PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Factors Influencing the Safety of Outpatient Coronary Computed Tomography Angiography – a Clinical Registry Study
AUTHORS	Andre, Florian; Fortner, Philipp; Emami, Mostafa; Seitz, Sebastian; Brado, Matthias; Gückel, Friedemann; Sokiranski, Roman; Sommer, André; Frey, Norbert; Görich, Johannes; Buss, Sebastian J.

VERSION 1 – REVIEW

REVIEWER	Verdoia, Monica Eastern Piedmont Univ
REVIEW RETURNED	19-Jan-2022

GENERAL COMMENTS	In the manuscript Florian et al. address the complications of coronary CT in a large cohort of patients. However since the population is so large and available data are relevant it or bot clear to me why they do bot try to get more information. Ex was the quality of imaging affected by heart rate? Why was it assessed only in 100 patients,? That seems to me an incomplete work. Were there differences for patients with established cad? The absence of a proper sistematic follow up does not allow to exclude missing adverse reactions. Limitations are generally lacking

REVIEWER	Andò, Giuseppe University of Messina - Messina University Hospital, Department of Cardiology
REVIEW RETURNED	24-Jan-2022

GENERAL COMMENTS	I believe the comparison between invasive coronary angiography and CT coronary angiography dose not make too much sense to the purpose of procedural safety and suggest to omit it. I also suggest the Authors to avoid discussing the issue of AKI after invasive angiography as no renal follow-up was endorsed in this study population.

REVIEWER	Swahn, Eva Linköping University, Department of Health, Medicine and Caring Science
REVIEW RETURNED	30-Jan-2022

GENERAL COMMENTS	Congratulations for performing a clinically important study regarding safety in an outpatient CTA setting. The aim is straight forward and the methods seem scientifically robust.

	Anyhow, the outcomes could be more clearly defined as well as the registry used. A first table with basic characteristics would also be nice to have a general feeling of the studied population.

VERSION 1 – AUTHOR RESPONSE

Dr. Monica Verdoia, Eastern Piedmont Univ

Comments to the Author:
In the manuscript Florian et al. address the complications of coronary CT in a large cohort of patients. However, since the population is so large and available data are relevant it or bot clear to me why they do bot try to get more information.
Ex was the quality of imaging affected by heart rate?
Why was it assessed only in 100 patients? That seems to me an incomplete work.
Were there differences for patients with established CAD?
The absence of a proper systematic follow up does not allow to exclude missing adverse reactions.
Limitations are generally lacking.

We thank Dr. Verdoia for these comments and suggestions. In the revised version of the manuscript, we included a table, which gives the basic characteristics of the study population showing its realworld nature. In addition, we could provide a histogram showing the age distribution, if desired by the reviewer. An example is given at the end of the response letter.
The assessment of influencing factors on image quality was beyond the scope of this study, which focuses on the safety of outpatient coronary CTA examinations. However, we could show in a prior study (doi: 10.1007/s00392-017-1077-2) that DSCT of the third-generation provides diagnostic image quality independent of heart rate and heart rhythm. Of note, the median heart rate of 62.0 (56.0-68.0) /min in the current study population was within the optimal range for DSCT image acquisition. To ensure that the reduction of the GTN dose does not impair diagnostic quality, the image quality was assessed in a subset of 100 randomly selected patients with half of them receiving the reduced GTN dose, which should be enough to detect clinically relevant changes in image quality. Neither the Agatston score as a measure of the calcified plaque burden (32.5 (0.0-245.0) vs. 38.0 (2.0-281.0), p>0.6) nor heart rate (58.0 (54.0-65.0) /min vs. 60.0 (57.0-65.0) /min, p>0.1) differed significantly between groups and, thus, did not confound the results on image quality. The limitations e.g., the retrospective nature of the trial and the lack of data on late and very late adverse reactions after contrast agent application, are given at the end of the discussion part. To highlight the limitations, we put them into a separate paragraph with a subheading in the revised version of the manuscript. Furthermore, we added further information on late and very late reactions after contrast agent administration. Of note, late reactions are commonly non-severe and selflimiting. The risk of very late reactions i.e., thyrotoxicosis, was negligible since contrast agent was not administered in patients with untreated Grave's disease or manifest thyroid hyperfunction. We clarified in the revised methods part, that the thyroid function was assessed in all patients before the potential contrast agent application, although this would not have been mandatory according to recently published recommendations (doi: 10.1159/000517175).

Dr. Giuseppe Andò, University of Messina - Messina University Hospital

Comments to the Author:
I believe the comparison between invasive coronary angiography and CT coronary angiography dose not make too much sense to the purpose of procedural safety and suggest to omit it. I also suggest

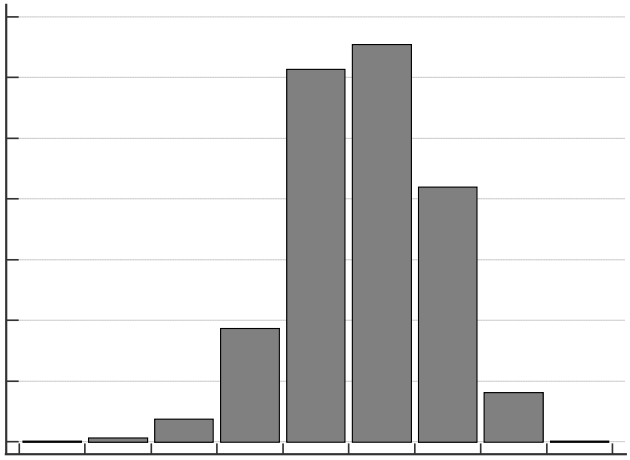
the Authors to avoid discussing the issue of AKI after invasive angiography as no renal follow-up was endorsed in this study population.

We appreciate the comments of Dr. Andò and removed the part in the revised version of the manuscript. Concerning the renal function after coronary CTA, we left a sentence in the limitations part because Reviewer 1 recommended a profound discussion of the limitations. Furthermore, we implemented the results of the recently published DISCHARGE trial showing that the risk of major adverse cardiovascular events is similar in coronary CTA and ICA diagnostic imaging strategies in patients with stable chest pain (doi: 10.1056/NEJMoa2200963).

Prof. Eva Swahn, Linköping University

Comments to the Author:
Congratulations for performing a clinically important study regarding safety in an outpatient CTA setting. The aim is straight forward and the methods seem scientifically robust. Anyhow, the outcomes could be more clearly defined as well as the registry used. A first table with basic characteristics would also be nice to have a general feeling of the studied population.

We thank Prof. Swahn for her comments and for raising these points. Outcomes i.e., periprocedural events, were defined as any event impairing the patient's well-being including not only relevant adverse events such as anaphylactoid reactions but also unpleasant symptoms e.g., transient nausea. This definition was included in the revised versions of the manuscript. We also provide a more detailed description of the CT registry, which aims to assess the real-world diagnostic and prognostic performance of cardiac CT examinations. Furthermore, we added a table with basic characteristics of the study population demonstrating its real-world nature, which we consider to be a strength of this study since it allows for the applicability of the results in clinical routine. If desired by the reviewer, we could add a histogram as follows showing the age distribution of the study population.



VERSION 2 – REVIEW

REVIEWER	Verdoia, Monica Eastern Piedmont Univ
REVIEW RETURNED	20-Apr-2022

GENERAL COMMENTS	The majority of the issues raised by the present and other reviewers have not been addressed. The only significant improvement is about limitations. In particular the characteristics o patients population should include other details, including ex the indications to CTA (established CAD, screening etc). Data on adequacy of heart rate etc have been stated but not included in the revision.

REVIEWER	Andò, Giuseppe University of Messina - Messina University Hospital, Department of Cardiology
REVIEW RETURNED	18-Apr-2022

GENERAL COMMENTS	All comments have been adequately addressed

VERSION 2 – AUTHOR RESPONSE

Reviewer: 2 Dr. Giuseppe Andò, University of Messina - Messina University Hospital All comments have been adequately addressed We thank Dr. Andò for the endorsement of the revised manuscript.

Reviewer: 1 Dr. Monica Verdoia, Eastern Piedmont Univ The majority of the issues raised by the present and other reviewers have not been addressed. The only significant improvement is about limitations. In particular the characteristics o patients population should include other details, including ex the indications to CTA (established CAD, screening etc). Data on adequacy of heart rate etc have been stated but not included in the revision. We appreciate the comment of Dr. Verdoia and revised the manuscript accordingly. Regarding the adequacy of the heart rate, the inclusion of patients with atrial fibrillation and the median heart frequency of 62.0 (56.0-68.0) /min are stated on page 11. Furthermore, we included the study of Ochs et al showing that the DSCT of the third generation is able to provide diagnostic image quality independent of heart rate and heart rhythm (doi: 10.1007/s00392-017-1077-2). Patients were referred for coronary CTA by their attending physicians considering their symptoms, cardiovascular risk profiles, and previous examination results. 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. We included these data in the methods and results parts. Furthermore, we added the figure showing the age distribution of the study population, which was initially proposed to reviewer 3. To give the reader an even better understanding of the study population, the age comparison between genders was added as well. We included the data on the image quality assessment, which were initially only given in the response letter, in the manuscript.