ERJ open research
THE BEST IN OPEN ACCESS BASIC, TRANSLATIONAL & CLINICAL RESPIRATORY RESEARCH

Early View

Original article

Treatable Cardiac Disease in Hospitalised COPD Exacerbations

Paul Leong, Martin I MacDonald, Paul King, Christian R Osadnik, Brian S Ko, Shane A Landry, Kais Hamza, Ahilan Kugenasan, John M Troupis, Philip G Bardin

Please cite this article as: Leong P, MacDonald MI, King P, *et al*. Treatable Cardiac Disease in Hospitalised COPD Exacerbations. *ERJ Open Res* 2021; in press (https://doi.org/10.1183/23120541.00756-2020).

Title: Treatable Cardiac Disease in Hospitalised COPD Exacerbations

Authors: Paul Leong (ORCID 0000-0002-7409-9328) MBBS, MPHTM, FRACP[*,1,2], Martin I MacDonald (0000-0003-1138-0590) MBChB, BMedSci, FRACP, PhD[*,1,2], Paul King MBBS, FRACP, PhD[1,2], Christian R Osadnik (0000-0001-9040-8007) B.Physio, PhD[1,3], Brian S Ko MBBS, FRACP, MD, PhD[2,4], Shane A Landry PhD[1,2], Kais Hamza PhD[5], Ahilan Kugenasan, BRadMedImg, MHlthSci[6], John M Troupis MBBS, MD, FRANZCR[2,6], Philip G Bardin (0000-0002-9596-574X) MBChB, FRACP, PhD[1,2]

[*]Joint first author

Affiliations: [1]Monash Lung and Sleep, Monash Health, Clayton, Victoria, Australia; [2]School of Clinical Sciences, Monash University, Clayton, Victoria, Australia; [3]School of Primary and Allied Health Care, Monash University; [4]Monash Heart, Monash Health, Clayton, Victoria, Australia; [5]School of Mathematical Sciences, Monash University, Clayton, Victoria, Australia; [6]Monash Imaging, Monash Health, Clayton, Victoria, Australia

Corresponding author: Dr Paul Leong, Monash Lung and Sleep, 246 Clayton Rd, Clayton, Victoria, Australia; paul.leong@monash.edu; Tel +61 (3) 9594 2900; Fax +61 (3) 9594 6311

Author contributions: Conception, design: PL, MIM, PK, CRO, BK, AK, JMT, PGB. Acquisition and analysis: PL, MIM, BK, SAL, KH, AK, JMT. Interpretation: PL, MIM, PK, CRO, BK, JMT, PGB. First draft: PL. All authors participated in revising work, agreed to submit this version for publication, and agree to be accountable for all aspects of the work.

Conflicts of interest: Dr Ko declares consulting fees from Canon Medical during the conduct of this study.

Funding: Dr Leong is supported by the Australian National Health and Medical Research Council Postgraduate Scholarship, the Royal Australasian College of Physicians Dixon Award and the Monash Lung and Sleep Institute. Dr Osadnik was the recipient of a Lung Foundation Australia COPD Research Fellowship and is the recipient of a Rebecca L Cooper Medical Research Foundation Project Grant, unrelated to the present work. Views expressed are those of the authors and may not represent those of the funding bodies. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Take home message: Severe, treatable cardiac disease is present during hospitalised COPD exacerbations – and is often clinically unsuspected. This cardiac disease can be detected with dynamic CT. Appropriate treatment could change outcomes.

Manuscript word count: 3380

Abstract

Introduction

Acute Exacerbations of Chronic Obstructive Pulmonary Disease (AECOPD) are accompanied by escalations in cardiac risk superimposed upon elevated baseline risk. Appropriate treatment for coronary artery disease (CAD) and heart failure with reduced ejection fraction (HFrEF) could improve outcomes. However, securing these diagnoses during AECOPD is difficult, so their true prevalence remains unknown, as does the magnitude of this treatment opportunity. We aimed to determine the prevalence of severe CAD and severe HFrEF during hospitalised AECOPD using dynamic computed tomography (CT).

Methods

Cross-sectional study of 148 patients with hospitalised AECOPD. Dynamic CT was used to identify severe CAD (Agatston score ≥ 400) and HFrEF (left ventricular ejection fraction $\leq$ 40% and/or right ventricular ejection fraction $\leq 35\%$).

Results

Severe CAD was detected in 51/148 patients (35%), left ventricular systolic dysfunction was identified in 12 cases (8%) and right ventricular systolic dysfunction was present in 18 (12%). Clinical history and examination did not identify severe CAD in approximately one-third of cases and missed HFrEF in two-thirds of cases. Elevated troponin and BNP did not differentiate subjects with severe CAD from non-severe CAD, nor distinguish HFrEF from normal ejection fraction. Under-treatment was common. Of those with severe CAD, only 39% were prescribed an antiplatelet agent, and 53% received a statin. Of individuals with HFrEF, 50% or less received angiotensin blockers, beta-blocker, or antimineralocorticoids.

Conclusion

Dynamic CT detects clinically covert CAD and HFrEF during AECOPD, identifying opportunities to improve outcomes via well-established cardiac treatments.

Abstract word count: 241

Manuscript

Introduction

Acute Exacerbations of Chronic Obstructive Pulmonary Disease (AECOPD) are complex, heterogenous events accompanied by a surge in cardiovascular risk and death[1–3]. Cardiac involvement, manifest as biomarkers of myocardial dysfunction, can be detected in up to 60% of acute exacerbations[2]. When present, this heralds reduced survival[2, 3]. Despite the frequency and importance of this signal, relationships between COPD and cardiovascular disease are imperfectly understood, particularly during AECOPD[4].

Two common, but eminently treatable cardiac diagnoses are associated with adverse outcomes at AECOPD: coronary artery disease (CAD)[5–8] and heart failure with reduced ejection fraction (HFrEF)[9, 10]. Both cardiac disorders have well established therapeutic pathways with clear reductions in mortality and morbidity[11–13]. They therefore represent obvious opportunities for intervention. However, their prevalence at AECOPD remains undefined, predominantly due to the limitations of routinely available diagnostic techniques.

The accurate bedside differentiation of pulmonary and cardiac diagnoses during AECOPD can be difficult. Clinical features such as dyspnoea and chest discomfort overlap and although evidence of missed ischemic events can be found on electrocardiograms, in the acute setting, these remain mostly non-specific[2, 14]. Standard cardiac imaging modalities have substantive limitations during AECOPD that render them inaccurate or impractical[2, 14]. For example, transthoracic echocardiography suffers from limited acoustic windows, and cardiac magnetic resonance imaging is typically not feasible in acutely dyspnoeic individuals[2].

Computed tomography (CT) has the potential to reveal treatable cardiac disease during AECOPD. For CAD, CT provides gold-standard quantitation of coronary artery calcium[15], an imaging marker pathognomonic of coronary atherosclerosis and atherosclerotic burden[15]. For left and right heart function, dynamic (i.e. video) CT yields extremely precise and accurate ejection fractions when judged against cardiac magnetic resonance imaging[16–20]. We combined these elements in a novel dynamic cardiopulmonary CT protocol[21] to enable rapid quantification of these key cardiac parameters in a single breath-hold.

In the current work, we hypothesised that during AECOPD, major cardiac pathology would be detectable by dynamic cardiopulmonary CT, and that a significant proportion would be otherwise clinically covert, representing a substantial treatment opportunity. We aimed to assess the prevalence and treatment of two key treatable entities: coronary artery disease as determined by coronary artery calcium burden[22] and HFrEF.

Methods

Patients and measurements

A prospective observational cohort study was conducted at a tertiary metropolitan Australian hospital between 9 December 2013 and 2 November 2019 (Australian and New Zealand Clinical Trial Registry ACTRN12617001562369). In this report, we detail cross-sectional data from the index admission, reporting according to STROBE[23]. Institutional ethics approval was obtained. Some results were previously presented in abstract format[24].

Eligible participants were diagnosed with AECOPD by treating physician(s) and was subsequently verified by pulmonologists using Global Initiative for Obstructive Lung Disease[25] clinical and spirometry criteria.

Following informed consent, dynamic cardiopulmonary CT was performed as described previously[21]. Briefly, a coronary artery calcium score was obtained using the gold-standard technique of electrocardiogram-gating, with results in Agatston units. This was followed by an intravenous iodinated contrast-enhanced examination simultaneously yielding left and right ventricular ejection fractions and a computed tomography pulmonary angiogram (Figure 1 and Online Supplement Video).

Imaging was performed on a 256-slice multidetector Philips iPatent iCT (Cleveland, USA) with a target dose of 4 millisieverts, iterative model-based reconstruction, and post-processing in Phillips Intellispace (V6, Cleveland, USA) by radiographers with >8 years of cardiac experience. CT was performed as early as possible in the hospital admission. All subjects had estimated glomerular filtration rate >30mL/min/1.73m^2 and sinus rhythm, and heart rate reduction therapy was not administered. Treating physicians were blinded to CT results during hospitalisation.

Key exclusion criteria were contrast allergy and the inability to grant informed consent. Chest x-ray, electrocardiogram and treatments were performed at the treating clinicians' discretion. Electrocardiogram analysis was performed for study purposes by a blinded clinician with abnormal ST segments and T wave inversion defined per the Fourth Universal Definition of Myocardial Infarction[26] (additional detail in Online Supplement).

At the time of study recruitment, serum samples were collected for this study. These were analysed for troponin I and B-type natriuretic peptide or N-terminal-pro B-type natriuretic peptide (hereafter collectively BNP). Results were considered abnormal if elevated above the manufacturer's upper reference limit (age and gender adjusted where recommended; additional detail in Online Supplement). Nasopharyngeal swabs were taken for viral

polymerase chain reaction and spontaneously expectorated sputum were submitted for bacterial culture.

Outcomes and statistical analyses

The primary outcomes were the prevalence of severe calcific CAD (Agatston score ≥400 [27]), and severe HFrEF defined by left ventricular ejection fraction (LVEF) ≤ 40% and/or right ventricular ejection fraction (RVEF) ≤35%. Secondary outcomes were the frequency of cardiac treatments at the time of hospital admission, and cardiac biomarkers.

Study data were collected and managed using REDCap electronic data capture tools[28]. Analyses were performed in IBM SPSS 25 and R 3.3.3. Normally distributed data are expressed as mean ± standard deviation and non-parametric data as median [interquartile range]. Group-wise comparisons were made with t-tests, Mann-Whitney U or Fisher's exact test as appropriate. Penalized likelihood logistic regression (logistif[6]) was used to explore predictors of 30 day readmission.

No *a priori* power calculations were performed and no corrections were made for multiple analyses. Alpha was two-sided and set at 0.05. Missing data were dropped from analyses.

Data sharing statement

Institutional ethics approval was obtained for data sharing in aggregated and de-identified formats only.

Results

331 patients were screened. Exclusions were predominantly for non-sinus rhythm and severe renal dysfunction (Figure 1). The final sample consisted of 148 participants (Table 1, Online Supplement Tables 1 and 2). The median time from emergency room arrival to CT was 1.8 [1.1, 2.9] days and the mean radiation dose was 4.0±1.5 millisievert. The mean heart rate at CT was 86.7 ± 14.1 beats per minute and the mean cardiac output indexed to body surface

area was 3.8 ± 0.9 L/min/m^2 (Table 2). The median coronary artery calcium score was 146.0 [28.3 – 821.3] Agatston units.

Patients were typical of hospitalised AECOPD cohorts[29, 30] with a mean age of 69.5 ± 9.5 years and severe airflow obstruction (FEV1 42.8 ± 18.5% predicted); 56 (38%) were current smokers. Viruses, most commonly rhinovirus, were found in 44 (30%) and bacterial pathogens were detected in 30 (20%). The median eosinophil count was 0.07 [0, 0.15] x10^9/L. The majority of patients (90/148, 61%) had been admitted to hospital for AECOPD in the previous 12 months.

CAD detection

In relation to the primary outcome, on CT, severe calcific CAD (Agatston score ≥400) was found in 51/148 patients (35%) (Table 2, Online Supplement Figure 2).

Conventional clinical evaluations under-detected severe CAD (Figure 2). On clinical history and examination, a diagnosis of atherosclerotic cardiovascular disease had only been made in 33/51 patients (61%) who had evidence of severe coronary calcification. Electrocardiograms exhibited ST or T wave abnormalities in 17/51 (33%) of patients with severe CAD on CT, and 16/89 (18%) with non-severe CAD (p=0.061).

Troponin and BNP did not distinguish individuals with and without severe CAD on CT (Online Supplement Table E3). Troponin was elevated in 14/47 (30%) with severe CAD versus 24/91 (26%) with non-severe CAD (p=0.69). Similarly, BNP was abnormal in 22/46 (48%) with severe CAD versus 41/90 (46%) under that threshold (p=0.86).

Six patients were diagnosed with an acute myocardial infarction by treating clinicians; all fulfilled the Fourth Universal Definition of Myocardial Infarction[26]. Two out of the six had CACS ≥ 400. Three patients underwent inpatient coronary angiography: one had a coronary

stent placed, and another underwent emergent coronary artery bypass grafting. The remaining three patients received a clinical diagnosis of type 2 myocardial infarction and based on current standards of care were managed non-invasively. When severe CAD was present, patients were more likely to be readmitted to hospital in the following 30 days (19/97 vs 19/51, p=0.029).

CAD treatment

Among patients with severe CAD, at admission, only 20/51 (39%) were taking an antiplatelet agent, and only 27/51 (53%) were prescribed a statin (Table 3).

HFrEF diagnosis

With regards to the primary outcome, using dynamic CT, LVEF≤40% was found in 12/148 (8%) and RVEF≤35% was present in 18/148 (12%) (Online Supplement Tables 4-5). Biventricular failure was present in six individuals.

Standard clinical assessments under-detected reduced LVEF (Figure 2). No prior diagnosis of heart failure had been made on clinical history or examination in 8/12 (67%) patients with low LVEF.

Chest-x rays were not predictive of reduced LVEF. In patients with reduced LVEF, only 2/12 (17%) chest x-ray radiologist reports noted signs of heart failure, in comparison to 11/123 (9%) who had normal LVEF (p=0.29).

Troponin was elevated in 9/11 (82%) of patients with low LVEF, but was also abnormal in 29/127 (23%) of those with normal LVEF. The prevalence of abnormal BNP did not differ between low LVEF and normal LVEF categories (5/12 (42%) vs. 58/124 (47%) respectively, p=0.77).

Findings were similar for RVEF ≤35%. No prior diagnosis of heart failure had been made on clinical history or examination in in 12/18 (67%) with low RVEF.

Chest x-rays were similarly non-diagnostic for reduced RVEF. In those with low RVEF, features of heart failure were reported in 2/17 (12%) versus 11/129 (9%) of those with normal RVEF (p=0.65).

Troponin elevation was more frequent when RVEF was reduced, but was not limited to patients with low RVEF (10/15 (67%) vs. 28/123 (23%), p=0.001). BNP elevation did not differentiate low RVEF and normal RVEF (5/17 (29%) vs. 58/119 (49%), p=0.19).

Individuals with reduced LVEF had higher median coronary artery calcium scores (1532 vs 119, p<0.001) and lower RVEF (34.0 ± 12.7% vs 49.9 ± 9.4%, p<0.001) compared with those with normal LVEF (Online Supplement Table 4). There was a tendency for higher 30-day readmission when left ventricular ejection fraction was depressed (6/12 (50%) vs 32/97 (33%), p=0.077).

Patients with reduced RVEF had lower LVEF (47.2 ± 17.5 vs 63.5 ± 11.9, p<0.001) and higher median coronary artery calcium scores (940 vs 126, p=0.022) (Online Supplement Table 5) than those with normal RVEF. Again, 30-day readmission was numerically higher in those with low RVEF (7/18 (39%) vs 31/130 (24%), p=0.25).

HFrEF treatment

At admission, in patients with low LVEF, 6/12 (50%) were prescribed angiotensin blockade, however beta blocker prescription was low at 2/12 (17%), and no individuals were prescribed a mineralocorticoid receptor antagonist.

Under-prescription was similarly found in patients with low RVEF. 5/18 (28%) received angiotensin blockade, 2/18 (11%) received beta blockers and 3/18 (17%) were prescribed a mineralocorticoid receptor antagonist.

27/148 (18%) patients received new or intensified heart failure treatment during admission. Of these, 15/27 (56%) had normal biventricular function on dynamic CT.

Patterns of dysfunction

Cardiac dysfunction at AECOPD was common (Figure 3). Overall, 62/148 (42%) patients had one or more severe treatable cardiac abnormalities (i.e. severe CAD, and/or HFrEF).

Most patients had detectable cardiac pathology: only 41/148 (28%) patients did not have one or more of severe coronary artery calcification, low LVEF, low RVEF, abnormal troponin or BNP.

Overall, 44/135 (33%) patients had a normal electrocardiogram, troponin and BNP. This combination made it extremely unlikely that a given individual had low left or right ventricular systolic dysfunction (which were present in 0/44 and 1/44 patients respectively). However, this combination did not differentiate those with severe CAD from those with non-severe CAD (13/44 (30%) vs 34/91 (37%), respectively, p=0.44).

30-day readmission

38/148 (26%) patients were readmitted in the 30 days following hospital discharge. 3 deaths occurred in this period, all of which were from respiratory causes. In univariate logistic regression, higher left ventricular ejection fraction and FEV_1 were associated with reduced odds of 30-day readmission (odds ratio 0.965, 95%CI 0.939-0.989, p=0.006 and 0.969, 95% CI 0.944-0.992, p<0.001 respectively) (Online Supplement Table 6). Conversely, higher coronary artery calcium score percentiles were associated with increased odds of admission

(odds ratio 1.013, 95%CI 1.001-1.025, p=0.028). Troponin and BNP were not associated with differences in 30-day readmission (p=0.293 and 0.642 respectively). In multivariate logistic regression, only FEV_1 was a significant independent predictor of 30-day readmission (odds ratio 0.976, 95%CI 0.949-1.0, p=0.049) (Online Supplement Table 7).

Discussion

We report the first application of dynamic cardiopulmonary CT in a cohort of hospitalised patients with AECOPD. Severe, but treatable cardiac disease was detected in 42% of patients: severe CAD was found in about one-third of patients, and severely reduced LVEF and/or RVEF was found in approximately 10% of cases. Standard tertiary hospital care assessments, including cardiac biomarkers performed relatively poorly to diagnose severe CAD and HFrEF. Unsurprisingly, undertreatment with disease-modifying agents was common. Taken together these findings imply that targeted disease finding in hospitalised AECOPD may aid diagnosis, treatment and prevention of future cardiac morbidity and mortality.

Hospitalised AECOPD are associated with substantial mortality and an enriched risk of subsequent major adverse cardiovascular events[2, 3]. Hospitalisation therefore represents a favourable opportunity to diagnose and intervene in cardiac disease by implementing well-established treatment pathways with recognised treatment benefits[11–13]. The finding that 42% of patients exhibited one or more of severe CAD or HFrEF, indicates that abundant treatment opportunities exist in this population of hospitalised AECOPD. Importantly, our findings are likely to be an underestimate of cardiovascular involvement in an unselected hospitalised AECOPD population since we excluded patients with severe renal disease and those who were not in sinus rhythm.

Dynamic CT highlighted that standard clinical assessments often grossly underdiagnosed CAD and HFrEF. One-third of severe CAD and two-thirds of severe HFrEF was clinically

unsuspected on standard history and examination and would have been overlooked in routine AECOPD management. Electrocardiograms were nonspecific for CAD, and chest x-rays were nonspecific for HFrEF as were troponin and BNP. Combining standard clinical assessments could be useful as the presence of a normal electrocardiogram, troponin and BNP rendered HFrEF unlikely. This combination was not entirely reassuring as important CAD was still detected in many of these individuals and our observations require replication in other cohorts.

It is unsurprising that cardiac biomarkers were not associated with specific cardiac diagnoses since these biomarkers are sensitive but not specific for cardiovascular diagnoses. Numerous factors including exacerbation severity, effects of tachycardia, hypoxia, and chronic changes including pulmonary hypertension and diastolic dysfunction could result in biomarker elevation[2, 31]. Consequently, biomarkers cannot be relied upon to directly determine therapeutic strategies outside of defined circumstances such as dynamic troponin elevations which might suggest acute coronary syndrome. However, biomarkers remain important sentinel markers of adverse outcomes including mortality[2] . Taken together, standard clinical assessments under-diagnosed cardiac disease and when abnormal, generally lacked the diagnostic accuracy required to institute disease-specific treatments.

The current studies show that 35% of patients had severe CAD, mirroring other cohorts including ECLIPSE, COPDGene and the Danish Lung Cancer Screening Trial[7, 8, 32]. In populations with COPD, CAD is associated with adverse outcomes including higher dyspnoea, lower exercise capacity and greater mortality [7, 8, 32]. Further, the incidence of acute myocardial infarction increases at AECOPD[3] beyond a baseline of elevated risk[33]. In aggregate, diagnosing CAD during AECOPD represents an opportunity for cardiac risk mitigation not only during that episode, but also towards improved longer-term outcomes. This notion is supported by data from COPD populations suggesting that antiplatelet and

lipid-lowering treatments may reduce dyspnoea, mortality and COPD exacerbations[1, 4]. A case-finding approach for CAD, such as that using CT, could define individuals with CAD and its severity, allowing targeted cardiac risk reduction.

HFrEF was less common in our cohort at about 10% prevalence, but this group may be of disproportionate clinical prominence since coexistent heart failure and COPD is associated with an increased frequency of hospitalisation[2, 4] and incipient heart failure may simulate AECOPD or even precipitate it[2, 4, 14]. Diagnosis and treatment of HFrEF appeared clinically difficult in our study. Two-thirds of those patients with HFrEF on dynamic CT related no clinical history or examination evidence of this diagnosis. Conversely, about half of patients with normal biventricular function received treatment for presumed heart failure. Identifying COPD patients with clear indications for HFrEF treatment such as angiotensin-blockade and beta-blockers would enhance the risk-benefit profile of these agents, as broader prescription may lead to adverse effects[34]. Finally, when HFrEF was detected a higher burden of CAD was present, suggesting CAD warrants consideration when HFrEF is detected.

Current AECOPD treatment paradigms[25] are dominantly aimed at pulmonary, rather than cardiac parameters, despite COPD populations demonstrating a 2.5-fold increased risk of cardiac disease[33]. Paradoxically, COPD management recommendations emphasise a thorough “precision medicine” approach, in which characteristics are defined and treated[35]. We found that some form of cardiac involvement at AECOPD was extremely common, with only 28% of patients not exhibiting one or more of severe CAD, HFrEF, or abnormal cardiac biomarkers. Without knowledge of influential cardiac diagnoses, a precision medicine strategy is difficult to fully implement and treatable cardiac diseases could be routinely overlooked. Overall, accurately diagnosing and treating cardiac comorbidities at an opportune occasion such as AECOPD could not only alter mortality and morbidity[1, 4, 11–13] but

could also ensure tailored pulmonary treatments that will minimise adverse cardiac effects. Our data demonstrated, however, that FEV_1 was the parameter most strongly associated with 30-day readmission, implying that optimising airway management may be the correct approach to preventing short-term readmissions for many patients.

The current study has caveats. Severely unwell patients including those with arrhythmias and with poor renal function were excluded from study. It is possible that results may not apply outside the study population of hospitalised AECOPD. However, findings are broadly consistent with previous global reports of under-diagnosis and under-treatment of coronary disease and systolic heart failure in COPD populations[1, 7, 36–38]. For example, quantitative coronary calcium burden in our patients was comparable to that in the ECLIPSE cohort[7], who also only received statins about one-quarter of the time; beta-blocker under-prescription for HFrEF is commonly also reported[1, 37, 39].

Diastolic dysfunction, and the clinical entity of heart failure with preserved ejection fraction are key comorbidities in patients with COPD that may explain cardiac biomarker elevation in some patients. However, methodologies to ascertain and quantify diastolic dysfunction on dynamic CT are not yet well established. Additionally, there is currently limited evidence that specific pharmacotherapies alter the course of heart failure with preserved ejection fraction, in contradistinction to HFrEF and CAD. Examining diastolic dysfunction therefore merits further study but was outside the scope of this work.

A limitation of this work is that multiple assays were used for both troponin and BNP. Because there are no validated ways to interchange values between assays, we were unable to draw inferences based on absolute biomarker levels. In addition, blood lipids were not measured and so could not be used to apply standard cardiovascular risk estimators.

A key strength is the use of dynamic CT to accurately assesses important cardiac parameters in a single, rapid imaging session requiring only one breath hold[21]. Coronary calcium was quantified using the gold-standard technique of prospective ECG-gated CT[15, 22]. For left and right ventricular parameters, dynamic CT is extremely precise and accurate, exhibiting near-perfect correlation (Pearson r 0.9 to 0.99) with the gold-standard of magnetic resonance imaging[16, 17, 19, 20]. CT however does require radiation exposure, adequate renal function and cannot directly measure pressures or vascular resistance.

The detection of coronary artery calcium reflects late-stage subclinical coronary atherosclerosis, and scores are proportionate to the area and volume of plaque [15, 22, 40]. Although we used the term severe CAD to refer to Agatston scores of ≥ 400 based on precedent [27], and worse outcomes when scores ≥ 400 [8, 41], it is a limitation that we did not conclusively demonstrate that these were associated with specific disease entities such as ischaemic heart disease.

During AECOPD, dynamic CT affords substantial pragmatic advantages in comparison to other cardiac imaging modalities. In many patients with COPD, transthoracic echocardiography parameters cannot even be obtained due to hyperinflation and poor acoustic windows[2, 21]. In addition to overcoming this practical disadvantage, dynamic CT is more accurate than echocardiography[16]. Magnetic resonance imaging requires prolonged acquisitions in a claustrophobic environment, an arduous and potentially dangerous undertaking during acute breathlessness. Neither echocardiography nor magnetic resonance imaging can quantitate CAD. Conversely, dynamic CT was practicable and well tolerated during hospitalised AECOPD, revealing two significant, treatable cardiac diseases.

Future studies could answer whether the HFrEF abnormalities observed are persistent or transient, and clarify associations between outcomes and other CT-derived measurements.

Key unresolved questions are identifying a subpopulation who would benefit from an invasive angiographic approach, and whether routine implementation of a CT-based case-finding strategy would be cost-efficient and improve long-term outcomes.

In conclusion, detection of cardiac disease employing dynamic cardiopulmonary CT is feasible during AECOPD with approximately 40% of patients having severe, but treatable cardiac disease. The ability to accurately delineate cardiac pathologies has potential to guide treatment and improve prognosis in people with COPD.

Acknowledgements

The authors thank Ms Anne Tran and Dr Gayan Kathriachchige for their important contributions to this work.

References

1. Morgan AD, Zakeri R, Quint JK. Defining the relationship between COPD and CVD: what are the implications for clinical practice? *Ther. Adv. Respir. Dis.* 2018; 12: 175346581775052.

2. MacDonald MI, Shafuddin E, King PT, Chang CL, Bardin PG, Hancox RJ. Cardiac dysfunction during exacerbations of chronic obstructive pulmonary disease. *Lancet Respir. Med.* 2016; 4: 138–148.

3. Wang M, Lin EP-Y, Huang L-C, Li C-Y, Shyr Y, Lai C-H. Mortality of cardiovascular events in COPD patients with preceding hospitalized acute exacerbation. *Chest* 2020; : S0012369220304438.

4. Rabe KF, Hurst JR, Suissa S. Cardiovascular disease and COPD: dangerous liaisons? *Eur. Respir. Rev.* 2018; 27: 180057.

5. Patel ARC, Donaldson GC, Mackay AJ, Wedzicha JA, Hurst JR. The Impact of Ischemic Heart Disease on Symptoms, Health Status, and Exacerbations in Patients With COPD. *CHEST* 2012; 141: 851–857.

6. McGarvey LP, John M, Anderson JA, Zvarich M, Wise RA. Ascertainment of cause-specific mortality in COPD: operations of the TORCH Clinical Endpoint Committee. *Thorax* 2007; 62: 411–415.

7. Williams MC, Murchison JT, Edwards LD, Agustí A, Bakke P, Calverley PMA, Celli B, Coxson HO, Crim C, Lomas DA, Miller BE, Rennard S, Silverman EK, Tal-Singer R, Vestbo J, Wouters E, Yates JC, Beek EJR van, Newby DE, MacNee W, Investigators for the E of CL to IPSE (ECLIPSE). Coronary artery calcification is increased in patients with COPD and associated with increased morbidity and mortality. *Thorax* 2014; 69: 718–723.

8. Bhatt SP, Kazerooni EA, Newell JD, Hokanson JE, Budoff MJ, Dass CA, Martinez CH, Bodduluri S, Jacobson FL, Yen A, Dransfield MT, Fuhrman C, Nath H. Visual estimate of coronary artery calcium predicts cardiovascular disease in COPD. *Chest* [Internet] 2018 [cited 2018 Jun 15]; Available from: http://linkinghub.elsevier.com/retrieve/pii/S0012369218308882.

9. Fuso L, Incalzi RA, Pistelli R, Muzzolon R, Valente S, Pagliari G, Gliozzi F, Ciappi G. Predicting mortality of patients hospitalized for acutely exacerbated chronic obstructive pulmonary disease. *Am. J. Med.* Elsevier; 1995; 98: 272–277.

10. Boudestein LCM, Rutten FH, Cramer MJ, Lammers JWJ, Hoes AW. The impact of concurrent heart failure on prognosis in patients with chronic obstructive pulmonary disease. *Eur. J. Heart Fail.* 2009; 11: 1182–1188.

11. Arnett DK, Blumenthal RS, Albert MA, Buroker AB, Goldberger ZD, Hahn EJ, Himmelfarb CD, Khera A, Lloyd-Jones D, McEvoy JW, Michos ED, Miedema MD, Muñoz D, Smith SC, Virani SS, Williams KA, Yeboah J, Ziaeian B. 2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation* [Internet] 2019 [cited 2020 Jun 17]; 140Available from: https://www.ahajournals.org/doi/10.1161/CIR.0000000000000678.

12. Grundy SM, Stone NJ, Bailey AL, Beam C, Birtcher KK, Blumenthal RS, Braun LT, de Ferranti S, Faiella-Tommasino J, Forman DE, Goldberg R, Heidenreich PA, Hlatky MA, Jones DW, Lloyd-Jones D, Lopez-Pajares N, Ndumele CE, Orringer CE, Peralta CA, Saseen JJ, Smith SC,

Sperling L, Virani SS, Yeboah J. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J. Am. Coll. Cardiol.* 2019; 73: e285–e350.

13. Yancy CW, Januzzi JL, Allen LA, Butler J, Davis LL, Fonarow GC, Ibrahim NE, Jessup M, Lindenfeld J, Maddox TM, Masoudi FA, Motiwala SR, Patterson JH, Walsh MN, Wasserman A. 2017 ACC Expert Consensus Decision Pathway for Optimization of Heart Failure Treatment: Answers to 10 Pivotal Issues About Heart Failure With Reduced Ejection Fraction: A Report of the American College of Cardiology Task Force on Expert Consensus Decision Pathways. *J. Am. Coll. Cardiol.* 2018; 71: 201–230.

14. Leong P, Macdonald MI, Ko BS, Bardin PG. Coexisting chronic obstructive pulmonary disease and cardiovascular disease in clinical practice: a diagnostic and therapeutic challenge. *Med. J. Aust.* 2019; 210: 417–423.

15. Hecht H, Blaha MJ, Berman DS, Nasir K, Budoff M, Leipsic J, Blankstein R, Narula J, Rumberger J, Shaw LJ. Clinical indications for coronary artery calcium scoring in asymptomatic patients: Expert consensus statement from the Society of Cardiovascular Computed Tomography. *J. Cardiovasc. Comput. Tomogr.* 2017; 11: 157–168.

16. Greupner J, Zimmermann E, Grohmann A, Dübel H-P, Althoff T, Borges AC, Rutsch W, Schlattmann P, Hamm B, Dewey M. Head-to-Head Comparison of Left Ventricular Function Assessment with 64-Row Computed Tomography, Biplane Left Cineventriculography, and Both 2- and 3-Dimensional Transthoracic Echocardiography. *J. Am. Coll. Cardiol.* 2012; 59: 1897–1907.

17. Maffei E, Messalli G, Martini C, Nieman K, Catalano O, Rossi A, Seitun S, Guaricci AI, Tedeschi C, Mollet NR, Cademartiri F. Left and right ventricle assessment with Cardiac CT: validation study vs. Cardiac MR. *Eur. Radiol.* 2012; 22: 1041–1049.

18. Sarwar A, Shapiro MD, Nasir K, Nieman K, Nomura CH, Brady TJ, Cury RC. Evaluating global and regional left ventricular function in patients with reperfused acute myocardial infarction by 64-slice multidetector CT: A comparison to magnetic resonance imaging. *J. Cardiovasc. Comput. Tomogr.* 2009; 3: 170–177.

19. Raman SV, Shah M, McCarthy B, Garcia A, Ferketich AK. Multi–detector row cardiac computed tomography accurately quantifies right and left ventricular size and function compared with cardiac magnetic resonance. *Am. Heart J.* 2006; 151: 736–744.

20. Wu Y-W, Tadamura E, Kanao S, Yamamuro M, Okayama S, Ozasa N, Toma M, Kimura T, Kita T, Marui A, Komeda M, Togashi K. Left Ventricular Functional Analysis Using 64-Slice Multidetector Row Computed Tomography: Comparison with Left Ventriculography and Cardiovascular Magnetic Resonance. *Cardiology* 2008; 109: 135–142.

21. Leong P, MacDonald MI, Ko BS, Lau KK, Troupis JM, Bardin PG. Single- breath comprehensive cardiopulmonary assessment utilizing computerized tomography. *Respirology* 2019; 24: 1026–1029.

22. Greenland P, Blaha MJ, Budoff MJ, Erbel R, Watson KE. Coronary Calcium Score and Cardiovascular Risk. *J. Am. Coll. Cardiol.* Journal of the American College of Cardiology; 2018; 72: 434–447.

23. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: Guidelines for Reporting Observational Studies. *Ann. Intern. Med.* American College of Physicians; 2007; 147: 573–577.

24. MacDonald MI, Wong A-M, King P, Lockwood S, Troupis J, Bardin P. Occult Cardiac Disease Can Be Identified by Dynamic 256-Slice CT During Chronic Obstructive Pulmonary Disease Exacerbation. *Am. Thorac. Soc. Int. Conf.* San Francisco; 2016.

25. Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global Strategy for the Diagnosis, Management and Prevention of COPD. 2020.

26. Thygesen K, Alpert JS, Jaffe AS, Chaitman BR, Bax JJ, Morrow DA, White HD. Fourth Universal Definition of Myocardial Infarction (2018). *J. Am. Coll. Cardiol.* 2018; 72: 2231–2264.

27. Raggi Paolo, Callister Tracy Q., Cooil Bruce, He Zuo-Xiang, Lippolis Nicholas J., Russo Donald J., Zelinger Alan, Mahmarian John J. Identification of Patients at Increased Risk of First Unheralded Acute Myocardial Infarction by Electron-Beam Computed Tomography. *Circulation* American Heart Association; 2000; 101: 850–855.

28. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)—A metadata-driven methodology and workflow process for providing translational research informatics support. *J. Biomed. Inform.* 2009; 42: 377–381.

29. Wark PAB, Tooze M, Powell H, Parsons K. Viral and bacterial infection in acute asthma and chronic obstructive pulmonary disease increases the risk of readmission. *Respirology* 2013; 18: 996–1002.

30. Ko FW, Chan KP, Hui DS, Goddard JR, Shaw JG, Reid DW, Yang IA. Acute exacerbation of COPD. *Respirology* 2016; 21: 1152–1165.

31. Anderson WJ, Lipworth BJ, Rekhraj S, Struthers AD, George J. Left Ventricular Hypertrophy in COPD Without Hypoxemia. *Chest* 2013; 143: 91–97.

32. Rasmussen T, Køber L, Abdulla J, Pedersen JH, Wille MMW, Dirksen A, Kofoed KF. Coronary artery calcification detected in lung cancer screening predicts cardiovascular death. *Scand. Cardiovasc. J.* 2015; 49: 159–167.

33. Chen W, Thomas J, Sadatsafavi M, FitzGerald JM. Risk of cardiovascular comorbidity in patients with chronic obstructive pulmonary disease: a systematic review and meta-analysis. *Lancet Respir. Med.* 2015; 3: 631–639.

34. Dransfield MT, Voelker H, Bhatt SP, Brenner K, Casaburi R, Come CE, Cooper JAD, Criner GJ, Curtis JL, Han MK, Hatipoğlu U, Helgeson ES, Jain VV, Kalhan R, Kaminsky D, Kaner R, Kunisaki KM, Lambert AA, Lammi MR, Lindberg S, Make BJ, Martinez FJ, McEvoy C, Panos RJ, Reed RM, Scanlon PD, Sciurba FC, Smith A, Sriram PS, Stringer WW, et al. Metoprolol for the Prevention of Acute Exacerbations of COPD. *N. Engl. J. Med.* Massachusetts Medical Society; 2019; 381: 2304–2314.

35. Agusti A, Bel E, Thomas M, Vogelmeier C, Brusselle G, Holgate S, Humbert M, Jones P, Gibson PG, Vestbo J, Beasley R, Pavord ID. Treatable traits: toward precision medicine of chronic airway diseases. *Eur. Respir. J.* 2016; 47: 410–419.

36. Brekke PH, Omland T, Smith P, Søyseth V. Underdiagnosis of myocardial infarction in COPD – Cardiac Infarction Injury Score (CIIS) in patients hospitalised for COPD exacerbation. *Respir. Med*. 2008; 102: 1243–1247.

37. Quint JK, Herrett E, Bhaskaran K, Timmis A, Hemingway H, Wedzicha JA, Smeeth L. Effect of beta blockers on mortality after myocardial infarction in adults with COPD: population based cohort study of UK electronic healthcare records. *BMJ* 2013; 347: f6650–f6650.

38. Pizarro C, Herweg-Steffens N, Buchenroth M, Schulte W, Schaefer C, Hammerstingl C, Werner N, Nickenig G, Skowasch D. Invasive coronary angiography in patients with acute exacerbated COPD and elevated plasma troponin. *Int. J. Chron. Obstruct. Pulmon. Dis.* 2016; 11: 2081–2089.

39. de Miguel Díez J, Morgan JC, García RJ. The association between COPD and heart failure risk: a review. *Int. J. Chron. Obstruct. Pulmon. Dis.* 2013; 8: 305–312.

40. Authors/Task Force Members, Piepoli MF, Hoes AW, Agewall S, Albus C, Brotons C, Catapano AL, Cooney M-T, Corrà U, Cosyns B, Deaton C, Graham I, Hall MS, Hobbs FDR, Løchen M-L, Löllgen H, Marques-Vidal P, Perk J, Prescott E, Redon J, Richter DJ, Sattar N, Smulders Y, Tiberi M, van der Worp HB, van Dis I, Verschuren WMM, Additional Contributor: Simone Binno (Italy), Document Reviewers:, De Backer G, et al. 2016 European Guidelines on cardiovascular disease prevention in clinical practice: The Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts): Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). *Eur. J. Prev. Cardiol.* 2016; 23: NP1–NP96.

41. Arad Y, Goodman KJ, Roth M, Newstein D, Guerci AD. Coronary Calcification, Coronary Disease Risk Factors, C-Reactive Protein, and Atherosclerotic Cardiovascular Disease Events: The St. Francis Heart Study. *J. Am. Coll. Cardiol.* 2005; 46: 158–165.

Figures

Figure 1: Dynamic cardiopulmonary Computed Tomography (CT) reveals severe but clinically undiagnosed coronary artery disease

Dynamic cardiopulmonary CT during hospitalised AECOPD in a 77-year-old female ex-smoker with post-bronchodilator FEV_1 of 46% predicted and no previously diagnosed cardiac disease. Representative cardiac images are shown in Panel A with upper panes (i, ii and iii) depicting end-diastole, and lower panes (iv, v, vi) depicting corresponding end-systolic images. CT revealed normal left ventricular ejection fraction (68%) and normal right ventricular ejection fraction (55%). Extreme coronary artery calcification was found (Panel B, serial descending images), with an Agatston score of 2048. Coronary calcification was dominantly in the left main stem (LMS) and left anterior descending (LAD) arteries, with lesser disease in the left circumflex (LCx) and right coronary arteries (RCA). Troponin and B-type natriuretic peptide were not elevated. Statin and angiotensin converting enzyme inhibitor were commenced. Following recovery from AECOPD, invasive angiography confirmed severe LMS and LAD disease requiring coronary artery bypass grafting. See also Online Video.

Figure 2: Treatable cardiac abnormalities on Computed Tomography (CT) are under-diagnosed by standard clinical assessments

With dynamic computed tomography (CT) as the gold standard, percentages of patients exhibiting relevant clinical parameter are depicted in grey. The additional yield from dynamic computed tomography is shown in black. Clinical diagnosis: clinical history and examination. Severe CAD: severe coronary artery disease (Agatston score ≥400), LVEF: left ventricular ejection fraction, RVEF, right ventricular ejection fraction, ECG: electrocardiogram, BNP: b-type natriuretic peptide.

Figure 3: Frequency and patterns of cardiovascular involvement in 148 patients with hospitalised acute exacerbations of Chronic Obstructive Pulmonary Disease

Frequency and patterns of associations between left ventricular ejection fraction ≤ 40% (LVEF ≤ 40%), right ventricular ejection fraction ≤35% (RVEF ≤35%), severely elevated coronary artery calcium score (Agatston ≥400, severe CAD), elevated troponin and elevated B-type natriuretic peptide (BNP). The upper bar chart shows the number of patients with the given combination of abnormalities in the lower panel. Combinations of abnormalities with a frequency of five or more individuals are shown.

Table 1: Characteristics of study participants at the time of admission (n=148 unless indicated)

Baseline Characteristic	**Value**
Age (years)	69.5 ± 9.5
Sex (n, %)	
Female	60 (41%)
Male	88 (61%)
Body-mass index (kg/m^2)	25.0 ± 7.2
Hospitalised exacerbations in prior 12 months (n, %)	
0	58 (39%)
1	31 (21%)
2	17 (12%)
3 or more	42 (28%)
Current smoker at admission (n, %)	56 (38%)
Smoking history (pack years)	47.3 ± 31.8
Postbronchodilator FEV_1/FVC (%)*	39.8 ± 15.2
Postbronchodilator FEV_1 (% predicted)*	42.8 ± 18.5
DLCO (% predicted)†	46.8 ± 20.8
Relevant medical history at admission (n, %)	
Ischemic heart disease	30 (20%)
Hypertension	58 (39%)
Dyslipidaemia	57 (39%)
Diabetes mellitus	19 (13%)
Cerebrovascular disease	16 (11%)

Heart failure	31 (21%)
Peripheral vascular disease	9 (6%)
Inhaled medications at admission (n, %)	
Long acting muscarinic antagonist	110 (74%)
Long acting beta agonist	112 (76%)
Inhaled corticosteroid	108 (73%)
Domiciliary oxygen or non-invasive ventilation	30 (20%)
Cardiovascular medications at admission (n, %)	
Angiotensin blocker	53 (36%)
Beta blocker	17 (12%)
Non-dihydropyridine calcium channel blocker‡	17 (12%)
Antiplatelet	41 (28%)
Anticoagulation§	8 (5%)
Statin	48 (32%)
Mineralocorticoid receptor antagonist	6 (4%)
Furosemide	26 (18%)

Values are mean±standard deviation, or n (%). * n=129. †Diffusion/transfer capacity of the lung for carbon monoxide, n=122. ‡Non-dihydropyridine calcium channel blocker: verapamil or diltiazem. §Anticoagulation: warfarin or directly acting oral anticoagulant.

Table 2: Cardiac parameters at acute exacerbation (n=148 unless indicated)

Variable	Value
Heart rate (bpm)	85.7 ± 14.1
Cardiac biomarkers (n, %)*	
Troponin elevated	38/138 (28%)
B-type natriuretic peptide elevated	63/136 (46%)
Cardiac parameters (dynamic computed tomography)	
Left ventricle	
EDVI (ml/m^2)	75.1 ± 23.0
ESVI (ml/m^2)	30.7 ± 22.1
Ejection fraction (%)	61.6 ± 13.7
Right ventricle	
EDVI (ml/m^2)	90.3 ± 25.7
ESVI (ml/m^2)	47.2 ± 22.7
Ejection fraction (%)	48.6 ± 10.6
Cardiac output indexed (left ventricular, l/min/m^2)	3.8 ± 0.9
Coronary artery calcium score (Agatston)†	
0 (none)	29 (20%)
1-99 (mild)	35 (24%)
100-399 (moderate)	30 (21%)
400-999 (severe)	20 (14%)
≥1000 (extreme)	31 (21%)

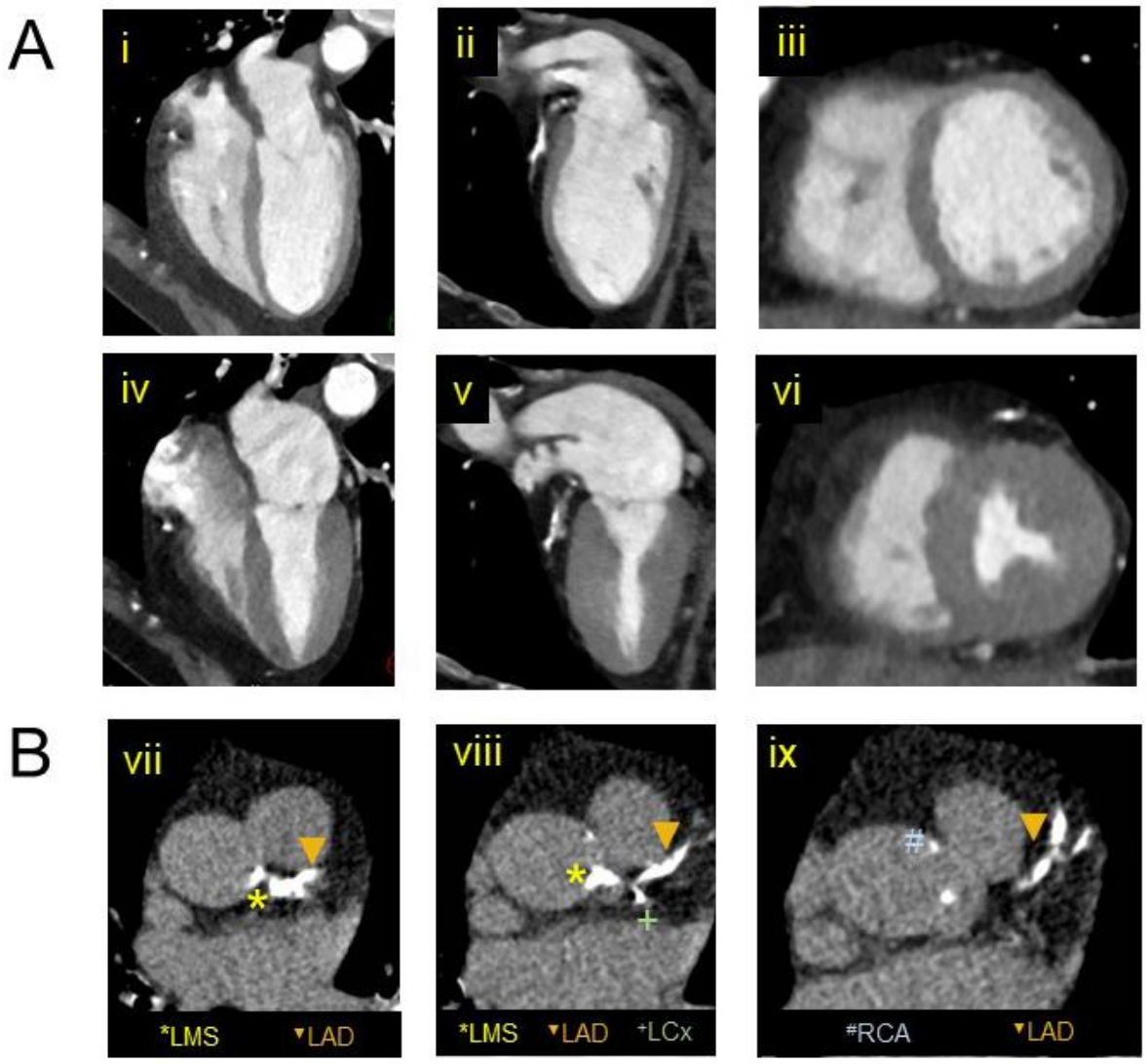
Mean ± standard deviation or n (%). *Above manufacturer's upper limit of normal. EDVI = end diastolic volume index, ESVI = end systolic volume index. Indexed values are raw values divided by body surface area. †n= 145 (two technical failures, one prior coronary bypass grafting).

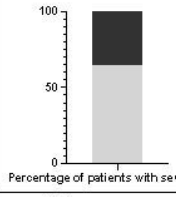
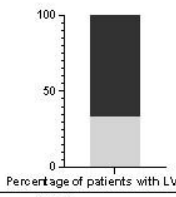
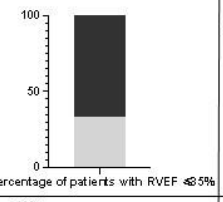
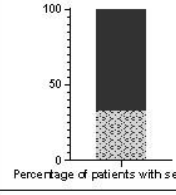
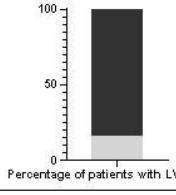
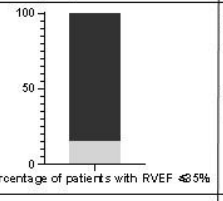
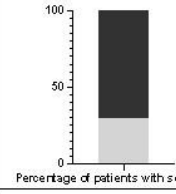
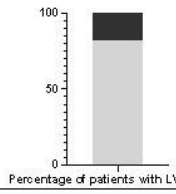
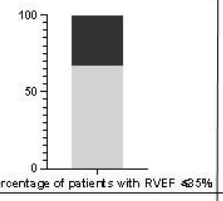
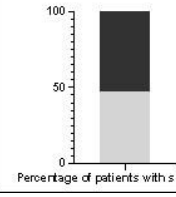
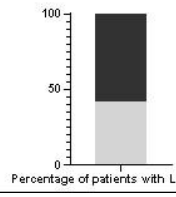
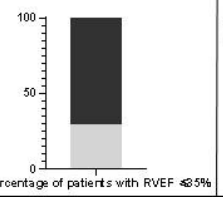
Table 3: Cardiovascular medications at admission in patients with severe cardiac disease diagnosed by computed tomography

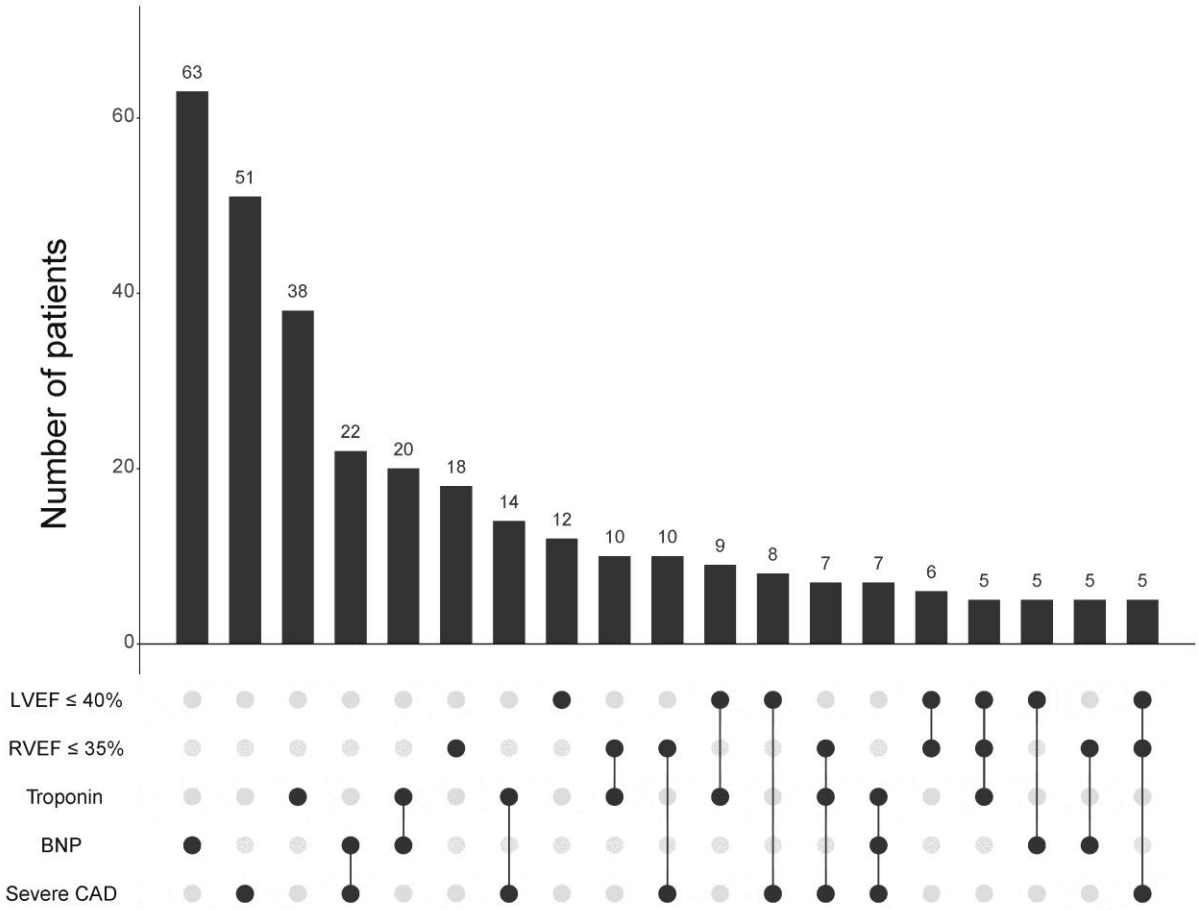
Treatment	Coronary artery calcium score ≥400, n=51	Left ventricular ejection fraction ≤40%, n=12	Right ventricular ejection fraction ≤35%, n=18
Angiotensin blocker	25 (49%)	6 (50%)	5 (28%)
Beta blocker	8 (16%)	2 (17%)	2 (11%)
Non-dihydropyridine calcium channel blocker*	6 (12%)	1 (8%)	2 (11%)
Antiplatelet	20 (39%)	6 (50%)	8 (44%)
Anticoagulation†	4 (8%)	1 (17%)	3 (17%)
Statin	27 (53%)	8 (67%)	8 (44%)
Mineralocorticoid receptor antagonist	2 (4%)	0	3 (17%)
Furosemide	11 (22%)	1 (8%)	6 (33%)

N (%). *Non-dihydropyridine calcium channel blocker: verapamil or diltiazem,

†Anticoagulation: warfarin or directly acting oral anticoagulant


A
i
ii
iii
iv
v
vi
B
vii
viii
ix
*LMS
▼LAD
*LMS
▼LAD
+LCx
#RCA
▼LAD

	Severe CAD	LVEF ≤ 40%	RVEF ≤ 35%	
Clinical diagnosis				No clinical diagnosis Clinical diagnosis
Electrocardiogram or chest x-ray				Normal ECG Abnormal ECG Chest x-ray normal Chest x-ray abnormal
Troponin				Troponin normal Troponin elevated
BNP				BNP normal BNP elevated


Number of patients
0
20
40
60
63
51
38
22
20
18
14
12
10
10
9
8
7
7
6
5
5
5
5
LVEF ≤ 40%
RVEF ≤ 35%
Troponin
BNP
Severe CAD