Benefits of the selective invasive strategy guided by CTA and CT-FFR in patients with coronary artery disease

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Benefits of the selective invasive strategy guided by CTA and CT-FFR in patients with coronary artery disease

**Short title:** CTA and CTA-derived FFR to guide invasive coronary angiography

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**WHAT’S NEW?**
Coronary computed tomography angiography (CTA) and CTA-derived fractional flow reserve (CT-FFR) may limit invasive coronary angiography to just one (diseased) vessel, or completely abolish the indication to invasive procedure. Using CTA and CT-FFR as a guiding tool in referral to invasive coronary angiography may result in substantial reduction in iodine contrast media volume and radiation exposure used during coronary artery disease diagnostic process. Aferomentioned benefits are greater for CT-FFR than CTA. Moreover, such approach reduces the number of catheters used, consequently reducing costs and the number of potential mechanical complications that may occur during catherization.

**ABSTRACT**
**Background:** Coronary computed tomography angiography (CTA) has high diagnostic accuracy in ruling out significant stenosis of coronary arteries. The additional use of CTA-derived FFR further enhances diagnostic utility of coronary CTA. Some of the patients interrogated non-invasively have diseased coronary arteries and undergo further diagnostic
testing, including invasive coronary angiography (ICA). Patients with one vessel disease may benefit from invasive interrogation limited to the diseased vessel only.

**Aims:** In 100 patients, we analysed the impact of a “diseased-vessel-only”, selective invasive diagnostic approach in patients undergoing ICA following coronary CTA (and CT-FFR) as compared to the traditional, “full ICA” approach. Our aim was to compare contrast volume and radiation dose used during ICA in both scenarios, seeking potential benefit for the patient in reducing those values by “diseased-vessel-only” approach.

**Results:** Sensitivity, specificity, positive predictive value and negative predictive value of CTA in prediction of subsequent revascularization were 96%, 75%, 51% and 99%, respectively, and for CT-FFR 90%, 90%, 69% and 97%, respectively. Using CTA as a method to guide ICA would reduce contrast volume and estimated radiation dose (ED), by 35% and 42.0% respectively ($P <0.0001$ for both). Taking into consideration CT-FFR results, contrast volume would be reduced by 57% and ED by 69% ($P <0.0001$ for both).

**Conclusion:** These real-world data support the concept that vessels with <50% diameter stenosis in QCT and hemodynamically insignificant in CTA-derived FFR may be skipped during ICA. Such approach would result in substantial reductions in contrast media volume used, as well as patient’s exposure to radiation during during ICA, while not leading to missed diagnoses.

**Key words:** coronary computed tomography angiography, coronary angiography, coronary artery disease, fractional flow reserve, CT-FFR

**INTRODUCTION**

Coronary computed tomography angiography (CTA) gained acceptance as a first line non-invasive diagnostic modality in triage of patients with chest pain [1]. The method has high diagnostic accuracy in ruling out significant stenosis of coronary arteries in patients with intermediate probability of coronary artery disease (CAD) [2–4]. The additional use of CTA-derived FFR further enhances diagnostic utility of coronary CTA, mainly by increasing its specificity [5–8]. By default, some of the patients interrogated non-invasively have diseased coronary arteries and undergo further diagnostic testing, including invasive coronary angiography (ICA). Conceivably, patients scheduled for ICA with one vessel disease may benefit from invasive interrogation limited to the diseased vessel only, presumably resulting in lower contrast media usage, lower radiation dose and less complications related to catheterization. The additional use of CT-FFR may further reduce the need for both arteries and
patients invasive interrogations. However, there are no guidelines addressing performing ICA after coronary CTA, and potential benefits of the sequential diagnostic strategies require evaluation.

Therefore, we prospectively sought to analyse the impact of a “diseased-vessel-only”, selective invasive diagnostic approach in patients undergoing ICA following coronary CTA (and CT-FFR) as compared to the traditional, “full ICA” approach. The potential benefits of such approach were defined as reduction of contrast media volume and radiation dose used during ICA, was the particular vessel subject to ICA or not. The costs of such novel approach were defined as missing significant coronary stenosis defined as either coronary stenosis ≥50% or coronary stenosis undergoing subsequent revascularization.

METHODS

Study group

From September 2015 to August 2016 we included 116 consecutive patients who underwent ICA following CTA performed at a single center (Institute of Cardiology, Warsaw, Poland). ICA were performed, if CTA findings suggested significant or borderline coronary artery stenosis (>50% diameter stenosis [DS]) in an artery amenable for intervention (at least 2.0 mm reference diameter), in the presence of clinical symptoms suggestive of CAD or additional tests indicating cardiac ischemia. We excluded patients who underwent ICA more than 6 months following CTA (n = 10) and those in whom CTA image quality prevented evaluation of the coronary artery lumen due to motion artifacts or severe calcifications (n = 6). Clinical and demographic information, medical history, and cardiovascular risk factors (hypertension, hyperlipidemia, diabetes, body mass index, smoking, being male) were prospectively collected during hospital stay of the patients, based on their medical records, laboratory blood test analysis and physical examination. The study was approved by the institutional ethical committee.

CTA examination and analysis

Coronary CTA was performed on dual source 2 × 192-slice Somatom Force (Siemens, Forcheim, Germany) scanner. Sublingual nitrates were administered prior to scanning in all patients. If necessary, beta-blockers were administered intravenously targeting a heart rate <70 beats per minute. The protocol for CTA image acquisition was recommended to comply with the Society of Cardiovascular Computed Tomography (SCCT) guideline [9]. Assessment of luminal diameter stenosis was performed using a 18-segment coronary model. Quantitative
diameter stenosis analysis (QCT) was performed with Syngo.via (Siemens Medical Systems) software by an experienced investigator blinded to results of ICA. Intraobserver correlation coefficient performed in 60 randomly chosen vessels was 0.98 (95% confidence interval [CI], 0.97–0.99; \( P < 0.0001 \) for correlation). Per-vessel maximum stenosis was categorized as 0%, 1%–24%, 25%–49%, 50%–69%, 70%–99%, 100% according to SCCT guidelines [10].

**CTA-derived FFR computation**

CT-FFR analysis was performed by a single observer using dedicated software (cFFR v.2.1, Siemens), based on machine learning algorithms [8]. A dedicated workstation was used to analyse mid-diastolic CTA data. Defining coronary lumen was a semi-automatic, two-step process- segmentation of coronary artery centerlines followed by coronary mesh delineation, both with manual correction if necessary. Tree-dimensional, colour-coded models of coronary trees were assessed by an observer blinded to QCA and FFR results. Any questionable results were consulted with the second observer and solved by consensus. In all major coronary arteries with stenosis above 40%, a point 40 mm distal to the MLA was used as a location to define CT-FFR result, as described by Solecki et al. [11].

**ICA examination and angiographic analysis**

ICAs were performed on a standard cardiology fluoroscopy equipment (Axiom, Siemens Healthcare, Forchheim, Germany), in pulsed fluoroscopy mode with default frame rate of 10 frames per second. Access site and utilization of additional tools (i.e. fractional flow reserve [FFR] assessment or intravascular ultrasound [IVUS]) was left to the discretion of the operator. Therapy decision was made on the basis of angiographic results in the context of the patient’s symptoms and other test results, such as stress ECG or echocardiography. Given data from literature that visual vessel assessment during ICA is highly subjective [12, 13], Quantitative Coronary Angiography (QCA) was chosen to define %DS in a repetitive manner. ICA images were submitted to Qangio XA (Medis, Leiden, The Netherlands) software for QCA analysis. Maximum diameter stenosis was automatically defined with subsequent manual aligning of the course of the vessel, if necessary. Per-vessel maximum stenosis was categorized as 0%, 1%–24%, 25%–49%, 50%–69%, 70%–99%, 100%. During diagnostic part of ICA, contrast media volume (with accuracy of up to 1ml) used for opacification of each of the main vessels (left and right coronary artery) was recorded. Similarly, the radiation doses used during each vessel imaging were recorded; air kinetic energy released per unit mass (air kerma [AK]; mGy) and the dose area product (DAP; \( \mu G\cdot m^2 \)), both measured using built-in software in the fluoroscopy
system (Axiom, Siemens Healthcare, Forchheim, Germany). Estimation of effective dose (ED) was based on a conversion coefficient of 0.185 mSv Gy$^{-1}$, as calculated by Boagert et al. [14]. In (QCA) DS of at least 50% was defined as CAD and Quantitative Computed Tomography (QCT) results were compared with QCA results.

**Statistical analysis**

The categorical variables are presented as numbers and percentages. The continuous variables are expressed as mean (SD) or median (interquartile range [IQR]) as appropriate. Descriptive statistics were used to analyse per-patient accuracy of CTA. The diagnostic performance of CTA in the detection of significant CAD was then determined by using the ROC curves, sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) parameters and their corresponding 95% confidence intervals (CIs), and was compared to QCA >50% DS as the reference standard. Wilcoxon test (for not normally distributed data), was used to assess the equality of values in continuous variables. A probability value of 0.05 or less was considered significant. All 3 groups (“routine”, “no ICA if >50 DS in QCT” and “no ICA if <0.8 in CTA-derived-FFR) were independently analyzed in pairs. All statistical analyses were conducted using MedCalc version 13.0 (MedCalc Software, Mariakerke, Belgium).

**RESULTS**

**Baseline characteristics**

In this study, 116 consecutive patients who underwent CTA and subsequently ICA were identified. After applying exclusion criteria, the final population consisted of 100 patients in whom 200 vessels (RCA, LCA) were assessed. Baseline characteristics of the population (mean age 67.1 (8.8), female 33%) are summarized in Table 1. The majority of patients (54%) presented with typical angina. In this group Canadian Cardiovascular Society grade 2 was most commonly observed. Thirty nine patients had undergone stress tests before coronary imaging-24 tests had been positive electrocardiographically, 6 clinically, 3 had been inconclusive and 6 negative. Among 17 patients with PCI history, all stents were imaged by CTA without significant blooming artifacts precluding stent patency evaluation. During ICA, either FFR or IVUS were used in 16 cases. Median time interval between CTA and ICA was 47 (IQR, 22–82) days. Overall, at least one >50%DS stenosis as assessed by QCA (including chronic total occlusions) was found in 78 patients. Subsequently, 64 patients were revascularized, including 52 PCIs and 12 coronary artery bypass grafting (CABG).
Selective, “diseased-vessel-only” diagnostics strategy based on CTA

Based on ROC curve (AUC, 0.977; 95% CI, 0.957–0.989; \( P < 0.001 \)) sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of CTA in detecting 50%DS in QCA were 99%, 97%, 94% and 100%, respectively (Table 2).

Based on ROC curve (AUC, 0.849; 95% CI, 0.810–0.882; \( P < 0.001 \)) sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of CTA in prediction of subsequent revascularization were 96%, 75%, 51% and 99%, respectively.

If CTA angiographic results were considered prior to ICA, 43 (43%) patients would undergo single (“diseased”) vessel diagnostic strategy, and 19 (19%) patients would not undergo ICA at all.

Comparisons of radiation doses and volume of contrast media used during the traditional diagnostic strategy vs. “diseased-vessel-only” ICA are presented in Figure 1 (radiation dose) and Figure 2 (contrast media volume). During the invasive procedure a median of 57.5 (IQR 44–70) ml of contrast agent, and median radiation dose of 6.17 (IQR, 3.64–8.56) mSv were used (Figure 1). Using CTA as a method to guide ICA would translate into diminution of median contrast volume and radiation dose, by 35% (from 57.5 ml to 37.5 ml), and 42.0% (from 6.17 mSv do 3.60 mSv) respectively \( (P < 0.0001 \) for both) (Figures 2 and 3). None of the arteries assessed by QCT as stenosed <50% was subsequently described as stenosed >50% by QCA, neither was subsequently treated invasively.

Selective, “diseased-vessel-only” diagnostics strategy based on CT-FFR

Diagnostic performance of CTA-FFR in prediction of subsequent revascularization (AUC, 0.899; 95% CI, 0.864–0.927; \( P < 0.001 \)) expressed as sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) was 90%, 90%, 69% and 97%, respectively.

Additional use of CTA-derived FFR as a method to guide ICA would result in deferral of ICA in 28 cases and excluding one of the coronary arteries from ICA in 50 cases (Figure 1). Investigated parameters’ medians would be reduced: contrast volume by 57% (from 57.5 ml to 25 ml) and ED by 69% (from 6.17 mSv to 1.97 mSv; \( P < 0.0001 \) for both) (Figures 2 and 3). Eight vessels assessed with CTA-derived FFR as not significantly stenosed (>0.8) were eventually revascularized. On the other hand, 19 vessels with CTA-derived FFR result ≤0.8 were treated conservatively- mainly due to small vessel caliber <2 mm (n = 15). Moreover, all of those values ranged within the grey zone (0.75 and 0.8).

DISCUSSION
It is estimated that 126 million people live with coronary artery disease worldwide, including 18 million in USA, accounting for 366 000 deaths and estimated $218 billion direct and indirect costs in USA only [15]. CTA, used to diagnose CAD non-invasively, is a rapidly expanding diagnostic modality, translating globally into substantial numbers of patients [1]. At least 10% of those patients (and due to changed pre-test-probability calculators in the latest European guidelines, likely more) may be diagnosed with >50% coronary stenosis and referred to ICA [16].

CAD diagnostic process with both CTA and ICA is associated with the use of radiation and contrast media. Considering their possible detrimental effect on skin, bone marrow and kidney function, different ways of minimizing their utilization are being developed, both on hardware and procedural level [17, 18]. There are no guidelines addressing performing ICA after CTA, and most interventionalists tend to catheterize all main epicardial coronary arteries in such situations (anecdotal information). Considering vast number of patients suspected of CAD, any change in contemporary diagnostic practice may profoundly affect radiation doses and contrast media volume used in the process.

In this single-center investigation of patients suspected of CAD we sought to determine how CTA findings may influence further invasive diagnostics in terms of contrast media volume and radiation exposure. In the present study, the sensitivity, specificity, PPV and NPV for coronary CTA were 99%, 97%, 94% and 100%, respectively, for diagnosis of >50% coronary stenosis on ICA. These values are similar to those reported in previous studies and confirm that CTA has reliable accuracy for both exclusion and diagnosis of significant CAD [19–21]. Given that, especially the high NPV reported here and in previous studies, we hypothesised that vessels assessed by CTA as free of >50% stenosis may not be examined during ICA.

The findings from our study indicate that consideration of CTA results to guide ICA may benefit patients with CAD with significant reduction of contrast media usage and radiation exposure. This benefit was most pronounced in the case of excluding LCA from ICA, as its visualization requires multiple contrast injections in different projections. Restraining ICA to RCA only would result in contrast media volume reduction by 64% if guided by CTA and 73% if guided by CTA-derived FFR. In case of LCA-ICA-only, radiation exposure in analogous scenario would be decreased by 61% and 78% for CTA and CTA-derived FFR, respectively.

In the analyzed group, no artery described as stenosed <50%DS in QCT was subsequently assessed as stenosed >50%DS in QCA.

In the present study, the basic and more advanced non-invasive diagnostics provide incremental benefit in consequent qualification for ICA. Implementing CTA-derived FFR would lead to
greater number of deferred and “single-vessel-only” procedures. Consequently, reduction in the investigated parameters was significantly higher for CTA-derived FFR algorithm than CTA-alone-based algorithm. The additive value of considering CTA-derived FFR result in the diagnostic process is depicted in Figure 4.

Importantly, restraining from unnecessary catheter manipulation/exchange and vessel ostium intubation may reduce rare, but very serious complications, including iatrogenic vessel dissection or embolic events. Given the increasing numbers of patients undergoing CTA, the “diseased vessel” invasive diagnostic strategy may lead to significant decrease in contrast media usage, radiation exposure, as well as- possibly- subsequent complications and procedural adverse events, without any deleterious consequences. Appreciating recent evidence, that CTA is a highly useful modality also in patients with high risk of CAD, one may anticipate that the importance of the discussed matter will prove to be even more pronounced [22]. Further improvement in the selection of patients requiring ICA may be achieved with additive information obtained with CT-based volumetric quantification of myocardial perfusion- a complementary functionality of modern CT equipment [23].

Study limitations

We acknowledge several limitations of the current study. The sample size is limited and is derived from a single center. The study was conceived as an observational, non-randomized project, based on prospectively collected data. Non-randomization and the fact that several operators performed ICAs may have influenced procedural aspects such as projections selection, number of contrast injections and additional tools (i.e. FFR, IVUS) utilization and therefore affected the radiation exposure and contrast media administration. This, however, reflects everyday practice. Moreover, agreement between non-invasive and invasive FFR measurement was performed based on only 12 cases. Nonetheless, robust evidence in the literature indicate good accordance between the two methods. Recognizing its inherent limitations, the study does have the advantage of representing a daily practice in a diverse patient population, as no clinical exclusion criteria were applied.

We aware that implementation of proposed changes in routine procedures may be deemed a deviation from the standard of care. Further, large-scale randomized investigations are needed to confirm safety of presented concept and provide well-established endpoints (i.e. differences in incidence of contrast-induced nephropathy, mechanical complications of ICA, etc.).
These real-world data support the concept that vessels with <50%DS in QCT and not hemodynamically significant in CTA-derived FFR may be skipped during ICA. Such approach would result in substantial reductions in contrast media volume used, as well as patient’s exposure to radiation during during ICA, while not leading to missed diagnoses.

Article information

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REFERENCES


### Table 1. Baseline patients’ characteristics and clinical assessment

<table>
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<tr>
<th>Characteristic</th>
<th>Value</th>
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<tr>
<td>Age, years, mean (SD)</td>
<td>67.1 (8.8)</td>
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<tr>
<td>Male gender, %</td>
<td>67</td>
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<tr>
<td>Height, m, mean (SD)</td>
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<td>Body weight, kg, mean (SD)</td>
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<td>Body mass index, kg/m^2, mean (SD)</td>
<td>28.5 (4.15)</td>
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<tr>
<td>Hypertension, %</td>
<td>91</td>
</tr>
<tr>
<td>Diabetes mellitus, %</td>
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</tr>
<tr>
<td>Hyperlipidemia, %</td>
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<tr>
<td>Smoking history, %</td>
<td>68</td>
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<tr>
<td>Pack-years, years, median (IQR)</td>
<td>20 (14–35)</td>
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<td>Current smoker, %</td>
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<tr>
<td>Ejection fraction, %, median (IQR)^a</td>
<td>60 (60–65)</td>
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<td>Atypical angina, %</td>
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<td>Typical angina, %</td>
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<tr>
<td>CCS 1, n (%)</td>
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<tr>
<td>CCS 2, n (%)</td>
<td>28/54</td>
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<tr>
<td>CCS 3, n (%)</td>
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<td>CCS 4, n (%)</td>
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<td>Chronic kidney disease, %</td>
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<tr>
<td>PCI history, %</td>
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<td>CABG history, %</td>
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<td>AMI history, %</td>
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<td>Family history of CAD, %</td>
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<td>Stress electrocardiograph:</td>
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<td>Performed, %</td>
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<tr>
<td>Clinically positive, n (%)</td>
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<td>ECG-positive, n (%)</td>
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<tr>
<td>Low-density lipoprotein cholesterol, mmol/l, mean (SD)</td>
<td>2.5 (0.9)</td>
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<td>1.4 (0.4)</td>
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<tr>
<td>Statin, %</td>
<td>90</td>
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<tr>
<td>ACE-inhibitor or ARB, %</td>
<td>86</td>
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Table 2. Diagnostic accuracy of CTA for detection of lesions >50%DS in QCA

<table>
<thead>
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<th></th>
<th>Per artery (n = 200)</th>
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<th>Per patient (n = 100)</th>
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<tr>
<td></td>
<td>Sensitivity (%)</td>
<td>Specificity (%)</td>
<td>PPV (%)</td>
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<tr>
<td>&gt;50% in QCT</td>
<td>99</td>
<td>97</td>
<td>94</td>
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Abbreviations: CTA, coronary computed tomography angiography; NPV, negative predictive value; PPV, positive predictive value; QCA, quantitative coronary angiography

Figure 1. Changes in invasive diagnostics based on non-invasive testing

Abbreviations: CT-FFR, computed tomography fractional flow reserve; ICA, invasive coronary angiography; QCT, quantitative computed tomography

Table 2. Diagnostic accuracy of CTA for detection of lesions >50%DS in QCA

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<tr>
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Figure 1. Changes in invasive diagnostics based on non-invasive testing

Abbreviations: CT-FFR, computed tomography fractional flow reserve; ICA, invasive coronary angiography; QCT, quantitative computed tomography
Figure 2. Estimated effective radiation dose used during coronary angiography routinely and in comparison with two strategies based on non-invasive testing
Abbreviations: see Figure 1

Figure 3. Contrast media volume used during coronary angiography routinely and in comparison with two strategies based on non-invasive testing
Abbreviations: see Figure 1
Figure 4. Incremental benefit of non-invasive diagnostic methods over routine, invasive coronary angiography. Quantitative coronary angiography (A) and quantitative coronary tomography (B) assessment of left anterior descending artery stenosis — both methods perform similarly, demonstrating borderline lesion. Computed tomography angiography-derived fractional flow reserve (C) value <0.8 indicates hemodynamic significance of the stenosis.