International Journal of Cardiology 286 (2019) 1–6

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Left ventricular hypertrophy contributes to Myocardial Ischemia in Non-obstructive Coronary Artery Disease (the MicroCAD study)

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ARTICLE INFO

Article history:
Received 16 October 2018
Received in revised form 15 February 2019
Accepted 27 March 2019
Available online 28 March 2019

Keywords:
Myocardial ischemia
Non-obstructive coronary artery disease
Left ventricular hypertrophy
Hypertension
Computed tomography coronary angiography

ABSTRACT

Background: The underlying mechanisms causing myocardial ischemia in non-obstructive coronary artery disease (CAD) are still unclear. We explored whether left ventricular hypertrophy (LVH) was associated with myocardial ischemia in patients with stable angina and non-obstructive CAD.
Methods: 132 patients (mean age 63 ± 8 years, 56% women) with stable angina and non-obstructive CAD diagnosed as <50% stenosis by coronary computed tomography angiography (CCTA) underwent myocardial contrast stress echocardiography. Left ventricular (LV) hypertrophy (LVH) was identified by LV mass index >46.7 g/m$^{2.7}$ in women and >49.2 g/m$^{2.7}$ in men. Patients were grouped according to presence or absence of myocardial ischemia by myocardial contrast stress echocardiography. The number of LV segments with ischemia at peak stress was taken as a measure of the extent of myocardial ischemia.
Results: Myocardial ischemia was found in 52% of patients, with on average 5 ± 3 ischemic LV segments per patient. The group with myocardial ischemia had higher prevalence of LVH (23 vs. 10%, $p = 0.035$), while age, sex and prevalence of hypertension did not differ between groups (all $p > 0.05$). In multivariable regression analyses, LVH was associated with presence of myocardial ischemia (odds ratio 3.27, 95% confidence interval [1.11–9.60], $p = 0.031$), and larger extent of myocardial ischemia ($\beta = 0.22$, $p = 0.012$), independent of confounders including age, hypertension, obesity, hypercholesterolemia, calcium score and segment involvement score by CCTA.
Conclusions: LVH was independently associated with both presence and extent of myocardial ischemia in patients with stable angina and non-obstructive CAD by CCTA. These results suggest LVH as an independent contributor to myocardial ischemia in non-obstructive CAD.
Clinical trial registration number: ClinicalTrials.gov, identifier NCT018535271.

1. Introduction

Management of patients with non-obstructive coronary artery disease (CAD) and stable angina represents a major clinical challenge [1,2]. Non-obstructive CAD is a common finding, in particularly among women [3,4]. During recent years it has been well documented that patients with non-obstructive CAD have increased cardiovascular morbidity and mortality, contrasting the original conception that it was a benign condition [2–6]. Myocardial ischemia is characterized by a mismatch between the myocardial oxygen supply and demand, and has adverse prognostic implications in patients with CAD [7]. Further, detection of myocardial ischemia in non-obstructive CAD may help to identify the patients with increased risk of impaired prognosis [8]. Moreover, the pathophysiologic mechanisms leading to myocardial ischemia in patients with non-obstructive CAD appear to be multifactorial. Several factors, including hypertension, atherosclerosis and microvascular dysfunction, have been reported as potential contributors to myocardial ischemia [1,9,10]. However, the underlying disease mechanisms contributing to myocardial ischemia in the individual patient may often not be identified during routine diagnostic work-up, and evidence based guidelines for personalized management of patients with non-obstructive CAD are still missing [1].

Left ventricular hypertrophy (LVH) is the hallmark of hypertension mediated organ damage and is an independent predictor of both all-cause mortality and cardiovascular morbidity in general and hypertensive population [11–14]. In hypertensive patients, LVH, in particular the concentric type, has been associated with presence of symptomatic myocardial ischemia even with normal coronary angiography [15]. It has previously been suggested that hypertensive patients with LVH have a lower threshold for myocardial ischemia and that this may explain the increased cardiovascular risk [16]. However, the impact of

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https://doi.org/10.1016/j.ijcard.2019.03.059
0167-5273/

LVH, a potential treatment target, on myocardial ischemia in patients with non-obstructive CAD has not previously been explored. Thus, the aim of this study was to assess whether presence of LVH may contribute to presence of myocardial ischemia in patients with stable angina and non-obstructive CAD.

2. Methods

2.1. Patient population

The Myocardial Ischemia in Non-obstructive Coronary Artery Disease (MicroCAD) study is a cross-sectional study that prospectively included patients referred to coronary computed tomography angiography (CCTA) at Department of Heart Disease, Haukeland University Hospital, Bergen, Norway in the period May 2013 until November 2014 by experienced cardiologist on a clinical suspicion of stable angina and that were diagnosed with non-obstructive CAD. Other inclusion criteria were age >30 years, clinical stable angina, defined as exercise induced angina pectoris and/or dyspnea for at least 6 months, and at least one cardiovascular risk factor (hypertension, hypercholesterolemia, diabetes, smoking or family history of premature CAD). Exclusion criteria were clinically unstable angina, severe valve disease, mechanical valve prosthesis, arrhythmias, severe pulmonary disease and known allergies to ultrasound contrast.

In total 153 patients were identified and invited, of whom 21 declined participation, leaving 132 patients included in the MicroCAD study. All participants signed informed consent. The MicroCAD project was approved by the regional ethical committee and was performed according to the 1975 Declaration of Helsinki. The MicroCAD project is registered at ClinicalTrials.gov with identifier NCT01853527.

2.2. Cardiovascular risk factors and symptoms

The patients reported cardiovascular risk factors, medical history and use of medication on a standardized questionnaire. Family history of premature CAD was considered present if documented CAD was present in a first-degree relative before the age of 65 years in women and 55 years in men. Hypercholesterolemia was defined as total serum cholesterol >6.5 mmol/l or use of cholesterol-lowering treatment. Body mass index (BMI) was calculated as body weight in kilograms divided by height in meters squared. Obesity was defined as BMI ≥30 kg/m^2. Hypertension was defined as known hypertension, use of antihypertensive drugs or high blood pressure at the clinic visit (systolic blood pressure ≥ 140 mm Hg and/or diastolic blood pressure ≥ 90 mm Hg) [17]. Fasting blood samples were collected to measure serum lipid profile, serum glucose and creatinine. Glomerular filtration rate was estimated by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula [18].

2.3. Conventional echocardiography

Echocardiography was performed following a standardized protocol and interpreted in line with current joint guidelines of the American Society of Echocardiography and the European Association of Cardiovascular Imaging [19]. We interpreted the images offline at the Bergen Echocardiography Core Laboratory blinded to clinical data. All images were proof-read by the same experienced reader (MTL). Left ventricular (LV) mass was calculated by Devereux's equation and indexed for height in meters in the allometric power of 2.7. We defined LVH by the prognostically validated sex specific cut-off values of LV mass index (LVMi) >46.7 g/m$^{2.7}$ in women and >49.2 g/m$^{2.7}$ in men [12,20]. LV ejection fraction was calculated by Simpson's biplane method. Relative wall thickness was calculated as posterior wall thickness/LV internal radius ratio and considered increased if ≥0.43 [19]. LV geometry was classified into four groups based on the presence of LVH and normal or increased relative wall thickness [19]. Accordingly, normal LV geometry was defined as no LVH and normal relative wall thickness, concentric remodeling as no LVH and increased relative wall thickness, concentric LVH as LVH and increased relative wall thickness, and eccentric LVH as LVH and normal relative wall thickness [19].

2.4. Myocardial contrast echocardiography for myocardial perfusion

Myocardial contrast echocardiography was performed using real-time low-mechanical index imaging and destruction replenishment following current guidelines [21]. Ultrasound contrast agent (SonoVue, Bracco, Milan, Italy) was given intravenously as 1 ml bolus followed by 1 ml/h infusion with a rotating infusion pump (VueJet, Bracco, Milan, Italy). Apical 2-, 3- and 4-chamber views were used to score wall motion and myocardial perfusion at rest and at peak dobutamine stress, defined as 85% of maximum age predicted (200 – age) heart rate during stress echocardiography [21]. Wall motion was scored visually as normal or abnormal, and myocardial perfusion as normal or delayed in the individual 17-segments of the LV. Stress induced myocardial ischemia was defined as presence of delayed contrast replenishment 2 heart beats after flash at peak stress in any LV segment. The number of LV segments with delayed perfusion at peak stress was taken as a measure of the extent of myocardial ischemia.

2.5. Coronary computed tomography angiography and non-obstructive coronary artery disease

CCTA was performed by a 256-slice dual source scanner (Somatom Definition Flash, Siemens, Germany) with electrocardiographic (ECG) -triggered acquisitions. Patients with heart rate >60 beats per minute were given metoprolol intravenously (1 mg/ml, maximum 20 mg) until heart rate was ≤60 beats per minute. The patients received non-ionic contrast intravenously as 80–115 ml iomeprol 400 mg I/ml (Iomeron®, Bracco, Milan, Italy) according to body weight. All patients received 0.4 mg sublingual nitroglycerin in order to optimize image quality. Experienced readers analyzed all images for detection of coronary artery stenosis using a modified 20-segment American Heart Association model [22]. Non-obstructive CAD was defined as presence of ≥ one stenosis with lumen diameter reduction 1–49% in any coronary artery segment. CCTA was revised in all patients where we detected myocardial ischemia in order to confirm diagnosis of non-obstructive CAD. Segment involvement score was calculated as the total number of coronary segments with atherosclerotic plaque [23].

2.6. Statistical analysis

Data analysis was performed using IBM SPSS Statistics version 24 (IBM Corporation, Armonk, NY, USA). The sample size was determined in order to have 80% power with statistical level of 0.05 to find 50% differences in prevalence of LVH between patients with and without myocardial ischemia, including an anticipated dropout rate of 5%. The study population was grouped into patients with and without myocardial ischemia. We compared groups by unpaired Student's *t*-test for continuous variables and Chi-Square test for categorical variables. The results are presented as mean ± standard deviation or median and interquartile range for continuous variables and number and percentages for categorical variables. Predictors of myocardial ischemia were assessed in uni- and multivariable logistic regression models and reported as odds ratio (OR) with 95% confidence intervals (CI). Independent covariables of the extent of myocardial ischemia were identified by uni- and multivariable linear regression analysis with standardized coefficients (β). A $p < 0.05$ was considered significant in all analyses.

Table 1
Clinical characteristics of the total study population and of groups of patients with and without myocardial ischemia.

	Total (n = 132)	Ischemia (n = 69)	No ischemia (n = 63)	p
Age (years)	63 ± 8	63 ± 9	62 ± 8	0.317
Female sex (%)	56	54	59	0.555
BMI (kg/m^2)	27.7 ± 4.5	27.2 ± 4.1	28.2 ± 4.8	0.206
Obesity (%)	24	16	32	0.032
Hypertension (%)	75	81	68	0.077
Diabetes (%)	13	12	13	0.919
Current cigarette smoking (%)	16	13	19	0.341
Family history of premature CAD (%)	64	58	70	0.192
Hypercholesterolemia (%)	48	54	41	0.156
Systolic blood pressure (mm Hg)	135 ± 16	135 ± 17	135 ± 16	0.795
Diastolic blood pressure (mm Hg)	79 ± 13	79 ± 13	79 ± 13	0.998
Heart rate (bpm)	69 ± 12	71 ± 13	68 ± 12	0.303
Serum glucose (mmol/L)	5.9 ± 1.6	5.9 ± 1.0	6.0 ± 2.0	0.727
Estimated GFR (mL/min/1.73 m^2)	86 ± 14	87 ± 15	85 ± 13	0.389
Total serum cholesterol (mmol/L)	5.0 ± 1.3	5.1 ± 1.4	5.0 ± 1.2	0.719
Serum HDL cholesterol (mmol/L)	1.5 ± 0.4	1.5 ± 0.5	1.5 ± 0.4	0.896
Serum LDL cholesterol (mmol/L)	3.2 ± 1.2	3.3 ± 1.3	3.2 ± 1.0	0.718
Serum triglycerides (mmol/L)	1.47 ± 0.96	1.55 ± 0.84	1.39 ± 1.08	0.340
Acetylsalicylic acid (%)	47	57	36	0.026
Statin (%)	38	40	36	0.627
Antihypertensive treatment (%)	58	59	56	0.729
Beta blocker (%)	30	23	36	0.126
Calcium channel blocker (%)	18	24	12	0.094
LV internal diastolic dimension (mm)	45.2 ± 5.5	45.0 ± 5.5	45.3 ± 5.5	0.764
LV internal systolic dimension (mm)	29.2 ± 5.3	29.0 ± 5.4	29.4 ± 5.2	0.678
Septal thickness (mm)	11.8 ± 2.0	12.3 ± 2.1	11.3 ± 1.8	0.003
Posterior wall thickness (mm)	9.3 ± 1.9	9.4 ± 2.1	9.1 ± 1.6	0.476
LV ejection fraction (%)	62 ± 7	63 ± 6	60 ± 7	0.019
LVMi (g/m$^{2.7}$)	40.1 ± 9.3	42.1 ± 9.7	37.9 ± 8.4	0.009
LVH (%)	17	23	10	0.035
Relative wall thickness	0.42 ± 0.11	0.42 ± 0.11	0.41 ± 0.10	0.487
Calcium score (HU)	42(14–107)	47(16–127)	37(11–83)	0.264
Number of diseased coronary arteries	1.6 ± 1.8	1.7 ± 0.8	1.5 ± 0.7	0.084
Multi-vessel disease (%)	54	60	48	0.168
Segment involvement score	2.6 ± 1.6	2.8 ± 1.8	2.4 ± 1.3	0.149

BMI, body mass index; CAD, coronary artery disease; bpm, beats per minute; GFR, glomerular filtration rate; HDL, high-density lipoprotein; LDL, low-density lipoprotein; LV, left ventricular; LVMi, left ventricular mass index; LVH, left ventricular hypertrophy; HU, Hounsfield units.

3. Results

3.1. Clinical characteristics and myocardial contrast stress echocardiography

All 132 study participants had symptomatic stable angina. Prior stress testing with exercise ECG was performed in 115 (89%) of the participants, and a total of 79 (67%) of the tests were reported to be negative or inconclusive due to low exercise capacity or left bundle branch block, leaving 36 patients (31%) with a positive exercise ECG. Myocardial ischemia by contrast stress echocardiography was found in 69 patients (52%), and among patients with a positive exercise ECG, 67% were diagnosed with myocardial ischemia by contrast stress echocardiography. The median time from CCTA to myocardial contrast echocardiography was 133 days (interquartile range 98–188 days). The group with myocardial ischemia had a 2-fold higher prevalence of LVH (Table 1), in particularly concentric LVH (Fig. 1). The groups did not differ in age, sex, prevalence of hypertension or antihypertensive treatment, however obesity was less common in the group with myocardial ischemia (Table 1).

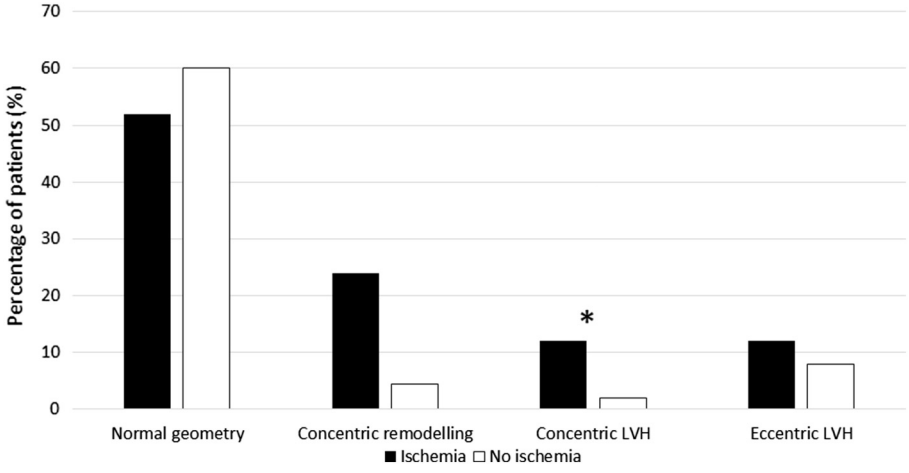

Fig. 1. Left ventricular geometry in patients with and without myocardial ischemia. Figure legend: LVH, Left ventricular hypertrophy. *p < 0.05 between groups.

Table 2
Covariables of myocardial ischemia identified in logistic regression analyses.

Variable	Univariable analysis			Multivariable analysis		
	OR	95% CI	p	OR	95% CI	p
LVH	2.87	1.04–7.88	0.041	3.19	1.04–9.76	0.043
Age (years)	1.02	0.98–1.06	0.315	0.99	0.94–1.04	0.623
Hypertension	2.05	0.92–4.59	0.080	2.24	0.97–5.65	0.059
Obesity	0.41	0.18–0.94	0.035	0.38	0.15–1.00	0.049
Hypercholesterolemia	1.65	0.83–3.28	0.157	1.98	0.92–4.28	0.083
Calcium score	1.00	0.99–1.01	0.461	1.00	0.99–1.01	0.874
Segment involvement score	1.18	0.94–1.49	0.159	1.19	0.87–1.65	0.280
Female sex	0.81	0.41–1.62	0.555			
Diabetes	0.95	0.33–2.70	0.919			
Current smoking	0.62	0.23–1.67	0.344			

OR, odds ratio; CI, confidence interval; LVH, left ventricular hypertrophy.

Coronary artery calcium score and segment involvement score (SIS), reflecting extent and severity of non-obstructive CAD, did not differ between the groups (Table 1).

By myocardial contrast stress echocardiography, 89% of patients reached age predicted maximal heart rate at peak stress. Nine of the 14 patients (65%) with lower than predicted maximal heart rate at peak stress had myocardial ischemia. Patients with and without myocardial ischemia had similar peak systolic blood pressure and heart rate (121 ± 23 vs. 123 ± 22 mm Hg, p = 0.616 and 132 ± 10 vs. 132 ± 11 beats per minute, p = 0.846). Fifteen patients (11%) had abnormal wall motion at peak stress. In 11 of these 15 patients wall motion abnormality was in the region supplied by the left anterior descending artery. The average extent of stress induced myocardial ischemia was 5 ± 3 LV segments. Wall motion abnormalities were significantly correlated with perfusion abnormalities during stress echocardiography, in which 13 (87%) of the patients with wall motion abnormalities also had perfusion abnormalities (p = 0.006). However, most patients with perfusion abnormalities had no concomitant wall motion abnormalities.

3.2. Covariates of myocardial ischemia

In univariable logistic regression analysis, myocardial ischemia was associated with presence of LVH and absence of obesity (Table 2). Myocardial ischemia remained independently associated with presence of LVH in multivariable analysis even after adjusting for age, hypertension, obesity, hypercholesterolemia, calcium score and SIS (Table 2).

In univariable linear regression analyses, larger extent of myocardial ischemia was associated with presence of LVH, hypertension and hypercholesterolemia (Table 3). In multivariable linear regression analysis, larger extent of myocardial ischemia remained associated with LVH independent of hypertension, obesity, hypercholesterolemia, calcium score and SIS (Table 3).

Table 3
Linear regression analyses of covariables associated with the extent of myocardial ischemia.

Variable	Univariable analysis		Multivariable analysis	
	β	p	β	p
LVH	0.19	0.034	0.23	0.010
Age (years)	0.002	0.984	−0.18	0.056
Hypertension	0.20	0.021	0.25	0.005
Obesity	−0.16	0.069	−0.18	0.044
Hypercholesterolemia	0.18	0.039	0.24	0.006
Calcium score	0.09	0.329	0.12	0.233
Segment involvement score	0.12	0.176	0.06	0.519
Female sex	−0.11	0.191		
Diabetes	0.09	0.325		
Current smoking	−0.09	0.335		

Multiple $R^2 = 0.18$, p = 0.001.
LVH, left ventricular hypertrophy.

4. Discussion

4.1. Myocardial ischemia and non-obstructive CAD

The present study demonstrates that about 50% of patients with stable angina and non-obstructive CAD have myocardial ischemia that can be detected by myocardial contrast stress echocardiography. The present results add to current knowledge by identifying the association of LVH with presence and extent of myocardial ischemia in these patients, independent of presence of hypertension.

Traditionally, myocardial ischemia has been perceived as secondary to coronary artery disease which directly obstructs blood flow to the myocardium [9,24]. However, we and others have previously demonstrated that myocardial ischemia may be present also in non-obstructive CAD [8,15,25]. The association between myocardial ischemia and LVH is well known as one of several mechanisms that may contribute to myocardial ischemia in patients with non-obstructive CAD, in addition to coronary vasospasm, coronary microvascular and endothelial dysfunction [1,10,26]. For instance, subendocardial ischemia and reduced myocardial blood flow have been detected by single photon computed tomography and positron emission tomography in patients with hypertrophic cardiomyopathy and in diabetes patients with LVH [27–29]. Reversible and irreversible ischemia was also detected in 35% of patients with LVH and exercise induced ST-depression, and was particularly prevalent in patients with concomitant CAD [30]. Further, in line with our results, it has previously been reported that LVH may contribute to lower the ischemic threshold in patients with hypertension and clinical evidence of CAD [31].

In animal studies, LVH has been suggested to contribute to myocardial ischemia through several mechanisms, such as reduced myocardial capillary density, increased LV filling pressure and increased myocardial oxygen demand [32,33]. In patients with ST elevation myocardial infarction, presence of LVH has been associated with higher incidence of microvascular obstruction as well as larger myocardial infarct size by cardiac magnetic resonance imaging [34]. The present results add to this by demonstrating that LVH may contribute to myocardial ischemia also in patients with stable angina and non-obstructive CAD.

As demonstrated, presence of hypertension was associated with larger extent of myocardial ischemia independent of LVH in our study. This suggests that hypertension contributes to myocardial ischemia through several mechanisms beyond the higher LV mass. As recently pointed out by Bairey Merz et al., hypertension may also influence myocardial perfusion in non-obstructive CAD through impaired vasomotion, endothelial dysfunction, atherosclerosis, reduced coronary microvascular density and thickened and stiffened microvessels with poor autoregulatory capacity [1].

In addition to LVH and hypertension, absence of obesity and presence of hypercholesterolemia were associated with a larger extent of myocardial ischemia in our study. The inverse association between obesity and myocardial ischemia was unexpected, and could not be explained by group-differences in sex or smoking. On the other hand, elevated total cholesterol is a well-established risk factor of CAD [35]. Furthermore, myocardial ischemia was not detected in all patients with LVH, suggesting that the etiology of myocardial ischemia was multifactorial also in our study.

Although the present study is small, our results may have potential important clinical implications for management of patients with non-obstructive CAD and stable angina. Current guidelines for management of patients with stable angina have pointed out the need for scientifically based management of non-obstructive CAD [36]. In particular, echocardiographic detection of LVH and myocardial ischemia may offer targets for a more personalized management of patients with non-obstructive CAD, pointing to the value of multimodality imaging in these patients. Moreover, antihypertensive treatment is associated with normalization of LV geometry and improved prognosis [11,37]. Our results also emphasize the importance of cardiovascular risk

control. In line with this, it has recently been demonstrated that in patients with non-obstructive CAD and myocardial infarction, the risk of new major cardiovascular events is predicted by established cardiovascular risk factors, including hypertension, diabetes and smoking [38]. Further, patients with non-obstructive CAD less often receive secondary preventive medication after myocardial infarction [39]. Accordingly, optimal medical treatment of non-obstructive CAD should be verified in prospective clinical studies.

4.2. Study limitations

We have selected a population with high risk of cardiovascular disease and our results cannot necessarily be generalized to a general angina population. The cross-sectional study design precludes identification of any causal relation between LVH and myocardial ischemia. The proportion of women was lower than what could be expected [40]. This might be explained by a referral bias, as only patients referred to CCTA by a cardiologist due to suspected CAD were eligible for inclusion. It is well documented from the Coronary CT Angiography Evaluation for Clinical Outcomes: An International Multicenter (CONFIRM) registry that women referred to CCTA have a higher pre-test probability of CAD then men [41]. In addition, the small study size did not allow stratification of the results by sex due to insufficient statistical power. However, our study population reflects a large group of patients in clinical practice who currently lack evidence-based guidelines for diagnostic work-up and management.

5. Conclusion

In patients with stable angina and non-obstructive CAD on CCTA, myocardial ischemia was found in half of the patients and was independently associated with presence of LVH. Our results suggest LVH as a potential treatment target in patients with stable angina and non-obstructive CAD to be explored in further clinical studies.

Funding

Financial support was obtained from the MedViz Consortium, a collaboration between the University of Bergen, Haukeland University Hospital and Christian Michelsen Research, all Bergen, Norway, and the Western Norwegian Regional Health Authorities. None of the sponsors had any involvement in study design, data collection, analysis or interpretation of data, writing of the report, or in the decision to submit the paper for publication.

Declarations of interest

The authors report no relationships that could be construed as a conflict of interest.

Acknowledgements

We thank Liv Himle (RN), Britt Gjellefall (RN), Liqun Zhang (staff engineer), Marina Kokorina (MD) and Synnøve Ygre Hauge (RN) for technical assistance with data collection, registration, and participant management.

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