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## Psychological distress is independently related to new coronary events at 8 years' follow-up in elderly primary care patients with hypertension

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### ABSTRACT

**Objective:** Occurrence of psychological distress in hypertensive patients could have a negative synergistic effect on future cardiovascular events (CVEs). The aim of this study was to determine the association between anxiety or depressive symptoms in elderly hypertensive primary care patients and the development of new CVEs and all-cause mortality.

**Methods:** A prospective cohort study was conducted in five Dutch general practices between June 2010 and January 2012. Patients with primary care managed hypertension, aged 60–85 years, were included and completed the GAD-7 and PHQ-9, measuring anxiety and depressive symptoms respectively. The incidence of new CVEs (coronary event, cerebrovascular disease, atrial fibrillation and heart failure) and all-cause mortality at 8 years' follow-up was recorded by data extraction of the digital information systems.

**Results:** Among the 555 included participants (mean age  $70 \pm 6.6$  years; 56% female), 29 (5.2%) had a new coronary event, 42 (7.6%) a cerebrovascular disease, 57 (10.3%) atrial fibrillation, 22 (4%) heart failure and 68 (12.3%) died. Elevated anxiety and depression scores increased the risk of a coronary event independently and significantly by 12% (HR 1.12; 95% CI [1.04–1.22],  $p = 0.005$ ) and 18% (HR 1.18; 95% CI [1.08–1.28],  $p < 0.0001$ ), respectively, adjusted for relevant (Framingham) baseline covariates. No associations were found with regard to other CVEs and all-cause mortality.

**Conclusion:** In a random sample of elderly primary care hypertension patients there was a significant association between psychological distress and the occurrence of new coronary events after 8 years' follow-up but not with other CVEs and all-cause mortality.

### 1. Introduction

Cardiovascular diseases (CVDs) are the most common causes of death worldwide, representing 32% of all global deaths [1], and comprises the second cause of deaths in the Netherlands and Europe after cancer, respectively, representing 25% vs. 30% of all deaths in the Netherlands [2]. Well-known risk factors for CVDs are hypertension, hypercholesterolemia, higher body mass index, smoking and increasing age [3,4]. Hypertension is very common in the general population (22%) [5] and increases with age [6]. Hypertension is also an important facet of the Framingham risk profile of CVD [4]. Nowadays in the Netherlands, patients with (uncomplicated) hypertension are primarily

treated in primary care within the context of the cardiovascular risk management program (CVRM). Within this primary care program, until now, there is little if any focus on psychological well-being and psychological distress of patients with hypertension as a risk factor for the development of future cardiovascular events (CVEs).

In recent decades, research has primarily focused on hospital (out-)patients with regard to psychological distress as a possible risk factor for CVDs. The possible role of psychological distress in primary care is still unclear [7,8], and primary care studies have mainly focused on the possible association between psychological distress and the occurrence of a second event after a first cardiovascular event [9–11]. Since 2012, the European Society of Cardiology included psychosocial factors – such

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as psychological distress, anxiety and depression – in their guidelines [12,13] as potential risk factors for CVD with a Class IIa, Level B evidence. Anxiety and depression in cardiovascular patients are related to a higher incidence of CVDs and increased costs [14]. The occurrence of both hypertension and psychological distress could have a negative synergistic effect on a future CVE. Although, the guidelines recommend psychological screening in the outpatient cardiology practice, this is far from implemented in cardiology practices in Europe, and its possible relevance in the primary care cardiovascular risk management program is even unknown.

Therefore, the aim of the current study was to determine the association between anxiety and/or depression symptoms in a sample of elderly patients with hypertension in the primary care setting and the subsequent development of new CVEs at 8 years' follow-up. The secondary aim was to determine the possible relation between anxiety and/or depression symptoms and all-cause mortality.

## 2. Methods

### 2.1. Participants

Patients in the current study were enrolled in the Chello cohort study (Chronic Heart Failure Prevention Program), of which the inclusion and exclusion criteria of participants have been described in detail elsewhere [15,16]. In short, primary care patients aged between 60 and 85 years diagnosed with essential hypertension were recruited for the Chello study from five general practices affiliated with the primary care organization PoZob [17], between June 2010 and January 2012. Exclusion criteria were previous diagnosis of heart failure, current treatment by a cardiologist and history of severe psychiatric illness other than mood or anxiety disorders. The study protocol was approved by the medical ethics committee of the Elisabeth Hospital in Tilburg, the Netherlands (NL38933.008.12).

### 2.2. Psychological assessments at baseline

Participants completed 2 standardized and validated questionnaires at study enrollment. Anxiety symptoms were assessed with the 7-item Generalized Anxiety Disorder scale (GAD-7) [18,19]. The 7 items are rated on a 4-point Likert scale, range 0 to 21, referring to the previous 2 weeks, with a higher score indicating more symptoms. A cut-off  $\geq 8$  is considered suitable for the detection of severe generalized anxiety disorder as well for the detection of any severe anxiety disorder for individuals,  $\geq 18$  years old, in primary care [18]. The GAD-7 has previously been validated in The Netherlands, showing adequate reliability (Cronbach's Alpha of 0.92) [20]. The Cronbach's Alpha of the GAD-7 questionnaire in the current study was 0.84.

Depression symptoms were assessed with the Patient Health Questionnaire 9 (PHQ-9) [21–24]. The PHQ-9 is a self-report questionnaire that consists of nine items that correspond to the DSM-V criteria for a depressive episode referring to the previous two weeks, with answers indicated on a 4-point Likert scale. The score range is from 0 to 27, with a higher score indicating more symptoms. The PHQ-9 has been validated in primary care populations ( $\geq 18$  years old), with a cut-off of  $\geq 5$  and  $\geq 10$ , indicative of mild and major depression, respectively [21,24,25] also in the Netherlands showing adequate reliability (Cronbach's Alpha of 0.88) [26]. The Cronbach's Alpha of the PHQ-9 questionnaire in the current study was 0.75.

### 2.3. The incidence of new cardiovascular events and all-cause mortality

In order to evaluate the incidence of new CVEs and all-cause mortality, a data extraction of the digital general practitioner (GP) information system was performed at 8 years' follow-up. Every GP in the Netherlands uses standard diagnosis codes for data entry into the electronic patient record form: international classification of primary care

(ICPC). The specific codes for CVD were extracted from the digital systems at follow-up. After inclusion, the occurrence of the following CVDs and deaths has been registered: the development of coronary events (acute coronary syndrome; unstable angina pectoris or acute myocardial infarction), heart failure, atrial fibrillation, cerebrovascular diseases (transient ischemic attack and cerebrovascular accident (CVA)) and all-cause mortality with respectively ICPC codes: K74, K75, K77, K78, K89, K90 and A96.

### 2.4. Statistical analyses

When comparing differences between groups, the Chi-square test was used for dichotomous variables and a Student's *t*-test for continuous variables. In case a variable was not normally distributed, a non-parametric test Mann-Whitney U was applied [27]. Multivariable Cox regression analyses was used to analyze the predictive value (Hazard ratios and 95% confidence intervals) of elevated anxiety and depression scores on developing a coronary event. Baseline covariates used: previous coronary events, use of antihypertensive medication, Framingham risk variables [4] (age, gender, smoking, cholesterol, systolic blood pressure) and Body Mass Index. Single logistic regression analyses (odds ratio, 95% CI) and diagnostic parameters (sensitivity, specificity and positive predictive value (PPV)) were performed with new coronary events at follow-up as dependent variable and depressive and anxiety symptoms scores at baseline as independent variables. All data were analyzed with commercially available statistical software (IBM SPSS Statistics Version 26).

## 3. Results

### 3.1. Study population

At baseline, a total of 592 participants provided written informed consent. For the current study, we excluded 3 patients with missing baseline information. At 8 years, of the remaining 589 participants, 34 patients were lost to follow-up. Baseline characteristics of patients who dropped out were similar to those who participated in the follow-up period. Therefore, data analyses in the current study include 555 patients.

### 3.2. Baseline characteristics

Baseline demographics of the patient cohort are displayed in Table 1. The mean age was 70 years ( $\pm 6.6$ ) and 56% of the study population was female, most participants ( $>75\%$ ) had a partner and 13% had a low (only primary) educational level. Regarding to lifestyle, 12% were active smokers and 32% regularly consumed alcohol. With regard to risk factors, 11% had diabetes, 5% had a previous myocardial infarction, 23% had a LDL cholesterol level on target [28] and 41% had a systolic blood pressure on target, according to the National Dutch guideline [28], see footnotes Table 1. A previous episode of depression or anxiety was found in 13% and 4% of the patients, respectively.

The scores on the GAD-7 and PHQ-9 were not normally distributed, with a skewness of respectively 2.7 and 2.2 and a Kurtosis of 8.8 and 6.3. The median scores for GAD-7 and PHQ-9 scores were respectively 1.0 [0–3.0] vs. 1.0 [0–3.0]. The correlation coefficient between GAD-7 and PHQ-9 scores was:  $r = 0.56$  (Spearman,  $p < 0.001$ , large effect size). The cut-offs of the GAD-7 ( $\geq 8$ ) and PHQ-9 ( $\geq 5$ ) in the literature corresponded respectively to the 96th and the 84th percentile in this study cohort of elderly primary care patients. There was no significant difference in elevated anxiety scores (GAD-7  $\geq 8$ ) between men ( $M = 0.04$ ,  $SD = 0.19$ ) and women ( $M = 0.06$ ,  $SD = 0.23$  t (553) = 1.18,  $p = 0.239$ ). There was also no significant difference in elevated depression scores (PHQ-9  $\geq 5$ ) between men ( $M = 0.01$ ,  $SD = 0.11$ ) and women ( $M = 0.03$ ,  $SD = 0.18$ , t (553) = 1.56,  $p = 0.119$ ). The characteristics of the current sample did not differ from the original Chello cohort [15,16] and

**Table 1**  
Baseline demographics of 555 hypertensive primary care patients with 8 years' follow-up.

Characteristic	N (%)	Mean (SD)	Median [IQR]
<b>Demographics</b>			
Age		69.9 ± 6.5	
Female	309 (55.7)		
Male	246 (44.3)		
<b>Socio-economics</b>			
Having a partner	418 (75.3)		
Low education *	73 (13.2)		
<b>Lifestyle</b>			
Current smoker	69 (12.4)		
Regular alcohol use **	175 (31.5)		
Recommended physical exercise ***	81 (14.6)		
<b>Clinical characteristics and risk factors</b>			
Previous myocardial infarction	27 (4.9)		
Previous CVA (TIA / stroke)	50 (9.0)		
Diabetes	59 (10.6)		
BMI		28.0 ± 4.4	
SBP		150.1 ± 19.4	
DBP		82.1 ± 10.4	
Blood pressure on target †	223 (40.5)		
Use of antihypertensive medication	427 (76.9)		
Total cholesterol		5.1 ± 1.0	
LDL		3.1 ± 0.9	
LDL on target ††	130 (23.4)		
Use of cholesterol lowering medication	239 (43.1)		
<b>Anxiety/depression (with overlap)</b>			
Previous diagnosis of anxiety	20 (3.6)		
Previous diagnosis of depression	73 (13.2)		
Anxiety / depressive symptoms score at baseline			
GAD-7 score		1.0 [0–3.0]	
PHQ-9 score		1.0 [0–3.0]	
Use of anxiolytic medication	35 (6.3)		
Use of antidepressant	28 (5.0)		

Values for categorial variables are given as number (percentage); values for continuous variables are given as mean ± standard deviation. Scores on the GAD-7 and PHQ-9 were not normally distributed, with a skewness of respectively 2.7 and 2.2 and a Kurtosis of 8.8 and 6.3. Therefore, we used Mann-Whitney U test [median, inter quartile range].

Abbreviations: CVA, cerebrovascular accident; TIA, transient ischemic attack; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; LDL, low-density lipoprotein; GAD-7, generalized anxiety disorder-7; PHQ-9, patient health questionnaire-9; CVD, cardiovascular disease.

\* Only primary elementary educated.

\*\* Defined as ≥ 2 glasses of alcohol per day on average.

\*\*\* Defined as ≥ 30 min exercise per day, at least 5 days per week.

† On-target systolic blood pressure defined as < 140 mmHg for persons aged <70 years and < 150 mmHg for persons aged 70 years or older, according to Dutch primary care guideline [28].

†† On-target LDL defined as < 1.8 for persons aged <70 years and previous CVD, <2.6 for persons aged <70 years without previous CVD and < 2.6 for persons aged 70 years or older, according to the Dutch primary care guideline [28].

patients who were lost to follow-up did not differ on age and gender.

### 3.3. CVEs and all-cause mortality during 8 years' follow-up

Table 2 shows the incidence of new CVEs and all-cause mortality during 8 years' follow-up. Of the participants, 29 (5.2%) had a new coronary event (unstable angina pectoris, acute myocardial infarction) during follow-up, 42 (7.6%) cerebrovascular disease (transient ischemic attack, cerebrovascular accident), 57 (10.3%) atrial fibrillation, 22 (4%) heart failure and 68 died (12.3%). For all CVEs and all-cause mortality no differences were found according to gender.

### 3.4. Psychological distress scores in relation to CVEs and all-cause mortality

Table 3 shows the median [IQR] scores on the GAD-7 and PHQ-9 at baseline, stratified by new CVEs and all-cause mortality. Patients who developed a coronary event had significantly higher median anxiety (Md = 3.0, U = 9763, z = 2.69, p = 0.007, r = 0.11) and depression symptom scores (Md = 2.0, U = 9212, z = 1.97, p = 0.048, r = 0.08) at baseline compared to those who did not develop a coronary event. No significant associations were found with regard to other CVEs and all-cause mortality.

### 3.5. Anxiety and depression scores in relation to coronary events

We performed multivariable Cox regression analyses to analyze the association of elevated anxiety and depression scores on developing a coronary event, adjusting for relevant covariates like previous coronary events, use of antihypertensive medication, age, gender, smoking, cholesterol, systolic blood pressure and Body Mass Index. Elevated anxiety scores (GAD-7) increased the risk of a coronary event independently and significantly by 12% (HR 1.12; 95% CI [1.04–1.22], p = 0.005). Elevated depression scores (PHQ-9) increased the risk of a coronary event independently and significantly by 18% (HR 1.18; 95% CI [1.08–1.28], p < 0.0001). To evaluate if all-cause mortality was not a competing risk we performed a sensitivity analysis, excluding all patients who had died during follow-up and we repeated the Cox regression analyses again, with similar results: elevated GAD-7 and PHQ-9 scores showed HR 1.12; 95% CI [1.03–1.22], p = 0.006 and HR 1.15; 95% CI [1.06–1.26], p = 0.001 respectively.

We subsequently defined subgroups of patients according to anxiety and depression scores using the cut-offs reported in the primary care literature. In single logistic regression analysis, patients with both GAD-7 (≥8) and PHQ-9 (≥5) scores above the cut-offs were 5.5 times more likely to develop new coronary events compared to those without elevated scores (OR 5.5; 95% CI: 1.68–17.81). However, these cut-offs refer to general primary care patients over 18 years and it is well

**Table 2**  
Incidence of new cardiovascular events and death at 8 years' follow up.

Cardiovascular event and death	Total	Men	Women	P value
	N = 555	N = 246	N = 309	
	N (%)	N (%)	N (%)	
Coronary event	29 (5.2%)	15 (6.1%)	14 (4.5%)	0.410
-Myocardial infarction	8 (1.4%)	2 (0.8%)	6 (1.9%)	0.268
-Unstable angina pectoris	21 (3.8%)	13 (5.3%)	8 (2.6%)	0.468
Cerebrovascular disease	42 (7.6%)	21 (8.5%)	21 (6.8%)	0.441
-TIA	21 (3.8%)	10 (4.1%)	11 (3.6%)	0.913
-stroke	21 (3.8%)	11 (4.5%)	10 (3.2%)	0.449
Atrial fibrillation	57 (10.3%)	28 (11.4%)	29 (9.4%)	0.441
Heart failure	22 (4.0%)	8 (3.3%)	14 (4.5%)	0.443
All-cause mortality	68 (12.3%)	34 (13.8%)	34 (11.0%)	0.315

Abbreviations: TIA, transient ischemic attack.

**Table 3**  
Median [IQR] anxiety and depression scores in relation to development of a CVE and all-cause mortality at 8 years follow-up.

Cardiovascular event and all-cause mortality	—	Anxiety GAD-7 score			Depression PHQ-9 score		
		N	Median [IQR]	P	N	Median [IQR]	P
Coronary event	+	29	3.0 [0–6.5]	<b>0.007</b>	29	2.0 [0–7.0]	<b>0.048</b>
	–	526	1.0 [0–2.0]		526	1.0 [0–3.0]	
Cerebrovascular disease	+	42	1.0 [0–3.0]	0.706	42	1.0 [0–3.0]	0.977
	–	513	1.0 [0–3.0]		513	1.0 [0–3.0]	
Atrial fibrillation	+	57	1.0 [0–2.5]	0.861	57	1.0 [0–3.0]	0.973
	–	498	1.0 [0–3.0]		498	1.0 [0–3.0]	
Heart failure	+	22	1.0 [0–1.3]	0.530	22	1.0 [0–3.3]	0.514
	–	533	1.0 [0–3.0]		533	1.0 [0–3.0]	
All-cause mortality	+	68	0.5 [0–2.0]	0.207	68	1.0 [0–3.0]	0.754
	–	487	1.0 [0–3.0]		478	1.0 [0–3.0]	

Abbreviations: CVE, cardiovascular event; GAD-7, generalized anxiety disorder-7; PHQ-9, patient health questionnaire-9.

known that in elderly patients, psychological distress is much less prevalent [29] and the female / male ratio changes [30]. Also, GAD-7 cut-off of  $\geq 8$  refers to severe anxiety disorder while the PHQ-9 cut-off of  $\geq 5$  refers to minor depression. This is also reflected in the current sample: the GAD-7 cut-off of  $\geq 8$  reflects the 96th percentile, while the PHQ-9 cut-off of  $\geq 5$  reflects the 84th percentile. This suggests that especially the cut-off of the GAD-7 seems too high for this elderly primary care population. Therefore, we looked at the possible association of new coronary events at follow-up and sub-groups of patients with both high anxiety and depression symptom scores using several cut-offs, see Table 4. Already, GAD-7 scores  $\geq 2$  (reflecting the 63rd percentile) and PHQ-9 scores  $\geq 3$  (reflecting the 69th percentile) significantly increased the likelihood of new coronary events at follow-up. The higher the cut-off the higher the specificity and the lower the sensitivity - the PPV was overall rather low. The combination of diagnostic parameters was most optimal when we used the 75th percentile cut-off of the GAD-7 ( $\geq 3$ ) and the PHQ-9 ( $\geq 4$ ), reflecting anxiety / depression symptom scores in the highest quartiles, with a sensitivity of 52% and 41%, a specificity of 76% and 79% respectively. Though the PPV values were low with 11 and 10% respectively.

#### 4. Discussion

##### 4.1. Summary

The current study indicates an association between psychological distress and the occurrence of new coronary events after 8 years' follow-up in a random sample of elderly (60–85 years) primary care patients with hypertension in the Netherlands. Patients with both anxiety and

depression symptom scores above cut-offs are especially more likely to develop a new coronary event during 8 years of follow-up compared to those without elevated symptom scores at baseline. This association existed at much lower symptom cut-off scores on the general anxiety scale (GAD-7) as generally reported in primary care settings. No associations were found between baseline anxiety / depression symptoms and the development of other CVEs and all-cause mortality.

##### 4.2. Strengths & limitations

One strength of the current study is the relatively large primary care sample with carefully registered follow-up data up to 8 years of follow-up. This enabled us to evaluate possible associations between distress symptoms and the development of new coronary events at different cut-offs, lower as commonly reported in the literature.

A limitation of this study is that we measured anxiety and depression scores at a symptom level instead of syndromal level. However, the DSM-V advocates more focus now on intensity of distress symptoms rather than using syndromal diagnoses [31,32]. Furthermore, we only assessed the psychological symptoms scores at baseline and did not repeat the assessment during 8 years of follow-up. However, a study conducted by Denollet et al. showed that only one measurement of anxiety scores at baseline predicted premature all-cause and cardiovascular death in middle-aged women [33].

Another limitation is the fact that we only have data on all-cause mortality and not data on cardiac death. Therefore, we are unable to specify reasons for dropout due to cardiac death. This is mainly to be explained by ethical limitations considering privacy of centrally registered mortality causes in the Netherlands.

**Table 4**  
Different cut-off scores of GAD-7 and PHQ-9 in relation to a new coronary event.

	N (total = 555)	Percentiles	OR (95% CI) for new coronary event	P-value	Sensitivity	specificity	PPV
GAD-7 $\geq 1$	295	47th	1.72 (0.79–3.77)	0.171	66%	48%	6%
GAD-7 $\geq 2$	206	63rd	2.53 (1.17–5.40)	0.014	59%	64%	8%
GAD-7 $\geq 3$	143	75th	3.33 (1.57–7.09)	0.001	52%	76%	11%
GAD-7 $\geq 4$	100	83rd	4.10 (1.90–8.83)	<0.001	45%	83%	13%
GAD-7 $\geq 5$	63	89th	3.93 (1.71–9.07)	0.001	31%	90%	14%
GAD-7 $\geq 6$	45	92nd	5.04 (2.09–12.14)	<0.001	28%	93%	18%
GAD-7 $\geq 7$	34	94th	5.88 (2.31–14.97)	<0.001	24%	95%	21%
GAD-7 $\geq 8$	27	96th	3.50 (1.12–10.89)	0.022	14%	96%	15%
PHQ-9 $\geq 1$	313	44th	1.50 (0.68–3.29)	0.309	66%	44%	6%
PHQ-9 $\geq 2$	243	57th	1.62 (0.76–3.44)	0.204	55%	57%	7%
PHQ-9 $\geq 3$	173	69th	2.15 (1.02–4.57)	0.041	48%	70%	8%
PHQ-9 $\geq 4$	125	78th	2.58 (1.20–5.56)	0.013	41%	79%	10%
PHQ-9 $\geq 5$	89	84th	2.98 (1.34–6.64)	0.005	35%	85%	11%
PHQ-9 $\geq 6$	65	89th	3.78 (1.64–8.70)	0.001	31%	89%	14%
PHQ-9 $\geq 7$	48	92nd	4.63 (1.93–11.11)	<0.001	28%	92%	17%
PHQ-9 $\geq 8$	33	95th	3.71 (1.31–10.44)	0.008	17%	95%	15%
PHQ-9 $\geq 9$	24	96th	2.78 (0.78–9.90)	0.102	10%	96%	13%
PHQ-9 $\geq 10$	13	98th	5.95 (1.55–22.94)	0.003	10%	98%	23%

Abbreviations: GAD-7, generalized anxiety disorder-7; PHQ-9, patient health questionnaire-9; PPV, positive predictive value.



Furthermore, elevated GAD-7 and PHQ-9 scores significantly increased the likelihood of new coronary events at follow-up but the PPV values at different cut-off's were overall rather low. Although we had a large sample size, the number of new coronary events at eight years follow-up was not substantially high, probably to be explained by the characteristics of the sample: an uncomplicated primary care hypertension population. Future research in a population at higher risk could elucidate on determining a more appropriate cut-off within a prediction model.

#### 4.3. Comparison with the existing literature

In the current study, 22% of the patients had a new CVE during 8 years' follow-up and specifically 5.2% of the patients developed a new coronary event. These results are in line with a recent study on the incidence and prevalence of CVEs of primary care subjects in the UK [34]: the prevalence of CVEs increased with age up to 25% between 70 and 79 years old. Specifically, the latter study found a prevalence of 3.5% of coronary events in the whole population, but they did not stratify by age category.

The prevalence of anxiety and depressive symptoms found in the current study of elderly primary care subjects is in line with other studies. A review by Roy-Byrne et al. indicates a prevalence of generalized anxiety disorder (GAD) in primary care between 3 and 9% [35]. In our study we found a GAD prevalence of 5%. Beekman et al. found a prevalence of 2% for major depressive disorder and 13% for minor depression in elderly primary care subjects [30], which is similar to our study; 2% and 16% with a score indicative of respectively, a major depressive disorder and minor depression. Interestingly, the patients reported more often a previous diagnosis of depression compared to a diagnosis of an anxiety disorder, while it is well-known that anxiety is more prevalent in the general population than depression [36]. However, it is also known that in primary care, both anxiety and depression are commonly overlooked problems, mostly to be explained by the aspecific presentation of these syndromes [35]. This 'under-diagnosis' prevalence is even much higher for anxiety than depression, comparable to the prevalence of the current study [18]. The prevalence of elevated psychological distress scores in our study may seem rather low, however, the prevalence of anxiety and depression decline with higher age [29] and our population was in the age range between 60 and 85 years. The classical finding of female / male ratio of 2 / 1 with regard to the prevalence of anxiety and depression in the age range of 18–65 years that disappears with increasing age was also demonstrated in the current study: there was no differences between the sexes [29,30,36].

There are hardly any data available on validation of cut-offs of GAD-7 and PHQ-9 in our specific population: primary care elderly subjects. We only found 4 reports of PHQ-9 cut-offs scores in elderly patients, three studies with a very small population [24,37,38] and the only large sample study had a selected population of chronic ill patients with diabetes and chronic obstructive pulmonary disease [39]. The current study also showed that the association between psychological distress and new coronary event already exists at much lower cut-offs as commonly reported in the scarce primary care literature.

There is abundant literature on possible explanations of the association between psychological distress and CVD as summarized recently in the European Heart Journal [40]. Although the title of the paper (Depression and cardiovascular disease: a clinical review) suggests cardiovascular disease in general, the authors consistently quoted papers referring to an association between depression and *cardiac* disease. To explain the interplay between cardiac disease and distress several mechanism have been proposed: biological mechanism (including genetics, neuro-hormonal, inflammation pathways, e.g.), behavioral mechanisms (well-known association between depression / cardiac disease and poor life style habits such as smoking, obesity, inactivity, poor diet) and psycho-social mechanism (including financial problems, (un)employment, loss of capabilities resulting in loss of independency,

sexual dysfunction e.g) [40]. Interestingly, the particular association between anxiety / depression with cardiac disease is confirmed in the current study: we found a significant association with new coronary events and baseline distress but not with other future cardiovascular diseases such as CVA. In the same review, the authors mention the frequently and consistently found association between anxiety and cardiac disease [40]. Anxiety and depression are co-morbid disorders with an overlap up to 40–50% [41–44]. In the current study, the correlation at baseline between anxiety and depression symptoms was 0.56, suggesting that up to 36% of the variance of anxiety symptom scores is explained by depressive symptoms or vice versa. There is a growing consensus, also in the DSM-V, that anxiety and depression symptoms should conceptually be regarded together as distress symptoms [31,32]. In the current study, the highest association was found between the development of new coronary events and distress symptoms above a certain cut-off in line with previous reports [42].

#### 4.4. Implications for practice

In the Netherlands, nowadays, there are large general health care management programs: diabetes care, COPD care and also CVRM [45]. Special trained nurses take care of patients with chronic diseases according to a protocol, developed by the Scientific Department of the National Dutch Primary Care Association [28]. In these protocols, there is growing focus on mental health problems of patients with chronic diseases but in daily practice, there is no standardized instrument implemented within, for example, CVRM. The current study underlines the relevance of implementing such an instrument to assess psychological distress. If implemented, patients with higher distress levels could be offered a simple intervention like for example mindfulness training. Using a randomized controlled design, cognitive based mindfulness interventions showed a benefit on emotional wellbeing in primary care elderly diabetes-II patients [46,47]. Nowadays, these mental health interventions are offered online: they are effective, easily accessible to the general population at minimal costs [48,49].

In psychiatry and psychology, most of the cut-offs on anxiety and depression scales are assessed using questionnaires as well as syndromal diagnostic interviews of anxiety and depression [50,51]. The established cut-offs are estimates with the highest positive predictive value at most optimal sensitivity and specificity predicting syndromal diagnosis of anxiety / depression. In the current study, we proposed an 'epidemiological' approach using percentiles or quartiles with regard to poor cardiac outcome. Using these substantially lower cut-offs compared to syndromal diagnostic research, we were able to show that elderly patients already at these lower cut-offs were significantly more likely to develop new coronary events during follow-up. This is comparable to large epidemiological follow-up studies of the last decades showing that lower levels of blood pressure, total cholesterol or LDL benefit health outcomes in patients at risk for cardiac disease [52]. In clinical practice, it could be beneficial for health outcomes to extrapolate symptom cut-off scores to poor cardiac outcomes [53].

In conclusion, the current study shows that elderly primary care hypertension patients with high levels of distress (anxiety / depression) are more likely to develop future coronary events.

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#### Authors' contributions

Conceptualization: JHK, SSP, SEM, RN and VP. Data curation: JHK and VP. Formal analysis: JHK and VP. Writing - original draft: JHK, SSP, SEM, RN and VP. Writing - review & editing: JHK, SSP, SEM, RN and VP. All the authors agreed on the final submitted version.

## Declaration of Competing Interest

The authors have no competing interests to report.

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