Original paper

Temporal changes in the pattern of invasive angiography use and its outcome in suspected coronary artery disease: implications for patient management and healthcare resources utilization

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Abstract

Introduction: Invasive coronary angiography (CAG), the 'gold standard' in coronary artery disease (CAD) diagnosis, requires hospitalization, is not risk-free, and engages considerable healthcare resources.

Aim: To assess recent (throught out 10 years) evolution of 'significant' (≥ 50% stenosis(es)) CAD prevalence in subjects undergoing CAG for CAD diagnosis in a high-volume tertiary referral center.

Material and methods: Anonymized medical records were compared from the last vs. the first 2-years of the decade (June 2007 to May 2018). Referrals for suspected CAD were 2067 of 4522 hospitalizations (45.7%) and 1755 of 5196 (33.8%) respectively ($p < 0.001$).

Results: The median patient age (64 vs. 68 years) and the prevalence of heart failure (24.1% vs. 42.2%) increased significantly ($p < 0.001$). The CAG atherosclerotic lesions, for all stenosis categories (< 50%; ≥ 50%; ≥ 70%; occlusion(s)), were significantly more prevalent in men. The proportion of subjects with any atherosclerosis on CAG increased (80.7% vs. 77.6%, $p = 0.015$). However, in the absence of any gross change in, for instance, the fraction of women (40.4% vs. 41.8%), the proportion of CAGs with significant CAD (lesion(s) ≥ 50%) decreased from 55.2% in 2007/2008 to below 1 in every 2 angiograms (48.9%) in 2017/2018 ($p < 0.001$). This unexpected finding occurred consistently across nearly all CAG referral categories.

Conclusions: Despite more advanced age and a higher proportion of subjects with 'any' coronary atherosclerosis on CAG, the likelihood of a 'negative' angiogram (lesion(s) < 50%; no further evaluation/intervention) has increased significantly over the last decade. The exact nature of this phenomenon requires further investigation, particularly as a reverse trend would be expected with the growing role (and current high penetration) of contemporary non-invasive diagnostic tools to rule out significant CAD.

Key words: diagnosis, angiography, coronary artery disease, coronary angiography, invasive evaluation, coronary angiogram.

Summary

Invasive coronary angiography (CAG), the 'gold standard' in coronary artery disease (CAD) diagnosis, requires hospitalization, is not risk-free, and engages considerable healthcare resources. We hypothesized that the current high penetration of non-invasive tools to rule out significant CAD (such as computed tomography angiography, single photon emission computed tomography or stress echocardiography) would lead to a reduction in CAGs showing an absence of significant lesions. By comparing the outcome of CAGs in the final vs. first 2 years of the last decade, we found – surprisingly – that despite more advanced patient age and a higher proportion of subjects with 'any' coronary atherosclerosis on CAG, the likelihood of a 'negative' angiogram has increased significantly. Such findings may have implications for patient management and healthcare resources utilization.

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Introduction

Cardiovascular diseases, responsible for nearly half of all deaths, are the main cause of death in Poland [1]. Among cardiovascular deaths, coronary artery disease (CAD) takes the biggest share (23.0% of all deaths in 2013; *n* = 40 869) [1]. Although not uncommon in middle-aged subjects, CAD affects mainly older patients, and it is seen more often in males than females [1]. The proportion of people aged over 65 is currently growing (and will grow further, by one fifth, by 2050) [1], thus significantly increasing the population of patients with cardiovascular diseases and increasing projected cardiovascular deaths [1]. Therefore prevention of CAD morbidity and mortality remains a crucial target, not only at the individual patient-physician level, but also at the level of national healthcare policy [1, 2].

In general, coronary artery lesions with below 50% diameter stenosis (considered angiographically 'insignificant') require no interventional management but rather modification of risk factors and pharmacotherapy to prevent or minimize lesion progression and the risk of lesion destabilization [3]. On the other hand, patients with lesion(s) ≥ 50% (considered angiographically 'significant' CAD [4–8]) may benefit from procedural intervention (particularly in the case of documented myocardial ischemia [3]) and lesions ≥ 70% are usually considered to require intervention [3]. Thus unequivocal determination of CAD severity continues to play a fundamental role in clinical decision-making in contemporary cardiology.

Invasive coronary angiography (CAG) remains the 'gold standard' in diagnosing CAD [3]. At present, nearly 55 000 diagnostic coronary angiograms are performed in Poland annually at the cost (inclusive of hospitalizations) of ca. 110 000 000 PLN (ca. 26 000 000 Euros) [9]. Although highly accurate, CAG is associated with X-ray exposure, use of a contrast medium, and is not free of complications [10]. The acceptable accuracy of non-invasive modalities (such as single-photon emission tomography, SPECT [11], computed tomography angiography [12] or stress echocardiography [13]) to rule out significant CAD [12] has led to increased adoption of these techniques in everyday clinical practice on both an outpatient and inpatient basis [14–17]. As all-comer patient data, by removing the bias of trial-non-represented patients and under-reporting bias [18], are critical in determining the practical role of new technologies [19], we hypothesized that high-volume tertiary referral center all-comer data from the last decade would provide evidence for (1) reduction in CAG use to determine CAD in all-comer hospitalizations, and (2) reduction in the proportion of those CAGs that show an absence of significant CAD.

Aim

This study was undertaken to assess the real-life evolution of CAG use for suspected CAD and the evolution of CAG angiographic results in a high-volume tertiary referral center by comparing large-volume all-comer samples from the beginning and the end of the decade.

Material and methods

We retrospectively investigated anonymized medical records of all consecutive hospital admissions to the Jagiellonian University Department of Cardiac and Vascular Disease at John Paul II Hospital, Kraków, Poland, in two distinct 2-year periods: at the beginning and the end of the 2007/2008–2017/2018 decade. The first sample consisted of patients admitted to our institution from 1 June 2007 to 31 May 2009 (period A); the second one included those hospitalized from 1 June 2016 to 31 May 2018 (period B). The 2-year (rather than typical 1-year) samples were chosen to minimize the likelihood of chance variations that might affect the study findings. For each period, the total number of admissions and the number of admissions including CAG for definitive CAD diagnosis (i.e., the actual study group) were determined. The non-study group involved, for both study periods, the patients hospitalized without CAG. Those included, amongst others, admissions for coronary revascularization following CAG performed elsewhere or admissions for another stage of revascularization, admissions for heart failure (HF) management in patients with already known coronary status, grown-up congenital heart disease admissions, admissions for arrhythmia diagnosis and management or hospitalizations for advanced diagnostic imaging or therapeutic and research procedures (e.g., pulmonary artery angioplasty or myocardial regeneration therapy) in patients considered not to require CAG [20–25]. A significant proportion of these non-study patients had previously determined CAG status or had undergone non-invasive testing to rule out significant CAD or were considered not to require coronary evaluation due to, for instance, young age [20].

All referrals for clinically-indicated invasive CAD diagnosis were grouped into 5 categories according to the principal referral diagnosis. These (non-overlapping) labels/categories were the following:

1. Stable unaccompanied CAD ('unaccompanied' understood as absence of any of the diagnostic labels below; cf., 2–5).
2. Acute coronary syndrome (ACS, including ST-elevation and non ST-elevation acute myocardial infarction and unstable angina).
3. Vascular disease (involving, in most cases, determination of the coronary status prior to vascular surgery or endovascular management of aortic, peripheral vascular or carotid disease).
4. Valvular heart disease (VHD; NB this category also included other, uncommon, conditions requiring coronary status determination prior to cardiac surgery).
5. Structural heart disease (mostly patients diagnosed for atrial septal defect, ASD, or permanent foramen

ovale (PFO) management or left atrial appendage exclusion) and pulmonary hypertension (PH) diagnosis and/or intervention (SHD/PH category).

Pilot analysis showed that heart failure (HF) could not be considered a separate referral category because of its significant overlap with the 5 exclusive categories given above. Nevertheless, because of its major individual and social impact [14, 15], the HF referral co-label was searched and recorded in each case to enable comparison of HF prevalence in patients undergoing CAG in the two studied periods.

According to the absence/presence of angiographically depicted lesions in a major epicardial vessel, CAGs were classified as showing the following: no CAD (normal coronary arteries, no luminal irregularity [26]) or CAD presence ('any' CAD) that was inclusive of stenosis(es) < 50% of the lumen diameter, stenosis(es) ≥ 50%, stenosis(es) ≥ 70%, occlusion(s) [3–8]. In addition, angiographic prevalence of the left main coronary artery (LM) stenosis ≥ 50% [3] was evaluated. 'Significant' CAD was defined, consistent with the existing convention, as the presence of atherosclerotic lesion(s) with ≥ 50% diameter stenosis [3–7]. In contrast, a 'negative' angiogram was defined as absence of lesion(s) ≥ 50% as this is grossly consistent with lack of indication for revascularization and absence of the need for further intravascular evaluation in the context of potential revascularization [3].

Statistical analysis

The frequencies of qualitative variables were presented as percentages and compared using the χ^2 test of proportions for categorical variables with Yates' correction, if applicable. Statistical analysis was performed using StatSoft Statistica 13.1 software for Windows (StatSoft Inc., Tulsa, OK, USA). *P*-values of < 0.05 were considered statistically significant.

Results

There were 4522 hospitalizations in period A and 5196 hospitalizations in period B (Table I and Figure 1; note the increase in hospitalization volume by 14.9%). The study cohort (CAG patients) included 2067 (834, 40.4% females) in period A and 1755 patients (734, 41.8% females) in period B. The proportion of patients undergoing CAG decreased from 45.7% in period A to 33.8% in period B ($p < 0.001$; Figure 1 A; absolute reduction by 11.9%, relative reduction by 26.1%). The median age of presentation increased by 4 years, from 64 (Q1–Q3: 56–72) to 68 years (Q1–Q3: 61–75) respectively ($p < 0.001$). The structure of CAG patients according to their referral diagnosis is shown in Figure 1 B, indicating no striking differences in the proportion of key categories (stable CAD – 52.8% vs. 50.8%; ACS 27.4% vs. 28.0%). However, a ≈40% increase in VHD and SHD/PH categories occurred at the end vs. beginning of the decade at the expense of CAG in vascular disease coronary evaluation (the latter became partly managed in a new department of the hospital). The proportion of HF, however, grew profoundly – from 24.1% of CAG patients in period A to 42.2% in period B (absolute increase by 18.1%, relative increase by 75.1%; $p < 0.001$; Figure 1 C).

Males were in general more prevalent across the referral categories (Table I) and the male gender was consistently higher (than the female sex) represented in all atherosclerotic lesion subsets; i.e., ≥ 50% stenosis, ≥ 70% stenosis, occlusion and LM stenosis in the groups (Table I).

Analysis as per the specific referral categories showed that the overall differences in the findings between period B vs. period A were driven mostly by unaccompanied stable CAD and ACS (Table I, Figure 2).

The finding of a 'positive' angiogram (defined, consistent with the fundamental clinical decision-making threshold, as presence of lesion(s) ≥ 50% diameter stenosis) decreased between period B and period A by 6.3% ($p < 0.001$, relative reduction by 11.4%, Figure 2). Data regarding the prevalence of coronary occlusion(s) and LM disease are shown in Table I and in Figure 2.

Discussion

The fundamental new findings from this work, in relation to the pattern of first-time CAGs for suspected CAD in a high-volume tertiary referral center over a decade, are the following:

Despite an increase in the overall hospitalizations volume by 14.9%, a reduction in referrals for suspected CAD occurred (from 45.7% to 33.8%; $p < 0.001$, Figure 1);

The proportion of CAGs depicting significant CAD (defined as presence of lesion(s) ≥ 50%) decreased from 55.2% in 2007/2009 to below 1 in every 2 angiograms in 2016/2018 (48.9%, $p < 0.001$). This unexpected finding was seen across nearly all CAG referral subgroups (Figure 2) and results for the prevalence of lesion(s) ≥ 70% were fully consistent (absolute reduction by 5.0% – from 48.8% to 43.8%, $p = 0.022$, relative reduction by 10.3%, Figure 2).

Other important observations, consistent with current CAD trends [1], include a significant increase in the median age (64 vs. 68 years) and the prevalence of heart failure (24.1% vs. 42.2%) increased significantly ($p < 0.001$ for both) while the proportion of women admitted for clinically indicated CAG remained similar (40.4% vs. 41.8%; Table I, Figure 1). As expected [6, 27], atherosclerotic coronary artery lesions, for all stenosis categories (i.e., any angiographic atherosclerosis, lesion(s) ≥ 50% , lesion(s) ≥ 70%, occlusion(s), left main (LM) coronary artery stenosis ≥ 50%) were more prevalent in males (Table I).

The most striking finding from the present study is a significant increase, for the last two versus the first 2 years of the decade, in the likelihood of a 'negative' angiogram (understood as absence of lesion(s) ≥ 50%,

Table I. Characteristics of the overall study cohort (**A**) and per suspected CAD referral categories (**B**)

A

Parameter	Period A				Period B				B vs. A *P*-value
	Total (*n* = 2067)	Men (*n* = 1233)	Women (*n* = 834)	*P*-value	Total (*n* = 1755)	Men (*n* = 1021)	Women (*n* = 734)	*P*-value	
Median age	64	62	66	< 0.0001	68	66	69.5	< 0.0001	< 0.0001
Any atherosclerosis	1603 (77.6%)	1026 (83.2%)	577 (69.2%)	< 0.0001	1417 (80.7%)	884 (86.6%)	275 (72.6%)	< 0.0001	0.0158
≥ 50% stenosis/es	1140 (55.2%)	796 (64.6%)	344 (41.2%)	< 0.0001	859 (48.9%)	604 (59.2%)	255 (34.7%)	< 0.0001	0.0001
≥ 70% stenosis/es	1008 (48.8%)	714 (57.9%)	294 (35.3%)	< 0.0001	769 (43.8%)	551 (54.0%)	218 (29.7%)	< 0.0001	0.0022
Occlusion/s	517 (25.0%)	405 (32.8%)	112 (13.4%)	< 0.0001	325 (18.5%)	239 (23.4%)	86 (11.7%)	< 0.0001	< 0.0001
LM stenosis	48 (2.2%)	37 (3.0%)	11 (0.5%)	0.0128	58 (3.3%)	47 (4.6%)	11 (1.5%)	0.0003	0.0810

B

Parameter	Period A				Period B				B vs. A *P*-value
	Total	Men	Women	*P*-value	Total	Men	Women	*P*-value	
Unaccompanied stable CAD:	(*n* = 1120)	(*n* = 64)	(*n* = 456)		(*n* = 892)	(*n* = 497)	(*n* = 395)		
Median age	64	63	66	< 0.0001	68	67	69	0.0001	< 0.0001
Any atherosclerosis	820 (73.2%)	522 (78.6%)	298 (65.4%)	< 0.0001	703 (78.8%)	428 (86.1%)	275 (69.6%)	< 0.0001	0.0036
≥ 50% stenosis/es	528 (47.1%)	372 (56.0%)	156 (34.2%)	< 0.0001	364 (40.8%)	254 (51.1%)	110 (27.9%)	< 0.0001	0.0045
≥ 70% stenosis/es	467 (41.7%)	330 (49.7%)	137 (30.0%)	< 0.0001	313 (35.1%)	219 (44.1%)	94 (23.8%)	< 0.0001	0.0025
Occlusion/s	226 (20.2%)	183 (27.6%)	43 (9.4%)	< 0.0001	109 (12.2%)	79 (15.9%)	30 (7.6%)	< 0.0001	< 0.0001
LM stenosis	32 (2.9%)	23 (3.5%)	9 (2.0%)	0.1977	25 (2.8%)	22 (4.4%)	3 (0.8%)	0.0001	0.9505
ACS:	(*n* = 528)	(*n* = 351)	(*n* = 177)		(*n* = 491)	(*n* = 326)	(*n* = 165)		
Median age	62	60	69	< 0.0001	67	65	69	< 0.0001	0.0002
Any atherosclerosis	484 (91.7%)	333 (94.9%)	151 (85.3%)	0.0002	440 (89.7%)	305 (93.6%)	135 (81.8%)	< 0.0001	0.2599
≥ 50% stenosis/es	438 (83.0%)	312 (88.9%)	126 (71.2%)	< 0.0001	373 (76.0%)	276 (84.7%)	97 (58.8%)	< 0.0001	0.0057
≥ 70% stenosis/es	422 (79.9%)	304 (86.6%)	118 (66.7%)	< 0.0001	356 (72.5%)	268 (82.2%)	88 (53.3%)	< 0.0001	0.0054
Occlusion/s	228 (43.2%)	173 (49.3%)	55 (31.1%)	0.0001	180 (36.7%)	136 (41.7%)	44 (26.7%)	0.0011	0.0338
LM stenosis	9 (1.7%)	8 (2.3%)	1 (0.6%)	0.2799	27 (5.5%)	22 (6.8%)	5 (3.0%)	0.1342	0.0010
Vascular disease:	(*n* = 234)	(*n* = 138)	(*n* = 96)		(*n* = 140)	(*n* = 92)	(*n* = 48)		
Median age	68	68	68	0.9025	70	70	70.5	0.5569	0.0059
Any atherosclerosis	206 (88.1%)	124 (89.9%)	82 (85.4%)	0.4098	126 (90.0%)	86 (93.5%)	40 (83.3%)	0.1091	0.6792
≥ 50% stenosis/es	136 (58.1%)	91 (65.9%)	45 (46.9%)	0.0036	75 (53.6%)	53 (57.6%)	22 (45.8%)	0.2512	0.4528
≥ 70% stenosis/es	91 (38.9%)	64 (46.4%)	27 (28.1%)	0.0049	66 (47.1%)	48 (52.2%)	18 (37.5%)	0.1409	0.1175
Occlusion/s	51 (21.8%)	41 (29.7%)	10 (10.4%)	0.0004	26 (18.6%)	20 (21.7%)	6 (12.5%)	0.2690	0.5392
LM stenosis	5 (2.4%)	5 (3.6%)	0 (0.0%)	0.1540	5 (3.6%)	2 (2.2%)	2 (4.2%)	0.8907	0.9272
VHD:	(*n* = 114)	(*n* = 46)	(*n* = 68)		(*n* = 128)	(*n* = 61)	(*n* = 67)		
Median age	65	63	66	0.0656	71	68	73	0.0689	0.0011
Any atherosclerosis	67 (58.8%)	30 (65.2%)	37 (54.4%)	0.3391	97 (75.8%)	44 (72.1%)	53 (79.1%)	0.4757	0.0047
≥ 50% stenosis/es	23 (20.2%)	10 (21.7%)	13 (19.1%)	0.9169	21 (24.2%)	15 (24.6%)	16 (23.9%)	0.9101	0.5489
≥ 70% stenosis/es	17 (14.9%)	8 (17.4%)	9 (13.2%)	0.7315	21 (16.4%)	10 (16.4%)	11 (16.4%)	0.8141	0.8872
Occlusion/s	7 (6.1%)	3 (6.5%)	4 (5.9%)	0.7963	7 (5.5%)	2 (3.3%)	5 (7.5%)	0.5153	0.9582
LM stenosis	1 (0.9%)	0 (0.0%)	1 (1.5%)	0.8434	0 (0.0%)	0 (0.0%)	0 (0.0%)		0.9537
SHD/PH:	(*n* = 71)	(*n* = 34)	(*n* = 37)		(*n* = 104)	(*n* = 45)	(*n* = 59)		
Median age	57	54	61	0.0081	65	62	68	0.0007	0.0001
Any atherosclerosis	26 (36.6%)	17 (50.0%)	9 (24.3%)	0.0459	51 (49.0%)	21 (46.7%)	30 (50.9%)	0.8223	0.1041
≥ 50% stenosis/es	15 (21.1%)	11 (32.4%)	4 (10.8%)	0.0537	16 (15.4%)	6 (13.3%)	10 (17.0%)	0.8165	0.4381
≥ 70% stenosis/es	11 (15.5%)	8 (23.5%)	3 (8.1%)	0.1427	11 (10.6%)	5 (11.1%)	6 (10.2%)	0.8673	0.4648
Occlusion/s	5 (7.0%)	5 (14.7%)	0 (0.0%)	0.0506	3 (4.6%)	2 (4.4%)	1 (1.7%)	0.8113	0.3553
LM stenosis	1 (1.4%)	1 (3.9%)	0 (0.0%)	0.9660	2 (1.9%)	1 (2.2%)	1 (1.7%)	0.5985	0.7373

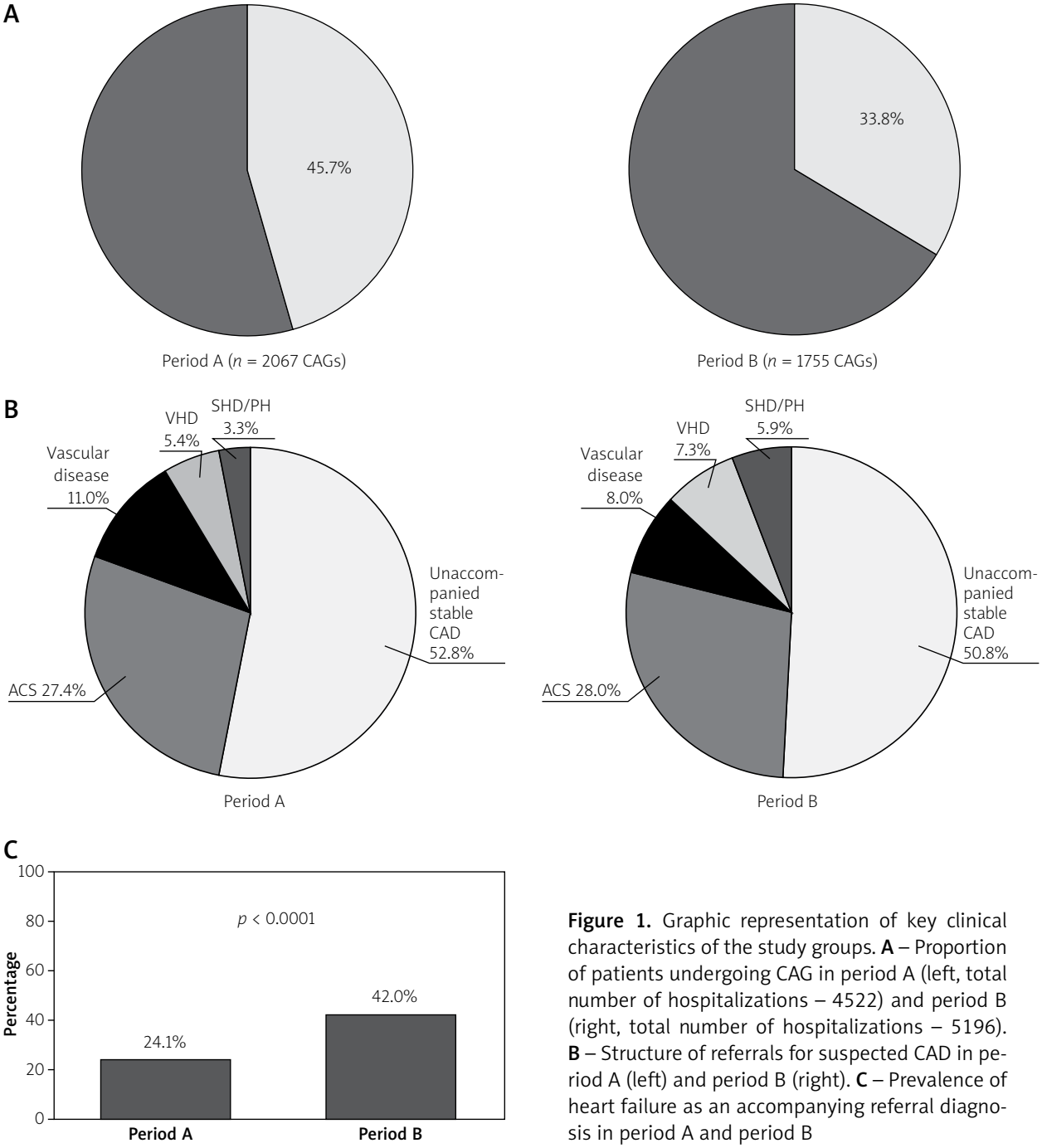

Figure 1. Graphic representation of key clinical characteristics of the study groups. **A** – Proportion of patients undergoing CAG in period A (left, total number of hospitalizations – 4522) and period B (right, total number of hospitalizations – 5196). **B** – Structure of referrals for suspected CAD in period A (left) and period B (right). **C** – Prevalence of heart failure as an accompanying referral diagnosis in period A and period B

grossly indicating no indication for further intravascular evaluation or intervention that might affect the patient's symptomatic status and/or prognosis [3]). Interestingly, this occurred despite a significantly smaller proportion of subjects undergoing clinically indicated CAG (Figure 1 A) that may be per se considered consistent with an increased role of non-invasive tests to rule out significant CAD [28]. However, an opposite trend might be anticipated with a significantly more advanced patient age in period B (median 68 vs. 64 years) and with significant increase (by 3.1%, $p < 0.001$) in the angiographic finding of 'any' atherosclerosis (a consistent across-the-referral-categories growth driven by an increase in prevalence of atherosclerotic lesions < 50%).

The exact nature of this phenomenon requires further investigation, particularly as a reverse trend (driven by contemporary ruling-out of non-significant CAD largely *prior* to the stage of hospital admission/CAG) should be expected with an increasing penetration (and role in decision-making) of the current generation of non-invasive diagnostic tools to rule out significant CAD. Those include, used today routinely on an out-patient and in-patient

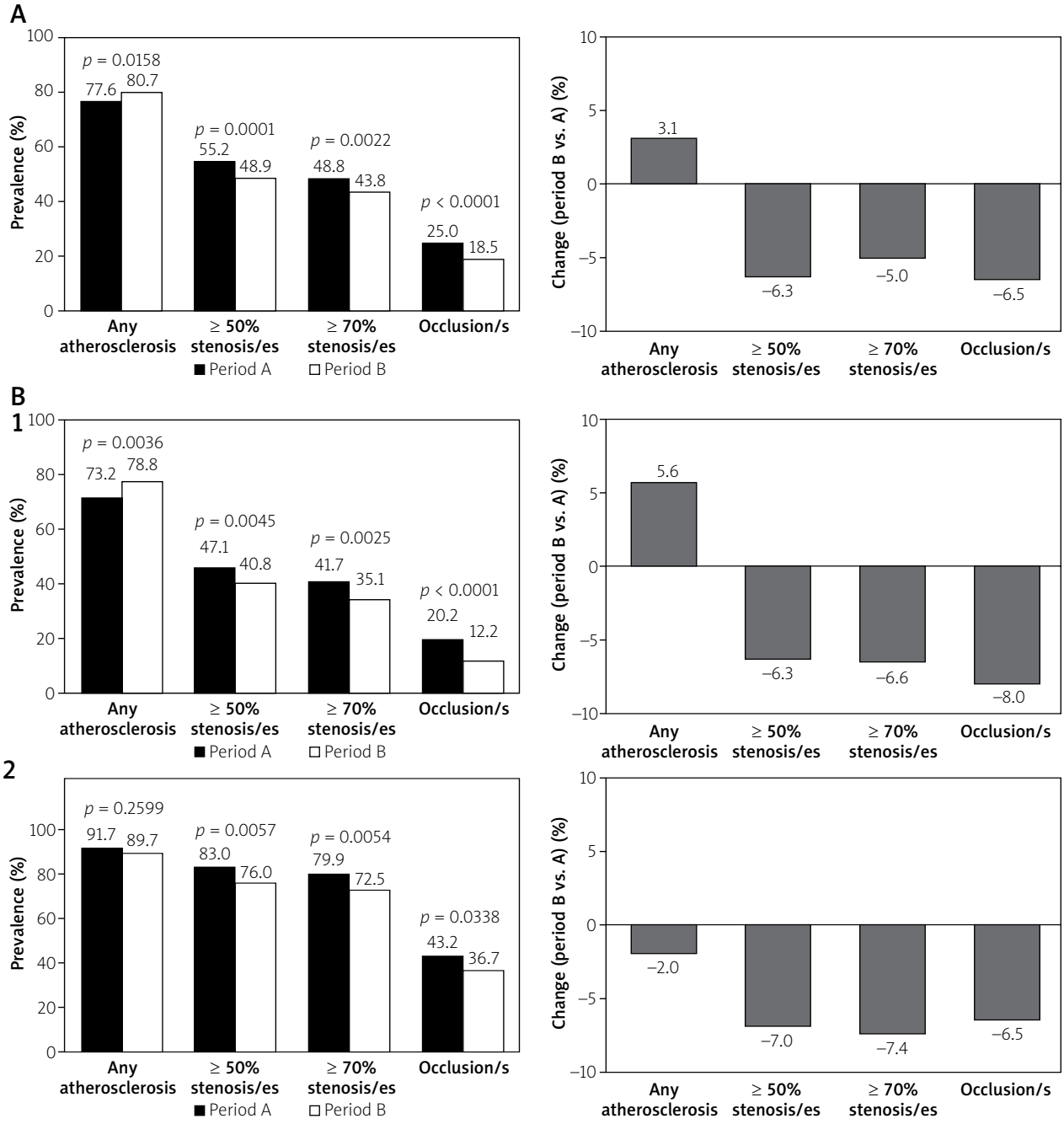

Figure 2. Angiographic prevalence (left) of coronary atherosclerotic lesions in CAGs performed in period A and period B and the change (right) in period B versus period A. **A** – Data for the whole study population. **B** – Data for specific referral diagnoses grouped into five categories (1 – unaccompanied stable CAD, 2 – ACS, 3 – vascular disease, 4 – VHD, 5 – SHD/PH). See text for abbreviations

basis, CT angiography, SPECT, and/or stress echo [11–16, 28–30]. Reasons beyond this unexpected finding, with its implications for patient management and healthcare resources utilization, are likely to be several-fold.

First, although the role of current generation non-invasive tests to rule out significant CAD has no doubt increased [28], and contemporary cardiology currently operates largely in the era of 'functional ischemia' [3], there is increasing understanding that non-invasive tests and imaging modalities (although generally adopted and generally useful in clinical decision-making practice [11–16, 28–30]) cannot universally replace CAG due to their patient population-dependent, device-dependent, and reporter-dependent issues leading to different optimal performance ranges and a (varying) proportion of the tests being non-diagnostic [12, 28, 31, 32]. For these

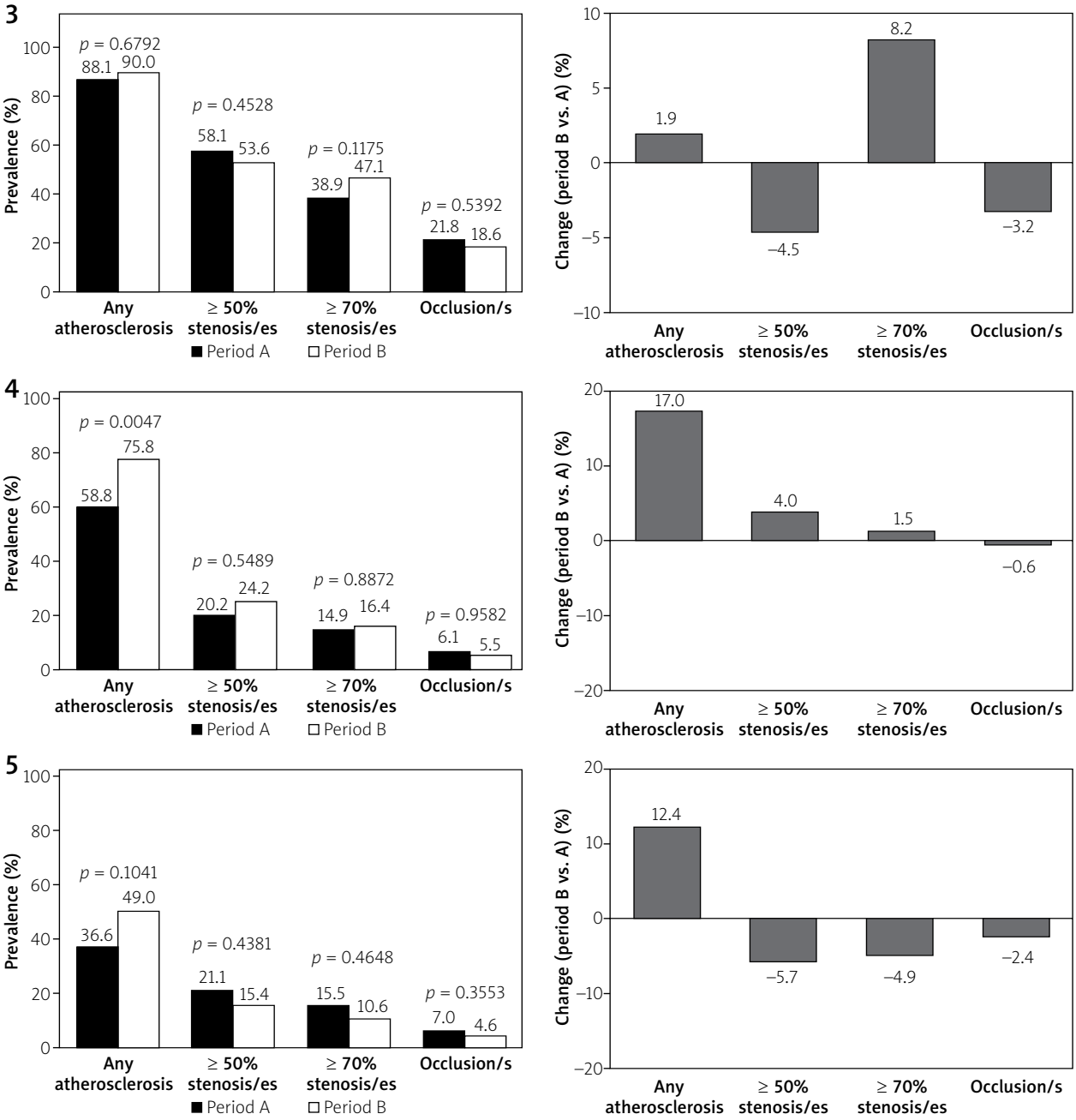

Figure 2. Cont.

reasons, the clinician's selection of 'the best' diagnostic technique for any given patient to rule in or rule out significant CAD remains challenging [28]. Moreover, a significant proportion of patients with 'negative' angiograms (up to 2/3 [27] exhibit myocardial ischemia not only on clinical presentation but also on imaging) [33]. Microvascular angina as well as vasospastic angina do require disease-specific management [34] and utilize significant healthcare resources [35], and a 'negative' CAG is the backbone of this diagnosis [27, 33, 34]. Thus, for today, it would be wrong to consider all 'negative' angiograms an unnecessary undertaking [36].

Increased prevalence of CAD decreases specificity of non-invasive tests, and – in a number of clinical scenarios in clinical practice – CAG is still performed after a non-invasive test rules out 'significant' CAD [12, 30, 31]. The timing of performing the (selected) non-invasive test(s) to rule out significant CAD has a profound effect on the data such as the one reported in the present study. We expect that most 'rejections' from CAG would occur at the pre-hospital state, but those also occur during hospitalization; thus we cannot rule out a considerable contribution of this population to the non-CAG patients, influencing the proportion between those subjected vs. not subjected to CAG (cf., Figure 1 A).

Another potentially important contribution to the temporal change in CAG referrals and outcome pattern observed in the present study may be linked to the profound increase in HF hospitalizations – both with and without CAG. In Europe and North America ≈30–50% of HF patients exhibit 'significant' CAD [15, 29]. Although 'simple' algorithms to rule out significant CAD in HF patients have been proposed based on evaluation of moderately sized populations [29, 37], they are not routinely applied and for the majority of HF patients there is a drive towards a definitive CAD diagnosis – i.e., performing CAG irrespective of the non-invasive tests that may (or may not) have taken place before. Thus the increased HF population (Figure 1) might contribute to the increase in 'negative' angiograms (Figure 2).

It is plausible that the growth of primary cardiology centers with CAG facilities may have influenced the referral structure to the tertiary centers, resulting in a higher proportion of (for a range of medical reasons) 'non-obvious' (rather than 'obvious') patients being currently evaluated in the tertiary centers. Assessment of the magnitude of this phenomenon, although extremely interesting and potentially impactful, is beyond the scope of our present work.

The pattern change depicted in the present study (growth of the proportion of patients with 'any' atherosclerosis driven by 'non-significant' lesions but fewer patients with 'significant' CAG lesions) may also result, in part, from the efficacy of aggressive pharmacologic and non-pharmacologic prevention in increased-risk subjects [2], leading to a modification in the course of the disease. Thus the present findings may be considered as a potential signal of the surfacing efficacy of adopting aggressive cardiovascular prevention measures.

It is worthwhile to realize that, despite the current era of 'functional ischemia' [3], there are credible contemporary data indicating that the structural burden of coronary disease (including angiographic lesions ≥ 50% [7]) is important – and that it may be prognostically far more relevant than the functional ischemia [7]. This further confirms that the primary cut-off of '50% diameter stenosis' between 'insignificant' and 'significant' coronary lesions used in our study (similar to a number of previous ones [3–7]) appears, at the present stage of knowledge, appropriate. Indeed, the anatomic burden of atherosclerotic disease (using the > 50% angiographic lesion severity cutoff) was recently demonstrated to be a consistent predictor of death and myocardial infarction whereas the ischemic burden was not [7].

Previous research on cardiovascular disease temporal trends in Poland has been focused on ACS with their clinical characteristics, treatment strategies, and outcomes [38, 39], leading to a series of crucial data used to improve patient care and utilization of resources in this specific patient cohort. In contrast, trends in stable CAD all-comer patient population characteristics and CAG outcomes have remained largely undetermined. Thus our work fills an important gap in the knowledge. Furthermore, the present study importantly supplements recent analysis from the Silesian Cardiovascular Database (SILCARD registry [40]). While the primary interest of SILCARD (which used pooled data from the primary, secondary and tertiary cardiology referral centers in Silesia, Poland) were the causes of hospitalization and prognosis in patients with cardiovascular disease in 2006–2014 [40], our work is focused on the angiographic outcomes in those hospitalized patients who underwent CAG. Importantly, both studies are consistent in their indication of a change in the population characteristics of hospitalized subjects, including a more advanced age (by 3–4 years in SILCARD [40]) and increasing prevalence of HF (in SILCARD absolute growth by 4.8%, relative growth by 29.3% [40]). Furthermore, the gender differences depicted in the present study (Table I) are similar to those in SILCARD [40] and those reported in other populations [4, 6, 26, 38, 39, 41, 42] and are thus consistent with internal integrity of the present data.

Finally, it needs to be noted that an increase in the 'negative' angiogram prevalence (Figure 2) does not necessarily indicate a trend that should automatically call for its reversal. Rather, this may indicate an increase in the proportion of patients who, for a number of clinical reasons, require a definitive diagnosis of their coronary status. Our findings regarding the beginning of the last decade are broadly consistent with data from the United States Veterans Affairs Healthcare System, where up to 48.5% of CAGs were 'negative' in 2007–2010 [43], but the temporal evolution in the US is unknown at present. Interestingly, in the US the numbers of CAGs appear constant over time (with CAG patients, similar to our results, getting older) [44] while rates of coronary revascularization have seen a significant decline in the last decade [45].

Limitations

While this work presents an accurate capture of the data from medical records in a large-volume center, one major limitation is that it is presently unknown whether, and to what extent, the findings are applicable to other tertiary cardiovascular referral centers. Although any major differences (at least within Poland, which has a similar patient referral structure across the country) and one (public) insurer are unlikely, some differences in the clinical characteristics of admission cohorts may exist in relation to specific interests and locations of expertise. Furthermore, it is unknown at present whether (and to what extent) trends similar to those depicted in the present study have occurred in the primary referral centers with CAG capacities. The growth of primary centers with CAG facilities, on the other hand, is likely to have affected changes in referrals to tertiary centers (including ours), affecting chang-

es in the proportion of patients subjected to CAG in the tertiary centers, and – possibly – also the CAG outcomes in the primary vs. tertiary centers. For these reasons, a large-scale overview of changes in the referral structure and CAG results across the country would be welcomed.

Another limitation is that we did not capture any detailed information regarding hospitalizations without performing CAG. The potential temporal changes in the non-CAG patients may affect findings in the CAG cohorts. For instance, an increase in the adoption of non-invasive tests to rule out significant CAD would be expected to result in reduced CAG referrals. Also, there is evidence from other healthcare systems that changes in reimbursement policies may affect patient referrals and clinical characteristics of the hospitalized patients [46–48]. It is unknown whether (and to what extent) this would contribute to temporal changes observed in the present study.

Finally, our present work did not involve re-review of the angiograms in a corelab fashion. Coronary stenosis severities, however, taken into consideration in the present study were routinely re-reviewed within the patient management teams including several interventionalists, and were the ones used in patient decision-making, resulting in their relevance to clinical practice. Indeed, any corelab re-review would be impractical in the present sample involving nearly 4000 angiograms, and we consider it highly unlikely that this could yield any greatly different angiographic outcomes.

Conclusions

Despite more advanced patient age and a higher proportion of subjects with 'any' coronary atherosclerosis on CAG, the likelihood of a 'negative' angiogram (lesion(s) < 50%, indicating no further evaluation/intervention) has increased significantly over the last decade. Consistent findings occurred for the reduced prevalence of angiograms depicting lesion(s) ≥ 70%. The exact nature of this phenomenon requires further investigation, particularly as a reverse trend would be expected with a growing role (and current high penetration) of contemporary non-invasive diagnostic tools to rule out significant CAD. Better strategies for risk stratification are needed to inform clinical decisions and to increase the diagnostic yield of CAG in routine clinical practice. These findings may have implications for patient management by clinicians on the one hand and, on the other, for healthcare resources utilization and insurance policies.

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Conflict of interest

The authors declare no conflict of interest.

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