragmatic score to support busy clinicians, faced with a rising workload and increasingly multimorbid caseload.[31] Although measurement of blood pressure in both arms has become more frequent over time it is not part of a routine review.[29 81] Therefore we derived a DROP score omitting inter-arm difference, which performed with similar sensitivity and specificity. For the same reasons, we prefer the unweighted score as a practical aide memoire to recognition of the risk of postural hypotension.

Further research

This study has examined the feasibility of identifying whom should be tested with sitting and standing blood pressure measurements to detect asymptomatic postural hypotension. It seems that a simple pragmatic scoring system can support this. We need to refine and externally validate this approach in larger samples more representative of UK primary care. Further work is needed to examine the feasibility and implications of medication review and antihypertensive withdrawal based on detection of postural hypotension in primary care.

Conclusion

We have described the derivation and validation of a score predicting the presence of postural hypotension. Initial testing suggests this approach to be feasible, and has identified the potential utility of the score in predicting mortality and cognitive decline over a nine year period of follow up. Further validation of the score in larger cohorts of individuals is warranted.

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Authors' contributions

CEC conceived and undertook this analysis. DT contributed to the analysis. FW contributed to the analysis and offered statistical advice and support. DL offered advice on analysis and interpretation of cognitive impairment indices. LF supported the study on behalf of the InCHIANTI investigators. JLC supervised study conduct. CEC drafted the manuscript, all authors revised and edited the manuscript and all authors have read, reviewed, and approved the final manuscript.

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Competing interests statement

All authors assert that they have no competing interests to declare

Previous dissemination

Interim reports on this work have been presented at annual scientific meetings of the European Society for Hypertension, Paris 2016 (Clark C, Thomas D, Warren F et al. Predicting postural hypotension, falls, and cognitive impairment: the InCHIANTI study. *J Hypertens* 2016; 34, e-Supplement 2: e32, September 2016) and the British and Irish Hypertension Society, Dublin, 2016 (Clark C, Thomas D, Mejzner N, et al. Can we predict who should be tested for postural hypotension? Derivation and validation of a prediction tool. *Journal of Human Hypertension* 2016;30 doi: doi:10.1038/jhh.2016.60)

Data sharing statement

The InCHIANTI datasets are available on application with a research proposal to the InCHIANTI investigators at http://inchiantistudy.net/wp/

Legends for tables and figures

Table 1. Risk markers included in univariable analysis

Table 2. Baseline characteristics of derivation and validation cohorts

Table 3. Univariable associations of risk markers with postural hypotension in derivation cohort

Table 4. Multivariable prediction models for postural hypotension

Table 5. DROP score associations with postural hypotension, mortality and cognitive decline

Figure 1. Prevalence of postural hypotension vs unweighted DROP Score without inter-arm difference term (Population prevalence indicated by horizontal line)

Figure 2. Kaplan Meier survival plot for DROP scores over 9 years follow up

Figure 3. Mean change in Mini Mental State Examination score over nine years per DROP score

Group	Risk marker included in analysis
Demographics	age
	gender
Medical History	hypertension
	heart failure
	myocardial infarction
	angina
	stroke
	diabetes
	Parkinson's disease
	cancer
	dementia
Examination	Mini Mental State Examination
Medications	antihypertensives
	antiarrhythmics
	antidepressants
	antipsychotics
	anxiolytics
	anticholinesterase inhibitors
Frailty	hospital admission, fall, or weight loss in last 12 months
	WHO physical disability level
	ADL disability score

Table 1. Risk markers included in univariable analysis

	Derivation Cohort	Validation Cohort	p
N	**649**	**668**	
	Mean (SD) or N/%	**Mean (SD) or N/%**	**t/ χ^2**
age	68.5 (15.7)	68.2 (15.3)	0.77
BMI	27.2 (4.3)	27.1 (4.0)	0.59
Supine SBP (higher arm)#	145.9 (21.3)	146.3 (21.6)	0.76
Supine DBP (higher arm)#	82.9 (8.8)	83.1 (9.5)	0.59
Standing SBP 1 min	140.4 (21.0)	141.2 (21.3)	0.51
Standing DBP 1 min	83.0 (8.9)	83.6 (9.4)	0.25
Standing SBP 3 min	141.4 (20.9)	141.9 (20.9)	0.66
Standing DBP 3 min	82.7 (9.0)	83.0 (9.4)	0.60
Female	368 (56.7)	358 (53.6)	0.27
Site (Greve vs Bagno a Ripoli)	320 vs 329	327 vs 341	0.91
Deceased @ 9 years	199 (30.7)	203 (30.4)	0.95
Systolic drop ≥20mmHg 1min	56 (8.6)	45 (6.7)	0.21
Diastolic drop ≥10mmHg 1min	41 (6.3)	40 (6.0)	0.82
Systolic drop ≥20mmHg 3 min	47 (7.2)	42 (6.3)	0.51
Diastolic drop ≥10mmHg 3min	46 (7.1)	48 (7.2)	1.00
Postural Hypotension present*	107 (16.5)	96 (14.4)	0.32
Systolic inter-arm difference ≥10mmHg	121 (18.8)	121 (18.1)	0.83
Previous stroke	44 (6.8)	45 (6.7)	1.00
Pre-existing diabetes	80 (12.3)	76 (11.4)	0.61
Pre-existing hypertension	279 (43.0)	292 (43.7)	0.82
Pre-existing CV disease	63 (9.7)	50 (7.5)	0.17
Pre-existing dementia	38 (5.9)	27 (4.0)	0.16
Pre-existing Parkinson's disease	9 (1.4)	6 (0.9)	0.45
Fall in preceding 12 months	143 (22.0)	130 (19.5)	0.28

#mean of 2nd and 3rd readings

*defined as a drop of ≥20mmHg systolic or ≥10mmHg diastolic within 3 minutes of standing

Table 2. Baseline characteristics of derivation and validation cohorts

Variable (n (%) unless otherwise stated)	PH absent (n=542)	PH present (n=107)	p value
Age (mean, SD)	67.7 (15.8)	72.2 (14.6)	0.005
Age over 60	438 (81)	96 (90)	0.027
Age over 65	421 (78)	90 (84)	0.160
Age over 70	302 (56)	73 (68)	0.018
MMSE score (mean, SD)	25.3 (4.9)	24.1 (5.1)	0.031
Female gender	301 (55.5)	67 (62.6)	0.200
Angiotensin converting enzyme inhibitors	103 (19)	23 (22)	0.552
Angiotensin-2 antagonists	6 (1)	4 (4)	0.066
Calcium channel blockers	62 (11)	15 (14)	0.451
Diuretics	48 (9)	17 (16)	0.027
Beta-blockers	20 (4)	4 (4)	0.981
alpha-blockers	11 (2)	1 (1)	0.442
aldosterone antagonists	2 (0.4)	0 (0)	0.529
Digoxin	27 (5)	14 (13)	0.004
Antiarrhythmics, class I and III	10 (2)	4 (4)	0.264
Psycholeptics: typical antipsychotics	8 (1)	4 (4)	0.119
Psycholeptics: atypical antipsychotics	6 (1)	1 (1)	1.000
Psycholeptics: anxiolytics	103 (19)	18 (17)	0.684
Psychoanaleptics: antidepressants	22 (4)	5 (5)	0.791
Drugs for dementia	5 (1)	0 (0)	1.000
Hypertension	217 (40)	62 (58)	0.001
Congestive heart failure	22 (4)	10 (9)	0.028
Myocardial infarction	23 (4)	6 (6)	0.607
Angina	21 (4)	7 (6)	0.421
Any CV disease	45 (8)	18 (17)	0.011
Stroke	28 (5)	16 (15)	0.001
Diabetes	64 (12)	16 (15)	0.420
Parkinson's disease	4 (1)	5 (5)	0.008
Any cancer	30 (6)	8 (8)	0.497
Dementia	29 (5)	9 (8)	0.257
MMSE score 22 to 26	150 (28)	27 (25)	0.637
hospital admission in past year	54 (10)	18 (17)	0.044
Weight loss ≥10lbs in past year	22 (4)	7 (6)	0.301
Any fall in past year	115 (21)	28 (26)	0.254
Any ADL disability	100 (19)	28 (26)	0.083
WHO disability level >1	66 (12)	24 (23)	0.045
Systolic blood pressure (mean, SD) mmHg	144.3 (20.1)	153.7 (25.3)	<0.001
Diastolic blood pressure (mean, SD) mmHg	82.2 (8.8)	86.2 (8.1)	<0.001

Systolic inter-arm difference (mean, SD) mmHg	2.0 (4.1)	4.7 (5.9)	<0.001
Systolic inter-arm BP difference ≥10mmHg	81 (15)	40 (37)	<0.001
Systolic inter-arm BP difference ≥ 15mmHg	10 (2)	6 (6)	0.007

p values derived from t-tests for continuous data, or Pearson chi-square for categorical data; Fisher's exact test reported where expected cell count <5

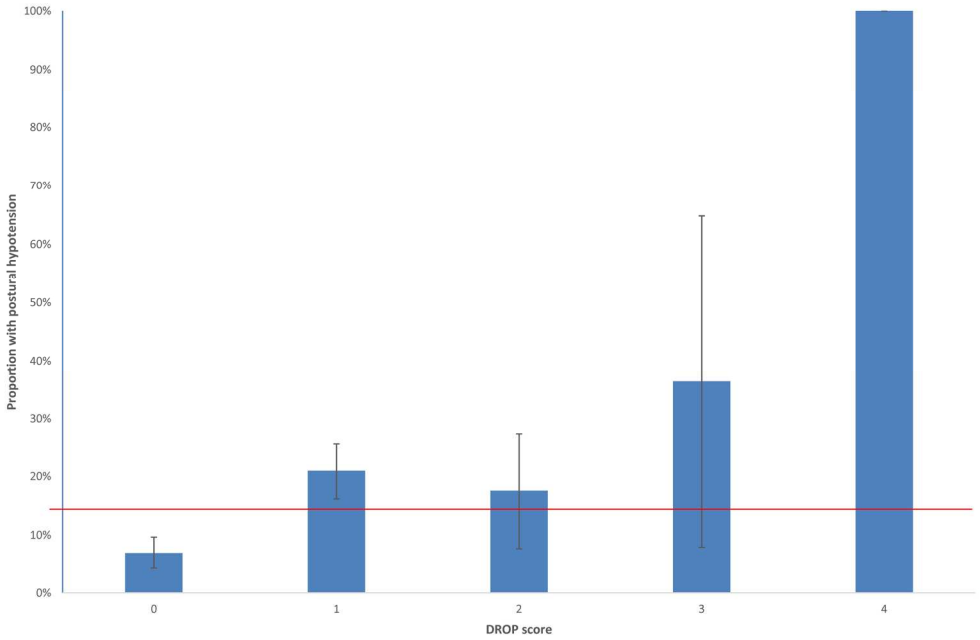
Table 3. Univariable associations of risk markers with postural hypotension in derivation cohort

Variable	Odds Ratio	95% Confidence Interval
Model 1		
Parkinson's disease	4.7	1.2 to 19.2
Previous stroke	2.2	1.1 to 4.5
Taking digoxin	2.2	1.0 to 4.7
Previous cardiac disease	1.9	1.0 to 3.6
Hypertension	1.7	1.1 to 2.6
Systolic inter-arm difference (continuous per mmHg)	1.1	1.1 to 1.2
Model 2		
Parkinson's disease	5.0	1.2 to 19.9
Previous stroke	2.2	1.1 to 4.4
Taking digoxin	2.4	1.1 to 5.1
Previous cardiac disease	1.9	1.0 to 2.6
Hypertension	1.7	1.1 to 5.1
Systolic inter-arm difference ≥10mmHg	3.3	2.0 to 5.3
Model 3		
Parkinson's disease	5.3	1.4 to 20.4
Previous stroke	2.4	1.2 to 4.8
Taking digoxin	2.0	0.9 to 4.3
Previous cardiac disease	1.8	0.9 to 3.4
Hypertension	1.9	1.3 to 3.0

Table 4. Multivariable prediction models for postural hypotension

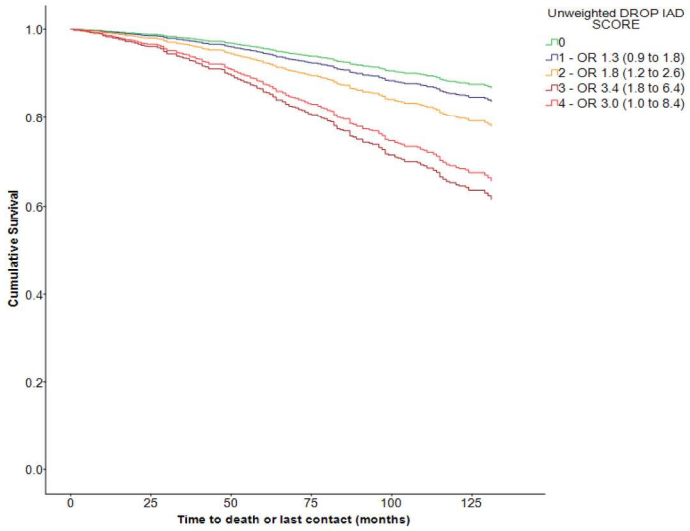
	Including inter-arm difference		Excluding inter-arm difference	
	Weighted	**Unweighted**	**Weighted**	**Unweighted**
Prediction of PH per unit increase of DROP score OR (95%CI)	1.9 (1.4 to 2.5)	1.8 (1.4 to 2.3)	2.4 (1.6 to 3.4)	2.0 (1.5 to 2.6)
Area under ROC curve (95%CI)	0.65 (0.59 to 0.70)	0.65 (0.60 to 0.71)	0.65 (0.59 to 0.71)	0.65 (0.59 to 0.70)
Mortality risk per unit score OR (95%CI)	1.9 (1.6 to 2.2)	1.8 (1.5 to 2.1)	2.8 (2.2 to 3.4)	2.1 (1.8 to 2.5)
Change in MMSE score over study (ANOVA)	N/A	P=0.004	N/A	P<0.001
Annual change in MMSE score (ANOVA)	N/A	P<0.001	N/A	P<0.001

Table 5. DROP score associations with postural hypotension, mortality and cognitive decline



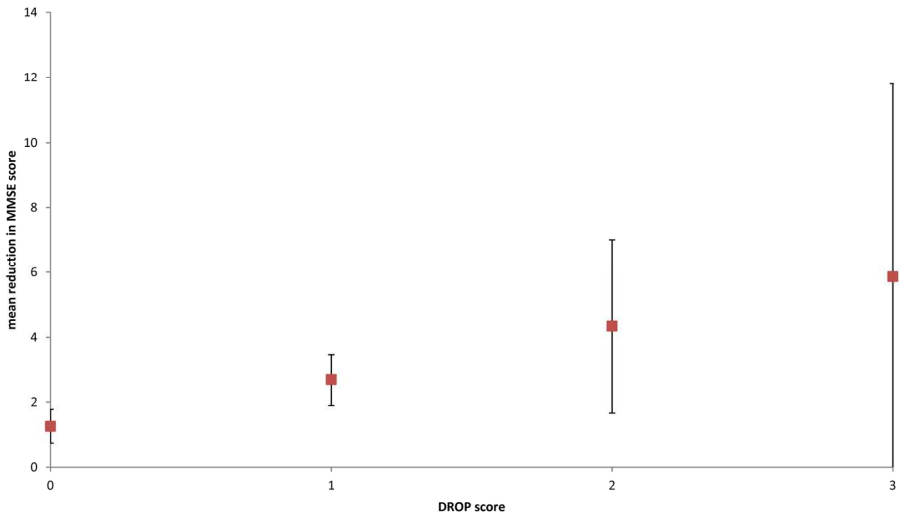
Prevalence of postural hypotension vs unweighted DROP Score without inter-arm difference term (Population prevalence indicated by horizontal line)

167x108mm (300 x 300 DPI)



Kaplan Meier survival plot for DROP scores over 9 years follow up

209x148mm (300 x 300 DPI)



Mean change in Mini Mental State Examination score over nine years per DROP score

165x108mm (300 x 300 DPI)

Appendix: Literature search for factors associated with postural hypotension

Demographics:	Increasing age[1-9]
	Female gender[10]
	Nursing home residence[11-15]
Medical History:	Hypertension[7-10 16-20] and uncontrolled hypertension[6 21 22]
	Diabetes and diabetic complications[17 23-28]
	Chronic Kidney Disease[10 29 30]
	Stroke[31-36]
	Ischaemic heart disease[36 37]
	Heart failure[38 39]
	Parkinson's disease[40-42]
	Cognitive impairment[43-50]
	Depression[51]
Medications:	Antiarrhythmic drugs[11]
	Antihypertensives[4 9-11 52-55] (negative association with ACE inhibitors)[10]
	Psychotropic agents (antipsychotics, sedatives, antidepressants)[23 53 56]
	Anticholinesterase inhibitors[50]
Biochemical:	Vitamin D deficiency (conflicting evidence)[1 23 57 58]
Frailty:[59 60]	Falls[61]
	Get up and go test[11]
	Reduced calf mass index[54 62]
	Activity of Daily Living disability score[1 11]
	Cumulative illness Rating Scale for Geriatrics score[23]
Environmental:	Seasons – prevalence higher in summer and in heatwaves[63 64]
	Time of day – higher in mornings[65-68]

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Medline and Embase Search Strategy

Date of search 20th October 2015

	Searches	Results
1	postural hypotension.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, nm, kf, px, rx, an, ui]	3109
2	orthostatic hypotension.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, nm, kf, px, rx, an, ui]	22694
3	1 or 2	21615
4	prevalence.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, nm, kf, px, rx, an, ui]	1202953
5	3 and 4	1678
6	limit 5 to humans	1565
7	limit 6 to aged <65+ years> [Limit not valid in Ovid MEDLINE(R),Ovid MEDLINE(R) In-Process; records were retained]	661
8	remove duplicates from 7	470

TRIPOD

TRIPOD Checklist: Prediction Model Development and Validation

Section/Topic	Item		Checklist Item	Page
Title and abstract				
Title	1	D;V	Identify the study as developing and/or validating a multivariable prediction model, the target population, and the outcome to be predicted.	1
Abstract	2	D;V	Provide a summary of objectives, study design, setting, participants, sample size, predictors, outcome, statistical analysis, results, and conclusions.	3
Introduction				
Background and objectives	3a	D;V	Explain the medical context (including whether diagnostic or prognostic) and rationale for developing or validating the multivariable prediction model, including references to existing models.	4
	3b	D;V	Specify the objectives, including whether the study describes the development or validation of the model or both.	4
Methods				
Source of data	4a	D;V	Describe the study design or source of data (e.g., randomized trial, cohort, or registry data), separately for the development and validation data sets, if applicable.	4
	4b	D;V	Specify the key study dates, including start of accrual; end of accrual; and, if applicable, end of follow-up.	4
Participants	5a	D;V	Specify key elements of the study setting (e.g., primary care, secondary care, general population) including number and location of centres.	4
	5b	D;V	Describe eligibility criteria for participants.	4
	5c	D;V	Give details of treatments received, if relevant.	N/A
Outcome	6a	D;V	Clearly define the outcome that is predicted by the prediction model, including how and when assessed.	5
	6b	D;V	Report any actions to blind assessment of the outcome to be predicted.	5
Predictors	7a	D;V	Clearly define all predictors used in developing or validating the multivariable prediction model, including how and when they were measured.	5 & table 1
	7b	D;V	Report any actions to blind assessment of predictors for the outcome and other predictors.	5
Sample size	8	D;V	Explain how the study size was arrived at.	6
Missing data	9	D;V	Describe how missing data were handled (e.g., complete-case analysis, single imputation, multiple imputation) with details of any imputation method.	N/A
Statistical analysis methods	10a	D	Describe how predictors were handled in the analyses.	5
	10b	D	Specify type of model, all model-building procedures (including any predictor selection), and method for internal validation.	5
	10c	V	For validation, describe how the predictions were calculated.	5
	10d	D;V	Specify all measures used to assess model performance and, if relevant, to compare multiple models.	5
	10e	V	Describe any model updating (e.g., recalibration) arising from the validation, if done.	N/A
Risk groups	11	D;V	Provide details on how risk groups were created, if done.	N/A
Development vs. validation	12	V	For validation, identify any differences from the development data in setting, eligibility criteria, outcome, and predictors.	None table 2
Results				
Participants	13a	D;V	Describe the flow of participants through the study, including the number of participants with and without the outcome and, if applicable, a summary of the follow-up time. A diagram may be helpful.	5
	13b	D;V	Describe the characteristics of the participants (basic demographics, clinical features, available predictors), including the number of participants with missing data for predictors and outcome.	table 2
	13c	V	For validation, show a comparison with the development data of the distribution of important variables (demographics, predictors and outcome).	table 2
Model development	14a	D	Specify the number of participants and outcome events in each analysis.	5
	14b	D	If done, report the unadjusted association between each candidate predictor and outcome.	table 3
Model specification	15a	D	Present the full prediction model to allow predictions for individuals (i.e., all regression coefficients, and model intercept or baseline survival at a given time point).	table 4
	15b	D	Explain how to the use the prediction model.	6
Model performance	16	D;V	Report performance measures (with CIs) for the prediction model.	6 table 5
Model-updating	17	V	If done, report the results from any model updating (i.e., model specification, model performance).	6
Discussion				
Limitations	18	D;V	Discuss any limitations of the study (such as nonrepresentative sample, few events per predictor, missing data).	6-7
Interpretation	19a	V	For validation, discuss the results with reference to performance in the development data, and any other validation data.	6-7
	19b	D;V	Give an overall interpretation of the results, considering objectives, limitations, results from similar studies, and other relevant evidence.	6-7
Implications	20	D;V	Discuss the potential clinical use of the model and implications for future research.	8
Other information				
Supplementary information	21	D;V	Provide information about the availability of supplementary resources, such as study protocol, Web calculator, and data sets.	N/A
Funding	22	D;V	Give the source of funding and the role of the funders for the present study.	14

TRIPOD Checklist: Prediction Model Development and Validation

*Items relevant only to the development of a prediction model are denoted by D, items relating solely to a validation of a prediction model are denoted by V, and items relating to both are denoted D;V. We recommend using the TRIPOD Checklist in conjunction with the TRIPOD Explanation and Elaboration document.