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Factors Influencing the Safety of Coronary Computed Tomography Angiography – a Clinical Registry Study

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Abstract

Objectives

Since safety of coronary CT angiography (CTA) is of great importance, especially with regard to widening indications and increasing morbidity, aim of this study was to assess influencing factors.

Methods

Patients undergoing coronary CTA in a third-generation dual-source CT in a radiological center were included in a clinical registry. Up to 20 mg metoprolol was administered intravenously to attain a heart rate ≤65/min. Glyceryl trinitrate (GTN) was administered in doses of 0.8 mg and 0.4 mg. Blood pressure was measured before the administration and after the CTA.

Results

Out of 5500 consecutive patients (3194 men, 62.3 (54.9-70.0) years), adverse events occurred in 68 patients (1.2%) with mild anaphylactoid reactions (0.4%), vasovagal symptoms (0.3%), and extravasation (0.3%) being most frequent. Anti-allergic drugs were given in 17 patients, atropine in 3 patients and volume in 1 patient. Drug administration resulted in a significant mean arterial pressure decline (96.0 (88.3-106.0) vs. 108.7 (99.7-117.3) mmHg; p<0.001). Patients, who suffered systolic blood pressure drops >20 mmHg or >40 mmHg, were older (66.5 (58.6-73.3) vs. 60.5 (53.6-68.3) years; 70.2 (63.3-76.5) vs. 62.1 (54.7-69.6) years), more often male (65.1% vs. 54.4%; 68.9% vs. 57.3%) and had higher Agatston score equivalents (83.0 (2.0-432.0) vs. 15.0 (0.0-172.0) and 163.0 (16.3-830.8) vs. 25.0 (0.0-220.0); all p<0.001). GTN dose reduction lowered the fraction of patients suffering from blood pressure drops >20 mmHg or >40 mmHg from 34.5% to 27.4% (p<0.001) and from 6.1% to 3.5% (p<0.001), respectively. The proportion of coronary segments with impaired image quality did not differ significantly.

Conclusions

Coronary CTA with intravenous beta-blocker administration is a safe procedure in an outpatient setting as adverse events are rare and mostly mild. Reduced GTN doses can further improve safety by lowering the rate of significant blood pressure drops, which occurred especially in elderly men with increased plaque burden.

Strengths and Limitations of this Study

- The study includes a large population of real-world patients and, thus, its results may be applicable in clinical routine.
- Adverse events, heart rate, and blood pressure characteristics were systematically recorded.
- Analyses were performed to identify patients at increased risk for adverse events.
- To our knowledge, this is the first study assessing the influence of GTN dosage on blood pressure and image quality in coronary CTA.
- Follow-up data on the effect of contrast agent administration, e.g., on renal function, were not available.

Keywords

Coronary Artery Disease, Cardiovascular Imaging, Computed Tomography, Clinical Pharmacology, Cardiology

Trial Registration: NCT03815123

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Introduction

Over recent years, cardiac computed tomography (CT) has emerged as an essential diagnostic modality for the detection and assessment of coronary artery disease (CAD). Calcium scoring measures the calcified plaque burden without the need for contrast agent application adding incremental prognostic value to standard cardiovascular risk factors [1 2]. Coronary CT angiography (CTA) offers a simultaneous visualization of the entire coronary tree. In contrast to invasive coronary angiography, coronary CTA not only allows for the quantification of coronary artery stenosis but also the evaluation of plaque morphology including the detection of high-risk plaque features indicating vulnerable lesions [3-5]. In addition, cardiac CT renders the evaluation of the cardiac morphology and adjacent anatomic structures like the aorta and the lungs possible [6]. Its high sensitivity and negative predictive value allow for the reliable exclusion of obstructive CAD. Thus, cardiac CT and especially coronary CTA have been implemented in current guidelines for the diagnosis and management of CAD even being the first-line imaging modality in the current NICE guidelines [7-10]. As cardiac CT is increasingly used and modern CT scanners enable the assessment of significantly calcified vessels or even coronary artery stents, the fragility and morbidity of the patients undergoing coronary CTA increase [11-13]. Thus, the safety of cardiac CT examinations is of paramount importance, especially in an outpatient setting. Although CT angiography is generally regarded to be safe, real-world data on coronary CT angiography assessing the impact of glyceryl trinitrate and intravenous beta-blocker administration are scarce.

The aim of this study was to assess the safety of coronary CTA in a real-world outpatient population and to evaluate the benefit of an optimized CTA examination protocol with a reduced glyceryl trinitrate (GTN) dose.

Methods

Patients were referred to coronary CTA by their attending physician and examinations were performed at a radiological center using a dual-source CT (DSCT) scanner of the third generation (SOMATOM Force, Siemens Healthcare, Erlangen, Germany). Subjects were enrolled in the Heidelberg Cardiac CT Registry and examinations, which were performed between May 2017 and April 2020, were included in this study. The workflow of the optimized coronary CTA examination protocol is given in Figure 1. Usually, an 18 G venous cannula was placed in the antecubital vein, but also 20 G cannulas were inserted into veins of the forearm or even the dorsum of the hand in individual cases. Patients were trained in breathing maneuvers as image acquisition was performed in inspiration breath-hold. Patients received up to 20 mg metoprolol tartrate (Lopressor, Recordati Pharma, Ulm, Germany) intravenously to achieve a heart rate of ≤65 /min. Glyceryl trinitrate (Nitrolingual, Pohl-Boskamp, Hohenlockstedt, Germany) was administered sublingually to improve the coronary artery visualization in standard doses of 0.8 mg (until April 2019) or 0.4 mg (from May 2019).

Of note, contraindications to the administrations of both drugs were excluded in advance. Patients with a known allergy to iodinated contrast agents were pretreated according to the current guidelines of the European Society of Urogenital Radiology [14 15]. Calcium scoring was performed before the contrast agent administration for the quantification of the coronary calcium burden and further optimization of the coronary CTA protocol. Between 40 ml and 80 ml prewarmed iomeprol with a concentration of 400 mg I/ml (Imeron 400, Bracco Imaging, Konstanz Germany) was administered at a flow rate between 4.5 and 5.5 ml/s depending on the respective protocol followed by a chaser of 30 ml isotonic saline at a flow rate of 5.0 ml/s. Axial or helical scan modes with automated attenuation-based tube potential selection and tube current (CARE Dose4D, Siemens Healthcare, Erlangen, Germany) were applied. The collimation was 96 x 0.6 mm and a slice acquisition of 192 x 0.6 mm using a z-flying focal was used. Advanced Modeled Iterative Reconstruction (ADMIRE) level 3 with dedicated cardiac kernels (usually Bv36 and Bv40) was applied for image reconstruction. The heart rate was recorded during the coronary CTA scan and blood pressure was measured before the drug

administration. In a subgroup, an additional blood pressure measurement was performed immediately after the coronary CTA examination. The intravenous access was left for 30 minutes after contrast agent administration as anaphylactoid reactions might occur delayed.

Image analysis was performed on a dedicated workstation (syngo.via, Siemens Healthcare, Erlangen, Germany) by an experienced cardiologist and radiologist (>4000 cardiac CT examinations). The CT examinations were reviewed visually before the patient was discharged to account for critical findings, which might have an immediate therapeutic consequence, whereas the detailed analysis was conducted afterwards. The results of the examination, as well as clinical data and adverse events, were documented in a dedicated database. Anaphylactoid reactions were graded according to severity as described before [16 17]. Briefly, four classes with increasing severity were employed: I: pruritus or dermal symptoms, II: abdominal, respiratory, or circulatory symptoms, III: more severe abdominal, respiratory, or respiratory symptoms including cyanosis and shock, IV: respiratory or cardiac arrest.

The cardiac CT examinations were clinically indicated by the referring physician and approval for the scientific data analysis was obtained from the ethics committee of the University of Heidelberg (S-226/2016 and S-758/2018).

The effect of the GTN dose on the proportion of coronary artery segments with impaired or non-diagnostic image quality was assessed by two experienced readers in 100 randomly selected patients with half of them receiving the reduced GTN dose.

Patient and Public Involvement

Patients, who were prospectively enrolled in the clinical registry, were informed about the general aims and research questions. Since the cardiac CT examinations were clinically indicated, patients could not be involved in the recruitment of the study population or in the conduct of the examinations. The results of this study will be implemented in clinical routine and, thus, be beneficial to future patients.

Statistics

Continuous data are uniformly given as a median and interquartile range as part of the data showed a non-parametric distribution. Normal distribution was assessed using the D'Agostino-Pearson test. Categorial data are given as numbers and proportions. The Mann-Whitney test was used for the comparison of two groups, the Wilcoxon test for paired samples, and the Kruskal-Wallis test with a posthoc analysis (Conover) for the analysis of several groups as appropriate. The Fisher's exact test was employed for the comparison of categorical data. Multivariate logistic regression analysis was used to model the effect of independent variables on a dichotomous characteristic of interest. In the case of missing values, the number of subjects included in the respective analysis is given at first mention. A p-value <0.05 was regarded as statistically significant. Analyses were conducted using dedicated statistical software (MedCalc Statistical Software version 19, MedCalc Software, Belgium).

Results

Coronary CTA examinations of 5500 consecutive patients (3194 men, 2306 women) with a median age of 62.3 (54.9-70.0) years were included in the final study population. Of note, safe venous access could not be established in 7 additional patients and another 2 patients aborted the examination after the calcium scoring scan due to a panic attack and severe claustrophobia. Male were significantly younger than female subjects (61.2 (53.9-69.3) years vs. 63.9 (56.5-71.1) years; p<0.001).

Adverse events occurred in 68 patients (1.2 %) with mild anaphylactoid reactions, vasovagal symptoms, and extravasation being most frequent. Of note, only mild forms of anaphylactoid reactions occurred in our study population. Another 36 patients (0.7 %) suffered from severe nausea which abated spontaneously within a few minutes in all subjects. An overview of all adverse events is given in Table 1 and Figure 2. Out of 24 patients (0.4 %) with anaphylactic reactions, 17 received a medication. Atropine was administered in 3 patients with symptomatic bradycardia and isotonic saline was administered in one patient with vasovagal symptoms. One patient was referred to the chest pain

unit due to critical coronary artery stenoses in combination with bradycardia after beta-blocker administration. Two patients were hospitalized due to unstable CAD and another one due to unexpected pulmonary embolism. In 5 of 16 cases of extravasation, only saline was injected extravascularly. Of note, all patients could be treated conservatively. Patients with adverse events were significantly younger (57.3 (50.8-61.6) years vs. 62.4 (55.0-70.1) years; p<0.001), which was mainly driven by the lower age of the subjects suffering from mild anaphylactoid reactions and vasovagal symptoms (p<0.05). The rate of adverse events did not differ significantly between the male and female patients (p=n.s.).

The administration of beta-blocker and GTN resulted in a significant decline of the systolic and mean arterial pressure (134.0 (122.0-150.0) mmHg vs. 150.0 (136.0-165.0) mmHg and 96.0 (88.3-106.0) mmHg vs. 108.7 (99.7-117.3) mmHg; both p<0.001, n=5185). Median heart rate was 62.0 (56.0-68.0) /min (n=5324) with men showing a little but significant lower frequency (61.0 (56.0-67.0) /min vs. 63.0 (68.0-69.0) /min; p<0.001) during the image acquisition. Patients suffering from systolic blood pressure drops of more than 20 mmHg and more than 40 mmHg were significantly older (66.5. (58.6-73.3) years vs. 60.5 (53.6-68.3) years and 70.2 (63.3-76.5) years vs. 62.1 (54.7-69.6) years; both p<0.001), were more often male (65.1 % vs. 54.4 %; p<0.001 and 68.9 % vs. 57.3 %; both p<0.001) and had a higher Agatston score equivalent (83.0 (2.0-432.0) vs. 15.0 (0.0-172.0) and 163.0 (16.3-830.8) vs. 25.0 (0.0-220.0), both p<0.001, n=5184). Age, sex and the Agatston score equivalent were significant predictors for systolic blood pressure drops of more than 40 mmHg in the multivariate regression analysis, whereas age and sex but not the Agatston score equivalent reached statistical significance for systolic blood pressure drops of more than 20 mmHg (n=5184).

The reduction of the standard GTN dose from 0.8 mg to 0.4 mg (n=3688; n=1812) resulted in small but significant decreases of the systolic blood pressure drop (15.0 (6.0-25.0) mmHg vs. 12.0 (3.0-21.5) mmHg) as well as the mean arterial pressure drop (12.3 (5.7-18.7) mmHg vs. 9.7 (3.7-16.3) mmHg; n=5185; both p<0.001). Of note, the proportions of patients suffering a drop of the systolic blood pressure of more than 20 mmHg (34.5 % vs. 27.4 %; p<0.001) as well as more than 40 mmHg (6.1 % vs

3.5 %; p<0.001) declined significantly with the reduction of the GTN dose (Figure 3). Age (62.6. (55.1-70.4) years vs. 62.2 (54.9-69.6 years), n=5185), sex (57.3 % men vs. 59.1 % men, n=5185) and the Agatston score equivalents (30.0 (0.0-261.0) vs. 25.0 (0.0-219.0) n=5184) did not differ significantly between the GTN groups included in the blood pressure analysis (all p=n.s.).

The proportion of coronary artery segments with impaired or non-diagnostic image quality did not differ significantly between the GTN dose groups (both p=n.s.).

Discussion

Coronary CTA is increasingly used as the first-line diagnostic modality for coronary artery disease replacing more and more diagnostic invasive coronary angiography for the primary assessment of coronary anatomy. Consequently, the fragility and morbidity of the patients referred to coronary CTA increase. Periprocedural safety is of great importance in clinical routine and especially in outpatient settings. Prior data indicate that adverse reactions may occur more frequently in outpatient than inpatient settings [18] and, additionally, the ability to address emergencies may be limited in some facilities. Thus, we assessed the safety of coronary CTA in a large real-world population and evaluated an optimized coronary CTA examination protocol. The key findings of our studies were as follows. 1) Adverse events as anaphylactoid reactions and extravasations are rare and mostly mild. 2) The intravenous administration of beta-blockers in combination with GTN can be regarded as safe when the dose is thoroughly adapted to the individual patient. 3) The fraction of patients suffering from significant blood pressure drops is increased especially in elderly men with increased plaque burden. 4) The reduction of the GTN dose reduces the rate of significant blood pressure drops without impairing the diagnostic image quality.

In the study population, anaphylactoid reactions were the most common adverse event with 0.4 % of cases of whom about two-thirds received medical treatment. Of note, only mild reactions occurred in our study population and none of the patients required hospitalization. About 0.7 % of the patients

reported transient nausea with none of them needing any medication which is in line with previously published studies [19-21]. Adverse reactions occurred more often in younger patients which is in agreement with a study by Gomi et al showing a higher incidence of adverse reactions in patients aged 59 years or less compared with older ones [20].

While the high degree of safety of the intravenous administration of current contrast agents was shown in several studies [22 23], the use of GTN and beta-blockers in cardiac patients requires an individual clinical assessment, especially in outpatient settings. Current guidelines approve the oral, intravenous, or both routes of beta-blocker administration, while an oral premedication followed by supplemental intravenous application, when necessary, is given as the most common approach [24]. The intravenous administration results in an immediate reduction of the heart rate and, thus, allows for a precise titration. In a retrospective study of 560 consecutive patients, the intravenous administration of atenolol resulted in a better heart rate reduction as well as in a faster preparation than the oral intake of metoprolol [25]. Although patients with atrial fibrillations were not excluded from our study, the median heart rate after beta-blocker administration was 62.0 (56.0-68.0) /min and, thus, suitable for coronary CTA using a third-generation DSCT scanner. Yet, safety data on the sole use of intravenous beta-blockers for rapid heart rate control is limited [25 26]. In our study population, the fraction of patients with symptomatic bradycardia was approximately 0.1 % and medical intervention was needed in less than half of the cases. Thus, we consider the intravenous administration of metoprolol immediately before CT image acquisition to be safe, when individually adapted to the patient.

GTN causes vasodilation, which can result in a drop in blood pressure and a reactive increase in the heart rate. While some protocols recommend the application of GTN immediately before the coronary CTA due to its short half-life of 2.5-4.4 min [27], we recommend its administration before the beta-blocker application for two reasons. First, the potential reactive heart rate increase can be counteracted by metoprolol administration adequately. Second, some patients may show an excessive blood pressure drop and may, therefore, need the reactive heart rate increase to sustain a sufficient mean arterial pressure, which would be impeded by prior administered beta-blockers. This

compensatory mechanism may be of importance especially in multimorbid patients, who often already suffer from a reduced heart rate adaptation. Of note, in our study, systolic blood pressure drops of more than 20 mmHg or even more than 40 mmHg occurred prevalently in elderly men with a high plaque burden indicated by the Agatston score equivalent.

In order to further improve the safety of coronary CTA examinations especially in fragile patients, we assessed the reduction of the standard GTN dose from 0.8 mg to 0.4 mg. This led to a reduction of the systolic as well as the mean arterial pressure drops of approximately 3 mmHg, respectively. Although being statistically highly significant, the clinical relevance of this reduction may seem to be low. However, the fraction of patients showing drops of more than 20 mmHg as well as more than 40 mmHg decreased significantly from 34.5 % to 27.4 % and 6.1 % to 3.5 %, respectively. Of note, the image quality of the coronary CTA was not impaired, being possibly due to the fact that the time of the maximal drug level of sublingually administered GTN ranges between 2 and 10 min and the half-life of its vasoactive metabolites is even longer covering the time of the coronary CTA [28]. Thus, the reduction of the GTN dose may improve patient safety without impairing diagnostic accuracy.

As the data analysis was conducted retrospectively, prospective trials are needed to confirm the improvement in patient safety by the optimized coronary CTA examination protocol. The number of adverse events was low hampering further statistical analyses, especially of subgroups. Since all patients were examined in an outpatient setting, follow-up data on late reactions after contrast agent administration as well as on renal function were not available. Of note, the risk of a contrast-induced acute kidney injury was very low as patients with an eGFR <45 ml/1.73m²/min were not examined routinely in this study [29 30].

The rate of major complications in diagnostic cardiac catheterization has been reported to be low (0.1-0.3 %) whereas the overall complication rate is approximately 0.8-1.4 % [31-33]. Of note, the definitions of complication and adverse events can differ substantially between studies on cardiac catheterization and cardiac CT with the latter using a more comprehensive approach even including mild forms of

adverse events as transient nausea. Aside from immediate periprocedural adverse events, acute kidney injury is more common after cardiac catheterization than after cardiac CT which is due to the different modes (intraarterial vs. intravenous) of contrast agent application [34]. Because of its lower invasiveness and the generally lower incidence and severity of adverse events, coronary CTA is the safer modality for CAD diagnostics unless in emergencies and in unstable patients when immediate treatment is necessary.

Conclusions

Coronary CTA with GTN and intravenous beta-blocker administration allows for a safe assessment of CAD in an outpatient setting showing a low rate of mostly mild adverse events. The use of an optimized coronary CTA examination protocol with a reduced GTN dose results in a lower fraction of patients with significant blood pressure drops and, thus, may further improve safety, especially in fragile patients.

Data Availability Statement

The data sets analyzed in this study are not publicly available due data protection regulation. They are available on reasonable request from the corresponding author.

Funding Statement

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Competing Interests Statement

The Radiology Center received a research grant from Siemens Healthineers. The authors declare, that there are no relationships that could be construed as conflict of interests.

Contributorship Statement

FA and SJB designed the study and performed the data analysis. PF, SJB, JG, MB, FG, RS and AS contributed to the data acquisition and ME and SS collected and administered the data. JG, AS and NF gave administrative support. All authors contributed to writing and editing of the manuscript and approved the final version.

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Tables

Table 1: Adverse events – Frequency and patient characteristics

	n	fraction	male	female	age [years]
Anaphylactoid Reaction I°/II°	24	0.4%	12	12	52.5 (48.0-59.5)
Anaphylactoid Reaction III°/IV°	0	0.0 %	0	0	
Vasovagal Symptoms	17	0.3%	11	6	56.0 (48.7-61.6)
Extravasation	16	0.3%	8	8	60.5 (53.4-67.1)
Symptomatic bradycardia	7	0.1%	7	0	59.1 (56.7-67.0)
Supraventricular tachycardia	1	0.02%	1	0	58.1
Dizziness/Presyncope	2	0.04%	0	2	53.6 (51.5-55.6)
Arterial Hypertension	1	0.02%	0	1	78.9
Nausea	36	0.7%	20	16	59.8 (52.9-65.7)

Figures Captions

Figure 1: Optimized coronary CTA examination protocol

i.v.: intravenously, G: gauge, SBP: systolic blood pressure, s.l.: sublingually

Common contraindications to metoprolol administration: hemodynamic instability, SBP < 90 mmHg, heart rate <50 /min, sick-sinus-syndrome, atrioventricular blockage II°/III°, severe asthma, intake of non-dihydropyridine calcium channel blockers, allergy to beta-blockers

Figure 2: Number of adverse events

a) The rate of all complications inclusive of transient nausea was low with 104 of 5500 patients (1.9 %).

b) Adverse events aside from nausea occurred in only 68 patients (1.2 %) being mostly mild.

Figure 3: Rate of significant blood pressure drops depending on glyceryl trinitrate dose

The reduction of the standard GTN dose from 0.8 mg to 0.4 mg resulted in significantly lower proportions of patients suffering a drop of the systolic blood pressure >20 mmHg as well as >40 mmHg. *p<0.001

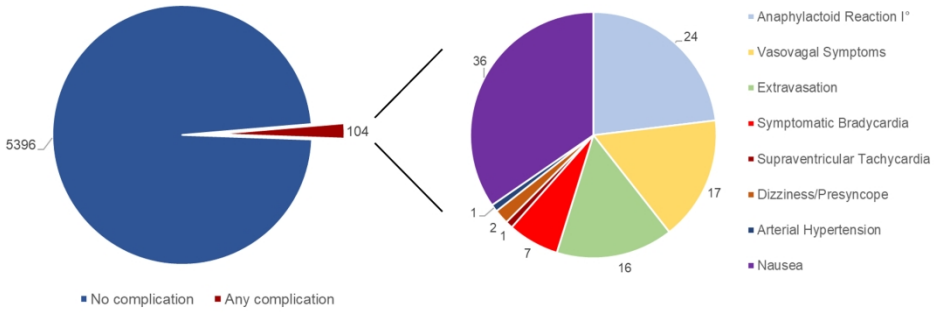

Figure 2: Number of adverse events
a) The rate of all complications inclusive of transient nausea was low with 104 of 5500 patients (1.9 %).
b) Adverse events aside from nausea occurred in only 68 patients (1.2 %) being mostly mild.

99x38mm (600 x 600 DPI)

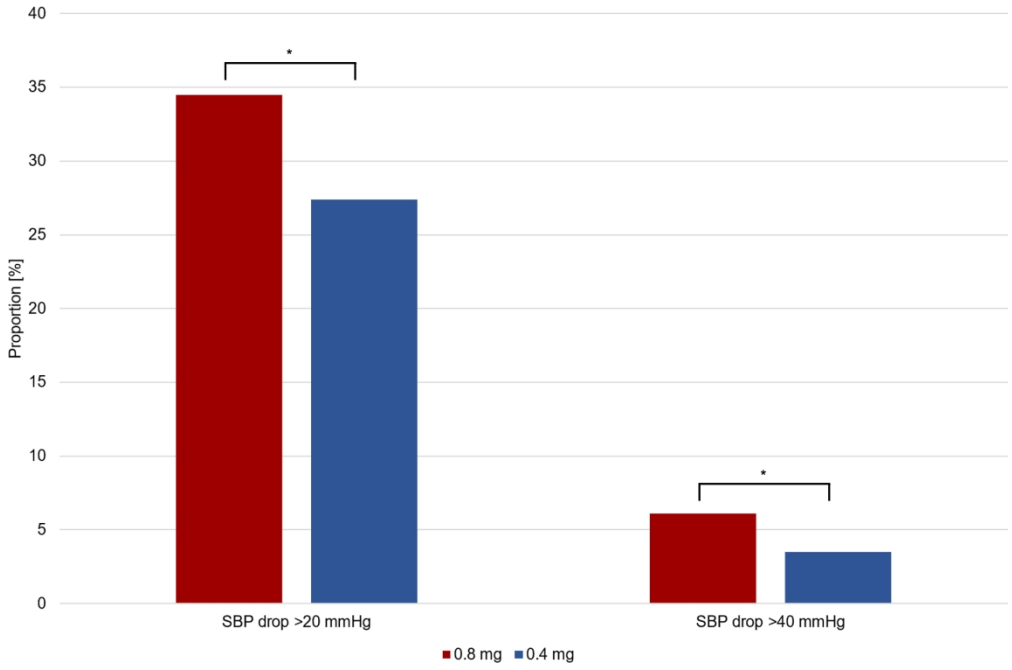

Figure 3: Rate of significant blood pressure drops depending on glyceryl trinitrate dose
The reduction of the standard GTN dose from 0.8 mg to 0.4 mg resulted in significantly lower proportions of patients suffering a drop of the systolic blood pressure >20 mmHg as well as >40 mmHg. *p<0.001

712x467mm (72 x 72 DPI)

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Factors Influencing the Safety of Outpatient Coronary Computed Tomography Angiography – a Clinical Registry Study

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Factors Influencing the Safety of Outpatient Coronary Computed Tomography Angiography – a Clinical Registry Study

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Abstract

Objectives

Since the safety of coronary CT angiography (CTA) is of great importance, especially with regard to widening indications and increasing morbidity, aim of this study was to assess influencing factors.

Methods

Patients undergoing coronary CTA in a third-generation dual-source CT in a radiological center were included in a clinical registry. Up to 20 mg metoprolol was administered intravenously to attain a heart rate ≤65/min. Glyceryl trinitrate (GTN) was administered in doses of 0.8 mg and 0.4 mg. Blood pressure was measured before the administration and after the CTA.

Results

Out of 5500 consecutive patients (3194 men, 62.3 (54.9-70.0) years), adverse events occurred in 68 patients (1.2%) with mild anaphylactoid reactions (0.4%), vasovagal symptoms (0.3%), and extravasation (0.3%) being most frequent. Anti-allergic drugs were given in 17 patients, atropine in 3 patients and volume in 1 patient. Drug administration resulted in a significant mean arterial pressure decline (96.0 (88.3-106.0) vs. 108.7 (99.7-117.3) mmHg; p<0.001). Patients, who suffered systolic blood pressure drops >20 mmHg or >40 mmHg, were older (66.5 (58.6-73.3) vs. 60.5 (53.6-68.3) years; 70.2 (63.3-76.5) vs. 62.1 (54.7-69.6) years), more often male (65.1% vs. 54.4%; 68.9% vs. 57.3%) and had higher Agatston score equivalents (83.0 (2.0-432.0) vs. 15.0 (0.0-172.0); 163.0 (16.3-830.8) vs. 25.0 (0.0-220.0); all p<0.001). GTN dose reduction lowered the fraction of patients suffering from blood pressure drops >20 mmHg or >40 mmHg from 34.5% to 27.4% and from 6.1% to 3.5% (both p<0.001), respectively. The proportion of coronary segments with impaired image quality did not differ significantly.

Conclusions

Coronary CTA with intravenous beta-blocker administration is a safe procedure in an outpatient setting as adverse events are rare and mostly mild. Reduced GTN doses can further improve safety by lowering the rate of significant blood pressure drops, which occurred especially in elderly men with increased plaque burden.

Strengths and Limitations of this Study

- The study includes a large population of real-world patients and, thus, its results may be applicable in clinical routine.
- Adverse events, heart rate, and blood pressure characteristics were systematically recorded.
- Analyses were performed to identify patients at increased risk for adverse events.
- To our knowledge, this is the first study assessing the influence of GTN dose on blood pressure and image quality in coronary CTA.
- Follow-up data on the delayed effects of contrast agent administration e.g., on renal function, were not available.

Keywords

Coronary Artery Disease, Cardiovascular Imaging, Computed Tomography, Clinical Pharmacology, Cardiology

Trial Registration: NCT03815123

Factors Influencing the Safety of Outpatient Coronary Computed Tomography Angiography – a Clinical Registry Study

Introduction

Over recent years, cardiac computed tomography (CT) has emerged as an essential diagnostic modality for the detection and assessment of coronary artery disease (CAD). Calcium scoring measures the calcified plaque burden without the need for contrast agent application adding incremental prognostic value to standard cardiovascular risk factors [1 2]. Coronary CT angiography (CTA) offers a detailed visualization of the entire coronary tree. In contrast to invasive coronary angiography, coronary CTA not only allows for the quantification of coronary artery stenosis but also the evaluation of plaque morphology including the detection of high-risk plaque features indicating vulnerable lesions [3-5]. In addition, cardiac CT renders the evaluation of the cardiac morphology and adjacent anatomic structures like the aorta and the lungs possible [6]. Its high sensitivity and negative predictive value allow for the reliable exclusion of obstructive CAD. Thus, cardiac CT and especially coronary CTA have been implemented in current guidelines for the diagnosis and management of CAD even being the first-line imaging modality in the current NICE guidelines [7-10]. As cardiac CT is increasingly used and modern CT scanners enable the assessment of significantly calcified vessels or even coronary artery stents, the fragility and morbidity of the patients undergoing coronary CTA increase [11-13]. Thus, the safety of cardiac CT examinations is of paramount importance, especially in an outpatient setting. Although CT angiography is generally regarded to be safe, real-world data on coronary CTA assessing the impact of glyceryl trinitrate (GTN) and intravenous beta-blocker administration are scarce.

The aim of this study was to assess the safety of coronary CTA in a real-world outpatient population, identify influencing factors, and evaluate the benefit of an optimized CTA examination protocol with a reduced GTN dose.

Methods

Patients were referred to coronary CTA by their attending physician and examinations were performed at a radiological center using a dual-source CT (DSCT) scanner of the third generation (SOMATOM Force, Siemens Healthcare, Erlangen, Germany). Subjects were enrolled in the Heidelberg Cardiac CT Registry and examinations, which were performed between May 2017 and April 2020, were included in this study. The workflow of the optimized coronary CTA examination protocol is given in Figure 1. Usually, an 18 G venous cannula was placed in the antecubital vein, but also 20 G cannulas were inserted into veins of the forearm or even the dorsum of the hand in individual cases. Patients were trained in breathing maneuvers as image acquisition was performed in inspiration breath-hold. Patients received up to 20 mg metoprolol tartrate (Lopressor, Recordati Pharma, Ulm, Germany) intravenously to achieve a heart rate of ≤65 /min. Glyceryl trinitrate (Nitrolingual, Pohl-Boskamp, Hohenlockstedt, Germany) was administered sublingually to improve the coronary artery visualization in standard doses of 0.8 mg (until April 2019) or 0.4 mg (from May 2019).

Contraindications to the administration of beta-blocker, GTN, or iodine-based contrast agents were assessed by checking the patients' medical history and records as well as the measurement of the renal and thyroid function. Patients with a known allergy to iodinated contrast agents were pretreated according to the current guidelines of the European Society of Urogenital Radiology [14 15]. Calcium scoring was performed before the contrast agent administration for the quantification of the coronary calcium burden and further optimization of the coronary CTA protocol. Between 40 ml and 80 ml prewarmed iomeprol with a concentration of 400 mg l/ml (Imeron 400, Bracco Imaging, Konstanz Germany) was administered at a flow rate between 4.5 and 5.5 ml/s depending on the respective protocol followed by a chaser of 30 ml isotonic saline at a flow rate of 5.0 ml/s. Axial or helical scan modes with automated attenuation-based tube potential and tube current selection (CARE Dose4D, Siemens Healthcare, Erlangen, Germany) were applied. The collimation was 96 x 0.6 mm and a slice acquisition of 192 x 0.6 mm using a z-flying focal spot was used. Advanced Modeled Iterative Reconstruction (ADMIRE) level 3 with dedicated cardiac kernels (usually Bv36 and Bv40) was applied

for image reconstruction. The heart rate was recorded during the coronary CTA scan and blood pressure was measured before the drug administration. In a subgroup, an additional blood pressure measurement was performed immediately after the coronary CTA examination. The intravenous access was left for 30 minutes after contrast agent administration as anaphylactoid reactions might occur delayed.

Image analysis was performed on a dedicated workstation (syngo.via, Siemens Healthcare, Erlangen, Germany) by an experienced cardiologist and radiologist (>4000 cardiac CT examinations). The CT examinations were reviewed visually before the patient was discharged to account for critical findings, which might have an immediate therapeutic consequence, whereas the detailed analysis was conducted afterwards. The results of the examination, as well as clinical data and periprocedural events, were documented in a dedicated database. Periprocedural events were defined as any incident impairing the patient's well-being including not only potentially dangerous adverse events e.g., anaphylactoid reactions, but also unpleasant symptoms e.g., transient nausea.

Anaphylactoid reactions were graded according to severity as described before [16 17]. Briefly, four classes with increasing severity were employed: I: pruritus or dermal symptoms, II: abdominal, respiratory, or circulatory symptoms, III: more severe abdominal, respiratory, or circulatory symptoms including cyanosis and shock, IV: respiratory or cardiac arrest.

The cardiac CT examinations were clinically indicated by the referring physician and approval for the scientific data analysis was obtained from the ethics committee of the University of Heidelberg (S-226/2016 and S-758/2018). The Heidelberg Cardiac CT registry aims to assess the real-world diagnostic and prognostic performance of cardiac CT examinations by including all patients undergoing cardiac CT examinations in an outpatient center.

The effect of the GTN dose on the proportion of coronary artery segments with impaired or non-diagnostic image quality was assessed by two experienced readers in 100 randomly selected patients with half of them receiving the reduced GTN dose.

Patient and Public Involvement

Patients, who were prospectively enrolled in the clinical registry, were informed about the general aims and research questions. Since the cardiac CT examinations were clinically indicated, patients could not be involved in the recruitment of the study population or the conduct of the examinations. The results of this study will be implemented in clinical routine and, thus, may be beneficial to future patients.

Statistics

Continuous data are uniformly given as a median and interquartile range as part of the data showed a non-parametric distribution. Normal distribution was assessed using the D'Agostino-Pearson test. Categorial data are given as numbers and proportions. The Mann-Whitney test was used for the comparison of two groups, the Wilcoxon test for paired samples, and the Kruskal-Wallis test with a posthoc analysis (Conover) for the analysis of several groups as appropriate. The Fisher's exact test was employed for the comparison of categorical data. Multivariate logistic regression analysis was used to model the effect of independent variables on a dichotomous characteristic of interest. In the case of missing values, the number of subjects included in the respective analysis is given at first mention. A p-value <0.05 was regarded as statistically significant. Analyses were conducted using dedicated statistical software (MedCalc Statistical Software version 19 and 20, MedCalc Software, Ostend, Belgium).

Results

Coronary CTA examinations of 5500 consecutive patients were included in the final study population. Of note, safe venous access could not be established in 7 additional patients and another 2 patients aborted the examination after the calcium scoring scan due to a panic attack and severe

claustrophobia. Male were significantly younger than female subjects (61.2 (53.9-69.3) years vs. 63.9 (56.5-71.1) years; p<0.001). The patient's characteristics are given in Table 1.

Adverse events occurred in 68 patients (1.2 %) with mild anaphylactoid reactions, vasovagal symptoms, and extravasation being the most frequent. Of note, only mild forms of anaphylactoid reactions occurred in our study population. Another 36 patients (0.7 %) suffered from severe nausea, which abated spontaneously within a few minutes in all subjects. An overview of all adverse events is given in Table 2 and Figure 2. Out of 24 patients (0.4 %) with anaphylactic reactions, 17 received a medication. Atropine was administered in 3 patients with symptomatic bradycardia and isotonic saline was administered in one patient with vasovagal symptoms. One patient was referred to the chest pain unit due to critical coronary artery stenoses in combination with bradycardia after beta-blocker administration. Two patients were hospitalized due to unstable CAD and another one due to unexpected pulmonary embolism. In 5 of 16 cases of extravasation, only saline was injected extravascularly. Of note, all patients could be treated conservatively. Patients with adverse events were significantly younger (57.3 (50.8-61.6) years vs. 62.4 (55.0-70.1) years; p<0.001), which was mainly driven by the lower age of the subjects suffering from mild anaphylactoid reactions and vasovagal symptoms (p<0.05). The rate of adverse events did not differ significantly between the male and female patients (p=n.s.).

The administration of beta-blocker and GTN resulted in a significant decline of the systolic and mean arterial pressure (134.0 (122.0-150.0) mmHg vs. 150.0 (136.0-165.0) mmHg and 96.0 (88.3-106.0) mmHg vs. 108.7 (99.7-117.3) mmHg; both p<0.001, n=5185). Median heart rate was 62.0 (56.0-68.0) /min (n=5324) with men showing a little but significant lower frequency (61.0 (56.0-67.0) /min vs. 63.0 (68.0-69.0) /min; p<0.001) during the image acquisition. Patients suffering from systolic blood pressure drops of more than 20 mmHg and more than 40 mmHg were significantly older (66.5 (58.6-73.3) years vs. 60.5 (53.6-68.3) years and 70.2 (63.3-76.5) years vs. 62.1 (54.7-69.6) years; both p<0.001), were more often male (65.1 % vs. 54.4 %; p<0.001 and 68.9 % vs. 57.3 %; both p<0.001) and had higher Agatston score equivalents (83.0 (2.0-432.0) vs. 15.0 (0.0-172.0) and 163.0 (16.3-830.8) vs. 25.0 (0.0-

220.0), both p<0.001, n=5184). Age, sex and the Agatston score equivalent were significant predictors for systolic blood pressure drops of more than 40 mmHg in the multivariate regression analysis, whereas age and sex but not the Agatston score equivalent reached statistical significance for systolic blood pressure drops of more than 20 mmHg (n=5184).

The reduction of the standard GTN dose from 0.8 mg to 0.4 mg (n=3688; n=1812) resulted in small but significant decreases of the systolic blood pressure drop (15.0 (6.0-25.0) mmHg vs. 12.0 (3.0-21.5) mmHg) as well as the mean arterial pressure drop (12.3 (5.7-18.7) mmHg vs. 9.7 (3.7-16.3) mmHg; n= 5185; both p<0.001). Of note, the proportions of patients suffering a drop of the systolic blood pressure of more than 20 mmHg (34.5 % vs. 27.4 %; p<0.001) as well as more than 40 mmHg (6.1 % vs. 3.5 %; p<0.001) declined significantly with the reduction of the GTN dose (Figure 3). Age (62.6 (55.1-70.4) years vs. 62.2 (54.9-69.6 years), n=5185), sex (57.3 % men vs. 59.1 % men, n=5185) and the Agatston score equivalents (30.0 (0.0-261.0) vs. 25.0 (0.0-219.0); n=5184) did not differ significantly between the GTN groups included in the blood pressure analysis (all p=n.s.).

The proportion of coronary artery segments with impaired or non-diagnostic image quality did not differ significantly between the GTN dose groups (both p=n.s.).

Discussion

Coronary CTA is increasingly used as the first-line diagnostic modality for CAD replacing more and more diagnostic invasive coronary angiography for the primary assessment of coronary anatomy. Consequently, the fragility and morbidity of the patients referred to coronary CTA increase. Periprocedural safety is of great importance in clinical routine and especially in outpatient settings. Prior data indicate that adverse reactions may occur more frequently in outpatient than inpatient settings [18] and, additionally, the ability to address emergencies may be limited in some outpatient facilities. Thus, we assessed the safety of coronary CTA in a large real-world population and evaluated an optimized coronary CTA examination protocol. The key findings of our studies were as follows. 1)

Adverse events such as anaphylactoid reactions and extravasations are rare and mostly mild. 2) The intravenous administration of beta-blocker in combination with GTN can be regarded as safe when the dose is thoroughly adapted to the individual patient. 3) The fraction of patients suffering from significant blood pressure drops is increased especially in elderly men with increased plaque burden. 4) The reduction of the GTN dose reduces the rate of significant blood pressure drops without impairing the diagnostic image quality.

In the study population, anaphylactoid reactions were the most common adverse event with 0.4 % of cases of whom about two-thirds received medical treatment. Of note, only mild reactions occurred in our study population and none of the patients required hospitalization. About 0.7 % of the patients reported transient nausea with none of them needing any medication which is in line with previously published studies [19-21]. Adverse reactions occurred more often in younger patients which is in agreement with a study by Gomi et al showing a higher incidence of adverse reactions in patients aged 59 years or less compared with older ones [20].

While the high level of safety of the intravenous administration of current contrast agents was shown in several studies [22 23], the use of GTN and beta-blockers in cardiac patients requires an individual clinical assessment, especially in outpatient settings. Current guidelines approve the oral, intravenous, or both routes of beta-blocker administration, while an oral premedication followed by supplemental intravenous application, when necessary, is given as the most common approach [24]. The intravenous administration results in an immediate reduction of the heart rate and, thus, allows for a precise titration. In a retrospective study of 560 consecutive patients, the intravenous administration of atenolol resulted in a better heart rate reduction as well as a faster preparation than the oral intake of metoprolol [25]. Although patients with atrial fibrillations were not excluded from our study, the median heart rate after beta-blocker administration was 62.0 (56.0-68.0) /min and, thus, suitable for coronary CTA using a third-generation DSCT scanner. Yet, safety data on the sole use of intravenous beta-blockers for rapid heart rate control is limited [25 26]. In our study population, the fraction of patients with symptomatic bradycardia was approximately 0.1 % and medical intervention was needed in less

than half of the cases. Thus, we consider the intravenous administration of metoprolol immediately before CT image acquisition to be safe, when individually adapted to the patient.

GTN causes vasodilation, which can result in a drop in blood pressure and a reactive increase in heart rate. While some protocols recommend the application of GTN immediately before the coronary CTA due to its short half-life of 2.5-4.4 min [27], we recommend its administration before the beta-blocker application for two reasons. First, the potential reactive heart rate increase can be counteracted by metoprolol administration adequately. Second, some patients may show an excessive blood pressure drop and may need the reactive heart rate increase to sustain a sufficient mean arterial pressure, which would be impeded by prior administered beta-blockers. This compensatory mechanism may be of importance, especially in multimorbid patients, who often already suffer from a reduced heart rate adaptation. Of note, in our study, systolic blood pressure drops of more than 20 mmHg or even more than 40 mmHg occurred prevalently in elderly men with a high plaque burden indicated by the Agatston score equivalent.

In order to further improve the safety of coronary CTA examinations, especially in fragile patients, we assessed the reduction of the standard GTN dose from 0.8 mg to 0.4 mg. This led to a reduction of the systolic as well as the mean arterial pressure drops of approximately 3 mmHg, respectively. Although being statistically highly significant, the clinical relevance of this reduction may seem to be low. However, the fraction of patients showing drops of more than 20 mmHg as well as more than 40 mmHg decreased significantly from 34.5 % to 27.4 % and 6.1 % to 3.5 %, respectively. Of note, the image quality of the coronary CTA was not impaired, being possibly due to the fact that the time of the maximal drug level of sublingually administered GTN ranges between 2 and 10 min and the half-life of its vasoactive metabolites is even longer covering the time of the coronary CTA [28]. Thus, the reduction of the GTN dose may improve patient safety without impairing diagnostic accuracy.

Limitations

As the data analysis was conducted retrospectively, prospective trials are needed to confirm the improvement in patient safety by the optimized coronary CTA examination protocol. The number of adverse events was low hampering further statistical analyses, especially of subgroups. Since all patients were examined in an outpatient setting, follow-up data on late reactions after contrast agent administration as well as on renal function were not available. Late reactions, occurring up to one week after contrast agent administration, are commonly mild to moderate skin manifestations e.g., maculopapular exanthema, which are self-limiting [29]. Since thyroid function was assessed in all patients and contrast agent was not given in those with contraindications such as manifest hyperthyroidism, the risk of very late reaction occurring after one week i.e., thyrotoxicosis, was negligible [14 30]. The risk of a contrast-induced acute kidney injury was very low as patients with an eGFR <45 ml/min/1.73 m² were not examined routinely in this study [31 32].

Coronary CTA has a lower frequency of major procedure-related complications than invasive coronary angiography, with a similar risk of major adverse cardiovascular events for both diagnostic imaging strategies in patients with stable chest pain as shown in a recent multi-center trial [33]. Since its general safety could be confirmed by our study, which analyzed an even larger population of real-world patients, coronary CTA can be considered an optimal diagnostic modality for CAD assessment in the outpatient setting.

Conclusions

Coronary CTA with GTN and intravenous beta-blocker administration allows for a safe assessment of CAD in an outpatient setting showing a low frequency of mostly mild adverse events. The use of an optimized coronary CTA examination protocol with a reduced GTN dose results in a lower fraction of patients with significant blood pressure drops and, thus, may further improve safety, especially in fragile patients.

Data Availability Statement

The data set analyzed in this study is not publicly available due to data protection regulations. It is available on reasonable request from the corresponding author.

Funding Statement

This work was supported by a research grant from Siemens Healthineers.

Competing Interests Statement

The Radiology Center received a research grant from Siemens Healthineers. The authors declare, that there are no relationships that could be construed as a conflict of interests.

Contributorship Statement

FA and SJB designed the study and performed the data analysis. PF, SJB, JG, MB, FG, RS and AS contributed to the data acquisition and ME and SS collected and administered the data. JG, AS and NF gave administrative support. All authors contributed to the writing and editing of the manuscript and approved the final version.

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Tables

Table 1 – Patient characteristics

Age [years]	62.3 (54.9-70.0)
Male	3194 men (58.1 %)
BMI [kg/m²; n=5285]	27.0 (24.4-30.4)
Systolic Arterial Pressure* [mmHg; n=5185]	150.0 (136.0-165.0)
Mean Arterial Pressue* [mmHg; n=5185]	108.7 (99.7-117.3)
Agatston Score [n=5499]	28.0 (0.0-242.0)

BMI: body mass index; *before the administration of beta-blocker and glyceryl trinitrate

Table 2: Periprocedural events – frequency and patient characteristics

	n	**fraction**	**male**	**female**	**age [years]**
Anaphylactoid Reaction I°/II°	24	0.4 %	12	12	52.5 (48.0-59.5)
Anaphylactoid Reaction III°/IV°	0	0.0 %	0	0	
Vasovagal Symptoms	17	0.3 %	11	6	56.0 (48.7-61.6)
Extravasation	16	0.3 %	8	8	60.5 (53.4-67.1)
Symptomatic Bradycardia	7	0.1 %	7	0	59.1 (56.7-67.0)
Supraventricular Tachycardia	1	0.02 %	1	0	58.1
Dizziness/Presyncope	2	0.04 %	0	2	53.6 (51.5-55.6)
Arterial Hypertension	1	0.02 %	0	1	78.9
Nausea	36	0.7 %	20	16	59.8 (52.9-65.7)

Figure Captions

Figure 1: Optimized coronary CTA examination protocol

i.v.: intravenously, G: gauge, SBP: systolic blood pressure, s.l.: sublingually

Common contraindications to metoprolol administration: hemodynamic instability, SBP <90 mmHg, heart rate <50 /min, sick-sinus-syndrome, atrioventricular blockage II°/III°, severe asthma, intake of non-dihydropyridine calcium channel blockers, allergy to beta-blockers

Figure 2: Number of periprocedural events

The rate of all periprocedural events inclusive of transient nausea was low with 104 of 5500 patients (1.9 %). Adverse events aside from nausea occurred in only 68 patients (1.2 %) and were mostly mild.

Figure 3: Rate of significant blood pressure drops depending on glyceryl trinitrate dose

The reduction of the standard GTN dose from 0.8 mg to 0.4 mg resulted in significantly lower proportions of patients suffering a drop of the systolic blood pressure >20 mmHg as well as >40 mmHg. *p<0.001

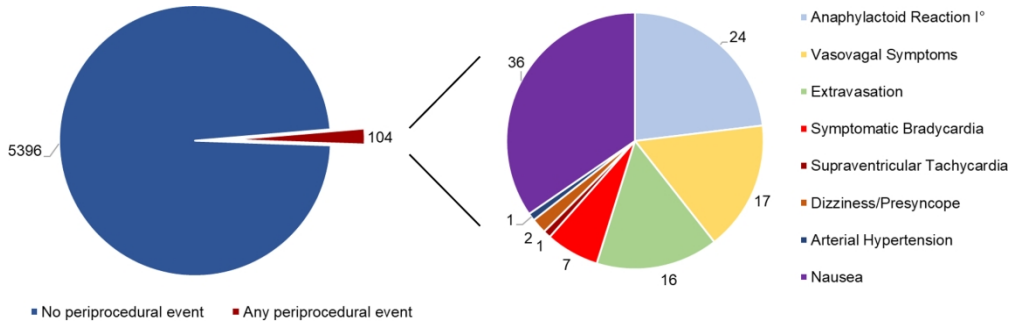

Figure 2: Number of periprocedural events<p>The rate of all periprocedural events inclusive of transient nausea was low with 104 of 5500 patients (1.9 %). Adverse events aside from nausea occurred in only 68 patients (1.2 %) and were mostly mild.

794x250mm (72 x 72 DPI)

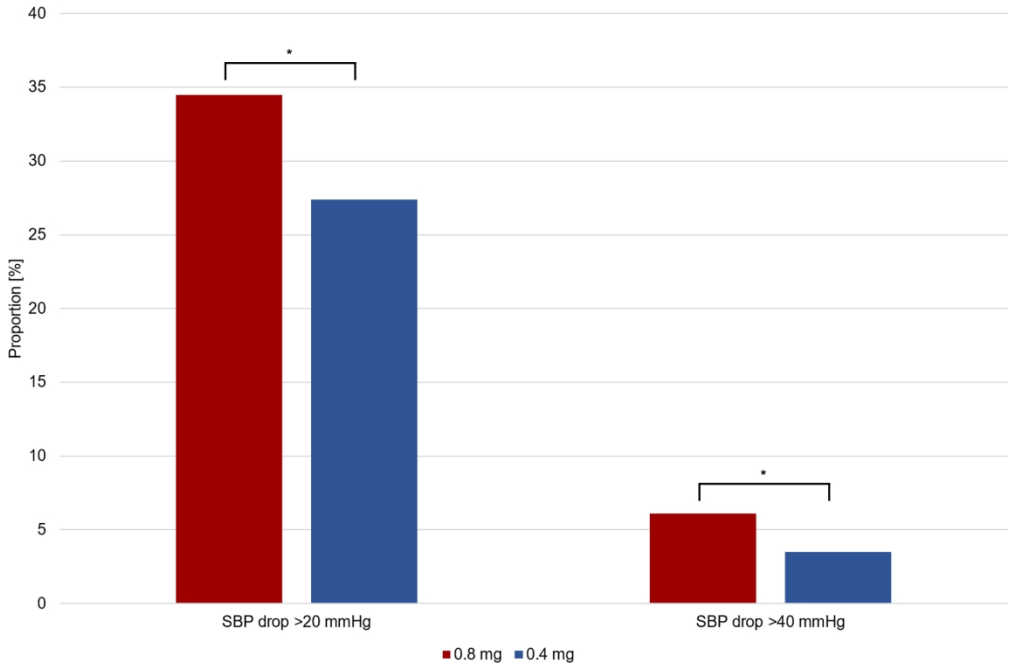

Figure 3: Rate of significant blood pressure drops depending on glyceryl trinitrate dose<p>The reduction of the standard GTN dose from 0.8 mg to 0.4 mg resulted in significantly lower proportions of patients suffering a drop of the systolic blood pressure >20 mmHg as well as >40 mmHg. *p<0.001

712x467mm (72 x 72 DPI)

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1 + 2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2-3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5-6
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	5
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	5
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5-6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6
Bias	9	Describe any efforts to address potential sources of bias	5
Study size	10	Explain how the study size was arrived at	5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6-7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7
		(*b*) Describe any methods used to examine subgroups and interactions	7
		(*c*) Explain how missing data were addressed	7
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	n.a.
		(*e*) Describe any sensitivity analyses	n.a.

Continued on next page

Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	7
		(b) Give reasons for non-participation at each stage	5-7
		(c) Consider use of a flow diagram	n.a.
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	7-8
		(b) Indicate number of participants with missing data for each variable of interest	7-9
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	n.a.
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	*8-9*
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	*8-9*
		(*b*) Report category boundaries when continuous variables were categorized	9
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	n.a.
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	9
Discussion			
Key results	18	Summarise key results with reference to study objectives	9-10
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	12
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	10-12
Generalisability	21	Discuss the generalisability (external validity) of the study results	12
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	13

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Factors Influencing the Safety of Outpatient Coronary Computed Tomography Angiography – a Clinical Registry Study

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Factors Influencing the Safety of Outpatient Coronary Computed Tomography Angiography – a Clinical Registry Study

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Abstract

Objectives

Since the safety of coronary CT angiography (CTA) is of great importance, especially with regard to widening indications and increasing morbidity, aim of this study was to assess influencing factors.

Methods

Patients undergoing coronary CTA in a third-generation dual-source CT in a radiological center were included in a clinical registry. Up to 20 mg metoprolol was administered intravenously to attain a heart rate ≤65/min. Glyceryl trinitrate (GTN) was administered in doses of 0.8 mg and 0.4 mg. Blood pressure was measured before the administration and after the CTA.

Results

Out of 5500 consecutive patients (3194 men, 62.3 (54.9-70.0) years), adverse events occurred in 68 patients (1.2%) with mild anaphylactoid reactions (0.4%), vasovagal symptoms (0.3%), and extravasation (0.3%) being most frequent. Anti-allergic drugs were given in 17 patients, atropine in 3 patients and volume in 1 patient. Drug administration resulted in a significant mean arterial pressure decline (96.0 (88.3-106.0) vs. 108.7 (99.7-117.3) mmHg; p<0.001). Patients, who suffered systolic blood pressure drops >20 mmHg or >40 mmHg, were older (66.5 (58.6-73.3) vs. 60.5 (53.6-68.3) years; 70.2 (63.3-76.5) vs. 62.1 (54.7-69.6) years), more often male (65.1% vs. 54.4%; 68.9% vs. 57.3%) and had higher Agatston score equivalents (83.0 (2.0-432.0) vs. 15.0 (0.0-172.0); 163.0 (16.3-830.8) vs. 25.0 (0.0-220.0); all p<0.001). GTN dose reduction lowered the fraction of patients suffering from blood pressure drops >20 mmHg or >40 mmHg from 34.5% to 27.4% and from 6.1% to 3.5% (both p<0.001), respectively. The proportion of coronary segments with impaired image quality did not differ significantly.

Conclusions

Coronary CTA with intravenous beta-blocker administration is a safe procedure in an outpatient setting as adverse events are rare and mostly mild. Reduced GTN doses can further improve safety by lowering the rate of significant blood pressure drops, which occurred especially in elderly men with increased plaque burden.

Strengths and Limitations of this Study

- The study includes a large population of real-world patients and, thus, its results may be applicable in clinical routine.
- Adverse events, heart rate, and blood pressure characteristics were systematically recorded.
- Analyses were performed to identify patients at increased risk for adverse events.
- To our knowledge, this is the first study assessing the influence of GTN dose on blood pressure and image quality in coronary CTA.
- Follow-up data on the delayed effects of contrast agent administration e.g., on renal function, were not available.

Keywords

Coronary Artery Disease, Cardiovascular Imaging, Computed Tomography, Clinical Pharmacology, Cardiology

Trial Registration: NCT03815123

Factors Influencing the Safety of Outpatient Coronary Computed Tomography Angiography – a Clinical Registry Study

Introduction

Over recent years, cardiac computed tomography (CT) has emerged as an essential diagnostic modality for the detection and assessment of coronary artery disease (CAD). Calcium scoring measures the calcified plaque burden without the need for contrast agent application adding incremental prognostic value to standard cardiovascular risk factors [1 2]. Coronary CT angiography (CTA) offers a detailed visualization of the entire coronary tree. In contrast to invasive coronary angiography, coronary CTA not only allows for the quantification of coronary artery stenosis but also the evaluation of plaque morphology including the detection of high-risk plaque features indicating vulnerable lesions [3-5]. In addition, cardiac CT renders the evaluation of the cardiac morphology and adjacent anatomic structures like the aorta and the lungs possible [6]. Its high sensitivity and negative predictive value allow for the reliable exclusion of obstructive CAD. Thus, cardiac CT and especially coronary CTA have been implemented in current guidelines for the diagnosis and management of CAD even being the first-line imaging modality in the current NICE guidelines [7-10]. As cardiac CT is increasingly used and modern CT scanners enable the assessment of significantly calcified vessels or even coronary artery stents, the fragility and morbidity of the patients undergoing coronary CTA increase [11-13]. Thus, the safety of cardiac CT examinations is of paramount importance, especially in an outpatient setting. Although CT angiography is generally regarded to be safe, real-world data on coronary CTA assessing the impact of glyceryl trinitrate (GTN) and intravenous beta-blocker administration are scarce.

The aim of this study was to assess the safety of coronary CTA in a real-world outpatient population, identify influencing factors, and evaluate the benefit of an optimized CTA examination protocol with a reduced GTN dose.

Methods

Patients underwent coronary CTA at a radiological center using a dual-source CT (DSCT) scanner of the third generation (SOMATOM Force, Siemens Healthcare, Erlangen, Germany). Patients were referred to the CT examination by their attending physicians considering their symptoms, cardiovascular risk profile, and previous examinations results. The indication was counter-checked by a radiologist. Subjects were enrolled in the Heidelberg Cardiac CT Registry and examinations, which were performed between May 2017 and April 2020, were included in this study. The workflow of the optimized coronary CTA examination protocol is given in Figure 1. Usually, an 18 G venous cannula was placed in the antecubital vein, but also 20 G cannulas were inserted into veins of the forearm or even the dorsum of the hand in individual cases. Patients were trained in breathing maneuvers as image acquisition was performed in inspiration breath-hold. Patients received up to 20 mg metoprolol tartrate (Lopressor, Recordati Pharma, Ulm, Germany) intravenously to achieve a heart rate of ≤65 /min. Glyceryl trinitrate (Nitrolingual, Pohl-Boskamp, Hohenlockstedt, Germany) was administered sublingually to improve the coronary artery visualization in standard doses of 0.8 mg (until April 2019) or 0.4 mg (from May 2019).

Contraindications to the administration of beta-blocker, GTN, or iodine-based contrast agents were assessed by checking the patients' medical history and records as well as the measurement of the renal and thyroid function. Patients with a known allergy to iodinated contrast agents were pretreated according to the current guidelines of the European Society of Urogenital Radiology [14 15]. Calcium scoring was performed before the contrast agent administration for the quantification of the coronary calcium burden and further optimization of the coronary CTA protocol. Between 40 ml and 80 ml prewarmed iomeprol with a concentration of 400 mg I/ml (Imeron 400, Bracco Imaging, Konstanz Germany) was administered at a flow rate between 4.5 and 5.5 ml/s depending on the respective protocol followed by a chaser of 30 ml isotonic saline at a flow rate of 5.0 ml/s. Axial or helical scan modes with automated attenuation-based tube potential and tube current selection (CARE Dose4D, Siemens Healthcare, Erlangen, Germany) were applied. The collimation was 96 x 0.6 mm and a slice acquisition of 192 x 0.6 mm using a z-flying focal spot was used. Advanced Modeled Iterative

Reconstruction (ADMIRE) level 3 with dedicated cardiac kernels (usually Bv36 and Bv40) was applied for image reconstruction. The heart rate was recorded during the coronary CTA scan and blood pressure was measured before the drug administration. In a subgroup, an additional blood pressure measurement was performed immediately after the coronary CTA examination. The intravenous access was left for 30 minutes after contrast agent administration as anaphylactoid reactions might occur delayed.

Image analysis was performed on a dedicated workstation (syngo.via, Siemens Healthcare, Erlangen, Germany) by an experienced cardiologist and radiologist (>4000 cardiac CT examinations). The CT examinations were reviewed visually before the patient was discharged to account for critical findings, which might have an immediate therapeutic consequence, whereas the detailed analysis was conducted afterwards. The results of the examination, as well as clinical data and periprocedural events, were documented in a dedicated database. Periprocedural events were defined as any incident impairing the patient's well-being including not only potentially dangerous adverse events e.g., anaphylactoid reactions, but also unpleasant symptoms e.g., transient nausea.

Anaphylactoid reactions were graded according to severity as described before [16 17]. Briefly, four classes with increasing severity were employed: I: pruritus or dermal symptoms, II: abdominal, respiratory, or circulatory symptoms, III: more severe abdominal, respiratory, or circulatory symptoms including cyanosis and shock, IV: respiratory or cardiac arrest.

The cardiac CT examinations were clinically indicated by the referring physician and approval for the scientific data analysis was obtained from the ethics committee of the University of Heidelberg (S-226/2016 and S-758/2018). The Heidelberg Cardiac CT registry aims to assess the real-world diagnostic and prognostic performance of cardiac CT examinations by including all patients undergoing cardiac CT examinations in an outpatient center.

The effect of the GTN dose on the proportion of coronary artery segments with impaired or non-diagnostic image quality was assessed by two experienced readers in 100 randomly selected patients with half of them receiving the reduced GTN dose.

Patient and Public Involvement

Patients, who were prospectively enrolled in the clinical registry, were informed about the general aims and research questions. Since the cardiac CT examinations were clinically indicated, patients could not be involved in the recruitment of the study population or the conduct of the examinations. The results of this study will be implemented in clinical routine and, thus, may be beneficial to future patients.

Statistics

Continuous data are uniformly given as a median and interquartile range as part of the data showed a non-parametric distribution. Normal distribution was assessed using the D'Agostino-Pearson test. Categorial data are given as numbers and proportions. The Mann-Whitney test was used for the comparison of two groups, the Wilcoxon test for paired samples, and the Kruskal-Wallis test with a posthoc analysis (Conover) for the analysis of several groups as appropriate. The Fisher's exact test was employed for the comparison of categorical data. Multivariate logistic regression analysis was used to model the effect of independent variables on a dichotomous characteristic of interest. In the case of missing values, the number of subjects included in the respective analysis is given at first mention. A p-value <0.05 was regarded as statistically significant. Analyses were conducted using dedicated statistical software (MedCalc Statistical Software version 19 and 20, MedCalc Software, Ostend, Belgium).

Results

Coronary CTA examinations of 5500 consecutive patients were included in the final study population. Of note, safe venous access could not be established in 7 additional patients and another 2 patients aborted the examination after the calcium scoring scan due to a panic attack and severe claustrophobia. Male were significantly younger than female subjects (61.2 (53.9-69.3) years vs. 63.9 (56.5-71.1) years; p<0.001). While in most patients an obstructive CAD was not known, 175 patients (3.2 %) had previously undergone percutaneous coronary intervention with coronary stent implantation and 48 patients (0.9 %) coronary artery bypass surgery or both. Further patient characteristics are given in Table 1 and displayed in Figure 2.

Adverse events occurred in 68 patients (1.2 %) with mild anaphylactoid reactions, vasovagal symptoms, and extravasation being the most frequent. Of note, only mild forms of anaphylactoid reactions occurred in our study population. Another 36 patients (0.7 %) suffered from severe nausea, which abated spontaneously within a few minutes in all subjects. An overview of all adverse events is given in Table 2 and Figure 3. Out of 24 patients (0.4 %) with anaphylactic reactions, 17 received a medication. Atropine was administered in 3 patients with symptomatic bradycardia and isotonic saline was administered in one patient with vasovagal symptoms. One patient was referred to the chest pain unit due to critical coronary artery stenoses in combination with bradycardia after beta-blocker administration. Two patients were hospitalized due to unstable CAD and another one due to unexpected pulmonary embolism. In 5 of 16 cases of extravasation, only saline was injected extravascularly. Of note, all patients could be treated conservatively. Patients with adverse events were significantly younger (57.3 (50.8-61.6) years vs. 62.4 (55.0-70.1) years; p<0.001), which was mainly driven by the lower age of the subjects suffering from mild anaphylactoid reactions and vasovagal symptoms (p<0.05). The rate of adverse events did not differ significantly between the male and female patients (p=n.s.).

The administration of beta-blocker and GTN resulted in a significant decline of the systolic and mean arterial pressure (134.0 (122.0-150.0) mmHg vs. 150.0 (136.0-165.0) mmHg and 96.0 (88.3-106.0) mmHg vs. 108.7 (99.7-117.3) mmHg; both p<0.001, n=5185). Median heart rate was 62.0 (56.0-68.0) /min (n=5324) with men showing a little but significant lower frequency (61.0 (56.0-67.0) /min vs. 63.0 (68.0-69.0) /min; p<0.001) during the image acquisition. Patients suffering from systolic blood pressure drops of more than 20 mmHg and more than 40 mmHg were significantly older (66.5 (58.6-73.3) years vs. 60.5 (53.6-68.3) years and 70.2 (63.3-76.5) years vs. 62.1 (54.7-69.6) years; both p<0.001), were more often male (65.1 % vs. 54.4 %; p<0.001 and 68.9 % vs. 57.3 %; both p<0.001) and had higher Agatston score equivalents (83.0 (2.0-432.0) vs. 15.0 (0.0-172.0) and 163.0 (16.3-830.8) vs. 25.0 (0.0-220.0), both p<0.001, n=5184). Age, sex and the Agatston score equivalent were significant predictors for systolic blood pressure drops of more than 40 mmHg in the multivariate regression analysis, whereas age and sex but not the Agatston score equivalent reached statistical significance for systolic blood pressure drops of more than 20 mmHg (n=5184).

The reduction of the standard GTN dose from 0.8 mg to 0.4 mg (n=3688; n=1812) resulted in small but significant decreases of the systolic blood pressure drop (15.0 (6.0-25.0) mmHg vs. 12.0 (3.0-21.5) mmHg) as well as the mean arterial pressure drop (12.3 (5.7-18.7) mmHg vs. 9.7 (3.7-16.3) mmHg; n= 5185; both p<0.001). Of note, the proportions of patients suffering a drop of the systolic blood pressure of more than 20 mmHg (34.5 % vs. 27.4 %; p<0.001) as well as more than 40 mmHg (6.1 % vs. 3.5 %; p<0.001) declined significantly with the reduction of the GTN dose (Figure 4). Age (62.6 (55.1-70.4) years vs. 62.2 (54.9-69.6 years), n=5185), sex (57.3 % men vs. 59.1 % men, n=5185) and the Agatston score equivalents (30.0 (0.0-261.0) vs. 25.0 (0.0-219.0); n=5184) did not differ significantly between the GTN groups included in the blood pressure analysis (all p=n.s.).

The proportion of coronary artery segments with impaired or non-diagnostic image quality did not differ significantly between the GTN dose groups (both p=n.s.). Of note, neither Agatston score nor heart rate differed significantly between groups (both p=n.s.).

Discussion

Coronary CTA is increasingly used as the first-line diagnostic modality for CAD replacing more and more diagnostic invasive coronary angiography for the primary assessment of coronary anatomy. Consequently, the fragility and morbidity of the patients referred to coronary CTA increase. Periprocedural safety is of great importance in clinical routine and especially in outpatient settings. Prior data indicate that adverse reactions may occur more frequently in outpatient than inpatient settings [18] and, additionally, the ability to address emergencies may be limited in some outpatient facilities. Thus, we assessed the safety of coronary CTA in a large real-world population and evaluated an optimized coronary CTA examination protocol. The key findings of our studies were as follows. 1) Adverse events such as anaphylactoid reactions and extravasations are rare and mostly mild. 2) The intravenous administration of beta-blocker in combination with GTN can be regarded as safe when the dose is thoroughly adapted to the individual patient. 3) The fraction of patients suffering from significant blood pressure drops is increased especially in elderly men with increased plaque burden. 4) The reduction of the GTN dose reduces the rate of significant blood pressure drops without impairing the diagnostic image quality.

In the study population, anaphylactoid reactions were the most common adverse event with 0.4 % of cases of whom about two-thirds received medical treatment. Of note, only mild reactions occurred in our study population and none of the patients required hospitalization. About 0.7 % of the patients reported transient nausea with none of them needing any medication which is in line with previously published studies [19-21]. Adverse reactions occurred more often in younger patients which is in agreement with a study by Gomi et al showing a higher incidence of adverse reactions in patients aged 59 years or less compared with older ones [20].

While the high level of safety of the intravenous administration of current contrast agents was shown in several studies [22 23], the use of GTN and beta-blockers in cardiac patients requires an individual clinical assessment, especially in outpatient settings. Current guidelines approve the oral, intravenous,

or both routes of beta-blocker administration, while an oral premedication followed by supplemental intravenous application, when necessary, is given as the most common approach [24]. The intravenous administration results in an immediate reduction of the heart rate and, thus, allows for a precise titration. In a retrospective study of 560 consecutive patients, the intravenous administration of atenolol resulted in a better heart rate reduction as well as a faster preparation than the oral intake of metoprolol [25]. Although patients with atrial fibrillations were not excluded from our study, the median heart rate after beta-blocker administration was 62.0 (56.0-68.0) /min and, thus, suitable for coronary CTA using a third-generation DSCT scanner, which is able to provide diagnostic image quality independent of heart rate and heart rhythm [13]. Yet, safety data on the sole use of intravenous beta-blockers for rapid heart rate control is limited [25 26]. In our study population, the fraction of patients with symptomatic bradycardia was approximately 0.1 % and medical intervention was needed in less than half of the cases. Thus, we consider the intravenous administration of metoprolol immediately before CT image acquisition to be safe, when individually adapted to the patient.

GTN causes vasodilation, which can result in a drop in blood pressure and a reactive increase in heart rate. While some protocols recommend the application of GTN immediately before the coronary CTA due to its short half-life of 2.5-4.4 min [27], we recommend its administration before the beta-blocker application for two reasons. First, the potential reactive heart rate increase can be counteracted by metoprolol administration adequately. Second, some patients may show an excessive blood pressure drop and may need the reactive heart rate increase to sustain a sufficient mean arterial pressure, which would be impeded by prior administered beta-blockers. This compensatory mechanism may be of importance, especially in multimorbid patients, who often already suffer from a reduced heart rate adaptation. Of note, in our study, systolic blood pressure drops of more than 20 mmHg or even more than 40 mmHg occurred prevalently in elderly men with a high plaque burden indicated by the Agatston score equivalent.

In order to further improve the safety of coronary CTA examinations, especially in fragile patients, we assessed the reduction of the standard GTN dose from 0.8 mg to 0.4 mg. This led to a reduction of the

systolic as well as the mean arterial pressure drops of approximately 3 mmHg, respectively. Although being statistically highly significant, the clinical relevance of this reduction may seem to be low. However, the fraction of patients showing drops of more than 20 mmHg as well as more than 40 mmHg decreased significantly from 34.5 % to 27.4 % and 6.1 % to 3.5 %, respectively. Of note, the image quality of the coronary CTA was not impaired, being possibly due to the fact that the time of the maximal drug level of sublingually administered GTN ranges between 2 and 10 min and the half-life of its vasoactive metabolites is even longer covering the time of the coronary CTA [28]. Thus, the reduction of the GTN dose may improve patient safety without impairing diagnostic accuracy.

Limitations

As the data analysis was conducted retrospectively, prospective trials are needed to confirm the improvement in patient safety by the optimized coronary CTA examination protocol. The number of adverse events was low hampering further statistical analyses, especially of subgroups. Since all patients were examined in an outpatient setting, follow-up data on late reactions after contrast agent administration as well as on renal function were not available. Late reactions, occurring up to one week after contrast agent administration, are commonly mild to moderate skin manifestations e.g., maculopapular exanthema, which are self-limiting [29]. Since thyroid function was assessed in all patients and contrast agent was not given in those with contraindications such as manifest hyperthyroidism, the risk of very late reaction occurring after one week i.e., thyrotoxicosis, was negligible [14 30]. The risk of a contrast-induced acute kidney injury was very low as patients with an eGFR <45 ml/min/1.73 m² were not examined routinely in this study [31 32].

Coronary CTA has a lower frequency of major procedure-related complications than invasive coronary angiography, with a similar risk of major adverse cardiovascular events, as shown in a recent multi-center trial comparing both modalities as initial diagnostic imaging strategies for guiding the treatment of patients with stable chest pain [33]. Since its general safety could be confirmed by our study, which

analyzed an even larger population of real-world patients, coronary CTA can be considered an optimal diagnostic modality for CAD assessment in the outpatient setting.

Conclusions

Coronary CTA with GTN and intravenous beta-blocker administration allows for a safe assessment of CAD in an outpatient setting showing a low frequency of mostly mild adverse events. The use of an optimized coronary CTA examination protocol with a reduced GTN dose results in a lower fraction of patients with significant blood pressure drops and, thus, may further improve safety, especially in fragile patients.

Data Availability Statement

The data set analyzed in this study is not publicly available due to data protection regulations. It is available on reasonable request from the corresponding author.

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Competing Interests Statement

The Radiology Center received a research grant from Siemens Healthineers. The authors declare, that there are no relationships that could be construed as a conflict of interests.

Contributorship Statement

FA and SJB designed the study and performed the data analysis. PF, SJB, JG, MB, FG, RS and AS contributed to the data acquisition and ME and SS collected and administered the data. JG, AS and NF gave administrative support. All authors contributed to the writing and editing of the manuscript and approved the final version.

Ethics statement

Universität Heidelberg, Ethikkommission der Medizinischen Fakultät, S-226/2016 and S-758/2018

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Tables

Table 1 – Patient characteristics

Age [years]	62.3 (54.9-70.0)
Sex	3194 men (58.1 %)
BMI [kg/m²; n=5285]	27.0 (24.4-30.4)
Systolic Arterial Pressure* [mmHg; n=5185]	150.0 (136.0-165.0)
Mean Arterial Pressue* [mmHg; n=5185]	108.7 (99.7-117.3)
Agatston Score [n=5499]	28.0 (0.0-242.0)

BMI: body mass index; *before the administration of beta-blocker and glyceryl trinitrate

Table 2: Periprocedural events – frequency and patient characteristics

	n	fraction	male	female	age [years]
Anaphylactoid Reaction I°/II°	24	0.4 %	12	12	52.5 (48.0-59.5)
Anaphylactoid Reaction III°/IV°	0	0.0 %	0	0	
Vasovagal Symptoms	17	0.3 %	11	6	56.0 (48.7-61.6)
Extravasation	16	0.3 %	8	8	60.5 (53.4-67.1)
Symptomatic Bradycardia	7	0.1 %	7	0	59.1 (56.7-67.0)
Supraventricular Tachycardia	1	0.02 %	1	0	58.1
Dizziness/Presyncope	2	0.04 %	0	2	53.6 (51.5-55.6)
Arterial Hypertension	1	0.02 %	0	1	78.9
Nausea	36	0.7 %	20	16	59.8 (52.9-65.7)

Figure Captions

Figure 1: Optimized coronary CTA examination protocol

i.v.: intravenously, G: gauge, SBP: systolic blood pressure, s.l.: sublingually

Common contraindications to metoprolol administration: hemodynamic instability, SBP <90 mmHg, heart rate <50 /min, sick-sinus-syndrome, atrioventricular blockage II°/III°, severe asthma, intake of non-dihydropyridine calcium channel blockers, allergy to beta-blockers

Figure 2: Age distribution

The majority of patients was between 50 and 70 years old and men were slightly but significantly younger than women (61.2 (53.9-69.3) years vs. 63.9 (56.5-71.1) years; p<0.001).

Figure 3: Number of periprocedural events

The rate of all periprocedural events inclusive of transient nausea was low with 104 of 5500 patients (1.9 %). Adverse events aside from nausea occurred in only 68 patients (1.2 %) and were mostly mild.

Figure 4: Rate of significant blood pressure drops depending on glyceryl trinitrate dose

The reduction of the standard GTN dose from 0.8 mg to 0.4 mg resulted in significantly lower proportions of patients suffering a drop of the systolic blood pressure >20 mmHg as well as >40 mmHg. *p<0.001

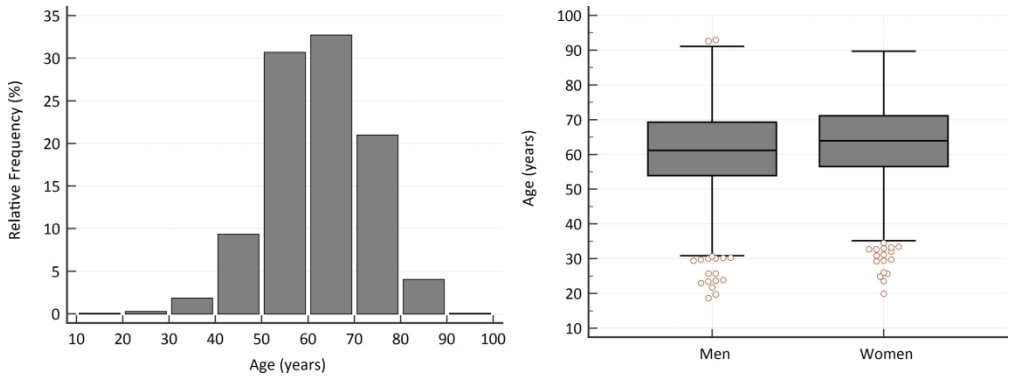

Figure 2: Age distribution<p>The majority of patients was between 50 and 70 years old and men were slightly but significantly younger than women (61.2 (53.9-69.3) years vs. 63.9 (56.5-71.1) years; p<0.001).

944x347mm (72 x 72 DPI)

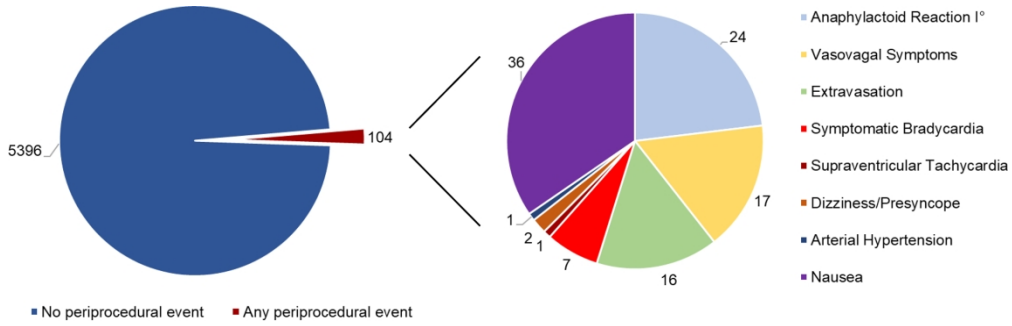

Figure 3: Number of periprocedural events<p>The rate of all periprocedural events inclusive of transient nausea was low with 104 of 5500 patients (1.9 %). Adverse events aside from nausea occurred in only 68 patients (1.2 %) and were mostly mild.

794x250mm (72 x 72 DPI)

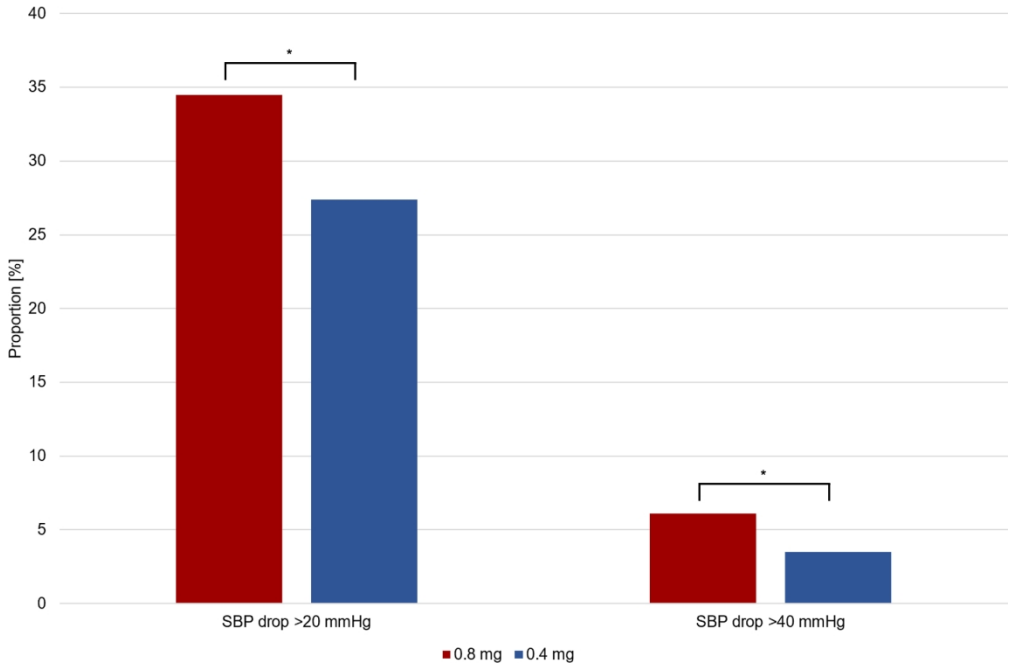

Figure 4: Rate of significant blood pressure drops depending on glyceryl trinitrate dose<p>The reduction of the standard GTN dose from 0.8 mg to 0.4 mg resulted in significantly lower proportions of patients suffering a drop of the systolic blood pressure >20 mmHg as well as >40 mmHg. *p<0.001

712x467mm (72 x 72 DPI)

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1 + 2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2-3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5-6
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	5
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	5
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5-6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6
Bias	9	Describe any efforts to address potential sources of bias	5
Study size	10	Explain how the study size was arrived at	5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6-7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7
		(*b*) Describe any methods used to examine subgroups and interactions	7
		(*c*) Explain how missing data were addressed	7
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	n.a.
		(*e*) Describe any sensitivity analyses	n.a.

Continued on next page

Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	7
		(b) Give reasons for non-participation at each stage	5-7
		(c) Consider use of a flow diagram	n.a.
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	7-8
		(b) Indicate number of participants with missing data for each variable of interest	7-9
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	n.a.
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	*8-9*
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	*8-9*
		(*b*) Report category boundaries when continuous variables were categorized	9
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	n.a.
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	9
Discussion			
Key results	18	Summarise key results with reference to study objectives	9-10
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	12
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	10-12
Generalisability	21	Discuss the generalisability (external validity) of the study results	12
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	13

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.