Correlates and Assessment of Excess Cardiovascular Risk in Bronchiectasis

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Abstract

Patients with bronchiectasis are at increased risk of cardiovascular disease. We aimed to identify factors associated with elevated cardiovascular risk in bronchiectasis, measured using aortic stiffness and cardiac biomarkers. We also sought to compare these direct measures against calculated QRISK2 scores.

Aortic stiffness, cardiac biomarkers and systemic inflammation were measured in 101 adults with stable bronchiectasis. Clinical and demographic data were also collected to allow calculation of QRISK 2 score and the Bronchiectasis Severity Index (BSI) for each patient.

The BSI score correlated with measured cardiovascular risk assessments, partly due to greater exacerbation frequency and lower FEV_1. Pulse-wave velocity was significantly higher in frequent (≥3 /year) than infrequent exacerbators (10.5 vs. 9.2ms^{-1}, p=0.01). Frequent exacerbators also had elevated serum CRP concentration suggesting increased systemic inflammation (4.8 vs. 2.2 mg/l, p=0.005). QRISK2 systematically underestimated cardiovascular risk in this population (median change in relative risk= 1.29). Under-estimation was associated with frequent exacerbations and male gender.

Patients with bronchiectasis have greater cardiovascular risk than published reference populations. Excess cardiovascular risk is associated with exacerbation frequency and impaired lung function. Cardiovascular risk assessment in bronchiectasis should be individualised as calculation tools are likely to underestimate the risk in this population.

Introduction

Bronchiectasis is defined as the persistent abnormal dilatation of bronchi in association with chronic purulent cough and/or frequent chest infections called exacerbations [1]. This pathological end point can result from a variety of diseases that affect mucociliary clearance and immunity. Consequent frequent or chronic lung infection further exacerbates mucosal damage and perpetuates the classic 'vicious' cycle [2]. Long neglected, UK mortality from bronchiectasis is currently around 1000 deaths per year and rising [3].

A large cohort analysis has demonstrated the significant burden of comorbidity carried by patients with bronchiectasis and the substantial impact this has on mortality [4]. Of interest, cardiovascular disease is likely to be causally linked to bronchiectasis as it is to other diseases which feature increased systemic inflammation [5]. We have previously defined a relationship between higher exacerbation frequency in COPD and elevated cardiovascular risk [6]. Bronchiectasis is also associated with increased systemic inflammation [7] and studies have reported that patients with bronchiectasis are at greater cardiac risk than matched controls [8, 9]. In order to reduce this excess cardiovascular risk in bronchiectasis, work is needed to better understand its correlates and how to identify bronchiectasis patients at higher risk of developing cardiovascular disease. The UK National Institute of Clinical Excellence recommends the use of the QRISK2 cardiovascular risk tool to aid decisions on blood pressure management and use of statins, but recognises that QRISK2 may not adequately assess risk in patients with systemic inflammatory disorders [10]. The QRISK2 algorithm uses epidemiological data, selected co-morbidities, cholesterol, blood pressure and body mass index to calculate the 10-year risk of myocardial infarction and stroke [11]. Rheumatoid arthritis, for example, is included in QRISK2 as a comorbidity, but bronchiectasis is not. We hypothesised that use of the QRISK2 score might systematically underestimate cardiovascular risk in patients with bronchiectasis, and therefore restrict the use of effective protective interventions.

The American College of Cardiology and American Heart Association 2013 guideline on the assessment of cardiovascular risk highlights the potential for technology such as cardiac biomarkers to better inform individual risk in patients otherwise classed as 'intermediate' [12]. One such technology is arterial stiffness, an independent predictor of cardiovascular risk in a number of patient groups [13-15]. As well as being correlated with advancing age and atherosclerotic burden, elevated arterial stiffness (measured by pulse-wave velocity) has a causal relationship with cardiovascular mortality through increased left ventricular afterload and impaired coronary perfusion [16]. Pulse-wave velocity (PWV) is a gold standard assessment of arterial stiffness providing additional predictive value beyond estimates based on existing cardiovascular risk factors [17]. Circulating cardiac biomarkers are also useful to better define individual cardiovascular risk. Troponins are markers of myocardial injury, and occult cardiac disease can result in minor elevation of circulating troponins. Troponin concentration predicts future cardiac events [18] and all-cause mortality [19] even when adjusted for standard risk factors. Brain Natriuretic Peptide (BNP) is another marker of myocardial and circulatory stress that can help predict future cardiac events and death in asymptomatic populations after adjustment for clinical risk factors [20]. An alternative approach to assessing cardiovascular risk using biomarkers is to assay markers of systemic inflammation, for example C-reactive protein (CRP) or fibrinogen which also correlate with risk of cardiovascular events [5].

We hypothesised that patients with bronchiectasis would have elevated cardiovascular risk, not adequately assessed using QRISK2. The aim of this study was to identify which disease factors were significantly associated with elevated cardiovascular risk measurements in bronchiectasis and furthermore, to determine whether measured risk was being accurately predicted by the calculated QRISK2 score.

Method

Study Subjects

101 patients with bronchiectasis were recruited as a convenience sample from clinics at the Royal Free London and University College London Hospital NHS Foundation Trusts. The study was approved by the local Research Ethics Committee (reference 10/H0720/43) and written informed consent was obtained from all participants.

Bronchiectasis was confirmed on computed tomography. Clinically significant bronchiectasis was defined as the presence of either chronic productive cough or recurrent respiratory infections together with a compatible CT scan [1]. Patients were investigated to determine the aetiology of bronchiectasis in accordance with the British Thoracic Society 2010 guideline [1]. Those with a primary diagnosis of COPD were excluded because of the recognised association of COPD with increased cardiovascular risk and since airway wall thickening and dilatation are common incidental radiological findings in COPD [21]. Patients were excluded if they were experiencing an acute worsening of respiratory symptoms, receiving treatment for an exacerbation, or had received treatment for exacerbation within two weeks.

Clinical Assessment

We collated variables allowing calculation of the Bronchiectasis Severity Index (BSI), available in 96 patients [22]. This composite score comprises age, Body Mass Index (BMI), Forced Expiratory Volume in one second (FEV_1), exacerbations within the last year, hospitalisations within the last two years, MRC (Medical Research Council) dyspnoea score, sputum colonisation with *Pseudomonas aeruginosa* or other potentially pathogenic micro-organisms, and the number of lobes involved on CT. Mild disease scores under 4 points, moderate scores 5-8 and severe disease over 8 points. Exacerbation history was defined according to healthcare utilisation and was based on patient recall [23]. Not all the variables were available in all patients: existing CT scans were available in 99

patients, sputum data were available from 77 patients and spirometry was available in 97 patients. In the absence of sputum culture results, non-colonisation was assumed but where other data were missing BSI was not calculated. Diameter of the pulmonary artery and ascending aorta was measured at the pulmonary artery bifurcation using an established method [24]. 86 CT scans were suitable for this measurement.

Pulse-wave Velocity (PWV)

Carotid-femoral PWV was measured in all patients as in our previous report [5], by one of two operators using the Vicorder system (Skidmore Medical, Bristol, UK). Values were measured in triplicate and the mean value used for analysis [6]. A pilot study carried out on 15 healthy volunteers by the two operators (ADS and BK) demonstrated good individual and inter-observer consistency assessed using intra-class correlation co-efficient (ICC): operator 1 ICC= 0.975, operator 2 ICC= 0.901, agreement between operators ICC= 0.969.

Reference ranges for PWV have been published by the 'Reference values for arterial stiffness collaboration' using large European populations of healthy subjects [25]. This is a composite analysis of multiple studies normalised to reflect values detected using the Sphygmocor device (AtCor Medical, West Ryde, NSW, Australia). These have been demonstrated to correlate well with measurements made with the Vicorder when path length is calculated using the mid-point of the femoral cuff [26].

Serum Analysis

CRP, N-terminal pro–BNP, and troponin T were measured in 100, 97 and 98 patients respectively on the day of the study visit using a Modular Analytics E 170 Module (Roche, Burgess Hill, UK) with limits of detection of 1mg/l, 2pg/ml, and 0.003mg/L respectively. Plasma fibrinogen was analysed in 78 patients using the Clauss method (IL ACL Top Coagulation Analyzer; Instrumentation Laboratories, Lexington, MA), with a limit of detection at 1.5g/L. As fibrinogen concentration was strongly correlated with CRP concentration the missing 23 fibrinogen values were imputed by regression against CRP. Results for CRP and Fibrinogen have previously been reported [27].

Statistical Analysis

Analysis was carried out using SPSS version 22 (IBM Corporation, Armonk, NY). Normality was assessed using the Kolmogorov-Smirnov test. Normally distributed data were expressed as mean ± standard deviation (SD) and skewed data as median and interquartile range (IQR). Pearson or Spearman rank correlations were applied when analysing two continuous variables as appropriate. Paired and unpaired t-tests and Mann-Whitney U tests were used when comparing means/ranks between two groups and one-way ANOVA or Kruskal-Wallis was employed for comparing means/ranks between multiple groups. Multivariate regression analysis was used to determine which components of BSI explained most variance in serum biomarkers. We assumed $p \leq 0.05$ as statistically significant unless specifically stated. Hochberg correction was performed for the multiple comparisons reported in table 2 [28]. This method controls the false discovery rate with a lower risk of type 2 error than the highly conservative Bonferroni correction [29]

Results

101 patients with bronchiectasis were recruited. Their baseline characteristics, bronchiectasis severity indices and the results of aortic stiffness (pulse-wave velocity) and cardiac biomarker measurements (pulsewave velocity, troponin T, NT-pro-BNP, fibrinogen and C-reactive protein) are reported in Table 1. As would be expected, the majority of subjects (63) were women; and the median age was 61 years. Whilst idiopathic and post-infectious disease were common (as would be seen in most cohorts) the single commonest aetiology in our subjects was primary immune deficiency (mainly common variable immunodeficiency), reflecting our local clinical practice

Correlates of elevated cardiovascular risk in bronchiectasis

The relationships between patient or disease characteristics and cardiovascular risk are reported in Table 2. There was a significant relationship between the overall severity of bronchiectasis as assessed by BSI score and all of the cardiac risk assessments. However, as age is a component of BSI and is associated with increasing cardiovascular risk (confirmed in the table) we went on to explore relationships between cardiovascular risk and key indices of bronchiectasis severity including exacerbation frequency, lung function impairment and extent of disease on CT.

Cardiovascular risk and systemic inflammation were both associated with exacerbation frequency. Patients with ≥3 exacerbations per year had a significantly higher median CRP concentration (4.8 (2.0-11.8) vs 2.2 (0.5-5.4) mg/l, p=0.005) as illustrated in Figure 1, higher mean PWV (10.5 vs. 9.2ms^{-1}, p=0.01) and elevated troponin suggesting sub-clinical myocardial injury. Multivariable analysis assessing which components of BSI predicted CRP confirmed an independent relationship with exacerbation frequency (β=0.38, p=0.001) and percent predicted FEV_1 (β=-0.23, p=0.029).

There was a correlation between radiological disease severity as assessed by the number of lobes involved on CT and the NT-pro-BNP concentration (r=0.24, p=0.02) although this was not statistically significant after Hochberg correction for multiple comparisons. To investigate whether any

association between radiological extent and cardiovascular strain (NT-pro-BNP) may be caused by pulmonary hypertension, we measured pulmonary artery (PA) diameter and the ratio between diameter of the PA and the ascending aorta (PA:A ratio), both of which correlate with invasive measures of pulmonary hypertension [30, 31]. As only 4 patients had a PA:A ratio greater than 1, we analysed the relationship between PA diameter or PA:A ratio and BNP. There were no significant correlations.

Lung function impairment (FEV_1 % predicted) was inversely correlated with troponin (r=-0.28, p=0.006), CRP (r=-0.34, p=0.001) and fibrinogen (r=-0.43, p<0.001). All of the markers were significantly and inversely related to absolute FEV_1 such that patients with lower FEV_1 have elevated markers of cardiovascular risk, and increased systemic inflammation.

Figure 1: **Exacerbation frequency in bronchiectasis is associated with increased systemic inflammation in the stable state as assessed by CRP concentrations (n=100, 2.2 vs. 4.8 mg/l, p=0.005).**

The inter-relationships between the four assessments of cardiovascular risk are reported in Table 3. All were significantly correlated with each other, with the exception of NT-pro-BNP with both CRP and fibrinogen. This suggests that assay of cardiac biomarkers, readily available in many health-care settings, may be able to reflect increased cardiovascular risk when compared to the 'gold standard' assessment of pulse-wave velocity.

Assessment of Cardiovascular Risk using QRISK2

Our cohort had significantly greater cardiovascular risk assessed using PWV than that published for age-matched controls [25]. 69 patients (68%) had a measured PWV higher than the healthy, age-adjusted mean. The mean difference between the expected and observed PWV of 0.9 ±1.6ms^{-1} was highly statistically significant (p<0.001), and associated with a median change in relative risk of adverse cardiovascular outcome of 1.29 (0.96-1.61) [32].

The QRISK2 calculator includes age, gender, ethnicity, postal (zip) code (as a marker of socio-economic status), family history of ischaemic heart disease, the presence of diabetes, chronic kidney disease, atrial fibrillation and/or rheumatoid arthritis, systolic blood pressure, cholesterol and body mass index. It estimates the 10-year absolute risk of myocardial infarction and stroke and the relative risk of these outcomes compared to a healthy individual of the same age, gender and ethnicity [11]. Compared to a healthy individual, 30 patients had their risk increased (30%) and 65 patients (64%) had their risk decreased after adjustment for these variables. Six patients' risk was unchanged.

Next we compared the QRISK2-derived relative risk with a relative risk estimate calculated as follows from the patient's measured PWV. Meta-analysis data of cardiovascular endpoints in relation to PWV has concluded that each standard deviation increase in $\log_e$ PWV is associated with a 1.45 increase in relative risk of cardiovascular events (myocardial infarction and stroke) at 5 years [32]. Using this assumption, the baseline relative risk of cardiovascular event was recalculated for each subject according to their PWV. For example, a subject aged 56 years with a PWV of 10.2ms^{-1} has a $\log_e$ PWV of 2.32 which lies 1.2 standard deviations above the median $\log_e$ PWV for healthy patients aged 50-60. Their relative risk therefore increases to 1.56 ($1.45^{1.2}$).

Calculated QRISK2 estimated lower relative risk of adverse cardiovascular outcomes than did measured pulsewave velocity in our population of patients with bronchiectasis. There was a mean difference between the relative risk calculated from QRISK2 and relative risk calculated from PWV of 0.42 ±0.78 ($p<0.001$). The different distribution of cardiovascular risk measured by PWV compared to that calculated by QRISK2 is illustrated as Figure 2. 73 patients (74%) had a higher cardiovascular risk measured by PWV than calculated by QRISK2.

FIGURE 2: Relative risk of adverse cardiovascular events calculated by QRISK2 (red) compared to risk conferred by measured pulse-wave velocity (blue), both in relation to that expected for age, gender, ethnicity and socio-economic status matched controls. Mean difference in risk = 0.42 ±0.78, p<0.001.

Finally, we went on to examine whether there were specific patient demographic or bronchiectasis characteristics that were associated with under-estimation of risk using QRISK2 compared to PWV. We examined this by comparing these variables against the magnitude of QRISK2 risk under-estimation. The data are presented as Table 4, which demonstrates that under-estimation of cardiovascular risk by QRISK2 compared to PWV was significantly associated with male gender and increased exacerbation frequency.

Discussion

The key findings of our study are that patients with bronchiectasis have greater measured cardiovascular risk than published reference control populations, that excess cardiovascular risk in bronchiectasis is associated with markers of bronchiectasis severity, specifically exacerbation frequency and impaired lung function, and that standard calculators of cardiovascular risk such as QRISK2 may underestimate measured cardiovascular risk in bronchiectasis – especially in men and in patients susceptible to frequent exacerbations. Given the biological plausibility of exacerbations driving cardiovascular damage through mechanisms such as plaque rupture [33] and microthrombosis tendency [34], it follows that exacerbation prevention may result in fewer cardiovascular events in these patients. These findings suggest that cardiovascular risk assessment in bronchiectasis should be individualised and not rely solely on calculation tools suitable for populations without the disease.

This is the largest study of individual cardiovascular risk in bronchiectasis ever reported. The first suggestion that bronchiectasis may be associated with cardiac dysfunction was a report by Alzeer in 2008 [35] demonstrating right ventricular impairment in association with pulmonary hypertension in patients with more severe, cystic disease. We have recently used population database analysis to

demonstrate a higher risk of ischaemic cardiovascular events in patients with bronchiectasis [9] and we therefore wished to investigate cardiovascular risk in a carefully phenotyped cohort of patients with bronchiectasis. Pulse-wave velocity (PWV) is a gold standard assessment of arterial stiffness that we have previously reported is stable over time and reproducible [6]. PWV provides additional predictive value beyond estimates based on existing cardiovascular risk factors [17]. Our findings are consistent with those published in cystic fibrosis [36] as well as those of Gale [8] who reported a higher aortic pulse wave velocity in 20 patients with bronchiectasis compared to controls. Greater aortic stiffness directly impacts cardiovascular events, as there is premature return of the reflected pulse-wave during late systole which impairs normal diastolic filling of the coronary arteries. In addition, stiffer central arteries impose a greater afterload on the heart and increase myocardial work, which over time may result in ventricular dysfunction [37]. In support of this, we found a significant correlation between aortic stiffness and the concentration of NT-pro-BNP.

We next went on to explore which features of bronchiectasis were associated with increased cardiovascular risk. Whilst the composite Bronchiectasis Severity Index (BSI) related strongly to aortic stiffness, both are age-dependent. Regarding specific features of bronchiectasis, the factors significantly associated with aortic stiffness were exacerbations and FEV_1. The elevation in pulse-wave velocity of $1.3ms^{-1}$ in patients experiencing three or more exacerbations annually, versus infrequent exacerbators, equates to a clinically significant excess risk of between 12 and 18% [38]. This difference is therefore large enough to be associated with adverse outcomes in patients susceptible to frequent exacerbations. We used a threshold of three exacerbations per year to define frequent exacerbations as this is used in the BSI score [22], and bronchiectasis guidelines [1]. It is known that exacerbations affect quality of life in bronchiectasis [39] and our findings extend the rationale for exacerbation prevention to include possible reduction in adverse cardiovascular outcomes.

We have previously defined an association between exacerbation frequency and cardiovascular risk in COPD [6]. Although this association in COPD may be confounded by smoking, chronic inflammatory conditions such as rheumatoid arthritis are also associated with elevated vascular risk supporting chronic inflammation itself as a driving force [40]. Similarly, in Systemic Lupus Erythematosus cardiovascular disease accounts for 50% of mortality and is strongly associated with markers of inflammation including fibrinogen and CRP [41]. Our finding of higher baseline CRP in frequent exacerbators supports a mechanism of chronic inflammation underlying their elevated cardiovascular risk. Whilst the concept of an independent exacerbation susceptibility phenotype associated with poor clinical outcomes is accepted in COPD [42], further work is required to establish whether the same is true in bronchiectasis. However, we have recently reported that increased systemic inflammation is seen even in community treated exacerbations [43].

Greater impairment in lung function, as assessed by FEV_1, was also associated with both increased systemic inflammation and elevation of cardiac risk. It has previously been reported that smaller lungs are associated with increased arterial stiffness and cardiovascular death in a general population which reflects our finding in this disease group [44]. The extent of disease on CT was associated with elevation of BNP (uncorrected analysis), in support of the study described earlier in which more severe cystic disease was associated with ventricular dysfunction [35]. We postulated that pulmonary hypertension may be the mechanism underlying this association and performed a univariate analyses between PA:A ratio and PA diameter, both established surrogates of pulmonary hypertension [30, 31], and BNP and CT lobar extent. We found no correlation between radiological extent and CT measures of pulmonary hypertension, similar to Deveraj *et al.*. We hypothesise that the link between BNP, a measure of cardiac impairment, and CT extent of disease is through systemic inflammation causing cardiac strain rather than specifically through pulmonary vascular disease.

Whilst CT extent was not related to arterial stiffness, the extent of disease did relate to cardiac impairment, and lung function to markers of myocardial damage and systemic inflammation. These findings suggest that preservation of lung function and minimisation of disease extent are also important goals in bronchiectasis management with regard to the mitigation of future cardiovascular disease.

Having identified increased cardiovascular risk in bronchiectasis, the next question we addressed was how this should best be assessed. We demonstrated that the QRISK2 score systematically under-estimated cardiovascular risk in bronchiectasis compared to calculating risk using PWV data, particularly in male patients, and those experiencing frequent exacerbations. We have shown that the latter group has elevated systemic inflammation in the stable state. We speculate that including inflammatory conditions such as bronchiectasis in cardiovascular risk calculators may improve predictive value. We suggest that an individual approach to cardiovascular risk assessment is required, with the use of additional tools where calculated risk is intermediate. This might include assessment of cardiac biomarkers (which correlated with pulse-wave velocity in this study) or pulse-wave velocity itself, or indeed alternative approaches such as coronary artery calcium score. The latter is attractive given the need for a chest CT scan to make the diagnosis of bronchiectasis. Biochemical analysis of cardiac biomarkers is likely the easiest measure to perform in routine practice but age-specific values from healthy populations are not available and we defined significant relationships between both troponin and BNP with age in this study. We cannot comment on whether other risk scores under-estimate cardiovascular risk in bronchiectasis; an idealised prospective study would be to measure risk with sufficient follow-up to record a significant number of future cardiovascular events.

Our results emphasis the importance of exacerbation prevention strategies in bronchiectasis not only to improve quality of life and to reduce lung morbidity, but also to potentially prevent cardiovascular disease events. Our data also suggest that anti-inflammatory therapies may have the

additional benefit of reducing cardiovascular risk, which should be considered as an exploratory end-point in future clinical trials. Although there are currently no licenced anti-inflammatory interventions available in bronchiectasis, we have recently demonstrated that specific components of systemic inflammation in bronchiectasis are related to disease severity and aetiology and elucidating the underlying pathways may identify novel therapeutic approaches [27].

There were some limitations to this study. Patients with bronchiectasis related to primary immunodeficiency are over-represented in this sample, reflecting our local referrals; this is a limitation of any single-centre study in bronchiectasis and there can never be a 'typical' population. The 28 subjects with primary immunodeficiency-related bronchiectasis were removed for an exploratory sub-analysis in order to determine whether overrepresentation of this group may have skewed results. Pulsewave velocity remained significantly greater in frequent exacerbators (≥3 exacerbations per year) compared to infrequent (10.8 vs 9.4ms^{-1}, p=0.005), as did CRP (3.9 (2.0-11.0) vs 2.3 (0.9-5.2) mg/L, p=0.019). Relative risk remained greater when measured by pulsewave velocity compared to QRISK score (0.86 (0.69-1.04) vs 1.33 (0.96-1.67), p=<0.001). This demonstrates that, despite reduced statistical power, our main results are robust to removal of patients with primary immunodeficiency from the analysis.

In other limitations, we may have been under-powered to detect weaker correlations, and did not perform an *a priori* power calculation. We cannot exclude the possibility that the relationship between frequent exacerbators and arterial stiffness represents, in part, elevated PWV persisting from the preceding exacerbation. We used a novel approach to calculate the excess cardiovascular risk attributable to elevated arterial stiffness. This relied on the use of a reference range for pulse-wave velocity and assumes that the relative risk increase attributable to a given increase in arterial stiffness is attributable to our study population. Ben-Shlomo *et al* [32] made PWV-based adjustments to the relative risk of cardiovascular events over five years, whereas QRISK calculates a

ten year risk. We made the assumption that changes in pulse-wave velocity would adjust the relative risk of cardiovascular events over five and ten years in a linear way.

In conclusion, we confirm that bronchiectasis is associated with increased cardiovascular risk, and define that this is related in part to the frequency of exacerbations and impairment in lung function. Assessment of cardiovascular risk using tools such as QRISK2 could underestimate risk in some patients, especially males and those susceptible to frequent exacerbations. Therefore an individual approach should be used for patients with intermediate risk. Awareness and mitigation of existing cardiovascular risk factors, and exacerbation prevention and anti-inflammatory therapy in bronchiectasis all have the potential to reduce cardiovascular events and require further study if we are to improve clinical outcomes in this neglected disease.

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Table 1: Baseline characteristics, bronchiectasis severity indices and assessment of pulse-wave velocity and cardiac biomarkers in 101 patients with bronchiectasis. *Data are presented as %, mean (±SD) or median (IQR) as appropriate.*

	Subjects n=101
Age (years)	61.0 (46.1-71.6)
Male	38 (38%)
Current Smoker	2 (2%)
Ex-smoker	28 (28%)
Pack Years (Current/Ex-smokers)	3.5 (1-15)
Body Mass Index (kg/m^2)	23.0 (20.9-25.7)
Systolic Blood Pressure (mmHg)	126 (115-139)
Diastolic Blood Pressure (mmHg)	80 (70-85)
Total Cholesterol (mmol/l)	4.8 ±0.4
Aetiology	
Primary Immunodeficiency[a]	28 (28%)
Idiopathic	21 (21%)
Post-infective	19 (19%)
Allergic Broncho-Pulmonary Aspergillosis	9 (9%)
Other[b]	24 (24%)
Long-term Macrolide	19 (19%)
Long-term Nebulised Antibiotic	3 (3%)
Inhaled Corticosteroid	42 (42%)
FEV_1 (% Predicted)	72.7 ±27.0
FEV_1 (l)	1.94 ±0.88
Exacerbation Frequency (/year)	2 (1-3)
Days since last exacerbation	171 (62-388)
Number of lobes involved on CT	4 (3-6)
Pulmonary Artery Diameter (mm)	25.5 ±4.0
Pulmonary Artery:Aorta Ratio	0.77 (0.70-0.84)
MRC Dyspnoea Score	2 (1-3)
Bronchiectasis Severity Index	5.5 (3-8)
Pulse Wave Velocity (ms^{-1})	9.3 (8.1-10.9)
Troponin T (μg/l)	0.006 (0.003-0.009)
NT-pro-BNP (pmol/l)	10.0 (4.5-17.0)
Fibrinogen (g/l)	3.31 (2.69-4.12)
C-reactive protein (mg/l)	3.2 (1.0-7.7)

[a]Common Variable Immunodeficiency (23), IgG Deficiency (4), X-Linked Agammaglobulinaemia (1)

[b]Aspiration (4), Kartagener's Syndrome (3), Tuberculosis (3), Rheumatoid Arthritis (3), HIV (3), Graft Versus Host Disease (2), Systemic Lupus Erythematosus (1), Sarcoidosis (1), Secondary Immunodeficiency (1), Surgery Related (1), Post radiotherapy (1), Non-Tuberculous Mycobacteria (1), Inflammatory Bowel Disease (1), Mounier-Kuhn Syndrome (1).

Table 2: Relationships between assessments of cardiovascular risk, and bronchiectasis severity index (BSI) / selected individual components. *Significant findings are in bold. Data are expressed as mean (±SD) or median (IQR), and r or rho as appropriate. * significant at α < 0.05, ** significant after Hochberg adjustment for multiple comparisons*

		PWV (m/s) n=101		Troponin (µg/l) n=98		NT-Pro-BNP (pmol/l) n=97		Fibrinogen (g/l) n=100		CRP (mg/l) n=100	
			p=		p=		p=		p=		p=
BSI		**0.45**	**<0.001****	**0.52**	**<0.001****	**0.34**	**0.001****	**0.39**	**0.001****	**0.24**	**0.017***
Age		**0.77**	**<0.001****	**0.59**	**<0.001****	**0.47**	**<0.001****	**0.28**	**0.012***	0.10	0.323
Annual Exacerbation Frequency	≥3 (n=40)	**10.5 ±2.7**	**0.011***	**0.008 (0.004-0.013)**	**0.047***	11.0 (5.0-18.5)	0.293	3.5 (2.7-4.3)	0.253	**4.8 (2.0-11.8)**	**0.005***
	<3 (n=61)	**9.2 ± 1.7**		**0.005 (0.003-0.008)**		9.0 (3.0-17.0)		3.2 (2.7-3.9)		**2.2 (0.5-5.4)**	
FEV_1 (l)		**-0.34**	**0.001****	**-0.42**	**<0.001****	**-0.34**	**0.001****	**-0.53**	**<0.001****	**-0.45**	**<0.001****
FEV_1 % Predicted		-0.02	0.832	**-0.28**	**0.006***	-0.11	0.301	**-0.43**	**<0.001****	**-0.34**	**0.001****
CT Lobes involved		0.14	0.159	0.17	0.091	**0.24**	**0.02***	-0.07	0.570	0.07	0.482

Table 3: Relationships between individual assessments of cardiovascular risk in 101 patients with bronchiectasis.

	Troponin (µg/l) n=98		NT-pro-BNP (pmol/l) n=97		Fibrinogen (g/l) n=78		CRP (mg/l) n=100	
		p=		p=		p=		p=
Pulse-wave velocity (ms^{-1})	**0.49**	**<0.001**	**0.27**	**0.008**	**0.24**	**0.036**	**0.20**	**0.043**
CRP (mg/l)	**0.20**	**0.045**	0.01	0.258	**0.55**	**<0.001**		
Fibrinogen (g/l)	**0.37**	**0.001**	0.19	0.090				
NT-pro-BNP (pmol/l)	**0.44**	**<0.001**						

TABLE 4: Relationships between patient and bronchiectasis indices, and the magnitude of cardiovascular risk under-estimation using QRISK2 compared with Pulsewave Velocity. *Data expressed as r or rho as appropriate, and mean* ***±****SD (gender).*

		Degree of relative risk underestimate by QRISK2	p=
Age		-0.16	0.12
Gender	Male	**0.62 ±0.85**	**0.037**
	Female	**0.29 ±0.70**	
BSI		0.06	0.59
FEV_1		0.06	0.54
FEV_1 % predicted		-0.12	0.23
Lobes involved on CT		-1.0	0.34
Exacerbation Frequency		**0.26**	**0.008**
MRC Score		0.04	0.68
Systolic BP		-0.03	0.78
Fibrinogen		0.01	0.94
Troponin		-0.05	0.65
NT-pro-BNP		-0.06	0.59
CRP		0.17	0.09