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Modified Criteria for Carotid Sinus Hypersensitivity are Associated with Increased Mortality in a Population Based Study.

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Abstract (250 words)

Aims

Carotid sinus hypersensitivity (CSH) is arbitrarily defined as ≥3 seconds asystole or vasodepression of ≥50 mmHg in response to carotid sinus massage (CSM). Using this definition, 39% of older people meet the criteria for CSH. It has been suggested that current criteria are too sensitive. Krediet et al and Kerr et al have proposed modified criteria. This population based study aimed to compare the prevalence of CSH defined according to standard, Krediet and Kerr criteria, and to establish if CSH defined according these criteria is associated with all-cause mortality.

Methods

272 community-dwelling people aged ≥65 were recruited at random. CSM was performed for five seconds in supine and head-up positions. Heart rate and blood pressure response were recorded using an ECG and photoplethysmography. Cox regression analysis was used to examine the association between each definition of CSH and all-cause mortality.

Results:

Prevalence of CSH defined according to standard, Krediet and Kerr criteria was 39%, 52% and 10% respectively. Seventy-one participants died over a mean follow-up of 8.6 years (SD 2.1). CSH defined according to standard and Krediet criteria was not associated with survival. CSH defined according to Kerr criteria was associated with all-cause mortality independent of age and sex [HR 2.023 (95% CI 1.131, 3.618) P=0.018)]. This remained significant after adjusting for cardiovascular risk factors [HR 2.174 (1.075, 3.900) P= 0.009].

Conclusions:

CSH defined according to Kerr criteria is associated with increased mortality. This raises an interesting question as to the suitability of the current criteria used to define CSH.

Key words

Carotid Sinus Hypersensitivity, Prevalence, All Cause Mortality

Condensed Abstract

Current criteria for CSH may be too sensitive. Kerr and Krediet proposed modified criteria. Community prevalence of CSH defined according to standard, Krediet and Kerr criteria was 39%, 52% and 10% respectively. Only CSH defined according to Kerr criteria was associated with increased all-cause mortality independent of age and cardiovascular risk factors.

What's New?

This is the first study to our knowledge to show an association between CSH and survival. We demonstrated that CSH characterised according to criteria, defined according to cut-offs derived from the normal response to CSM in older people, is associated with increased mortality.

Introduction

Carotid sinus hypersensitivity (CSH) is currently defined as ≥3 seconds asystole, and / or ≥50 mmHg drop in systolic blood pressure in response to carotid sinus massage[1]. When it occurs in conjunction with syncope or presyncope it is called Carotid Sinus Syndrome (CSS). Although these criteria are widely accepted it has been suggested that current criteria are too sensitive, particularly in older people[2]. Kerr et al found that 39% of community dwelling adults aged ≥65 years have CSH defined according to these criteria and CSH was present in 35% of asymptomatic individuals[3]. The group reported the 95th percentile for carotid sinus massage response was 7.3 seconds asystole and a 77 mmHg drop in systolic blood pressure. Based on these data and data from Menozzi et al[4] and Brignole et al[5], Krediet et al suggested that current criteria are over sensitive and proposed future studies evaluate modified criteria such that CSM is positive if it triggers an asystole >6 seconds or a fall in mean arterial pressure below 60 mmHg for >6 seconds [2].

CSH is associated with significant morbidity including falls, fractured neck of femur and head injury [6,7,8]. Surprisingly, despite the significant association between CSH and injury, studies to date have failed to show an association between CSH and mortality[9, 10]. The uncertain specificity of current CSH criteria may account for the failure of studies to identify an association between CSH and mortality.

This study compared the prevalence of CSH in a community cohort defined according to standard criteria, the Krediet criteria and criteria derived from the 95th percentile for response to CSM; the Kerr criteria. Secondly, we aim to establish if CSH defined according to standard criteria or modified criteria is associated with ten-year all-cause mortality in a cohort for whom CSH status is known for all participants.

Methods

Between April 2002 and October 2003, 375 community-dwelling people age 65 and older took part in the first phase of a longitudinal study examining the prevalence and clinical associations of carotid sinus hypersensitivity (CSH). Participants were recruited at random from a single general practice (GP) in the North of England. Persons living in residential or nursing care were excluded. Full details of recruitment have been previously described [11].

Carotid Sinus Massage

All assessments were carried out in a temporary community clinic based close to the participants' general practitioner. Carotid sinus massage (CSM) was performed in consenting participants without contraindication. Contraindications included myocardial infarction, stroke or transient ischemic attack in the preceding 3 months, history of significant carotid stenosis, carotid bruit or clinical suspicion of carotid stenosis.

Subjects rested supine for five minutes before CSM. CSM was performed by the same doctor (SJK) in every case. The point of maximum pulsation over the carotid artery, between the angle of the mandible and thyroid cartilage was identified. Firm longitudinal massage was applied for five seconds. A three-lead ECG was used to monitor cardiac response to the test. Continuous beat-to-beat blood pressure was recorded from the hand using digital photoplethysmography (Portapress, TNO- Biomedical, Amsterdam). The subject's hand was supported at heart level throughout all measurements.

CSM was stopped before five seconds if >3 seconds asystole was recorded. CSM was first performed on the right hand side in the supine position followed by the left hand side in the supine position. Participants were then tilted to the 70-degree head-up tilt position and CSM repeated on the right hand side followed by the left hand side. One minutes rest was allowed between each period of massage. The longest RR interval post-CSM and greatest vasodepression post-CSM were used to calculate response to CSM.

Definitions of CSH

Three definitions of CSH are evaluated:

1. **Standard Criteria**

A pause in heart rate of ≥3 seconds in response to CSM and /or vasodepression of ≥ 50 mmHg drop in systolic blood pressure or both of the above.

2. **Krediet Criteria**

   A pause in heart rate of ≥6 seconds in response to CSM and / or a fall in mean arterial pressure to a value <60 mmHg for ≥6 seconds.

3. **Kerr Criteria**

   A pause in heart rate in response to CSM >95th percentile of the population response (7.3s asystole), and / or vasodepression in response to CSM >95th percentile of the population response (>77 mmHg fall in systolic blood pressure), or both.

Clinical Assessment

Past medical history was obtained by direct interview of all subjects. Particular attention was paid to the presence or absence of cardiovascular disease and risk factors. If participants were unsure of their past medical history, GP medical notes were reviewed. Ischemic heart disease was defined as a clinical history of angina or myocardial infarction.

Participants were asked to bring a list of all medications they were taking with them to the assessment. A composite variable, "use of Cardioactive medication", was defined as using antihypertensive medication, diuretic medication, antianginals, or antiarrhythmics.

Height and weight were recorded and body mass index calculated. Presence or absence of signs of cardiac failure was noted.

Participants were fitted with a twenty-four hour ambulatory blood pressure monitor (ABPM) (Spacelabs 90207 – Spacelabs Medical Inc, Redmond, Washington USA). An appropriate sized cuff was fitted to the non-dominant arm. Subjects were instructed to relax their arm when the cuff was inflating. Monitors were programmed to take a BP recording every 30 minutes during the day (7 am to 10 pm) and every hour overnight (10 pm to 7 am). Mean systolic and diastolic blood pressure were calculated for the 24 hour period, daytime and night-time.

Survival Data

Participants' GP electronic medical records were reviewed in September 2012 to identify if participants were alive or their date of death. If participants were no longer registered with the GP, the National Register of Births, Deaths and Marriages ending September 2012 was reviewed to confirm if participants had died and verify their date of death.

Ethical Approval

Ethical approval was granted by local research and ethics committees. Written informed consent was obtained from all participants.

Statistics

All data were analysed using Statistical Package for Social Science (SPSS) version 19. For all tests the level of statistical significance was set at <0.05.

Normally distributed continuous data is shown as mean and standard deviation and differences between 2 groups compared using Student's t test. Differences between 3 or more groups are compared using an ANOVA with post-hoc Bonferroni correction. Non-parametric continuous data is shown as median and interquartile range and group differences compared using Mann Whitney-U test. Categorical data are shown as percentages and compared using Chi square or Fishers exact tests as appropriate.

Time to event is defined as time between date of carotid sinus massage and death or end of the study; 1st October 2012. Risk factors associated with mortality were analysed using Cox regression analysis initially controlling only for age and sex. Subsequent models adjusted for relevant covariates.

Results

Of the 375 individuals participating in the study, 35 refused consent for CSM and 68 had a contraindication to CSM. Thus, 272 participants underwent CSM. Participants undergoing CSM were significantly younger than participants not undergoing CSM [Median age 72 v. 76 years respectively, P=<0.001], had significantly lower burden of ischemic heart disease [21% v. 50%, P<0.001] and were less likely to be taking cardioactive medications [46% v. 96%, P<0.001].

Prevalence of CSH

As previously reported, of the 272 participants who underwent CSM, 106 participants (38.9%) had CSH defined using conventional diagnostic criteria[11]. One hundred and forty-one participants (51.8%) had CSH defined according to Krediet criteria and 28 (10.3%) had CSH defined according to Kerr criteria. Table 1 shows the prevalence of CSH subtypes according to each of these criteria.

The high prevalence of participants meeting the Krediet criteria resulted from the large number of individuals meeting the Krediet criteria for vasodepression (Table 1). Figure 1 compares baseline mean arterial pressure (MAP) for participants according to CSH criteria met. Participants meeting the Krediet criteria but not the standard criteria for CSH had significantly lower mean arterial BP at baseline (figure 1).

The clinical characteristics of participants according to the presence or absence of CSH defined using the three different criteria are shown in Table 2. Regardless of the criteria used to define CSH, participants with CSH were older. In addition, participants with CSH defined by standard and Kerr criteria were more likely to be male.

Twenty-two patients reported syncope or presyncope during CSM. Table 3 shows the proportion of participants reporting symptoms according to CSH status defined by the 3 sets of criteria. All 3 sets of criteria were significantly associated with syncope during CSM ($P<0.001$). Only standard and Kerr criteria were associated with presyncope.

Survival

Of the 272 participants consenting to CSM, 71 had died at the end of follow-up; mean follow-up interval 8.6 years (SD 2.1). When conventional criteria were used to define CSH, rates of death in the CSH group were higher compared to the group without CSH but this did not differ significantly [32% v 22% respectively, $P=0.073$]. Mortality was significantly greater in the group with CSH defined according to the Krediet criteria compared to those without CSH [33% v. 19% respectively, $P=0.009$]. Use of the Kerr criteria revealed the most significant difference in mortality between those with and without CSH [53% versus 23% respectively, $P<0.001$].

Cox regression analysis was used to examine if CSH was associated with all-cause mortality. Three models were developed. Model 1 adjusted for age and sex. Model 2 made additional adjustments for cardiovascular factors associated with CSH and known to influence mortality including: body mass index, smoking history (pack years), history of hypertension, diabetes, ischemic heart disease and congestive cardiac failure. Finally, in model 3, use of cardioactive medication was added to the model.

CSH defined according to conventional criteria and Krediet criteria was not associated with survival after adjusting for age and sex. CSH defined according to Kerr criteria was, however, independently associated with mortality [HR 2.023 (95% CI 1.131, 3.618) P=0.018)] (Table 4). CSH defined according to Kerr criteria remained a significant independent predictor of mortality after adjusting for cardiovascular risk factors [HR 2.174 (95% CI 1.075, 3.900) P= 0.009]. Further adjustment for use of cardioactive medication did not substantially attenuate the model [HR 2.154 (95% CI 1.198, 3.873) P=0.010] (Table 4). Thus, in all three models, CSH defined according to Kerr Criteria was a significant independent predictor of all-cause mortality at ten-year follow-up. In addition, age and male gender were independently associated with increased all-cause mortality. Mortality decreased with increasing body mass index.

Survival and Symptoms during CSM

To examine if symptoms during CSM were important predictors of mortality, cox regression analysis was repeated comparing participants with CSH and syncope or presyncope during CSM to participants who were asymptomatic. There were no associations between survival and symptoms in association with CSH defined by any of the criteria (Table 5).

Discussion

In this study, we have shown the prevalence of CSH defined by standard, Krediet and Kerr criteria is 39%, 52% and 10% respectively. The Krediet criteria were developed due to concerns that standard criteria are insufficiently strict. It is therefore surprising that prevalence of CSH is higher when Krediet criteria are applied compared applying the standard criteria to diagnose CSH. Review of baseline BP revealed that participants meeting the Krediet, but not the standard criteria, had a significantly lower baseline MAP. Blood pressure in these participants therefore fell below a MAP of 60mmHg without the drop in

systolic blood pressure reaching 50 mmHg as stipulated by conventional criteria. Conversely, in a small number of participants with significantly higher baseline MAP, systolic BP fell by more than 50mmHg without meeting a MAP of 60mmHg or below.

Krediet et al developed their modified criteria in an attempt to strengthen the association between CSH and symptoms. Interestingly, all 3definitions of CSH were significantly associated with syncope during the test but only standard and Kerr criteria associated with presyncope. The positive predictive value for syncope and presyncope during the test was greatest for the Kerr criteria and lowest for the Krediet criteria suggesting the Krediet criteria are not superior to standard criteria in terms of association with symptoms.

Krediet et al defined vasodepressive CSH as a fall below a MAP of 60mmHg for 6 seconds in response to CSM based on clinicopathological reasoning. They argued that when the heart stops beating, MAP starts to decline rapidly and reaches a level below 60 mmHg in 3–5 seconds[2]. Falls in systemic pressure below the lower limit of cerebral auto-regulation result in cerebral hypoperfusion[12]. The time span from the start of critical cerebral hypoperfusion to loss of consciousness is known as 'cerebral ischemic anoxia reserve time'. The 6 second duration of hypotension in response to CSM suggested by Krediet et al is based on studies conducted in young men that have shown critical ischemic anoxic reserve time of 5-8 seconds[13]. It is, therefore, interesting that although 139 (51%) participants had a MAP of $\leq$60 for $\geq$6 seconds only 19 of these participants (13%) reported presyncope or syncope during CSM.

Traditional criteria stipulate a relative change in blood pressure whereas the Krediet criteria require a fall in MAP below a fixed value; 60mmHg. As discussed, participants with a lower MAP prior to CSM, only require small decreases in blood pressure in order to meet the Krediet criteria for CSH. Conversely, in individuals with chronic hypertension, in whom the cerebral autoregulatory curve has shifted to the right, large drops in BP, enough to cause cerebral hypoperfusion may occur at a MAP above 60 mmHg. Traditional criteria and Kerr criteria for CSH have the advantage that the required change in BP is relative to baseline blood pressure.

CSH defined according to the Kerr criteria, derived from the normal range of responses to CSM among community-dwelling older people, is associated with increased mortality. This is the first study to demonstrate an association between CSH and mortality. The association was independent of age, hypertension and history of ischemic heart disease, suggesting the association between CSH and mortality is not merely a result of the link between CSH and cardiovascular disease and raises interesting questions about the monitoring and management of patients with CSH meeting the Kerr criteria.

CSH defined according to standard criteria and Krediet was not associated with survival. This is in keeping with two previous studies[9,10]. Hampton et al examined mortality among 1504 patients with CSH identified from a single syncope centre. Standardised mortality rates (SMRs) were compared with regional age matched SMR data from the office of national statistics. There was no difference between CSH patients (CSH defined according to standard criteria) and the general population in SMRs for all-causes, or for cerebrovascular or cardiovascular deaths[9]. In a similar study, Brignole et al followed-up 262 patients with a history of syncope or presyncope in whom CSM resulted in CSH and reproduced their symptoms. Mortality over a 6-year follow-up was compared to mortality among 55 patients with unexplained syncope and SMR of the Italian general population with similar age and sex distribution. Mortality rates in all three groups were similar[10].

Both the Hampton et al and the Brignole et al studies recruited symptomatic participants with CSH from syncope clinics and compared to SMR[9,10]. Kerr et al, however, found over 25% of individuals with CSH defined according to standard criteria had no prior history of syncope, presyncope or dizziness and the majority of symptomatic patients with CSH had not been referred to a specialist clinic[11]. The high prevalence of CSH (defined according to standard criteria) among asymptomatic older individuals means it is likely the control populations from which the SMR were derived included a significant proportion of asymptomatic patients with undiagnosed CSH. Our study was the first study examining the association between CSH and mortality among a community cohort in whom CSH status of all participants had been assessed and documented.

Current guidelines for implantation of pacemakers for cardioinhibitory CSH stipulate that CSM should be associated with reproduction of symptoms of presyncope or syncope[1]. In this study, CSH according to Kerr criteria, but not symptoms were associated with mortality.

This raises interesting questions as to whether pacing should be considered for asymptomatic individuals meeting the Kerr criteria. Even though it is recommended by current guidelines, previous clinical trials evaluating pacing for the treatment of cardioinhibitory CSS have failed to reliably show benefit with pacing. Although there are several possible explanations for this, it may reflect the lack of specificity of standard criteria.

A number of limitations to this study should be acknowledged. Firstly, participants undergoing CSM were significantly younger and less likely to have cardiovascular disease than the participants who did not undergo CSM. This is an inevitable consequence of the contraindications to CSM (recent stroke, myocardial infarction, persistent arrhythmia). The prevalence of CSH increases with age and CSH is associated with hypertension and cardiovascular disease. Given that older individuals with a history of cardiovascular disease were excluded from the study it is likely that the true prevalence of CSH in the wider population may have been underestimated.

This study did not examine cause-specific mortality. Mortality due to CSH may result from morbidity associated with related falls and syncope. Approximately one in ten falls are associated with injury, including hip fracture, subdural haemorrhage, or soft tissue injury[14]. Of people admitted to hospital with a fall, about 50% are alive at 1 year[15]. CSH is associated with autonomic dysfunction and it has also been suggested that CSH related deaths may be due to prolonged asystole or malignant arrhythmias triggered by severe vasodepression[9]. Future studies are needed that examine the association between the Kerr criteria and cause-specific mortality and to examine the association between CSH defined by Kerr criteria and falls and / or syncope.

Larger studies are also needed to compare mortality related to the different subtypes of CSH. The small number of individuals with pure cardioinhibitory and mixed CSH, particularly when CSH was defined according to Kerr criteria, prohibited comparison of subtypes.

Readers should also note that the favoured protocol for preforming CSM has been modified since this study began. In line with guidelines available at the time of the studies inception CSM was performed for 5 seconds[16, 17]. Since 2009, the European Society of Cardiology have recommended carotid sinus massage should be performed for 10 seconds[18]. No comparator studies have been conducted to assess the optimum duration of CSM but some

authors suggest longer CSM may be associated with higher rates of syncope. Although this has not been proven, increasing duration of CSM may result in increased prevalence of CSH and / or CSS.

Summary

This is the first study to our knowledge to show an association between CSH and survival. We demonstrated that CSH characterised according to the Kerr criteria, defined according to cut-offs derived from the normal response to CSM in older people, affects 10% of the population aged 65 and over and is associated with increased mortality. In addition, it showed that over 50% of community-dwelling older people have a response to CSM that meets modified criteria for CSH proposed by Krediet et al. These criteria and standard criteria were not associated with survival. Future studies should evaluate the prognostic value of the 3 definitions of CSH in terms of predicting future falls, syncope and the ability of the criteria to identify patients who would benefit from pacing.

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Figures

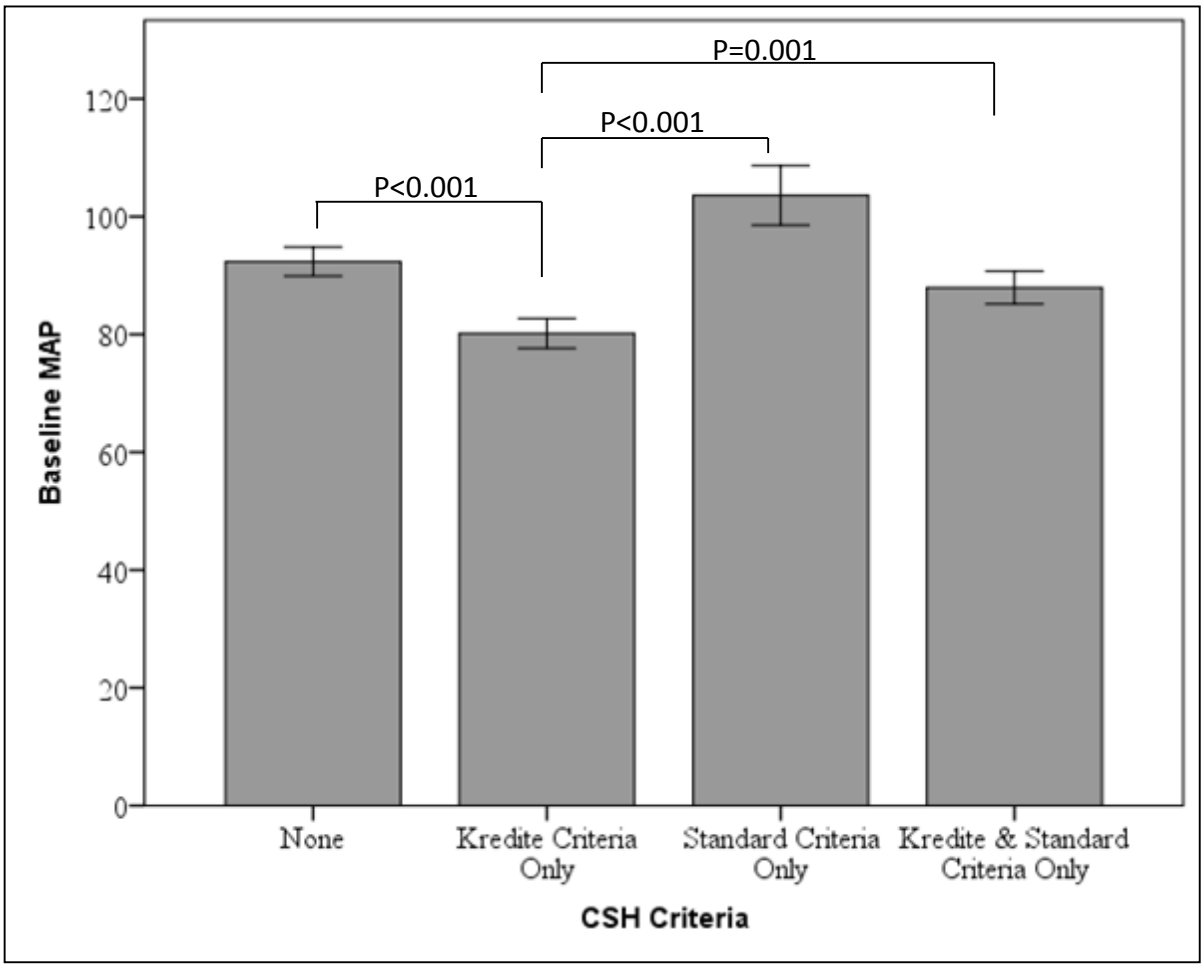

Figure 1 Comparison of baseline mean arterial pressure according to CSH criteria met. Error bars show 95% confidence intervals. P values are calculated using one way ANOVA with Bonferroni correction.

Tables

Table 1 Prevalence of CSH and CSH subtypes according to different criteria

	Standard Criteria N (%)	**Krediet Criteria N (%)**	**Kerr Criteria N (%)**
Carotid Sinus Hypersensitivity	106 (39)	141 (52)	28 (10)
• **Cardioinhibitory**	6	2	6
• **Vasodepressive**	42	116	16
• **Mixed**	58	23	6

Table 2 Demographic and Clinical Characteristics for Participants with and without CSH According to the 3 Different Definitions of CSH

	Conventional Criteria			**Krediet Criteria**			**Kerr Criteria**		
	No CSH	**CSH**	**P**	**No CSH**	**CSH**	**P**	**No CSH**	**CSH**	**P**
	N=166	**N = 106**		**N=131**	**N= 141**		**N=244**	**N=28**	
Age [median (IQR)]	71 (67, 76)	73 (69,79)	**0.015**	70 (67, 75)	74 (69. 78)	**<0.001**	71 (68, 76)	75 (71, 79)	**0.013**
Sex [male (%)]	86 (51.8)	68 (64.2)	**0.045**	67 (51.1))	87 (61.2)	0.079	133 (54.5)	21 (75.0)	**0.038**
BMI	27 (4.0)	26 (3.4)	**0.039**	27 (3.9)	27 (3.8)	0.657	26.8 (3.9)	26.7 (2.9)	0.866
Pack years	3 (0, 20)	9 (0, 26)	0.082	2 (0, 20)	10 (0, 25)	**0.031**	4 (0, 20)	16 (0, 30)	0.075
Mean Daytime Ambulatory BP									
• **Systolic BP [mean (SD)]**	134 (15.0)	135 (14.2)	0.481	135 (14.7)	134 (14.1)	0.406	134 (14.7)	132 (14.4)	0.345
• **Diastolic BP [mean (SD)]**	75 (9.6)	78 (8.9)	**0.006**	77.8 (9.3)	75.4 (7.5)	**0.021**	75.6 (9.6)	77.5 (8.2)	0.345
	N (%)	**N(%)**	**P**	**N (%)**	**N(%)**	**P**	**N (%)**	**N(%)**	**P**
Ischemic Heart Disease	33 (19.9)	25 (23.6)	0.467	20 (15.3)	38 (30.0)	**0.019**	52 (21.3)	6 (21.4)	0.989
Hypertension	53 (31.9)	47 (44.3)	**0.038**	45 (34.4)	55 (39.0)	0.426	86 (35.2)	14 (50.0)	0.125
Cardiac Failure	11 (6.6)	10 (9.4)	0.398	9 (6.9)	12 (8.5)	0.613	19 (7.8)	2 (7.1)	1.000
Diabetes	11 (6.6)	5 (4.7)	0.514	5 (3.8)	11 (7.8)	0.163	15 (6.1)	1 (3.6)	1.000
Hypercholesterolemia	49 (29.5)	30 (28.3)	0.829	36 (27.5)	43 (30.5)	0.584	71 (29.1)	8 (28.6)	0.954
Cardioactive Medication	73 (44.0)	51 (48.1)	0.504	53 (40.5)	68 (48.2)	0.365	109 (44.7)	15 (53.6)	0.371

Table 3 Proportion of patients with each form of CSH who reported symptoms during CSM

	Standard CSH N=106 n (%)	**Krediet CSH N=141 n (%)**	**Kerr CSH N=28 n (%)**
Syncope	17 (16)*	16 (11)*	13 (46)*
Presyncope	9 (8)*	7 (5)	5 (18)*
Syncope or Presyncope	22 (20)*	19 (13)*	14 (50)*
*Chi square test used to examine significance of association between criteria and symptoms during CSM, *indicates significant associations (P<0.001 in all cases).*			

Table 4 Cox Regression Models. Relative risk of all-cause mortality associated with CSH according to conventional, Krediet and Kerr criteria.

	Conventional Criteria			**Krediet Criteria**			**Kerr Criteria**		
	HR	**95% CI**	**P**	**HR**	**95% CI**	**P**	**HR**	**95% CI**	**P**
Model 1									
CSH	1.286	0.809, 2.046	0.288	1.319	0.799, 2.177	0.280	2.023	1.131, 3.618	**0.018**
Age	1.121	1.082, 1.162	**<0.001**	1.117	1.076, 1.159	**<0.001**	1.115	1.075, 1.156	**<0.001**
Sex	1.792	1.094, 2.934	**0.020**	1.773	1.081, 2.906	**0.023**	1.793	1.092, 2.946	**0.021**
Model 2									
CSH							2.174	1.212, 3.900	**0.009**
Age							1.091	1.048, 1.135	**<0.001**
Sex							1.713	1.011, 2.901	**0.045**
BMI							0.913	0.851, 0.980	**0.012**
Pack Years							1.011	0.999, 1.022	0.061
Hypertension							1.546	0.951, 2.512	0.079
Diabetes							1.626	0.720, 3.670	0.242
IHD							0.931	0.517, 1.676	0.812
CCF							1.878	0.887, 3.974	0.099
Model 2									
CSH							2.154	1.198, 3.873	**0.010**
Age							1.090	1.048, 1.134	**<0.001**
Sex							1.718	1.014, 2.909	**0.044**
BMI							0.911	0.848, 0.979	**0.011**
Pack Years							1.011	1.000, 1.022	0.060
Hypertension							1.531	0.941, 2.941	0.087
Diabetes							1.599	0.706, 3.620	0.260
IHD							0.868	0.457, 1.651	0.667
CCF							1.791	0.831, 3.860	0.137
CV Meds							1.159	0.650, 2.067	0.616

BMI =body mass index, IHD = ischemic heart disease, CCF= congestive cardiac failure, CV meds = cardioactive medication

Table 5 Cox Regression Models. Hazard ratio of all-cause mortality associated with symptomatic CSH defined according to standard criteria, Krediet criteria and Kerr criteria.

	Conventional Criteria			**Krediet Criteria**			**Kerr Criteria**		
	HR	**95% CI**	**P**	**HR**	**95% CI**	**P**	**HR**	**95% CI**	**P**
Model 1									
CSH + Symptoms	1.589	0.760, 3.326	0.219	1.814	0.867, 3.796	0.114	2.021	0.870, 4.695	0.102
Age	1.124	1.084, 1.165	**<0.001**	1.123	1.084, 1.165	**<0.001**	1.125	1.085, 1.166	**<0.001**
Sex	1.833	1.120, 3.000	**0.016**	1.805	1.102, 2.955	**0.019**	1.783	1.089, 2.918	**0.022**

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