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Examining the prevalence of left atrial appendage thrombus in a cohort of acute stroke patients with an extended CT angiographic protocol

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Abstract

Introduction: Current guidelines recommend transthoracic echocardiography (TTE) for routine screening of cardiac emboli, however the visualisation of the left atrial appendage (LAA) where the thrombi are commonly found is poor. Transesophageal echocardiography (TEE) would provide better detectability of LAA thrombus, but it is time-consuming and semi-invasive method. Extending non-gated carotid computed tomography angiography (CTA) examination to the LAA could reliably detect thrombi, and could also aid treatment and secondary prevention of stroke.

Methods: We extended the CTA scan range of acute stroke patients 4cm below the carina to include the left atrium and appendage. During the review we evaluated LAA thrombi based on contrast relations. We then used gradient boosting to identify the most important predictors of LAA thrombi from a variety of different clinical parameters.

Results: We examined 240 acute stroke patients' extended CTA scans. We detected LAA thrombi in eleven cases (4.58%), eight of them had atrial fibrillation. 23.75% of all patients (57 cases) had recently discovered or previously known atrial fibrillation. Windsack morphology was the most commonly associated morphology with filling defect on CTA. According to the gradient-boosting analysis, LAA morphology showed the most predictive value for thrombi.

Conclusion: Our extended CTA scans reliably detected LAA thrombi even in cases where TTE did not, and showed that two patients' LAA thrombus would have been untreated based on electrocardiogram (ECG) monitoring and TTE. We also showed that the benefits of CTA outweigh the disadvantages arising from the slight amount of excess radiation.

Keywords:

Cardioembolic Stroke, CT angiography, Atrial Appendage

Introduction

Ischemic stroke is a major cause of disability and death worldwide, with a significant impact on public health. According to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification, ischemic stroke can be categorized into five subtypes based on their etiology: large artery atherosclerosis, cardioembolism, small vessel occlusion, stroke of other determined etiology, and stroke of undetermined etiology [1]. Large artery atherosclerosis accounts for approximately 15-20% of all ischemic strokes, while cardioembolic stroke represents 20-30% of all cases. Small vessel occlusion and stroke of other determined etiology are less frequent, accounting for 20-25% and 5-15% of all ischemic strokes, respectively. The remaining cases, which cannot be attributed to any specific cause, are classified as "stroke of undetermined etiology" or "unknown subtype". According to earlier studies, this latter „unknown" or „undetermined" subtype can account for up to 26-42% of all ischemic strokes [2–6]. Since the cause of stroke remains unknown in the majority of the cases, it is vital to develop new methods or establish novel biomarkers that can facilitate and improve the diagnostic process, so that treatment and secondary prevention can be more effective. It could be further elaborated that a significant proportion of strokes with an undetermined etiology may actually be cardioembolic, but they are difficult to detect due to the limitations of current diagnostic methods. For instance, detecting paroxysmal atrial fibrillation (AF) can be challenging, as it may be present intermittently and not during the time of diagnostic testing. In addition, imaging techniques such as computed tomography (CT) and echocardiography may not provide sufficient information to identify the source of the stroke. Moreover, there is a possibility that the thrombus in the heart could have dissolved either spontaneously or due to thrombolytic therapy, making it difficult to detect. Therefore, the development of more sensitive and specific diagnostic tools, for example advanced imaging techniques, could significantly improve the detection and secondary prevention of cardioembolic strokes.

Based on a recent study [7] we have used an extended version of the non-gated carotid CTA scan in our stroke protocol for the patients who have been admitted to the ER with symptoms of acute stroke. Our objective with this study is to assess the percentage of ischemic stroke in the Eastern European population that can be attributed to thrombi originating from the LAA. From the acquired database we also try to establish clinical features that have the highest risk for developing thrombi in the LAA.

Materials & Methods

All participants provided their written informed consent according to the Declaration of Helsinki and the Scientific and Research Ethics Board of the Medical Research Council Hungary has approved all experimental protocols (BMEÜ/4381- 1 /2022/EKU). All research was performed in accordance with relevant guidelines and regulations.

All authors have contributed equally to the conceptualisation of the study. S.I.A. has prepared the initial draft of the manuscript, which was then revied by all the other authors.

Image acquisition & evaluation

In our prospective study we have included patients who had been referred to the emergency department of Albert Szent-Györgyi Clinical Center, University of Szeged between September 2021 and August 2022 with symptoms of acute stroke. They underwent multimodal CT evaluation for reperfusion therapy based on our stroke protocol, which included non-contrast CT; non-gated, single-phase CTA (from LAA to vertex, for details see below); and CT perfusion if outside the time window for thrombolysis (4.5-9 hours after symptom onset) or mechanical thrombectomy (6-24 hours after symptom onset). We have altered the angiography scan of this protocol according to Senadeera et al. [7] by extending the scan-range 4 cm below the carina to visualise the LAA (Figure 1). Patients were examined by either a GE EVO Revolution 64 slice or a Philips iCT 256 slice scanner with helical scanning mode. Scan parameters for the Philips scanner were set to the following: 0.33s rotation time, 128x0.625mm collimation, 100kV tube potential, 0.763 pitch, 244mA tube current. Angiographic scans were obtained using 15ml Xenetix 350 (Guerbet) at a flow rate of 2,5 ml/s followed by 45ml Xenetix 350 at a flow rate of 4ml/s, then 20ml saline chaser at a flow rate of 4ml/s. Threshold for automatic bolus tracking was set to 150 Hounsfield Units (HU) in the aortic arch. An iterative reconstruction algorithm was chosen (iDose^4) to reconstruct the data with 0.9mm slice thickness in a 512x512 matrix. The data was then automatically transferred to our

Picture Archiving and Communication System (PACS). Scan parameters for the GE scanner were set to the following: 0.5s rotation time, 64x0.625mm collimation, 100kV tube potential, 0.984 pitch. Tube current was adjusted automatically, using Auto mA and Smart mA with a current range of 150-400 mA and a reference noise index of 12. Angiographic scans were obtained using 60ml Omnipaque 350 (GE Healthcare) at a flow rate of 4 ml/s. Threshold for automatic bolus tracking was set to 100 HU in the aortic arch. An iterative reconstruction algorithm (ASiR-V) was chosen to reconstruct the data with 0.625mm slice thickness in a 512×512 image matrix and data was automatically transferred to our PACS.

Two experienced radiologists (Z.T.K., R.K.) have reviewed the scans and evaluated LAA thrombi, and a third radiologist was invited, had there been any disagreements. Only scans from patients with ischemic stroke were assessed, irrespective of having large vessel occlusion or not. Thrombi were evaluated according to Senadeera et al.:

- Positive: A well-defined ovoid/round LAA filling defect not caused by motion artifact or atrial trabeculae, which has a HU < 100.
- Indeterminate: Not fulfilling either positive or negative criteria
- Negative: LAA completely opacifies with contrast medium, with the exception of changes that can be explained by motion artifact or atrial trabeculae.

Example images for all categories are shown in Figure 2.

Clinical data collection

S.I.A. and N.Sz. have collected patient demographics and clinical data with special emphasis on the result of 24 hour ECG monitoring during hospitalisation, the result of the TTE and TEE (if it was performed), anticoagulation therapy and related lab tests at admission, NIHS score at admission and at discharge [8] , CHADS-VASc score [9], pre stroke and 90 day modified Rankin score [10,11], and Alberta Stroke Programme Early CT (ASPECT) score [12] on the non-enhanced CT. We have also assessed the morphology of the LAA and have categorised it according to Di Biase et al. and Yaghi et al. [13,14]. The patency of the intra- and extracranial vessels, plaque morphology and degree of stenosis have also been evaluated on the CTA scan.

To measure excess radiation received by the patients, total dose length product (DLP) was calculated and extracted from the scanners.

Inclusion & exclusion criteria, data quality control

In our study we have included patients with age of at least 18 years, who had been referred to the Department of Neurology, Emergency Outpatient Clinic with symptoms of acute stroke withing 24 hours of onset and CTA was indicated due to suspected large vessel occlusion. We have also retrospectively identified and included a group of patients who had been scanned according to a previous, non-extended CTA protocol, which started from the aortic arch in order to assess excess radiation resulting from the extension of the scan.

Exclusion criteria were pregnancy and prior allergyform reaction for contrast medium. In these cases magnetic resonance imaging (MRI) and MR angiography was performed according to the local protocol.

Those patients, whose scan range did not reach the desired height, and whose examinations revealed other conditions that could have caused their initial symptoms (e.g., epilepsy, cerebral neoplasm or excessive alcohol or drug intake) had been excluded from the study. Inclusion and exclusion criteria were conceptualised by S.I.A., N.Sz. and P.K.

Statistical analysis

Next to descriptive statistics, we have analysed patient clinical data using the R implementation of extreme gradient boosting[15] to identify the most important predictors of LAA thrombus formation. Boosting works by iteratively building short decision trees, each trained on the errors of the previous decision tree. With this approach, progressively better decision trees are constructed over each iteration by combining weaker models to collectively build a strong model. In gradient boosting this process is formalised as a gradient descent algorithm over an objective funtcion, which leads to a more accurate description of the dataset. We used RStudio version 2022.12.0+353 (R version 4.2.2 [16]) to write the code used in the analysis. The following R packages were used: *xgboost*[17], *readxl*[18]. After importing the data we used the xgboost() function to build a model with the following settings: objective='reg:linear', nrounds=100, max_depth=5, eta=0.3. Importance values were extracted from the model, which were then used to create a variable importance plot (Figure 3).

To estimate excess radiation, we have performed a two-sample t-test in R between two groups of patients: those who had been scanned using the conventional low-dose protocol and those who had been scanned according to the new extended protocol. Statistical significance level was set at α=0.05. The statistical methods were conceptualised by S.I.A. and reviewed by Z.T.K., P.K. and R.K. Analysis were carried out by S.I.A. and R.K. Visualisation was done by S.I.A.

Results

We have examined a total number of 294 patients, who had been referred to the emergency room with symptoms of acute stroke. Closer examination revealed that 48 of these patients had other conditions that caused symptoms similar to that of stroke (e.g., epilepsy, cerebral neoplasm or excessive alcohol or drug intoxication), and so they were excluded from the study. Peer review of the CTA scans to detect LAA thrombi had yielded 'indeterminate' result in 6 cases, which were also excluded from our study.

Demographics

The demographics and basic clinical data of the remaining 240 cases are summarised in Table 1. 57 patients had been diagnosed with atrial fibrillation, and 22 of these (38.6%) were newly discovered (i.e., during their hospitalisation).

LAA thrombi

We have found thrombi in the LAA in 11 cases (4.58%), whose majority were found in LAAs with windsock morphology. 8 of these 11 patients (72.7%) had been diagnosed with AF, and 2 of these were newly discovered (25%). In total 28 patients had received anticoagulant therapy: 19 had received direct oral anticoagulant, 2 had received LMWH, and 7 had received vitamin-K antagonist according to their clinical reports. Of the 35 patients with known atrial fibrillation 22 (62.85%) were on anticoagulant therapy (16 had received direct oral anticoagulant, 2 had received LMWH, and 4 had received vitamin-K antagonist). Among patients *without* LAA thrombi 23 patients were under anticoagulation therapy (direct oral anticoagulant: 15, vitamin-K antagonist: 7, low molecular witght heparin: 1) and 55 were under antiaggregation therapy (acetylsalicylic acid: 30, clopidogrel: 18, both: 7). Two of these patients received both anticoagulant and anticoagulation therapy. Among patients *with* LAA thrombi two received anticoagulant therapy and four were under anticoagulation therapy prior to the examination. We also examined the morphology of the left atrial appendage (LAA) in individuals with identified LAA thrombus, discovering that in most instances (54.5%), thrombi were present in LAAs with "windsock" morphology. Moreover, a significant proportion of patients with LAA thrombus (72.7%) were found to have either previously diagnosed or newly discovered atrial fibrillation.

Predictors of thrombus formation

Our gradient boosting-based analysis showed that the morphology of the LAA has the best predictive value for thrombus formation. The complete list of predictors is depicted in Figure 4.

Excess radiation

The extended group received higher radiation dose on average. This difference, according to a two-sample t-test revealed statistically significant excess radiation in the 'Extended' group (Total DLP: 1191.6 ± 241.94 vs 1294.58 ± 192.34 mGy*cm^2, p<0.001). The plots resulting from the two-sample t-test are shown in Figure 4.

Discussion

In this prospective study we used an extended version of the carotid CTA scan of our stroke imaging protocol to assess the occurrence of thrombi in the left atrial appendage in acute stroke patients. We found the cause of stroke, is thrombus in the LAA in 4.58% of stroke patients, which is in accordance with a previous study[7]. We found that the LAA morphology had the highest predictive value for LAA thrombus formation. The amount of excess radiation received by patients that results from the extension of the CTA protocol to the LAA level, was statistically higher, but considering the clinical benefit, probably neglectable.

Ischemic stroke is one of the most common causes of disability in developed countries worldwide. The underlying etiology in most ischemic stroke cases remains unknown, although in some cases cardiac origin is discovered. According to the most recent guideline [19] prolonged electrocardiogram (ECG) monitoring along with the use of echocardiography are recommended for the diagnostic workup of cryptogenic stroke to help identify the source of emboli or cardiac abnormalities, such as atrial fibrillation as soon as possible.

Prolonged ECG monitoring can detect intermittent or paroxysmal atrial fibrillation, which is present in 25% of patients with ischemic stroke and it is associated with a fivefold increased risk of stroke [20]. Although relatively common, it can be missed during a shorter duration ECG monitoring [21].

Echocardiography, which is usually transthoracic echocardiography can detect potential sources of embolism, such as atrial or ventricular thrombi, patent foramen ovale, or atrial septal defects, although the visualisation of the LAA where the thrombi are commonly found is poor [22]. Transoesophageal echocardiography is a highly accurate and sensitive method that can provide better visualisation of the LAA (and potential thrombi within). It is considered the gold standard for detecting thrombi in the LAA; however, it is an invasive method which requires sedation of the patient, and it is also relatively time-consuming [23].

ECG-gated CTA can provide high-resolution images of the heart, including the left atrial appendage, potentially allowing for the detection of embolic sources, such as thrombi [24]. However, ECG-gating is not easy to accomplish, and it is not always feasible, especially in an emergency situations such as stroke, where the elapsed time between the first imaging step and the initial therapy is critical.

In our study we used an extended version of the non-gated CT angiography scan of our stroke protocol according to Senadeera et al [7]. Using this extended method, we were able to detect thrombi in the LAA in 11 cases, most of which were found in LAAs with windsock morphology. Atrial fibrillation was detected in eight cases, which was discovered during hospitalisation in two of them.

Our analysis based on extreme gradient-boosting [15] showed that the top 3 predictive factors were LAA morphology, serum Troponine T level and CHADS-VASC score. In a recent study the authors used a similar, GBM-based approach and have found that BNP, LAA width, CRP, Fibrinogen and eGFR are closely related to the risk of LAA thrombosis in nonvalvular atrial fibrillation [25].

Thrombus formation in the LAA is influenced by several factors, including LAA morphology. A multicenter study revealed significant correlation between LAA morphological types and the prevalence of stroke in patients with atrial fibrillation[26]. This association can be attributed to the impact of LAA shape and structure on blood flow velocity. Specifically, certain LAA morphologies, such as larger, more complex, or trabeculated appendages (referred to as non-chickenwing morphologies), are linked to decreased blood flow velocity. Consequently, slower blood flow (measuring ≤20cm/s) increases the likelihood of blood stasis, creating an environment favorable for thrombus formation. It should be noted that – in contrast to our investigation – the authors of these studies focused on patients with atrial fibrillation rather than patients with acute stroke, which might refer to different

populations [27–29]. According to Di Biase et al. the distribution of the non-chickenwing morphologies is as follows: cactus 30%, windsock 19%, cauliflower 3%, and the associated stroke or TIA prevalence is 12%, 10% and 18% respectively. According to this the cauliflower morphology, while it is the rarest of morphologies, it has the highest risk of stroke or TIA occurrence. On the other hand, windsock and cactus morphologies are more frequent but are less likely to be associated with cerebrovascular events [26].

In addition, certain clinical biomarkers play a crucial role in predicting LAA thrombus formation. It has been shown by previous studies that markedly elevated levels of Troponin T and pro B-type natriuretic peptide (pro BNP) – which are indicators of cardiac damage and strain – contribute to an increased risk of thrombus formation within the LAA [30–32]. Monitoring of these biomarkers can help identify patients who may require closer surveillance and targeted interventions.

The CHA_2DS_2-VASc score is a widely used clinical risk stratification tool for predicting stroke risk in patients with atrial fibrillation. A recent study has demonstrated that patients with LAA thrombi tend to have elevated CHA_2DS_2-VASc scores [30]

Excess radiation is undoubtedly the biggest pitfall of extending the CTA scan range, however, while it is statistically significant, we argue that the potential clinical benefit gained from the extension (namely the immediate diagnostic result) outweighs this cost.

Our study is not without limitations. We purposely chose not to use ECG-gating as it hinders the diagnostic workflow. However, it is certain that using ECG-gating would significantly improve image quality by reducing the amount of motion artifacts. It is our intention to implement a gating method that is fast enough to be used in the imaging of stroke, while also producing a minimal amount of motion artifacts. Another limitation of our study is the single-phase nature of our scans, meaning that we did not repeat nor have we delayed the scans after initial contrast medium administration. A study on cardiac CT by Spagnolo et al. showed that by delaying the acquisition of the angiographic scan, the amount of false positives can be significantly reduced, and that a delay of 6 minutes after contrast administration could be considered optimised for the diagnosis of LAA thrombi [33]. It is possible that with delayed scanning the number of filling defects – and therefore the number of false positives – could be reduced, however, we believe that with a viable gating method there would be no need to perform additional delayed scans, as they would also prolong the diagnostic process.

Conclusion

In our study we successfully replicated the methods by Senadeera et al in the Eastern-European population and were able to identify the cause of cryptogenic stroke in 4.58% of patients at the first imaging step of stroke diagnosis. Moreover, we showed that, in accordance with previous studies, the morphology of the left atrial appendage predicts thrombus formation the most. We also showed that the extension of the scan range results in statistically higher radiation dose for the patients, however we believe that the diagnostic information gained has more benefit for the patient as well as the clinician.

Therefore we recommend that the extension of the scan range should be considered as part of the routine imaging of stroke since the benefits outweigh the additional risk caused by excess radiation.

Data availability statement

The datasets presented in this article are not readily available because they contain sensitive clinical and personal details; anonymized data will be shared by the corresponding author upon reasonable request, after consideration by the local ethics committee. Requests to access the datasets should be directed to ZK, kincses.zsigmond.tamas@med.u-szeged.hu.

Ethics statement

The Scientific and Research Ethics Board of the Medical Research Council Hungary has approved all experimental protocols in this study (BMEÜ/4381- 1 /2022/EKU). Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

SA: conceptualization, data curation, visualization, software, writing – original draft. NS: conceptualization, data curation, formal analysis. RK: data curation, investigation, validation, writing – review and editing. PK and ZK: conceptualization, funding acquisition, supervision, , resources, writing – review and editing. All authors contributed to the article and approved the final version.

Conflict of Interest

The authors of this manuscript declare no relationships with any companies, whose products or services may be related to the subject matter of the article.

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Word count: 3526

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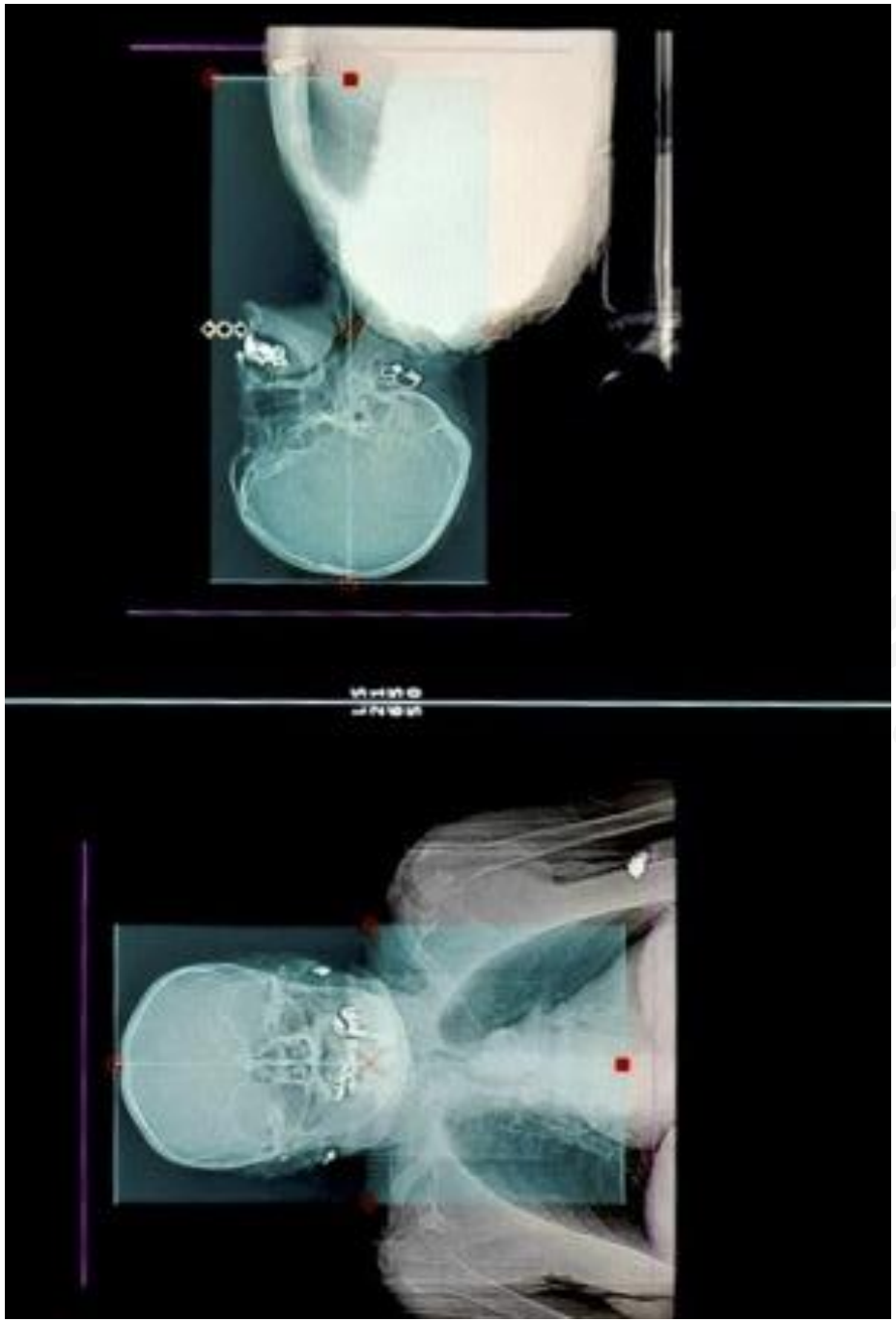
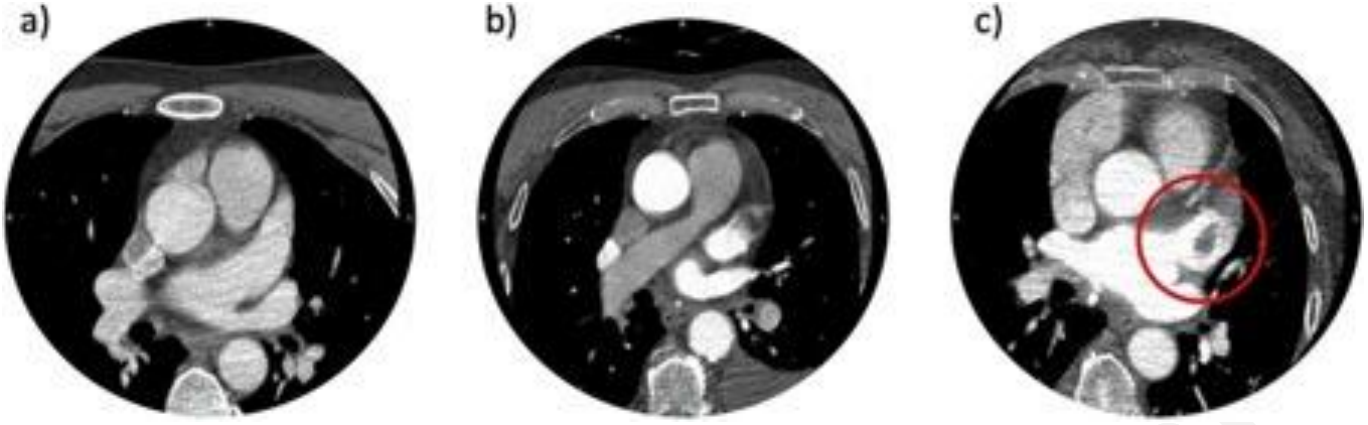
Figure 1.: Example scout image with selection box (light blue) to visualise the scan range in our extended protocol.

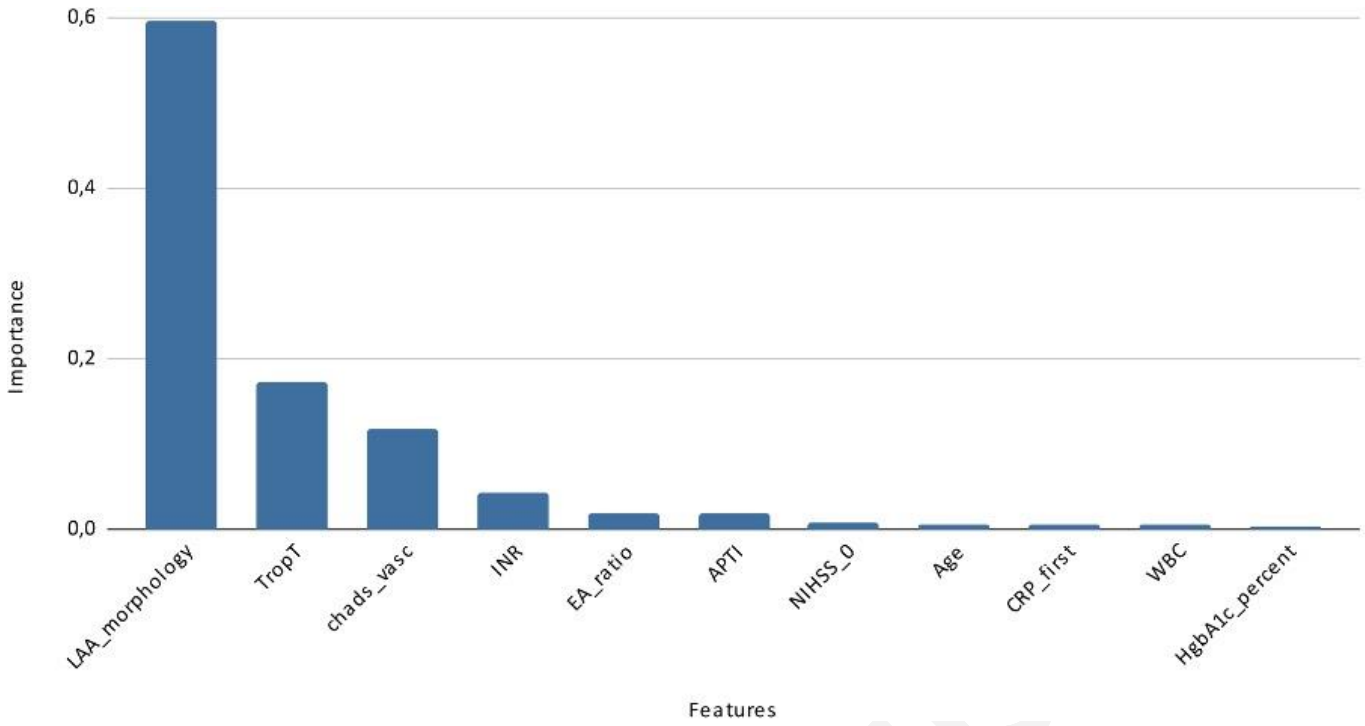
Figure 2.: Example computed tomography (CT) angiography images of the three categories created while evaluating for thrombi: a)negative: the left atrial appendage (LAA) completely opacifies with contrast; b) indeterminate: does not fulfill either criteria; c) positive: well defined filling defect in the LAA (red circle).

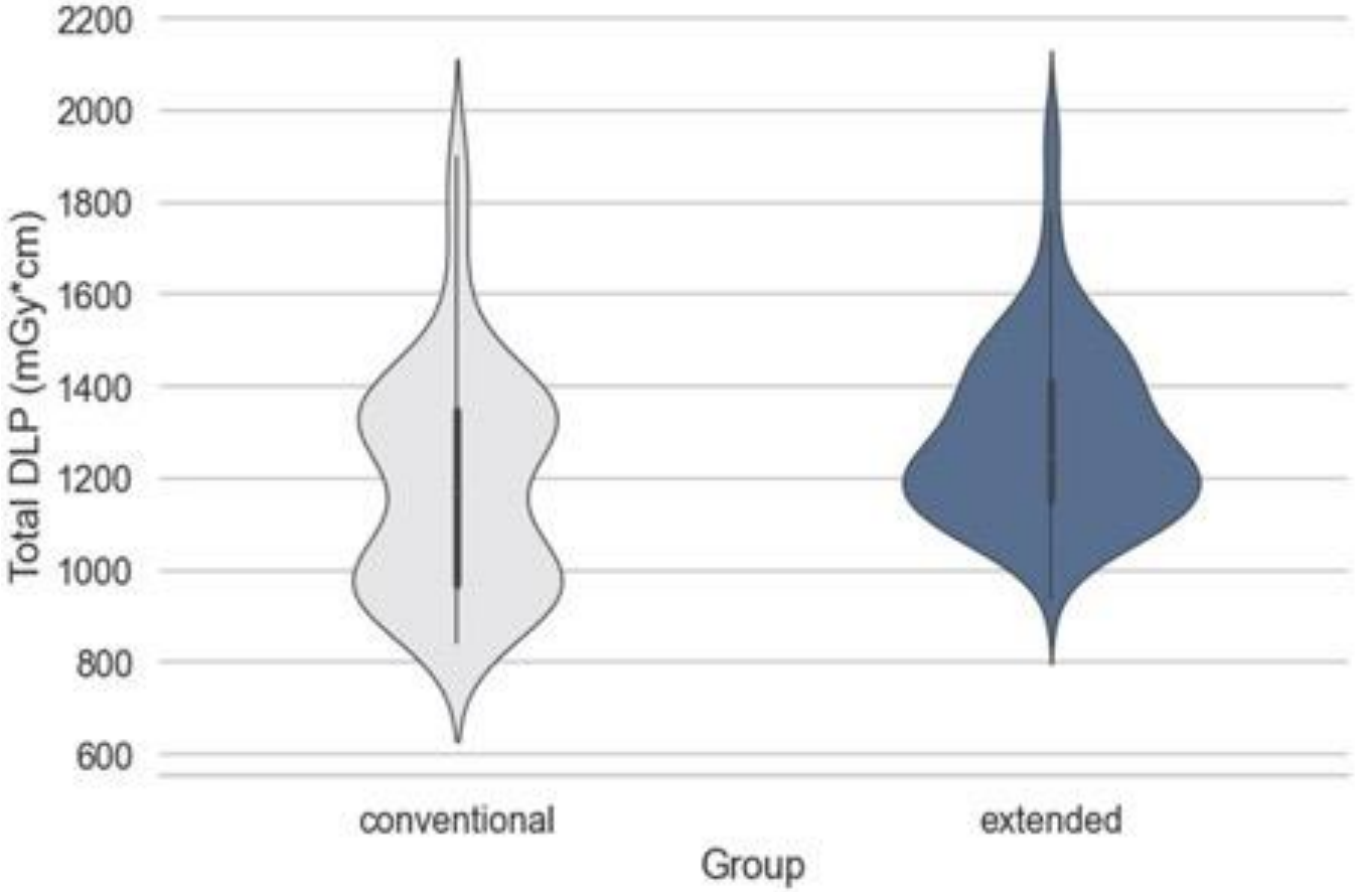
Figure 3.: Result of the gradient-boost analysis. The graph shows clinical factors in order of their predictive values calculated with gradient-boost. Our analysis showed that left atrial appendage morhology, followed by serum Troponine-T and CHADS-VASc score have the highest predictive value for thrombus formation.

Figure 4.: Violin plot of the two-sample t-test between two groups of patients: X-axis: conventional (grey): patients who had been scanned according to the original protocol; extended (blue): patients who had been scanned according to the new, extended protocol. Y-axis: Total Dose Length Product that was calculated by the scanners.









Age of patients (mean ± standard deviation)	71.28 ± 11.88 years
Number of female patients	122 (50.8%)
Number of patients with atrial fibrillation	57 (22 newly discovered[a])
Number of patients with hypertension	202 (84.17%)
Number of patients with diabetes	75 (31.25%)
Generalised atherosclerosis / cardiovascular disease[b]	79 (32.92%)
Number of patients receiving prior anticoagulant therapy	28 (11.67%; DOAC[c]: 19; LMWH[d]: 2; vitamin-K antagonist: 7)

Table 1.: Demographic and basic clinical data of the patients.[a]Atrial fibrillation that was discovered during the patient's hospitalisation at our institute. [b]"Generalised atherosclerosis / cardiovascular disease" were defined retrospectively and included patients who had documented ischemic heart disease, atherosclerosis, heart failure or previous myocardial infarction. [c]DOAC=direct oral anticoagulant, [d]LMWH=low molecular weight heparin.