

Heart rate-reducing therapy with add-on ivabradine and bisoprolol before coronary computed tomographic angiography in a fast-track ambulatory setting

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Abstract

Objective: This study was performed to determine whether add-on oral ivabradine in patients treated with beta blockers 1 hour before coronary computed tomographic angiography (CCTA) is effective in lowering the heart rate and thus improving CCTA quality.

Methods: In this single-center cohort study, the data of 294 patients referred for ambulant CCTA were retrospectively screened. Patients with an initial heart rate of ≥ 75 bpm ($n = 112$) were pretreated with either a combination of bisoprolol and ivabradine or with bisoprolol alone.

Results: During the scan, there was no difference in heart rate between the two groups. Likewise, there was no significant difference in additionally administered intravenous bradycardic agents, the number of motion artifacts, or the radiation dose. Both drug regimens were tolerated well.

Conclusion: Additive oral ivabradine 1 hour before CCTA does not result in a further reduction of the heart rate. Consequently, neither movement artifacts nor radiation dose can be reduced. Therefore, pretreatment with ivabradine does not seem reasonably appropriate in an outpatient clinical setting with short patient contact.

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Keywords

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Introduction

Coronary computed tomographic angiography (CCTA) has emerged in recent years as a promising noninvasive cardiac imaging test for the assessment of patients with suspected coronary artery disease (CAD).¹ Because it is the most sensitive of all non-invasive diagnostic imaging tests for detection of CAD in patients with stable angina,² and because of its high negative predictive value (close to 100%),³ CCTA has become an important technique for both detecting and ruling out CAD. It is mainly used in outpatient settings with short-term, single-patient contact.

CCTA prevents the need for invasive procedures if significant CAD is ruled out;⁴ however, CCTA has not been adequately developed for complete replacement of invasive coronary angiography as a diagnostic examination method. With the implementation of 64-multislice computed tomography (CT), image resolution has improved; however, the coronary arteries of some high-risk patients still cannot be imaged precisely enough to attain a definite diagnosis.^{5,6} Because the main limiting factors are tachycardia and motion artifact, a stable and low heart rate is strongly recommended to achieve the best possible image quality.^{3,7,8}

A heart rate of 65 bpm is usually recommended before starting CCTA. If required, a short-acting beta blocker or other heart rate-reducing agents can be administered⁹ since the target heart rate of 65 bpm cannot be achieved in all patients with beta blockers alone. Various studies have shown the successful use of ivabradine

alone or in addition to beta blockers before CCTA; however, the required dose of either drug was higher than tested in large, pivotal trials or the time from drug administration to imaging was several hours to days and therefore unsuitable for an outpatient fast-track setting.^{10–15} A recent meta-analysis on CCTA pretreatment revealed a higher percentage of achieving heart rates of <65 bpm with ivabradine than with beta blockers.¹⁶ Therefore, the use of ivabradine, an inhibitor of the I_f channel of the sinus node, might be an alternative option for patients in sinus rhythm¹⁷ before CCTA.

The aim of the present study was to determine whether the combination of orally administered bisoprolol and ivabradine only 1 hour before the scan within a fast-track ambulatory setting resulted in superior CCTA quality due to a lower heart rate during the scan. Quality was assessed by the number of artifacts, the radiation dose, and the use of additional intravenous beta blocker.

Materials and methods

Heart-rate lowering treatment before CCTA has changed at our center from bisoprolol alone to a combination of bisoprolol and ivabradine. In this study, we compared patients treated before this protocol change to those treated with the new protocol. Because this was a retrospective analysis, an intention-to-treat approach was not used. We analyzed the data of patients who were referred to our center for CCTA and had heart rates of >75 bpm. Patients

pretreated with only a single dose of bisoprolol were compared with patients pretreated with single doses of bisoprolol and ivabradine. These drugs were given to the patients in the waiting room by the medical staff of the center 1 hour before the scan. Patients excluded because of a heart rate of ≤ 75 bpm showed no significant differences in age, sex, hypertension, diabetes, nicotine abuse, dyslipidemia, known CAD, or family history of CAD compared with patients included in the study.

CCTA protocol

The medical history, heart rate, and blood pressure were taken for all patients in both groups 1 hour prior to CCTA. If their heart rate was ≥ 75 bpm, the patients immediately received premedication. Patients in the treatment group received 10 mg of bisoprolol and 7.5 mg of ivabradine orally. Patients in the control group received only 10 mg of bisoprolol orally.

CCTA was performed in all patients using a Somatom Sensation Cardiac 64 CT system (Siemens, Munich, Germany), and archived maximum intensity projection (MIP) files were assessed with Syngo Plaza software (Siemens Healthcare, Erlangen, Germany). The time windows used were the mid-to-end diastolic phase (60%–80% of the R–R interval).

The heart rate during CCTA was assessed and monitored. For the assessment of motion artifacts, streak artifacts were counted by a blinded person not involved in the routine analysis of the scan using an MIP reconstruction file.

The difference in the heart rate during scan acquisition between the groups (control vs. treatment) was assessed as the primary outcome. The differences in the radiation dose, motion artifacts, and heart rate changes were assessed as the secondary outcomes using linear mixed models. Use of an additional intravenous beta blocker to

further reduce the heart rate was also tested. The normality assumption was visually checked by Q–Q plots. A nonparametric equivalent, executed by applying the SAS macro “npar,” was also used in case the normality assumption was violated.^{10,18} The covariance type of the linear mixed model was selected based on a likelihood ratio test (homogenous vs. heterogeneous variance between the groups). Statistical analysis between the two groups was performed using Statistical Analysis Software version 9.2 (SAS Institute Inc., Cary, NC, USA).

This study was approved by the local ethics board, which waived the requirement for written informed consent because of the retrospective study design. The study is registered at clinicaltrials.gov with the number NCT02764970.

Results

Of 294 consecutive patients referred to our center for CCTA, 112 presented with heart rates >75 bpm and were therefore eligible for the study. In total, 47 (32%) patients were pretreated with only a single dose of bisoprolol and 65 (44%) were pretreated with single doses of bisoprolol and ivabradine. A flow chart of the study population is shown in Figure 1, and the baseline characteristics of the patients are shown in Table 1.

To confirm the assumption that an elevated heart rate during the CT scan results in impaired scan quality as measured by the increased number of artifacts and higher exposure to radiation, we correlated these parameters as shown in Figure 2. There was a strong correlation between heart rate and the number of artifacts. The correlation was present using the initial baseline heart rate upon arrival at the center ($p = 0.006$) (Figure 2(a)) and became stronger when calculated using the heart rate measured during the CT scan ($p < 0.0001$)

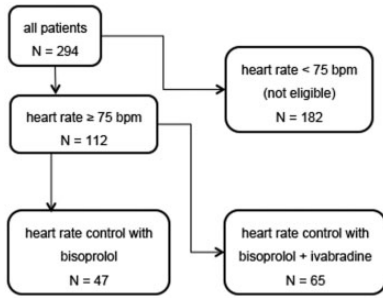


Figure 1. Flow chart of study population.

Table 1. Patients' characteristics.

	Overall	Controls	Treatment	p for trend
Patients	112	47	65	
Age, years	61 ± 11	63 ± 10	60 ± 11	0.14 (A)
Male sex	63 (56)	24 (51)	39 (60)	0.09 (F)
Hypertension	63 (56)	31 (65)	32 (49)	0.47 (F)
Diabetes	12 (11)	4 (9)	8 (12)	0.34 (F)
Nicotine abuse	34 (30)	11 (23)	23 (35)	0.07 (F)
Dyslipidemia	50 (38)	27 (57)	23 (35)	0.14 (F)
Known CAD	7 (6)	1 (2)	6 (9)	0.12 (F)
Family history of CAD	55 (49)	23 (49)	32 (49)	0.46 (F)

Data are presented as n, n (%), or mean ± standard deviation. CAD, coronary artery disease. A = ANOVA; F = Fisher Exact Test.

(Figure 2(b)). Figure 2(c) and (d) depict the correlation between the heart rate and radiation dose. There was a significant correlation between the scan heart rate and radiation dose ($p = 0.0018$), but no correlation between the baseline heart rate and radiation dose (Figure 2(c) and (d)).

To analyze differences between the control and treatment groups, 47 patients received 10 mg of oral bisoprolol for heart rate reduction and 65 patients received a combination of 10 mg of oral bisoprolol and 7.5 mg of oral ivabradine.

Statistical analysis of the heart rate reduction showed no significant difference between the treatment and control groups (treatment group: 84.1 ± 6.7 bpm before

medication and 65.1 ± 9.8 bpm after medication, 19.0 bpm; control group: 80.7 ± 5.1 bpm before medication and 62.7 ± 9.1 bpm after medication, 18.0 bpm) (Figure 3(a)), indicating a lack of an additive frequency-reducing effect of ivabradine. Moreover, subgroups differentiated by sex (male: 63.8 ± 10.3 bpm vs. female: 64.4 ± 8.7 bpm) or age (≤ 60 years: 63.5 ± 9.2 bpm vs. ≥ 60 years: 64.6 ± 9.9 bpm) revealed no significant differences (Figure 3(b) and (c)).

Because some patients still had elevated heart rates immediately before the scan, they were further treated with 5 to 25 mg of metoprolol intravenously. Neither the number of patients (19 of 65 in the treatment group and 17 of 47 in the control group) nor the amount of additionally added intravenous beta blocker (13.9 ± 5.4 mg and 11.2 ± 5.5 mg, respectively) was significantly different between the two groups (Figure 4(a)).

Although these patients received an additional beta blocker, the number of artifacts ($r = 0.30$, $p < 0.01$), radiation dose ($r = 0.17$, $p = 0.08$), and heart rate ($r = 0.36$, $p < 0.001$) were positively correlated with the amount of additional intravenous metoprolol (Figure 4(b)–(d)). In addition, despite the more intense treatment, the heart rate during the examination was higher in patients who received the additional beta blocker than in patients on oral medication only (69.2 ± 7.8 vs. 61.9 ± 9.2 bpm, $p < 0.001$) (Figure 4(e)).

None of the patients in the study had any symptoms (such as dizziness, fainting, or a severe drop in blood pressure) that would have required any further medical treatment.

Discussion

This study underlines the clinical value of low heart rates during CCTA because the scan quality deteriorates and radiation increases with higher heart rates. In this

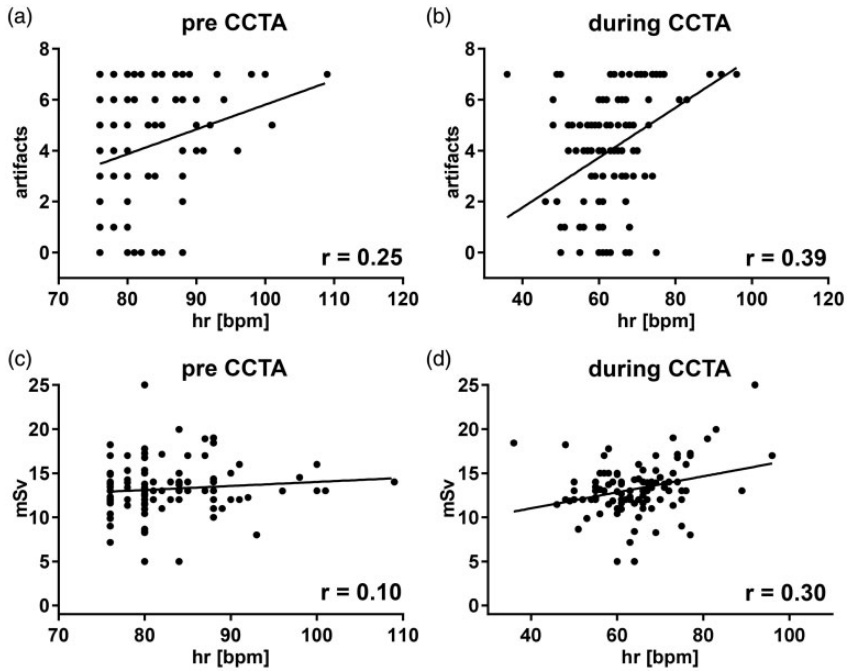


Figure 2. Impact of heart rate on (a, b) the number of artifacts and (c, d) the radiation dose. CCTA, coronary computed tomographic angiography; HR, heart rate.

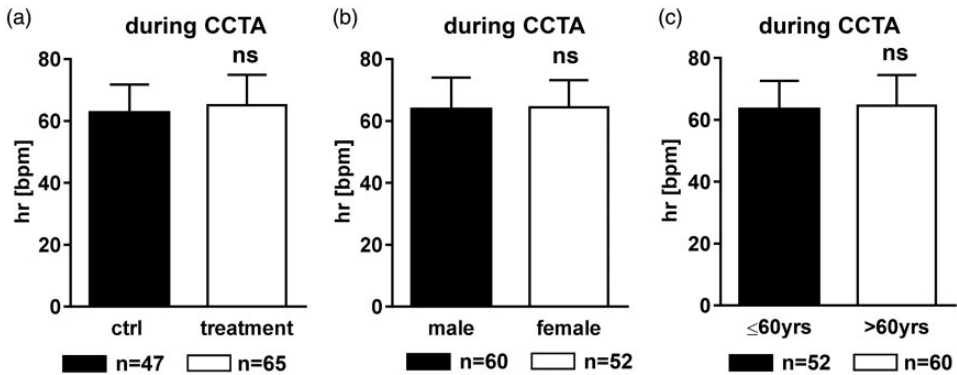


Figure 3. Heart rate during scan in (a) control vs. treatment, (b) male vs. female, and (c) patients aged ≤ 60 vs. >60 years. HR, heart rate; CCTA, coronary computed tomographic angiography; Ctrl, Control.

study, however, we have demonstrated that 7.5 mg of oral ivabradine as an add-on to baseline beta-blocker treatment 1 hour before CCTA is not sufficient to

significantly reduce the heart rate. No subsequent changes in motion artifacts or the radiation dose were observed with this additional therapy.

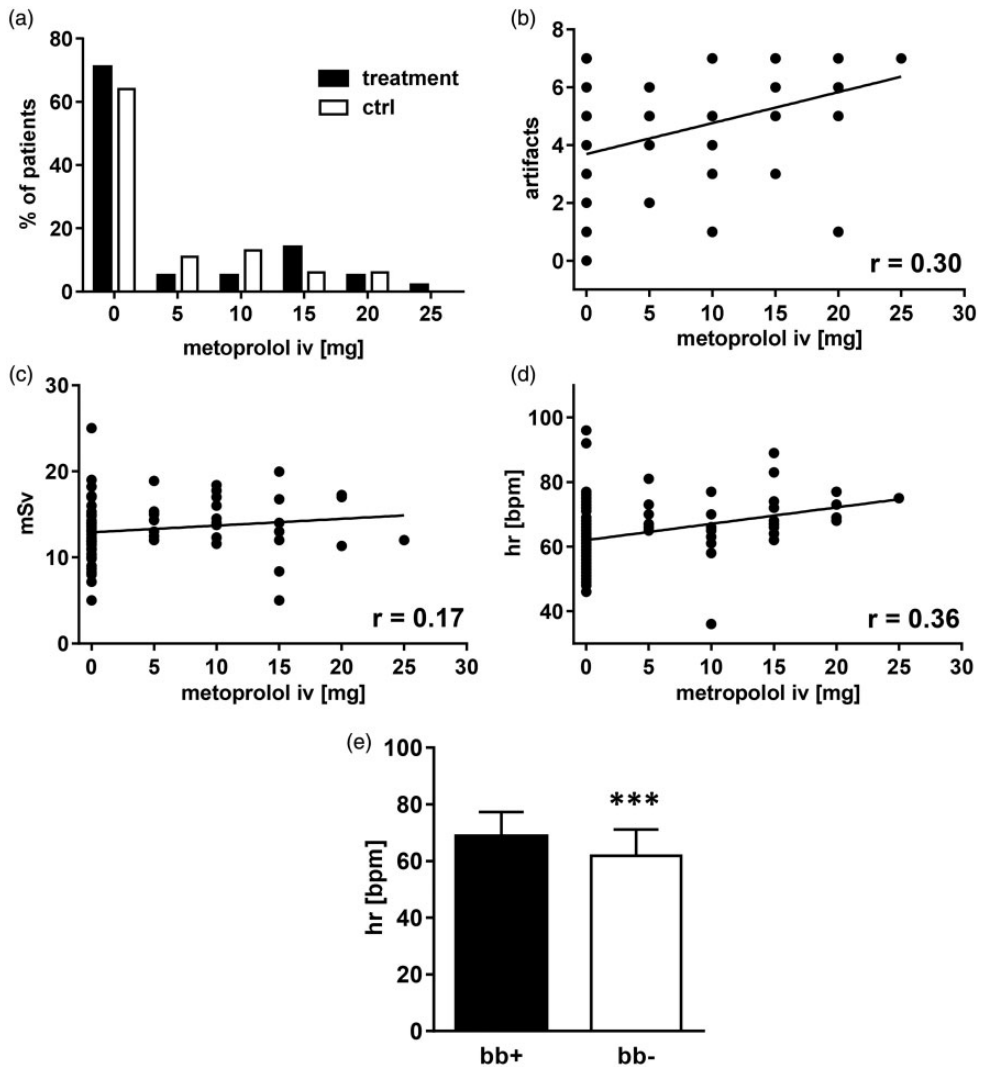


Figure 4. Additional administration of metoprolol. (a) Used dose. (b) Correlation with artifacts. (c) Correlation with radiation dose. (d) Correlation with heart rate. (e) Heart rate in patients with/without additional intravenous use of beta blockers. iv, intravenous; HR, heart rate; BB, beta blocker.

Heart rate

Because previous studies and a recent meta-analysis have shown the effectiveness of ivabradine as a heart rate-lowering therapy before CCTA, other confounding factors need to be considered, such as the time from oral administration to CCTA and the dosage used.

Previously, only high doses (20 mg) of ivabradine resulted in significant heart rate reduction if administered 2 hours before the scan. In contrast, single doses of 5 or 10 mg did not significantly reduce the heart rate.¹¹ Notably, the decline in heart rate with 20 mg of ivabradine was associated with a considerable decrease in systolic blood pressure, despite the fact that ivabradine is

considered to be a specific I_f channel inhibitor that does not affect blood pressure. Significant decreases in blood pressure, however, might imply the need for continuous blood pressure monitoring, which does not seem feasible in an ambulatory fast-track setting.

Slightly lower doses of 10 or 15 mg of ivabradine before CCTA have been shown to be sufficient to achieve a significant heart rate reduction.¹⁴ However, compared with our study, higher single doses of ivabradine were administered (10 or 15 mg vs. 7.5 mg in our study), and a longer period from drug administration to the CCTA scan (2.5 vs. 1 hour) was used. The finding of a significant reduction of heart rate in patients who received oral ivabradine in doses proven to be safe in larger clinical trials (5 mg or 7.5 mg) twice daily 1 day prior to CCTA supports the importance of the time duration from drug administration to the scan. Moreover, ivabradine was able to significantly reduce the dose of intravenously administered beta blockers required to achieve the target heart rate of 65 bpm during the scan.¹² Lower oral and intravenous beta-blocker doses were also achieved in a recent dose-adjusting approach using ivabradine in a prospective and randomized open-label study.¹⁵

Motion artifacts

During the cardiac cycle of contraction and relaxation, CCTA scans are taken at the end of diastole when myocardial movement is minimal. Slow and stable heart rates enable scan acquisition without motion artifacts. Because the heart rate was not altered after ivabradine treatment compared with the control group, we did not observe differences in the number of motion artifacts between the groups. However, there was a correlation between the heart rate and the number of artifacts calculated for all patients and a positive

correlation between artifacts and the use of an intravenous beta blocker immediately before the scan, emphasizing the role of heart rate reduction in patients undergoing CCTA. Breathing, gross body movement, or heart rate irregularity⁸ can also lead to misalignment artifacts. However, the number of misalignment artifacts is not necessarily a measurement of the evaluability and or accuracy of CCTA if MIP reconstructions are used.

Radiation dose

Lower heart rates facilitate the use of flash sequences with a reduced radiation dose and are likely to reduce motion artifacts that can lead to non-analyzable scans that need to be repeated and thus result in additional radiation doses. Because no differences in heart rate were detectable in this study, we did not observe differences in the radiation dose between the two groups.

In addition to the scan protocol, patient characteristics such as height and weight as well as the field of view used for the scan play a role in the radiation dose.¹⁹ In the present study, however, only a weak and non-significant correlation between the body mass index and radiation dose was found (correlation coefficient of 0.132).

The relatively large field of view, which included the central parts of the lungs, partially explains the higher radiation doses in the present study than in most other studies. With the algorithm used, incidental findings besides the coronary arteries were reported for 15% of the patients. A pulmonary nodule was reported in nine patients, supporting the statement from the National Lung Screening Trial Research Team America that patients with a high risk of pulmonary cancer benefit from CCTA because the scan can be used for screening.²⁰

Safety

No adverse effects of ivabradine were documented during the evaluation period. This supports the thesis that a single dose of 7.5 mg of ivabradine is safe,^{11,14,21} as previously reported in a comparable setting for ivabradine in combination with and without beta blockers.¹⁴ In that study, none of the patients exhibited significant blood pressure changes and only one patient developed severe bradycardia.

In conclusion, the combination of ivabradine and bisoprolol before CCTA is safe but does not provide additional benefits over a beta blocker alone. It is not effective for a clinical fast-track ambulatory setting with a 1-hour period between the arrival of the patient and the CT scan. Therefore, it cannot be recommended as a clinical standard for heart rate control before CCTA in this setting.

Declaration of conflicting interests

The authors declare that they have no conflict of interest.

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References

1. Budoff, MJ, Dowe D, Jollis JG, et al. Diagnostic performance of 64-multidetector row coronary computed tomographic angiography for evaluation of coronary artery stenosis in individuals without known coronary artery disease: results from the prospective multicenter ACCURACY (Assessment by Coronary Computed Tomographic Angiography of Individuals Undergoing Invasive Coronary Angiography) trial. *J Am Coll Cardiol* 2008; 52: 1724–1732.
2. Windecker, S, Kolh P, Alfonso F, et al. 2014 ESC/EACTS guidelines on myocardial revascularization. *EuroIntervention* 2015; 10: 1024–1094.
3. Mollet, NR, Cademartiri F, van Mieghem CA, et al. High-resolution spiral computed tomography coronary angiography in patients referred for diagnostic conventional coronary angiography. *Circulation* 2005; 112: 2318–2323.
4. Paech DC and Weston AR. A systematic review of the clinical effectiveness of 64-slice or higher computed tomography angiography as an alternative to invasive coronary angiography in the investigation of suspected coronary artery disease. *BMC Cardiovasc Disord* 2011; 11: 32.
5. Vanhoenacker PK, Heijenbrok-Kal MH, Van Heste R, et al. Diagnostic performance of multidetector CT angiography for assessment of coronary artery disease: meta-analysis. *Radiology* 2007; 244: 419–428.
6. Wehrschuetz M, Wehrschuetz E, Schuchlenz H, et al. Accuracy of MSCT coronary angiography with 64 row CT scanner-facing the facts. *Clin Med Insights Cardiol* 2010; 4: 15–22.
7. Ropers U, Ropers D, Pflederer T, et al. Influence of heart rate on the diagnostic accuracy of dual-source computed tomography coronary angiography. *J Am Coll Cardiol* 2007; 50: 2393–2398.
8. Leipsic J, Abbara S, Achenbach S, et al. SCCT guidelines for the interpretation and reporting of coronary CT angiography: A report of the Society of Cardiovascular Computed Tomography Guidelines Committee. *J Cardiovasc Comput Tomogr* 2014; 8: 342–358.
9. Task Force Members, Montalescot G, Sechtem U, et al. 2013 ESC guidelines on the management of stable coronary artery disease: the Task Force on the management of stable coronary artery disease of the European Society of Cardiology. *Eur Heart J* 2013; 34: 2949–3003.
10. Akritas MG and Politis DN. *Recent advances and trends in nonparametric statistics.*

- 1st ed. Amsterdam, The Netherlands, San Diego, CA: Elsevier, 2003, p. x, 512.
11. Jiang J, Tian L, Huang Y, et al. Pharmacokinetic and safety profile of ivabradine in healthy Chinese men: a phase I, randomized, open-label, increasing single- and multiple-dose study. *Clin Ther* 2013; 35: 1933–1945.
 12. Lambrechtsen J and Egstrup K. Pre-treatment with a sinus node blockade, ivabradine, before coronary CT angiography: a retrospective audit. *Clin Radiol* 2013; 68: 1054–1058.
 13. Adile KK, Kapoor A, Jain SK, et al. Safety and efficacy of oral ivabradine as a heart rate-reducing agent in patients undergoing CT coronary angiography. *Br J Radiol* 2012; 85: e424–e428.
 14. Celik O, Atasoy MM, Erturk M, et al. Comparison of different strategies of ivabradine premedication for heart rate reduction before coronary computed tomography angiography. *J Cardiovasc Comput Tomogr* 2014; 8: 77–82.
 15. Kacijan, B, Novak Z, Jug B, et al. Heart-rate reduction with adjusted-dose ivabradine in patients undergoing coronary computed tomographic angiography: a randomized trial. *J Comput Assist Tomogr* 2017; 41: 360–363.
 16. Qiu S, Shi S, Ping H, et al. Efficacy of ivabradine versus beta-blockers for heart rate reduction during computed tomography coronary angiography: a meta-analysis of randomized controlled trials. *Cardiology* 2016; 135: 133–140.
 17. DiFrancesco D. The role of the funny current in pacemaker activity. *Circ Res* 2010; 106: 434–446.
 18. Brunner E, Domhof S and Langer F. *Nonparametric analysis of longitudinal data in factorial experiments*. Wiley series in probability and statistics. 2002, New York, NY: J. Wiley, p. xvii, 261.
 19. Hausleiter J, Meyer T, Hermann F, et al. Estimated radiation dose associated with cardiac CT angiography. *JAMA* 2009; 301: 500–507.
 20. National Lung Screening Trial Research Team, Aberle DR, Adams AM, et al. Reduced lung-cancer mortality with low-dose computed tomographic screening. *N Engl J Med* 2011; 365: 395–409.
 21. Bayraktutan U, Kantarci M, Gundogdu F, et al. Efficacy of ivabradin to reduce heart rate prior to coronary CT angiography: comparison with beta-blocker. *Diagn Interv Radiol* 2012; 18: 537–541.