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POCT-assisted Diagnosis for Acute Coronary Syndrome, Heart Failure and Venous Thromboembolism in Primary Care: A Longitudinal Analysis

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Abstract

Objective: Evaluating symptoms indicating acute Coronary Syndrome (ACS), Heart Failure (HF) or Venous Thromboembolism (VTE) poses a particular challenge at primary care level. Cardiac troponin T (cTnT), N-terminal pro-brain natriuretic peptide (NT-proBNP) and D-dimer serve as crucial diagnostic tools in such assessments. Evidence of the clinical benefit of 3-in-1 Point-of-Care Testing (POCT) for these biomarkers are very limited. The current study is to further investigate the benefit of POCT-assisted diagnosis for cardiovascular risk stratification in primary care.

Methods: In the first phase of a previously reported prospective multicentre controlled trial, primary care physicians were randomised to POCT assisted diagnosis or conventional diagnosis (controls). In the second phase, the controls received the POCT analyser and continued patient recruitment. The accuracy of the working diagnosis made during the baseline consultation of adults presenting with the respective symptoms was evaluated in a follow-up examination. The resulting accuracy was compared with the accuracy from the controls.

Results: Controls and POCT patients were similar in terms of baseline characteristics, symptoms and pre-existing diagnoses, but differed in working diagnosis frequencies. After the follow-up visit, except for the musculoskeletal problems, which were more prevalent in the controls, no statistically significant difference could be determined in regard to the confirmed diagnosis frequencies. In the POCT group, working diagnoses were more frequently correct (79.2% vs. 59.6%, p<0.001) and diagnostic accuracy for ACS, HF, and VTE was higher (58.3% vs. 45.2%, p<0.001).

Conclusion: The POCT device improved the diagnostic accuracy for patients with symptoms indicative of ACS, HF, or VTE.

Keywords: Point-of-care testing; Primary care; Cardiovascular biomarkers; Acute coronary syndrome; Heart failure; Venous thromboembolism; Sensitivity; Specificity

Introduction

The evaluation of patients with chest pain and/or dyspnoea is a routine part of primary care practice. These cardinal symptoms can be caused by the following diseases and disorders: stable angina pectoris, infections of the upper respiratory tract, myocardium or pericardium, pneumothorax, exacerbated COPD, gastrointestinal disease, musculoskeletal pain and panic disorder. The three most important differential diagnoses are Acute Coronary Syndrome (ACS), Heart Failure (HF) and Venous Thromboembolism (VTE) [1-4]. Establishing a reliable primary care diagnosis on the basis of clinical findings and the readily available diagnostic tools, such as ECG and X-ray, can be difficult. A number of useful cardiovascular biomarkers help facilitate the diagnosis and more are currently under development [5,6]. The most frequently employed biomarkers in this context are cardiac troponin T (cTnT), N-terminal pro-brain natriuretic peptide (NT-proBNP) and D-dimer [7-9]. New multifunctional devices are capable of measuring all three in a matter of minutes [10].

As a protein found only in the heart, cTnT is a highly specific and sensitive biomarker of myocardial damage and, if elevated, diagnoses myocardial infarction in the setting of myocardial ischemia (ST changes, chest pain) [11-14]. In addition, cTnT is recognised as an important prognostic marker in ACS [15-18].

NT-proBNP enables rapid differentiation between cardiac and non-cardiac causes of dyspnoea, as a value in the normal range can rule out HF with near certainty [19,20]. Moreover, NT-proBNP has a high prognostic value among patients with ACS. Elevated NT-proBNP at the point of initial presentation predicts an increased risk of mortality from myocardial infarction [21-24]. In combination with symptoms, clinical findings, ECG and troponin, it also aids in the risk stratification of patients with ACS and non ST-segment elevation myocardial infarction (NSTEMI) [25].

D-dimers are degradation by-products of fibrinolysis, which are typically elevated in patients with VTE (deep vein thrombosis (DVT) and Pulmonary Embolism (PE)). In ambulatory patients with a low pre-test probability, a negative D-dimer value can safely rule out DVT and PE [26]. As increased D-dimer levels are seen in many other non-thrombotic situations such as pregnancy, malignancies, sepsis, pneumonia, erysipelas and others, the specificity of the D-dimer test is low [27].

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The aim of this second analysis based in part on the previous study by Tomonaga et al. [10], was to confirm the benefit of POCT-assisted diagnosis for cardiovascular risk stratification in primary care. We assumed that the 40 Swiss general practitioners originally randomised as conventional diagnosis controls would attain a more accurate diagnosis of ACS, HF and VTE with the aid of POCT for cTnT, NT-proBNP, and D-dimer.

Methods

Study design and patients

In a previous prospective multicentre cluster-randomised trial, by Tomonaga et al. [10], conducted in the Canton of Zurich (Switzerland) from May 2006 to August 2007, 33 primary care practices (39 physicians) were assigned to diagnostic aid from a POCT analyser and 35 primary care practices (40 physicians) were assigned to conventional diagnosis employing best clinical practice (controls) [10]. In August 2007, the controls received the same diagnostic device and continued patient recruitment until August 2008. The present analysis thus represents a before-and-after comparison of the same 40 physicians.

All adult patients presenting in the randomised primary care practices between May 2006 and August 2008 with chest pain, tightness, shortness of breath and other symptoms indicating a potential cardiovascular event were encouraged to take part in the study. All individuals included in the study gave their prior written consent. In addition, the study received approval from the local medical ethics committee (Kantonale Ethikkommission Zürich), in accordance with the Declaration of Helsinki (1996) and Good Clinical Practice guidelines. Excluded from the study were patients with a presentation >5 days after symptom onset, severe renal insufficiency, recent anticoagulant treatment and/or ongoing cancer therapy. The cited exclusion criteria were chosen to minimise the distortion of results stemming from a positive or negative influence on the biomarkers due to secondary diagnoses or treatments [28-30]. During the initial consultation, the general practitioner established the patient's medical history, principal symptoms and a comprehensive clinical status. It was up to the treating physician to decide whether to order such additional tests as ECG, conventional X-ray and, in the second phase of the study, analysis of the three biomarkers (the physician had the possibility to choose if and which biomarker test was necessary). The results of the initial consultation formed the basis for a working diagnosis in the following five categories: ACS, HF, VTE, musculoskeletal or other problems. At least three weeks after the baseline consultation, the same physician re-evaluated his or her working diagnosis in a follow-up examination. Additionally taking into account the results of any hospitalisations and/or further examinations by specialists, the follow-up examination yielded the confirmed diagnosis.

Technical information

After completion of the first study phase, the physicians were provided with the bedside Cardiac Reader® (Roche Diagnostics, Switzerland), a 3-in-1 device that determines cTnT, NT-proBNP and D-dimer in heparinised venous blood within 8 to 12 minutes. The quantitative measurement of the parameters was carried out in the ranges from 0.05-2.00 ng/ml, 60-3000 pg/ml and 0.1-4.0 µg/ml with 0.1 ng/ml, 125 pg/ml and 0.5 µg/ml as the positive/negative cut-offs. The instruction of the general practitioners regarding operation of the POCT device and interpretation of the test results was always conducted by the same specialist from Roche Diagnostics to ensure consistency [10]. The quality of the tests was monitored in accordance with the internal and external quality controls mandated by Swiss federal law and the Swiss Commission for Quality Assurance in Medical Laboratories (QUALAB) [31].

Statistical analysis

The data were analysed using IBM SPSS 19.0 (IBM Corporation, Somers, NY, USA) and Microsoft Office Excel 2007 (Microsoft Corporation, Redmond, WA, USA). Chi-square tests and t tests were used for categorical and continuous variables, respectively. A two-tailed p value of <0.05 was considered statistically significant. To evaluate the quality and performance of the diagnostic test, we generated receiver operating characteristic (ROC) curves, which were defined as test sensitivity on the Y-axis and 1-specificity on the X-axis. The area under the ROC curve (AUC) combining sensitivity and specificity was used to assess the overall performance of the diagnostic tests. This area was interpreted as the average sensitivity value for all potential specificity values [10].

Results

Study population and baseline characteristics

Of the 302 patients included in the study from May 2006 to August 2008, 151 (50%) were recruited as controls and diagnosed conventionally, whereas the remainder were assigned to the POCT group and received a diagnosis supported by the analysis of cTnT, NT-proBNP and/or D-dimer. The relevant baseline characteristics of age, gender, body mass index, creatinine, glucose, triglycerides, HDL and LDL did not differ significantly between the two groups. The interval between symptom onset and baseline visit was longer in the POCT group because some patients presented over 5 days after symptom onset (non-inclusion criterion). We contacted the practices for specific explanations. In almost all cases the patients had visited the physician in the previous weeks/months (>>5 days) with cardiovascular problems. Due to new or exacerbated symptoms (on setting in the previous 5 days) they revisited their physician who reported the date of their first or previous visit incorrectly. After patients with incorrect symptom onset were excluded, the average interval between symptom onset and baseline visit became similar in the two groups (Table 1).

Presenting symptoms

The majority of patients in both groups presented with the principle symptoms of ACS, namely acute chest pain, tightness, pressure or squeezing in the chest and/or dyspnoea. Other symptoms typical of manifest heart failure alongside dyspnoea, such as oedema, distended neck veins, nocturia and cyanosis, were rarely documented. The groups statistically differed in acute chest pain, tightness, pressure/squeezing in the chest, and neck vein congestion (Table 2).

Medical history

The most frequently recorded cardiovascular risk factors were arterial hypertension, diabetes mellitus and current smoking. Hypertension, heart failure and smoking seemed to be more prevalent in the POCT patients, whereas thrombosis/embolism and pathological ECG were more prevalent in the controls. However no statistically significant difference was found between the two groups (Table 3).

Working and confirmed diagnoses

The frequencies of the working diagnoses between the two groups were similar for HF (p=0.850), VTE (p=0.219) and MS (p=0.681) (Figure 1). In contrast, in the POCT group there were significantly

Variable	Controls	POCT	P value
	n=151	n=151	
	n(%)	n(%)	
	or mean ± SD	or mean ± SD	
Men	83/143 (58.0)	83/148 (56.1)	0.735
Age (years)	64 ± 17	61 ± 16	0.424
Body mass index (kg/m^2)	27 ± 6	27 ± 5	0.797
Glucose (mmol/l)	6.3 ± 2.1	6.1 ± 2.0	0.403
Creatinine (mmol/l)	84.4 ± 22.4	81.8 ± +20.2	0.285
High-density lipoprotein (mmol/l)	1.4 ± 0.5	1.3 ± 0.5	0.640
Low-density lipoprotein (mmol/l)	3.3 ± 1.0	3.0 ± 1.3	0.247
Triglycerides (mmol/l)	1.7 ± 1.0	1.9 ± 0.9	0.982
Interval between symptom onset and baseline visit (all patients, days)	1.7 ± 1.7	2.2 ± 8.2	0.194
Interval between symptom onset and baseline visit (patients presenting <5 days after symptom onset, days)	1.5 ± 1.4	1.3 ± 1.5	0.228
Time period	May 2006-August 2007	August 2007-August 2008	

Table 1: Baseline demographics, clinical chemistry and interval between symptom onset and baseline presentation.

Symptome	Controls	POCT	P value
	n=151	n=151	
	n(%)	n(%)	
Acute chest pain	96 (64)	75 (50)	0.015
Tightness, pressure, or squeezing in the chest	92 (61)	64 (42)	0.001
Dyspnoea	69 (46)	53 (35.1)	0.061
Heartburn-like sensation	19 (13)	19 (13)	1.000
Heaviness and tension sensations in the leg	5 (3)	6 (4)	0.759
Calf pain	4 (3)	10 (7)	0.101
Neck vein congestion	4 (3)	0 (0)	0.044
Oedema	9 (6)	9 (6)	1.000
Nocturia	4 (3)	1 (1)	0.176
Cyanosis	3 (2)	1 (1)	0.317

Table 2: Presenting symptoms.

fewer ACS diagnoses (p=0.006) and more other diagnoses (e.g. stable angina, pleuritis, pericarditis, viral infection, psychiatric problems; p=0.029) if compared to the controls.

In the confirmed diagnosis, the diagnoses of ACS, HF, VTE and other problems scarcely differed between the two groups (p=0.845, p=0.545, p=0.296 and p=0.251 respectively) (Figure 2). Only MS problems showed a significant difference and were more prevalent in the controls (35.1% vs. 24.0%, p=0.035). In both groups, the majority of the patients were diagnosed with either MS or other problems.

Diagnostic Accuracy of the Working Diagnosis

In the POCT group, 118/151 (79.2%) working diagnoses were correct compared to 90/151 (59.6%) in the control group (p<0.001). Considering the three most important differential diagnoses ACS, HF and VTE, 58.3% of the working diagnoses were correct in the POCT group and 45.2% in the control group (p<0.001), with 25 false positive diagnoses (41.7%) in the POCT group and 40 false positive diagnoses (54.8%) in the control group. For the remaining working diagnoses (MS or other problems), there were 83/89 (93.3%) correct diagnoses in the POCT group and 57/78 (73%) in the control group (p<0.001). The sensitivity was higher in the POCT group for all working diagnoses except ACS and VTE (Table 4). The specificity was similar for all working diagnoses in both groups, except for ACS, which exhibited much better specificity in the POCT group. The Negative Predictive Values (NPV) for ACS, HF and VTE were practically identical. Overall, the accuracy of the working diagnoses in the POCT group was somewhat better than in the control group. Compared to the aforementioned predecessor study by Tomonaga et al. [10], however, the results of this second before-and-after analysis were less pronounced.

Biomarker Performance in the POCT group

Considering the sensitivity, specificity and NPV of all cardiovascular biomarkers in the POCT group, it is clear that the sensitivity for the confirmed diagnoses was markedly higher than for the working diagnoses, especially for the ACS diagnoses. The NPV was only minimally higher and the specificity was nearly identical in both groups. In terms of individual biomarkers, the cTnT test exhibited a higher diagnostic power for the confirmed diagnoses than the working diagnoses: the sensitivity was 40% higher while the NPV was 10% higher (Table 5). One patient had a false-negative result and risked a wrong diagnosis. Despite the false-negative result, the patient was diagnosed correctly based on his medical history and symptoms.

Unlike the cTnT test, NT-proBNP results were nearly identical in the working diagnoses and the confirmed diagnoses with a sensitivity of 92-93%, specificity of 65-68% and NPV of 93%. Only one patient received a false negative test. It was an 88-year-old female who had a history of angina pectoris and diabetes and polymedication (ACE inhibitors, beta-blockers, oral anti-diabetic medication). Again, despite the false-negative result, the patient was diagnosed correctly based on her medical history and symptoms. The sensitivity of the D-dimer test was high. Only one patient had a false-negative test. He was a male, 65 years old, with a BMI of 38 kg/m^2 and a medical history of DVT. He was correctly diagnosed based on his history and symptoms. Sixteen of 49 individuals with positive D-dimer were not found to have thrombosis, which is reflected in a specificity of 75%.

The cTnT ROC curve based on the confirmed diagnoses exhibited an irregular shape as the physicians often simply recorded the result as

	Controls	POCT	P value
	n=151	n=151	
	n(%)	n(%)	
Myocardial infarction	11 (7)	13 (9)	0.670
Angina pectoris	15 (10)	12 (8)	0.545
Peripheral arterial disease	5 (3)	2 (1)	0.251
Aneurysm/dissection	2 (1)	1 (1)	0.562
Hypertension	23 (15)	34 (23)	0.106
Diabetes mellitus	15 (10)	17 (11)	0.708
Smokers	24 (16)	32 (21)	0.236
Chronic obstructive pulmonary disease	5 (3)	1 (1)	0.099
Pathological electrocardiagram	59 (39)	48 (32)	0.171
Heart failure	5 (3)	13 (9)	0.052
Renal failure	8 (5)	5 (3)	0.395
Thrombosis/embolisme	13 (9)	6 (4)	0.097
Malignant tumor	7 (5)	7 (5)	1.000
Hospitalisation in previous 12 month	25 (17)	17(11)	0.183

Table 3: Medical history.

positive or negative (<0.1ng/ml). In such cases positives and negatives values were arbitrarily entered as 0.1 ng/ml and 0.0 ng/ml respectively. The AUC of 89% demonstrated the high quality of the test (Figure 3). The ROC curves for NT-proBNP and D-dimer were more regular and showed AUCs of 86% and 91% respectively.

Discussion

The results of the current study emphasise the importance of POCT for cTnT, NT-proBNP and D-dimer in the evaluation of patients presenting in primary care practices with potential cardiovascular symptoms. Diagnoses were more accurate with the use of a POCT device. In particular, the POCT-assisted general practitioners were able to avoid numerous false positive working diagnoses of ACS, HF and VTE. This, in turn, meant that many additional diagnostic measures could be spared. Analysis of the three biomarkers cTnT, NT-pro BNP and D-dimer in primary care settings offers a relevant diagnostic advantage by more reliably ruling ACS, HF and VTE in or out among a non-selected patient population. Overall, compared with the data stem from the study by Tomonaga et al. [10] the results of this second analysis where slightly less pronounced.

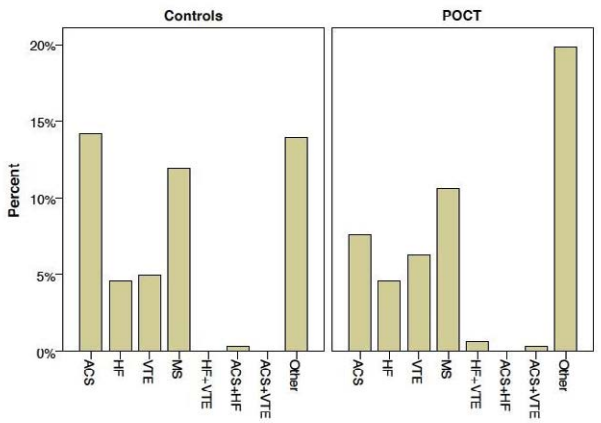

Figure 1: Working diagnoses at baseline. ACS diagnoses were more frequent and other diagnoses less frequent in the controls (p=0.006 and p=0.029). HF, VTE and MS were similar in both groups (p=0.850, p=219 and p=0.681 respectively). One patient in the control group was diagnosed with both ACS and HF, one POCT patient with ACS and VTE and two patients in the POCT group with HF and VTE. (ACS, acute coronary syndrome; HF, heart failure; MS, musculoskeletal problems; VTE, venous thromboembolism).

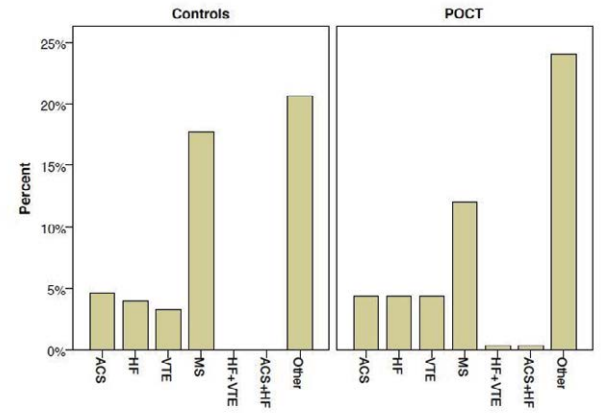

Figure 2: Confirmed diagnoses. The incidence of ACS, HF, VTE and other problems were similar in both groups (p=0.845, p=0.545, p=0.296 and p=0.251 respectively). Musculoskeletal and other problems were the predominant diagnoses in both groups. MS were significantly more frequent in the controls (p=0.035). (ACS, acute coronary syndrome; HF, heart failure; MS, musculoskeletal problems; VTE, venous thromboembolism.

		Sensitivity		Specificity		NPV	
		n	%	n	%	n	%
ACS	POCT	12/15	80	124/136	91	124/127	98
	Controls	14/14	100	107/137	78	107/107	100
HF	POCT	14/15	93	134/136	99	134/135	99
	Controls	10/12	83	134/139	96	134/136	99
TE	POCT	11/15	73	125/136	92	125/129	97
	Controls	9/10	90	135/141	96	135/136	99
MS	POCT	29/36	81	111/114	97	111/118	94
	Controls	34/53	64	96/98	98	96/115	84
Other	POCT	55/71	77	75/78	96	75/91	82
	Controls	37/62	60	84/89	94	84/109	77

Table 4: Diagnostic accuracy of the working diagnoses – sensitivity, specificity and NPV.

Biomarker	In relation to	Sensitivity		Specificity		NPV	
		N	%	N	%	N	%
cTnT	Working ACS	8/19	42	83/89	93	83/94	88
	Confirmed ACS	9/11	82	92/97	95	92/94	98
NT-pro BNP	Working HF	13/14	93	13/19	68	13/14	93
	Confirmed HF	12/13	92	13/20	65	13/14	93
D-dimer	Working VTE	17/19	89	47/56	84	47/49	96
	Confirmed VTE	10/11	91	48/64	75	48/49	98

Table 5: Sensitivity, specificity and NPV of cTnT, NT-pro BNP and D-dimer **in relation to the working and confirmed diagnoses of ACS, HF and VTE.**

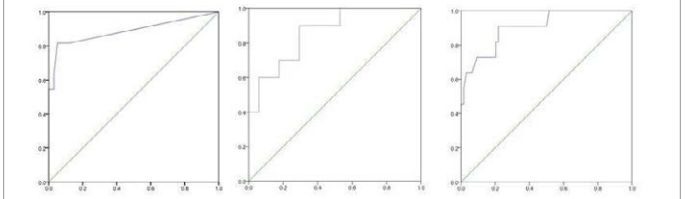

Figure 3: cTnT(left), NT-proBNP (center) and D-dimer (right) ROC curves. X-axis: 1-specificity; Y-axis: Sensitivity. Areas under the curv (AUC): 89% (95% confidence interval [CI]: 0.75-1.00), 86% (95% CI: 0.72-1.00) and 91% (95% CI: 0.81-1.00).

Diagnoses of ACS

Encompassing unstable angina pectoris, NSTEMI and ST-segment elevation myocardial infarction (STEMI), ACS is responsible for rising morbidity and mortality worldwide [32]. Coronary heart disease is the leading cause of death in western countries. In the United States, it was responsible for one in six deaths in 2007 [33]. A study conducted by Murray et al. [34] suggests that by the year 2020, it will become the main cause of death in developing countries as well. The rapid identification of patients with suspected ACS is critical for the

initiation of evidence-based medical treatment, which has a major influence on clinical and economic outcomes [11,12,35]. Relying on symptoms to recognise acute myocardial infarction is often difficult, especially because a third of the patients present with other symptoms than chest pain [36]. In the current study, the number of ACS diagnoses was unexpectedly high among the working diagnoses, in particular in the control group. We surmised that the study topic may have sensitised physicians to typical and atypical chest pain as a potential cause of ACS, leading them to overestimate its incidence. In numerical terms, approximately two-thirds of the ACS working diagnoses in the control group were not confirmed in the follow-up examination. This was reflected in the high sensitivity and low specificity. In the POCT group, by contrast, fewer cases of ACS were suspected, which resulted in poorer sensitivity but a better specificity. In 90% of the POCT group and in 80% of the control group, ACS was correctly included or excluded. Overall, the data from this analysis based in part on the data of the previously reported trial by Tomonaga et al. [10] support the idea that measuring cTnT in combination with the clinical presentation, patient history and ECG enhances diagnostic accuracy, in line with the American College of Cardiology/American Heart Association guidelines on managing patients with unstable angina or NSTEMI and the European Society of Cardiology Guidelines for the diagnosis and treatment of non-ST-segment elevation ACS [11,12]. Except for the sensitivity results discussed above, our data reflect the 94% sensitivity and 97% NPV of the cTnT test for ACS reported by Lüscher et al. [37] in 92 patients with chest pain, and the 100% sensitivity, 42% specificity and 100% NPV reported by Fehr et al. [38] in a cross-sectional study of asymptomatic haemodialysis patients. The high AUC value for the cTnT ROC curve was largely attributable to the high test specificity. To exclude ACS on the basis of a negative cTnT reading, at least 6 hours need to have elapsed following symptom onset (time to increase above the reference range). The maximum time limit up to which troponin can be used for diagnostic purposes is 5-7 days (time for biomarker level normalisation). Table 1 confirms that most patients fulfilled this time criterion.

Diagnoses of HF

HF is a growing health problem worldwide. According to the latest statistics, over 5.5 million Americans and approximately 15 million inhabitants in the 51 ESC member countries suffer from HF. The incidence of HF among those over 65 years of age is 10 per 1000 [33,39]. In addition, it is the most frequent cause of hospitalisation for people over 65 [33]. With effective treatments and lower mortality rates from hypertension and coronary heart disease, the two largest causes of HF, more people are surviving to experience HF in old age and hence the incidence and absolute numbers of patients with HF can be expected to rise significantly in coming decades [40]. The diagnosis of HF in a primary care context is difficult as symptoms and clinical examinations are often not sensitive enough to make a reliable diagnosis [41]. Furthermore, while echocardiography is the most frequently used and most dependable method of evaluating systolic and diastolic heart function [39,42], the technique is relatively expensive and beyond the means of most general practitioners [42,43].

In our analysis, like the previous study by Tomonaga et al. [10], the diagnosis of HF in the POCT group exhibited high sensitivity, specificity and NPV. Specificity and NPV were also high in the control group. However, sensitivity was lower, suggesting that HF was better identified in the POCT group, presumably due to the NT-proBNP. The high AUC of the NT-proBNP ROC curve (Figure 3) reflected the high diagnostic accuracy of the test.

Diagnoses of VTE

The incidence of symptomatic VTE – which includes DVT and PE – ranges from 71 to 117 cases per 100,000 of the population. According to studies, which exclude autopsy data, approximately two-thirds of the above mentioned VTE range are DVT and one-third are PE [44,45]. In order to diagnose patients with suspected VTE at the primary care level and decide if additional diagnostic measures are necessary, the patient history and clinical examination alone are not sufficient [46,47]. With the introduction of the non-invasive D-dimer blood test, extended to the primary care setting, the accuracy of diagnosis was significantly improved [48-50]. A negative D-dimer test in combination with a low clinical pre-test probability can exclude DVT without requiring an ultrasound [50,51]. In our study, specificity and NPV were good in both groups for the diagnosis of VTE. Sensitivity was slightly better in the control group. The D-dimer assay showed a moderately good specificity while the sensitivity and NPV were excellent: almost all patients with VTE also had an elevated D-dimer. The NPV of 98% confirms the assay's power in regard to the exclusion of VTE. Here too, the results of the current analysis correspond to the previous study by Tomonaga et al. [10] as well as the findings of other studies, e.g. Ten Cate-Hoek and Prins et al., Leclercq et al. or Schutgens et al. [51-53].

Study limitations and future research

This study is partially based on a previous prospective multicentre cluster-randomised trial investigating the benefit of POCT-assisted diagnosis for cardiovascular diseases in primary care [10]. The aim of this analysis was to investigate whether the use of the same POCT-device in the controls leads to a similar increase in diagnostic accuracy. A simple, uncontrolled before and after study design was used.

A second limitation concerns the used POCT-device and the interval between sampling year and publication of this second analysis (ca. 6 years): the Cardiac Reader® used in this study has been already substituted with new and more accurate devices. However, this should not necessarily alter the value of the results in demonstrating the utility of POCT for the evaluation of patients with chest pain and/or dyspnoea at primary care, since the new device should be more accurate, reducing the percentage of false positive and false negative diagnoses.

Third, our study restricted its geographic scope to Canton of Zurich. Although the results can be assumed to apply to more rural areas as well, this would need to be confirmed in a further study. Forth, the recruiting of patients proved to be surprisingly difficult. Especially in the first phase, the initial number of recruited patients was low and we had to call the physicians several times to remind them to continue patient recruitment. In the second phase with the POCT device, patient recruiting was greatly improved compared to the previous phase. We surmised that the in-practice presence of the Cardiac Reader® automatically made the physicians more aware of the study and increased their motivation to recruit patients. Another reason for the lower than expected recruitment numbers is that patients with chest pain in today's modern medicine tend to directly seek out emergency care. Fifth, the working diagnosis and the confirmed diagnosis were determined by the same physician. An evaluation by an independent second physician was not possible due to data protection concerns. This could have led to underreporting of incorrect working diagnoses, artificially inflating the accuracy of the working diagnoses or resulting in a false low difference

between the study phases. On the other hand, all the results of further ambulatory or inpatient investigations were incorporated in the final assessment, which reduced the risk of potential bias. A sixth and final limitation concerns the general practitioners who ignored the results of the biomarkers, especially in the diagnosis of ACS. It was not clear if this was due to a lack of confidence in the biomarkers and hence a greater weighting of the medical history and clinical examination, or if the physicians incorrectly interpreted the results of the biomarkers. This aspect emphasises the importance of continued education and training of primary care providers.

Very little data has been collected on the socioeconomic benefit of cardiovascular risk stratification in primary care using POCT. A number of studies published to date have analysed the advantages of individual biomarkers, particularly in connection with the reduction of further diagnostic procedures and hospitalisations, which can be presumed to offer socioeconomic benefits [10]. For instance, Ten Cate-Hoek et al. [51] determined that the number of unnecessary ultrasound examinations can be reduced by 30% for patients with suspected VTE who have a negative D-dimer and a low pre-test probability of VTE. Nielsen et al. [54] concluded from their data that NT-proBNP testing obviated the need for an echocardiogram in 50% of patients presenting with dyspnoea in primary care practices. A similar study by Siebert et al. [55,56] even registered a 58% reduction in the number of echocardiograms. Moreover, this study was able to show that 13% of hospitalisations could be avoided and hospitalisation periods could be shorted by 12% when the diagnosis was made using NT-proBNP. To identify the true positive socioeconomic benefit of POCT for ACS, HF and VTE in primary care medicine, further studies need to be conducted [10].

Conclusions

This second analysis based in part on the data of the previously reported study by Tomonaga et al. [10], demonstrated again the benefit of 3-in-1 POCT for cardiovascular risk stratification in primary care medicine. The rapid analysis of the three biomarkers cTnT, NT-proBNP and D-dimers enabled more accurate diagnoses of ACS, HF and VTE. In view of the advantageous socioeconomic potential, a further investigation is already being planned based on the clinical outcome of this study [10].

Competing Interests

The authors declare that they have no conflict of interest.

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