APPROPRIATENESS OF PRESCRIBING OF DIRECT ORAL ANTICOAGULANTS IN A UNIVERSITY TEACHING HOSPITAL NETWORK

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Introduction Direct oral anti-coagulants (DOACs) have been developed that provide simplified, fixed dose regimes over variable dosing with vitamin K anticoagulants. However, DOAC dosing is dependent on indication, demographics and co-morbidities, such as renal impairment. Inappropriate dosing is associated with harm with both unintentional under- and excessive-dosing [1]. The purpose of this study is to describe the appropriateness of DOAC prescribing with respect to the criteria set out in summary of product characteristics (sPC) and British National Formulary [2,3].

Methods A retrospective audit of consecutive in-patients, over a 3-month period, prescribed DOACs in St Bartholomew's and Royal London hospitals from November 2018 was performed. Data was extracted from electronic healthcare and pharmacy records. Inclusion criteria: prescribed a DOAC (apixaban, dabigatran, edoxaban and rivaroxaban), recorded dose and frequency, patient sex, age and weight; serum creatinine (sCr). Exclusion criteria: use of non-DOAC anticoagulant, record duplication and incomplete records. Dosing appropriateness was compared for each of the drugs with respect to indication and criteria set in individual sPCs.

Results 360 patients were prescribed DOACs, of whom 203 (56%) satisfied inclusion/exclusion criteria. Main reasons for non-inclusion were incomplete records (n=54) and record duplication (n=91). Mean age was 76±24 years, with 23% of patients >80 years-old and 15% <60 kg. Renal function (creatinine clearance (CrCl), calculated using Cockcroft-Gault method) was <50 mL/min in 42% of patients. The majority of DOAC prescribing was for atrial fibrillation (71%). For the

individual DOACs, dose appropriateness was best for dabigatran (93.3%, n=14/15 patients) and edoxaban (95.2%, 20/21 patients). Rivaroxaban was prescribed appropriately in 81% (n=58/72) of patients and apixaban was prescribed appropriately in 82% (n=78/95) of patients. Majority of dose inappropriateness was due to non-indicated underdosing (n=29/34). For rivaroxaban, this was apparent in patients with a significant discrepancy between renal function measured by eGFR (CKD-EPI equation) and calculated CrCl (Cockcroft-Gault method, recommended in sPC and used in the clinical trials). For patients requiring reduced dosage, this was correctly prescribed in 92% (n=35/38) patients.

Conclusion In our university hospital network, more patients were underdosed relative to their indication than was expected. This may be due to usage of clinically available eGFR, which is routinely available as part of hospital systems, rather than using manually calculated CrCl and the multiple criteria required to dose apixaban correctly. Further education of prescribers and ward-based pharmacists is required to improve the prescribing quality with the aim of improving treatment efficacy and safety outcomes.

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Conflict of Interest nil

CARDIOVASCULAR RISK PROFILE AND DISEASES IN PATIENTS WITH SARCOIDOSIS IN THE ACALM BIG DATA REGISTRY

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Abstract 120 Table 1 Prevalence of comorbid cardiovascular disease in patients with sarcoidosis

	Sarcoid Prevalence	Control Prevalence	Adjusted Risk
	n (%)	n (%)	Odds ratio (95% CI)
Hypertension	256 (28.4%)	1,562 (17.3%)	1.724 (1.430-2.078)***
Hyperlipidemia	102 (11.3%)	605 (6.7%)	1.310 (1.014-1.691)*
T1DM	19 (2.1%)	107 (1.2%)	1.284 (0.769-2.144)
T2DM	152 (16.9%)	682 (7.6%)	1.961 (1.587-2.425)***
IHD	97 (10.8%)	801 (8.9%)	0.849 (0.656-1.097)
ACS	13 (1.4%)	242 (2.7%)	0.394 (0.220-0.707)**
Heart Failure	51 (5.7%)	209 (2.3%)	2.202 (1.549-3.130)***
AF	46 (5.1%)	283 (3.1%)	1.215 (0.855-1.727)
CKD	43 (4.8%)	122 (1.4%)	2.862 (1.967-4.164)***
Cerebrovascular	17 (1.9%)	156 (1.7%)	0.814 (0.482-1.375)
PVD	8 (0.9%)	104 (1.2%)	0.473 (0.221-1.010)

Odds ratio for comorbid cardiovascular disease adjusted by multivariate logistic regression accounting for demographics and cardiovascular diseases * = p<0.05 ** = p<0.01 *** = p<0.001
T1DM = Type 1 Diabetes Mellitus. T2DM = Type 2 Diabetes Mellitus. IHD = Ischemic Heart Disease. ACS = Acute Coronary Syndrome.
AF = Atrial Fibrillation. CKD = Chronic Kidney Disease. PVD = Peripheral Vascular Disease.

Background Sarcoidosis is a chronic systemic disease associated with cardiovascular manifestations. Although various inflammatory conditions have become recognized as non-traditional risk factors for cardiovascular disease (CVD), the risk profiles in sarcoidosis remain uncharacterised due to its rarity. Using a big data approach we evaluated the burden of CVD on patients with sarcoidosis.

Methods The Algorithm for Comorbidities, Associations, Length of Stay and Mortality (ACALM) study consists of 1816230 patients admitted hospitals in England between 2000–2014. All patients admitted with sarcoidosis were compared to age and gender matched control groups and multivariate logistic regression analyses were used to evaluate the risk of CVD.

Results 902 sarcoid patients were compared to an age and gender matched control group of 9020 patients (mean age 50±15, 50.4% male). Both groups were predominantly Caucasian (sarcoid 50.3% vs. control 78%) but as expected, higher proportions of sarcoid patients were Afro-Caribbean (18.2% vs. 3.0%) and South Asian (20.2% vs 7.3%). Sarcoid patients were significantly more likely to have heart failure (Odds ratio, OR 2.2), chronic kidney disease (OR 2.9), hypertension (OR 1.7), hyperlipidaemia (OR 1.3), and type 2 diabetes (OR 2.0). They were less likely to have acute coronary syndrome (OR 0.4).

Conclusion Sarcoidosis is associated with a marked increase in heart failure and kidney disease, as well as a range of traditional CVD risk factors which need to be managed. These results are illustrated in Table 1.

Conflict of Interest none

Valve Disease/Pericardial Disease/ Cardiomyopathy

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RE-EVALUATING THE GENETIC CONTRIBUTION OF MONOGENIC DILATED CARDIOMYOPATHY

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Introduction Dilated cardiomyopathy (DCM) is genetically heterogeneous, with >100 purported disease genes tested in clinical laboratories. However, many genes were originally identified based on candidate-gene studies that did not adequately account for background population variation. Here we define the frequency of rare variation in 2538 DCM patients across protein-coding regions of 56 commonly tested genes and compare this to both 912 confirmed healthy controls and a reference population of 60,706 individuals in order to identify clinically interpretable genes robustly associated with dominant monogenic DCM.

Methods We used the TruSight Cardio sequencing panel to evaluate the burden of rare variants in 56 putative DCM

genes in 1040 DCM patients and 912 healthy volunteers processed with identical sequencing and bioinformatics pipelines. We further aggregated data from 1498 DCM patients sequenced in diagnostic laboratories and the ExAC database for replication and meta-analysis.

Results Specific variant classes in TTN, DSP, MYH7 and LMNA were associated with DCM in all comparisons. Variants in BAG3, TNNT2, TPM1, NEXN and VCL were significantly enriched specific patient subsets, with the last 3 genes likely contributing primarily to early-onset forms of DCM. Overall, rare variants in these 9 genes potentially explained 19–26% of cases. Whilst the absence of a significant excess in other genes cannot preclude a role in disease, such genes have limited diagnostic value since novel variants will be uninterpretable and therefore non-actionable, and their diagnostic yield is minimal.

Conclusion In the largest sequenced DCM cohort yet described, we observe robust disease association with 9 genes, highlighting their importance in DCM and translating into high interpretability in diagnostic testing. The other genes evaluated have limited value in diagnostic testing in DCM. This data will contribute to community gene curation efforts, and will reduce erroneous and inconclusive findings in diagnostic testing.

Conflict of Interest None

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ENDOTHELIAL LOSS AS A CAUSE OF IMPAIRED MYOCARDIAL PERFUSION RESERVE IN SEVERE AORTIC STENOSIS

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Introduction Impaired myocardial perfusion reserve occurs in pressure overload hypertrophy such as in severe aortic stenosis (AS) despite unobstructed epicardial coronaries. However the pathological mechanisms underlying this are poorly understood. We sought to assess myocardial perfusion reserve in severe AS by stress perfusion cardiovascular magnetic resonance (CMR), and examine the findings in relation to the histological evidence of vascular changes in the myocardium.

Methods Fourteen patients with severe AS and unobstructed epicardial coronaries underwent adenosine stress perfusion CMR before and 6 months after surgical aortic valve replacement (AVR). Myocardial biopsies were obtained during AVR and stained using CD31+ for endothelium, smooth muscle actin (SMA) for smooth muscle, and picosirius red for fibrosis. Nine age- and sex- matched post-mortem myocardial samples served as histological controls.

Results When compared to controls, the myocardium of patients with severe AS had reduced vessel density, total quantity of SMA+ve and CD31+ve, in addition to the expected increase in fibrosis. (figure 1) There was absence of CD31+ve endothelium in SMA+ve arterioles, indicating endothelial loss. Importantly, patients with an aortic valve area (AVA) $\leq 0.8\text{cm}^2$ had greater endothelial loss compared to those with an AVA > 0.8 and $\leq 1.0\text{cm}^2$ ($1.34 \pm 0.44\%$ vs $2.84 \pm 1.03\%$, $p=0.006$), and endothelial loss also correlated with myocardial perfusion reserve index (MPRI), $r=0.66$, $p=0.019$. MPRI improved significantly post AVR (from 0.95 ± 0.17 to 1.50 ± 0.43 , $p=0.018$).