MEDDOCS Open Access Publisher

ISSN: 2639-4383

Annals of Cardiology and Vascular Medicine

Open Access | Research Article

Growth Differentiation Factor 15 in Heart Failure with Preserved Ejection Fraction

Assia Haddad[1,2]*; Nadia Ould Bessi[3,4]; Mohamed Karim Guerchani[1,5]; Ammar Chikouche[3,4]; Salim Benkhedda[1,5]

[1]Faculty of medicine of Benyoucef Benkhedda Algiers University.

[2]Mohamed Abderrahmani Specialized Hospital, Cardiac surgery department.

[3]Pierre and Marie Curie Center. Biochemistry department, Algiers.

[4]Faculty of pharmacy of Benyoucef Benkhedda Algiers University.

[5]Mustapha Bacha University Hospital. Epidemiology department. Algiers.

***Corresponding Author(s): Assia Haddad**

Faculty of medicine of Benyoucef Benkhedda Algiers University.

Email: assiah7@yahoo.fr

Received: Dec 18, 2023

Accepted: Feb 15, 2024

Published Online: Feb 22, 2024

Journal: Annals of Cardiology and Vascular Medicine

Publisher: MedDocs Publishers LLC

Online edition: http://meddocsonline.org/

Keywords: Growth differentiation factor; Heart failure with preserved ejection fraction; Prognosis.

Abbreviations: AF: Atrial Fibrillation; BNP: Brain Natriuretic Peptide; CRI: Chronic Renal Insufficiency; COPD: Chronic Obstructive Pulmonary Disease; EF: Ejection Fraction; ESC: European Society Of Cardiology; GDF: Growth Differentiation Factor; GLS: Global Longitudinal Strain; HF: Heart Failure; HFPEF: Heart Failure With A Preserved Ejection Fraction; HFREF: Heart Failure With A Reduced Ejection Fraction; LA: Left Atrium; LAV: Left Atrial Volume; LV: Left Ventricle; LVEF: Left Ventricular Ejection Fraction; LVH: Left Ventricular Hypertrophy; LVM: Left Ventricular Mass; MACE: Main Acute Cardiovascular Events; 6M-WT: 6Minutes' Walk Test MSD: Mean Standard Deviation; NT-Probnp: N Terminal Pro Brain Natriuretic Peptide; PAH: Pulmonary Arterial Hypertension; WHO: World Health Organization.

Abstract

Background: Heart failure with preserved ejection fraction (HFpEF) is a growing burden in the world, and its pathophysiology is complex and its understanding remains insufficient. Following the comorbidity-inflammation paradigm, biomarkers are a promising screening tool.

Purposes: This study aims to assess the prognostic value of Growth differentiation factor 15 (GDF 15) in an Algerian cohort of patients with HFpEF as well as its association with other factors.

Results: 111 patients were collected. The average age of our patients was 72 +/- 11 years ranging from 40 to 89 years old, and 60% of the participants were female. Among non-cardiac comorbidities, GDF 15 was significantly associated with age (P=0.015), chronic renal insufficiency (P= 0.020), anemia (P=0.0 28), chronic obstructive pulmonary disease (0.028), coronary artery disease (P= 0.038). Among the cardiac parameters, GDF 15 was significantly associated with the presence of atrial fibrillation (P= 0.001), increased left atrial volume (P=0.001), and increase pulmonary arterial systolic pressure (P=0.0004). The discriminatory capacity of GDF-15 (area under the receiver-operator curve (AUC) = 0.717) was almost similar to that of NT-proBNP (AUC = 0.737). However, after multivariate analysis, only NT-pro BNP was independently associated with outcome. GDF-15 levels did not predict prognosis after a 1-year follow-up period.

Conclusion: GDF-15 was associated with the presence of atrial fibrillation, increased left atrial volume, and pulmonary arterial hypertension. Thus, Plasma GDF-15 levels could reflect the cardiac remodeling and fibrosis, but did not predict prognostic at 1 year.

Cite this article: Haddad A, Bessi NO, Guerchani MK, Chikouche A, Benkhedda S. Growth Differentiation Factor 15 in Heart Failure with Preserved Ejection Fraction. Ann Cardiol Vasc Med. 2024; 7(1): 1080.

Introduction

Heart Failure (HF) represents a real global public health issue due to its high prevalence, its morbidity, mortality, and its socio-economic impact on the health system. HF with preserved Ejection Fraction (HFpEF) accounts for 40%-70% of heart failure cases [1,2]. The pathophysiology of HFpEF is complex and its understanding remains insufficient. Following the comorbidity-inflammation paradigm, comorbidities and especially metabolic comorbidities promote the development and worsening of heart failure with preserved ejection fraction through a cascade of events ranging from systemic inflammation to myocardial fibrosis [34,5].

The actors of this cascade are the biomarkers. GDF 15, a member of the TGF-β cytokine family, is one of the various biomarkers that increase following inflammation or tissue aggression [6,7]. In addition to its diagnostic role, recent studies have highlighted its prognostic role alongside natriuretic peptides and troponins [8]. To further characterize HFpEF patients and to look for new therapeutic options in these patients, we conducted a prospective study of HFpEF patients with acute or chronic heart failure at an Algerian university hospital. This report aims to assess the prognostic value of GDF 15 in HFpEF as well as its association with other factors.

Material and methods

Our study is a prospective observational monocentric cohort with the primary objective to determine whether the growth differentiation factor 15 (GDF15) independently affects the prognosis in patients with heart failure and preserved ejection fraction. We enrolled patients with clinical signs and symptoms of heart failure consecutively referred to the echocardiography laboratory of the A2 cardiology department of Mustapha Bacha university hospital, between April 2018 and April 2020 for acute or chronic heart failure. The diagnosis of HFpEF was retained according to the criteria of the ESC 2016 [9]. Were excluded from study patients with more than moderate valve disease, Pulmonary Arterial Hypertension (PAH) class 1, 3, 4, or 5 of the World Health Organization (WHO), arrhythmogenic dysplasia of the right ventricle, congenital heart disease, right ventricular infarction, pericardial disease, and specific cardiomyopathy. Circulating GDF-15 and NT-proBNP levels were measured using electrochemiluminescence. This is the technique used by the e 601 immunoassay module of the Cobas® 6000 analytical controller designed by Roche diagnostics. Associations between GDF-15 and one-year outcomes were assessed. The primary outcome measure was a composite of all-cause mortality and hospitalizations due to HF. All the patients were followed up for 1 year.

Statistical analysis

The basic characteristics, echocardiography, and biological data are expressed as mean ± standard deviation. Proportions are shown as percentages and continuous parameters are reported as Mean Standard Deviation (MSD). Dichotomous parameters were analyzed by the chi-square test and continuous variables by the Kruskal Wallis rank sum test. Logistic regression analysis was used to determine the independent prognostic power of each variable to predict the risk of all-cause mortality, hospitalization for HF, and major acute cardiovascular events. All statistical analyzes were performed using R 4.0 software. For all tests, a p-value ≤ 0.05 is considered statistically significant.

Results

111 patients were enrolled with an average age of 72 years ± 11, and 60% were women. 67% of patients had isolated left signs of HF while 33 had congestive signs of decompensated HF.

Comorbidities and risk factors: The majority of patients (86%) were hypertensive and diabetics (70%) with a history of Atrial Fibrillation (AF) (47%). Nearly half of patients (49%) had anemia (Hemoglobin < 13 g/dl for men and < 12 g/dl for women), 44% had Chronic Renal Insufficiency (CRI) defined as a glomerular filtration rate <60 mL/min/1.73 m2). 38% of patients were obese with a history of coronary artery disease (29%), and chronic obstructive pulmonary disease (COPD) (21%) (Table 1).

Echocardiographic findings: The average LVEF is 58.76% ± 6.24, ranging from 50 to 74%. The average GLS is 14.37 ± 4.17 ranging from 3.2 to 24%. 58% of patients had a GLS < 16% in absolute value. The average indexed left ventricular mass is 121 g/m² ± 37 ranging from 55 to 331 g/m². 74% of patients have Left Ventricular Hypertrophy (LVH) with 54% of the eccentric type. 10% of patients had isolated LV remodeling. The average E/e' ratio is 15 ± 5 ranging from 6 to 32. The average indexed volume of the Left Atrium (LA) is 49.79 ml/m² ± 20 ranging from 18 to 150 ml/m². 82% of patients had dilatation of the Left Atrium (indexed LA volume > 34ml/m²). The mean peak Tricuspid Regurgitation (TR) velocity is 2.82 m/s ± 0.42 ranging from 1.94 to 4 m/s. 50% of patients had a peak velocity > 2.8m/s. The average pulmonary arterial systolic pressure (PASP) was 42 mmHg ± 13 ranging from 20 to 84 mmHg (Table 1).

Table 1: Baseline characteristics of population study.

Characteristics	
Age (n, sd)	72 ±11
Women (n, %)	67 (60)
Hypertension (n, %)	96 (86)
Diabetes (n, %)	78 (70)
Obesity (n, %)	42 (38)
Chronic renal insufficiency (n, %)	49 (44)
Anemia (n, %)	54 (49)
Chronic obstructive pulmonary disease (n,%)	23 (21)
Smoking (n, %)	6 (3.92)
Ischemic heart disease (n, %)	32 (29)
Atrial fibrillation (n,%)	52 (47)
Left ventricular ejection fraction (%)	59± 6
Indexed left ventricular mass (g/m²)	121± 37
Indexed left atrial volume (g/m²)	50 20
Mean E/é ratio	15± 5
Pulmonary arterial systolic pressure (mmHg)	42± 13
Pick of velocity of tricuspid regurgitation (m/s)	2.82 ± 0.4
Global longitudinal strain (%)	14 ± 4
NT-Pro BNP (pg/ml)	2814 ± 463
Growth differentiation Factor (GDF) 15 (pg/ml)	4045 ± 437
6 Minute's walking test (meters)	274 ± 149

Blood biomarkers

GDF 15: The average value of GDF 15 was 4045 pg/ml ± 4367 ranging from 400 to 25630 pg/ml. GDF 15 was not associated with gender (P= 0.69), the presence of diabetes (P= 0.60), hypertension (P= 0.09), obesity (P=0.37) or smoking (P= 0.48). On the other hand, GDF 15 was significantly associated with age (P=0.015), right heart failure (P= 0.040), CRI (P= 0.020), anemia (P=0.028), COPD (0.028), CAD (P= 0.038), and the presence of atrial fibrillation (P= 0.001). Among the echographic parameters, GDF 15 was significantly associated with LA volume (P=0.001), the presence of left atrial dilation (P= 0.01), the peak velocity of TR (P=0.003), and PASP (P=0.0004) while it was not associated with LVEF (P= 0.66), GLS (P=0.57), indexed LV mass (P= 0.629), the presence of LVH (P=0.669) or the E/e' ratio (P=0.294). It was also significantly associated with NT-proBNP values (P= 0.008) (Table 2).

NT-proBNP: the mean value of NT-proBNP was 2814 pg/ml ± 462.7 ranging from 133 to 35000 pg/ml.

Functional statue: The 6-minute walking test could be performed in only 44% of our patients (n=49), due to inappropriate physical conditions, physical deconditioning or osteoarticular pathology. The average value of the 6-minute walk perimeter was 274 ± 148.6 meters ranging from 100 to 512 meters. 51% of patients had a perimeter < 300 meters (Table 1).

Table 2: Association between levels of GDF-15 and other parameters.

	GDF<1200pg/ml N= 19	1200-1800pg/ml N= 14	GDF>1800pg/ml N= 78	P
Age, n (%)	62.89	67.57	75.37	0.052*
Women, n (%)	9 (47.37)	6 (42.86)	29 (37.18)	0.693**
Hypertension, n (%)	14 (73.68)	11 (78.57)	71 (91.03)	0.091**
Diabetes n (%)	12 (63.16)	9 (64.29)	57 (73.08)	0.608**
Obesity, n (%)	5 (26.32)	7 (50)	30 (38.46)	0.374**
Chronic renal insufficiency, n (%)	3 (15.79)	6 (42.86)	40 (51.28)	0.020**
Anemia n (%)	4 (21.05)	7 (50)	43 (55.13)	0.028**
Atrial fibrillation, n (%)	2 (10.53)	6 (42.86)	44 (56.41)	0.001**
Chronic obstructive pulmonary disease (%)	0 (0)	5 (35.71)	18 (23.08)	0.028**
Ischemic heart disease, n (%)	10 (52.63)	4 (28.57)	18 (23.08)	0.039**
Left ventricular ejection fraction (%)	59.47	59.71	58.41	0.474*
Global longitudinal strain (%)	15.12	14.86	14.1	0.661*
Indexed left atrial volume (ml/m²SC)	38.17	50.5	52.49	0.001*
Indexed left ventricular mass (g/m²)	122.3	129.9	119.5	0.271*
Ratio E/e'	15.07	13.67	15.92	0.131*
Peak of tricuspid regurgitation (m/s)	2.589	2.654	2.911	0.004*
Pulmonary arterial systolic pressure (mmHg)	33.84	35.79	44.96	0.0002*
N-terminal pro B natriuretic peptide (pg/ml)	1068	1356	3501	0.008*
6 minute's walk test (meter)	366.6	316.2	241.8	0.073*

* Kruskal Wallis rank sum test; ** Pearson's Chi squared test with Yates' continuity correction.

Prognosis:

The rate of mortality of all causes, hospitalization for heart failure, and acute cardiovascular events at 1 year was 35% with a mortality rate at 1 year of 13.5%. In univariate analysis, congestive heart failure (P= 0.003; OR= 3.7), CRI (P= 0.007; OR=3), anemia (P=0.006. OR=3.14), obesity (P= 0.03; OR= 2.39), atrial fibrillation (P=0.02; OR=2.5), peak velocity of TR (P= 0.028; OR=2.9), PASP (P= 0.0006), GDF 15 (P= 0.002), NT-pro BNP (P=0.005), and 6 minutes' walk test (P= 0.0003 were significantly associated with outcome at one year (Table 3). The discriminatory capacity of GDF-15 (area under the receiver-operator curve (AUC) = 0.717) was almost similar to that of NT-proBNP (AUC = 0.737) (Figure 1). However, after multivariate analysis, only NT-pro BNP and congestive heart failure were independently associated with one-year outcome (Table4).

Discussion

Growth Differentiation Factor 15 (GDF-15), a member of the TGF-β cytokine family, is secreted by cardiac tissues as well as other tissues, including adipose, immune and vascular tissue, in response to various pathologies or stimuli, such as inflammation, oxidative stress, tissue damage, and adverse remodeling [4]. Elevated levels of GDF-15 have been associated with an increased risk of developing heart failure in the general population [1011], patients with chronic kidney disease [12,13], and risk of mortality in patients without heart disease [9]. The combination of NT-proBNP with increased GDF-15 levels increased t14he diagnostic accuracy of HFpEF [1516]. Its prognostic value in HF was initially reported in heart failure with Reduced Ejection Fraction (HFREF) 17[181920,21], and recently validated in HFpEF22 [232425,26] even after adjustment for NT-pro BNP 27and high-sensitivity troponin T28 [2930]. One of the challenges of using GDF-15 as a biomarker for HFpEF is the apparent lack of specificity, as GDF-15 levels increase over time in HFREF and are also seen with elder diabetes and CRI an31d are correlated with mortality [32]. Currently, it has been well established that GDF15 level can stratify prognostic. However, in a recent study GDF-15 levels did not predict prognosis after a 1-year follow-up period [33]. In our study we performed a com-

parison and combination of plasma GDF-15 and NT-proBNP to evaluate the prognosis of 1-year adverse events, including all-cause death and hospitalization for HF. GDF 15 didn't predict the outcome at one year in HFPEF after multivariate analysis. This discrepancy may be related to the small sample size, but also because of lacking of clinical studies to suggest relevant cut-off values that can help in clinical decision especially in patients with HFpEF. In another hand, our results were based on the initial levels of GDF 15 and not the serial measurements, while some studies showed that the elevation of GDF15 in heart failure patients is reversible upon treatment [34]. Also, the specific implications of increased levels of GDF 15 remain unclear, as they lack specificity. So still evidence from large cohorts of patients with HFpEF is lacking.

In line with other data, we found in our series that high levels of GDF 15 were significantly associated with age [21], the functional statute, [15,22] coronary artery disease [23], and the presence of atrial fibrillation [24,25]. We also found that GDF-15 was associated with anemia in agreement with other data [26] and emerging evidence showing that in response to anemia, erythroblasts secrete GDF-15 [27] with a strong positive correlation with iron deficiency parameters in anemic patients [28]. Our results join other studies finding a significant association between high levels of GDF-15 and the presence of Chronic Obstructive Pulmonary Disease (COPD) and Pulmonary Arterial Hypertension (PAH) [29-30].

Among echocardiographic parameters, GDF 15 was associated with atrial volume and PASP. Few data showed that serum GDF-15 levels correlate positively with LV mass in the elderly [31], and elevated plasma GDF-15 is an independently associated with LV hypertrophy in hypertensive patients. [32] In our study, we did not find an association between GDF-15 levels and Left Ventricular Mass Index (LVMI). The same results were found by Hage [33] and Rimbas [34] who demonstrated that GDF-15 was associated with left atrial indexed volume but not with the indexed LV mass [35], and that diastolic dysfunction parameters, are mainly correlated with inflammatory biomarkers, in particular GDF 15, and endothelial dysfunction, but only LAVI was correlated with myocardial fibrosis [35]. Perhaps because those echocardiographic measurements remain poor markers of the severity of HFpEF syndrome.

Conclusion

Our study indicated that plasma GDF-15 levels increased with age, the presence of anemia, chronic renal insufficiency, coronary artery disease, and COPD. Moreover, GDF-15 is associated with the presence of atrial fibrillation, increased left atrial volume, and pulmonary arterial hypertension. Thus, GDF 15 could play a role in cardiac remodeling and myocardial fibrosis pathophysiology. However, GDF15 levels did not predict prognostic at 1 year in our study. Our results underline the complexity of structural and biological determinants of HFpEF, which remain incompletely understood. A potential approach using a panel of biomarkers could help to identify the main cardiac structural phenotype for more appropriate therapeutic strategies. So still evidence from large cohorts of patients with HFpEF is needed.

Table 3: Factors associated with one-year outcome in patients with HFpEF.

	MACE -	MACE +	OR	CI.95	P. Value
Male, n (%)	26 (59.09)	18 (40.91)	1.516	0.6806, 3.379	0.3029
Age, mean (sd)	71.51 (11.78)	73.62 (9.93)	1.018	0.981,1.056	0.3436
Congestive heart failure, n (%)	8 (26.67)	22 (73.33)	11.79	4.302, 32.29	0.0030
Diabetes, n (%)	49 (62.82)	29 (37.18)	1.361	0.5631, 3.291	0.4887
Hypertension, n (%)	62 (64.58)	34 (35.42)	1.097	0.3421, 3.516	0.8751
Smoking, n (%)	5 (83.33)	1 (16.67)	0.3526	0.03876, 3.208	0.3495
Chronic renal insufficiency, n (%)	25 (51.02)	24 (48.98)	3.008	1.33, 6.804	0.0075
Obesity, n (%)	22 (52.38)	20 (47.62)	2.392	1.062, 5.392	0.0333
Anemia, n (%)	28 (51.85)	26 (48.15)	3.143	1.375, 7.181	0.0060
Chronic obstructive pulmonary diseases, n (%)	16 (69.57)	7 (30.43)	0.7656	0.2817, 2.081	0.5965
Ischemic heart disease, n (%)	25 (78.12)	7 (21.88)	0.4113	0.1572, 1.076	0.0670
Atrial fibrillation, n (%)	28 (53.85)	24 (46.15)	2.514	1.119,5.648	0.0239
LV ejection fraction, mean (sd)	59.44 (6.17)	57.49 (6.257)	0.9489	0.888, 1.014	0.1164
Global longitudinal strain of LV (%), mean (sd)	14.92 (3.90)	13.35 (4.525)	0.9123	0.8281, 1.005	0.0600
Indexed LV mass (g/m²), mean(s	122.1 (38.36)	119.8 (35.38)	0.9983	0.9875, 1.009	0.758
LV hypertrophy, n (%)	60 (65.22)	32 (34.78)	0.9143	0.3239, 2.581	0.8641
E/é, mean (sd)	15.11 (5.34)	16.2 (4.64)	1.043	0.9654, 1.126	0.2828
Indexed Left atrial volume (ml/m²), mean (sd)	47.22 (16.85)	54.54 (24.15)	1.019	0.9978, 1.04	0.0763
Velocity of tricuspid regurgitation (m/s) mean (sd)	2.756 (0.43)	2.947 (0.41)	2.916	1.109,7.665	0.0282
Pulmonary arterial systolic pressure (mmHg),mean (sd)	38.55 (11.48)	48.08 (13.53)	1.063	1.026,1.102	0.0006
NT-proBNP (Pg/ml),mean (sd)	1754 (235)	477 (6752)	1.23	1.06, 1.428	0.0057
GDF15 (Pg/ml), mean (sd)	3127 (3707)	574 (4999)	1.015	1.004,1.025	0.0067
6 Minute's walk test (meter), mean (sd)	344	165 (91)	0.99	0.98- 0.99	0.0003

MACE: Main Acute Cardiovascular Events; LV: Left Ventricule; NT pro-BNP: N-Terminal Pro-B-Type Natriuretic Peptide; GDF 15: Growth Differentiation Factor-15.

Table 4: Independent prognostic factors associated with one-year outcome in patients with HFpEF after logistic regression.

	OR	CI.95.Low	CI.95.Upp	P Value
Congestive Heart Failure	8.945	2.471	32.38	0.0008
Chronic renal insufficiency	1.537	0.5293	4.461	0.4296
Obesity	1.825	0.6316	5.273	0.2664
Anemia	2.199	0.7542	6.41	0.1409
Atrial fibrillation	0.8543	0.2749	2.655	0.7855
Velocity of tricuspid regurgitation (m/s)	0.4251	0.01685	10.72	0.6035
Pulmonary arterial systolic pressure (mmHg)	1.038	0.9205	1.171	0.5404
N-terminal pro-B-type natriuretic peptide (pg/ml)	1.205	1.017	1.428	0.0316
Growth differentiation factor 15 (pg/ml)	1.001	0.9872	1.015	0.8850

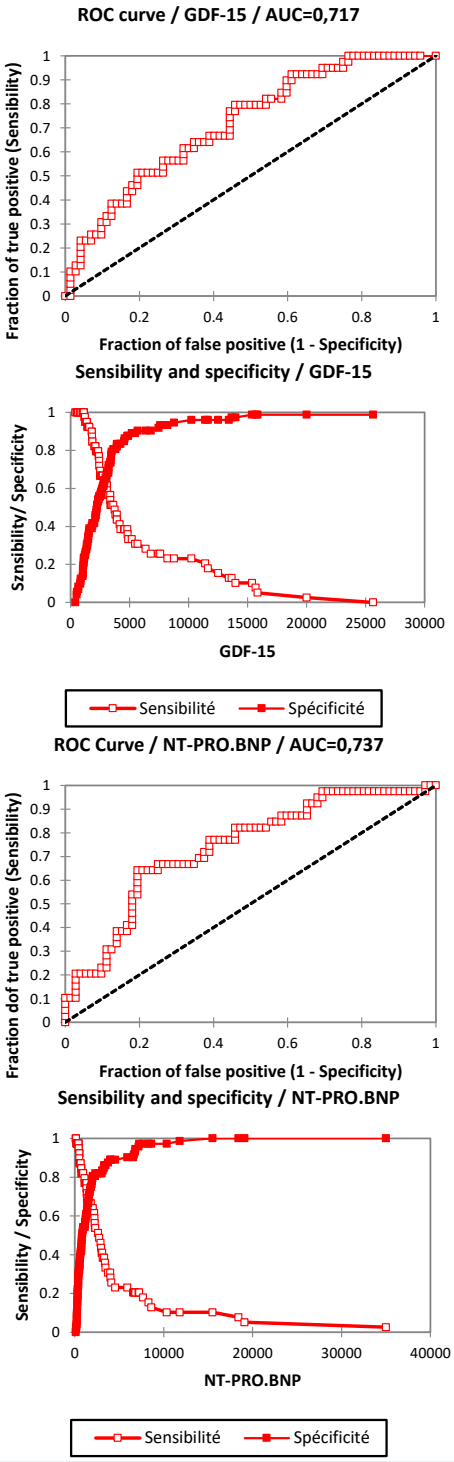

Figure 1: Comparison between AUC (Area under the receiver-operator curves (ROC) of GDF 15 and NT Pro-BNP.

Limitations of our study: Potential limitations of this study were related to the small sample size and the low rate of events, but also because of GDF-15 was measured only at inclusion in the study, so we didn't assess its interaction and fluctuation over time during the progression of HF and upon treatment. This issue should be explored in future research.

Disclosure of any funding to the study: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors OR Conflict of interest: None declared.

Disclosure of any conflict of interest

Conflict of interest: None declare.

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