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Potential recruitment into a clinical trial of vascular secondary prevention medications in cerebral small vessel disease, based on concomitant medication use

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A B S T R A C T

Background: Blood pressure-lowering medications, antiplatelet drugs and statins are often prescribed to asymptomatic patients with white matter hyperintensities (WMH). A clinical trial is needed, but potential trial participants would be excluded if they already had another indication to take the medication. It is likely that many patients with WMH would already have a recognised vascular-related indication for these drugs.

We used data from the UK Biobank study to determine what proportion of people with WMH were not taking these drugs and would be potentially able to enter a clinical trial of antiplatelet drugs, statins, or BP-lowering medication.

Methods: We used the UK Biobank MRI sub-study of healthy volunteers aged 40–70 years as our cohort. We considered that WMH volumes in the top quartile (2.7–89 mls) were severe enough for a patient to be at risk of progression and be offered treatment. Such patients could also be included in a hypothetical clinical trial if there were no contraindications. Using the product licenses, we defined exclusion criteria for four hypothetical clinical trials of aspirin, clopidogrel, statins, and tight BP control. We then calculated what proportion of patients would still be eligible if these criteria were applied.

Results: 5794/23,179 patients had WMH in the top quartile. Of these, 4006/5794 69% (95% CI 68–70%) would be eligible for a trial of aspirin; with 81% (95% CI 80–82%) eligible for a trial of clopidogrel; 56% (95% CI 55–58%) of patients would be eligible to enter into a trial of a lower BP target, and 58% (95%CI 57–59%) would be able to enter a trial of a statin.

Conclusions: Over 80% of patients with WMH in the UK biobank would be eligible to enter a trial of an antiplatelet and just over half would be eligible to enter a trial of a statin or BP-lowering medication.

1. Introduction

White matter hyperintensities on MRI (WMH) are a widely recognised imaging feature of cerebral small vessel disease (SVD). SVD is associated with increased risk of stroke, dementia, disability, and death [1,2]. Whilst there is no proven evidence based treatment, many clinicians treat small vessel disease (including WMH) by targeting vascular risk factors with blood pressure (BP) lowering medications, antiplatelet agents and statins [3].

To date both established [4] and proposed [5] trials of potential treatments for SVD have focused on the patient with a lacunar stroke: a symptomatic lacunar stroke is a time when a patient can be identified as having currently active SVD. However, it may be beneficial to start treatment of SVD in its earlier, largely asymptomatic, stages.

Logically, antihypertensives, antiplatelets and statins may be beneficial. Intensive blood pressure control may reduce the size of WMH [6,7] as uncontrolled hypertension in midlife increases the risk of dementia in later life [8]. Antihypertensive treatment, antiplatelet drugs and statins are gold standard treatment in people presenting with an ischaemic stroke (including lacunar stroke), therefore it is reasonable to assume that people with WMH, without a symptomatic stroke, would benefit from treatment. However, the secondary prevention of small subcortical strokes (SPS3) trial found dual antiplatelet agents to increase mortality and haemorrhage risk in patients with lacunar stroke [9].

Given that antiplatelets, antihypertensives, and statins are already prescribed by some practitioners; given the clinical uncertainty about the benefit of using these drugs for incidental asymptomatic SVD, a large-scale trial is needed to determine if these are justifiable therapies. However, recruitment to such a trial may be difficult as many potential

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participants may either be taking the medication for another indication or have a known contra-indication.

Due to the above, we aimed to establish what proportion of asymptomatic study participants with WMH on imaging would be able to enter a hypothetical clinical trial. We used the neuroimaging, and self-reported clinical and medication data from the UK Biobank. This is a large prospective observational study of healthy volunteers whose aim is to improve the prevention, diagnosis and treatment of a wide range of illnesses [10].

2. Methods

All participants provided written consent to be included in the UK Biobank and had a full understanding of the resource's aims and purpose. We operated and used the data under the framework of the UK Biobank's ethics and governance council (https://www.ukbiobank.ac.uk/wpcontent/uploads/2011/05/EGF20082.pdf), this analysis was completed under application number 17,689. This study was covered by the generic ethical approval for UK Biobank studies from the NHS National Research Ethics Service (approval letter dated 17th June 2011, Ref 11/NW/0382).

2.1. Participants

Adult volunteers were recruited between 2006 and 2010 and were assessed with a standard protocol. At baseline recruitment into the UK Biobank, health and lifestyle data were collected for each participant through a questionnaire, physical measurements, and biological samples [11]. Baseline assessment included comprehensive medication data, both prescribed and over the counter. A subset of participants had subsequent neuroimaging with MRI, beginning in 2014.

2.2. Small vessel disease assessment

The UK biobank imaging protocol compromises MRI sequences including T1, T2 FLAIR, diffusion and susceptibility-weighted imaging [10,12]. For our assessment of SVD; we used T1 and T2 FLAIR images, focusing on WMH and assessing lesion volume as a continuous variable [2]. The methodology for acquiring the MRI data, including the method for calculating WMH volumes, has been described previously [10, 13]. Briefly, all images were acquired using a Siemens 32-channel head coil [14,15]. T2 FLAIR images were also acquired in the sagittal orientation but with a resolution of $1.05 \times 1 \times 1$ mm [10]. The image processing was carried out using an automated sequence, which extracted volume of different tissues including WMH from the T1 and T2 FLAIR sequences.

We defined SVD status according to WMH volume quartiles, with those in the top quartile of WMH volumes defined as having SVD eligible for treatment in a trial. In the absence of a recognised threshold above which WMH is considered pathological, we considered that this was a population of people who had some WMH and were well enough to take part in a research study, and thus were analogous to the population who would be considered for a clinical trial.

2.3. Defining eligibility criteria for clinical trials

We then defined and applied a series of trial inclusion/exclusion criteria to this SVD cohort and assessed the proportion eligible for study inclusion. We chose four possible strategies that may have benefit in SVD: BP lowering, statins, aspirin and clopidogrel. In designing each trial protocol, we consulted the Electronic Medicine Compendium and British National Formulary (BNF) version 77 to determine cautions, indications and contraindications [16,17]. Additionally, for the trial of BP lowering we used a modified version of the inclusion and exclusion criteria of the 2015 SPRINT trial, which was a trial of BP lowering to a target rather than using particular medications [18] (Fig. 1).

Broadly, we assumed that patients would not be able to participate in the clinical trial if they had either an existing indication for treatment, or an existing contraindication or caution for treatment. Therefore patients with previous symptomatic stroke or TIA would not be recruited to a trial, as that is a well-recognised indication for treatment with antihypertensives, antiplatelets or statins. We also assumed that a patient with a relative contraindication would be unlikely to be recruited into a clinical trial. The exclusion criteria for trials of BP lowering and statins are shown in Table 1 and for antiplatelets are shown in Table 2.

We used simple descriptive statistics for baseline characteristics of those defined as having SVD eligible, for treatment in a trial, and for those who could be included in each of our theoretical trials. We also assessed baseline differences in demographics and vascular risk factors between those defined as having SVD eligible for treatment in a trial, and compared these with the rest of the UK Biobank cohort using parametric and proportion tests as required. All statistical analysis was carried out on Minitab version 9. If data was missing from physiological measurements carried out at study visits, the patient was excluded from analysis requiring that measurement. If data on whether a patient had a condition was missing, the patient was assumed not to have the condition.

As relatively few biobank participants had severe WMH, we carried out a subgroup analysis in which the analysis was repeated for the subgroup of participants with a WMH volume of 20 mls or greater.

3. Results

At the time of data extraction (19/05/2018), brain imaging data were available for 23,179 participants of the 502,628 recruited to UK biobank. 5794 of the 23,179 had a total WMH volume in the highest quartile with a range of 2.7–89mls, and median 5.2mls. The second-highest quartile had a median of 1.6mls WMH volume; both the third and fourth quartiles had a median of 0mls of WMH volume. Data on blood pressure was missing from 57 participants. The participants with high WMH (Table 3) had a mean age of 69 years, 52% were male, 44% were either current or previous smokers, 37% had pre-existing vascular disease, and 9% had pre-existing cardiac disease. The mean BP was 141/80, and the majority - 67% (3966/5794) - were on at least one BP-lowering drug.

The participants with high WMH who could be entered into a clinical trial were less likely to have a pre-existing vascular or cardiac condition and were slightly younger, than those that could not be entered into the clinical trial.

3.1. Aspirin and Clopidogrel

4006/5794 (69.1%, 95% CI: 68.0–70.3%) were eligible for a trial of aspirin compared to 4710/5794 (81.3%, 95% CI: 80.3–82.3%) being eligible for a trial of clopidogrel. Reasons for exclusion are shown in Fig. 2: 792 patients (13%) would have been excluded as they were already on an antiplatelet or anticoagulant drug. More patients were eligible for a trial of clopidogrel, as 593 patients were excluded from the aspirin trial due to a diagnosis of asthma, which is a relative contraindication.

3.2. Antihypertensives

3262/5794 (56.3%, 95% CI: 55.0–57.6%) could be recruited to a study of BP lowering to a target of 120 mmHg using similar eligibility criteria to the SPRINT trial. 1606 were excluded as they had a systolic BP below 130, and 1802 did not have hypertension which would have made them eligible to be included in SPRINT [19], (i.e. 130–180 mmHg on ≤1 medication, 130–170 mmHg on ≤2 medications, 130–160 mmHg on ≤3 medications, 130–150 mmHg on ≤4 medications). SPRINT used stratified recruitment to maximize the cohort more likely to benefit from treatment.

Table 1
Exclusion Criteria for trial of BP- lowering or statin.

BP Lowering exclusion criteria	Statin exclusion criteria
Indication for a specific BP medication*	Currently on any of the following medications:Any lipid lowering therapy including statins, fibrates, and othersCiclosporinDiagnosis of one of the following:High cholesterolAny arrhythmiaLiver DiseaseAny hepatitis, liver failure, cirrhosis, chronic liver disease, any other liver/biliary/pancreas problemHypothyroidismAny pancreatic disease (including pancreatitis)Any biliary tree diseaseBowel obstruction or malabsorption (including coeliac disease)Any haemorrhagic disorder
Secondary Hypertension	
Diabetes	
History of Stroke	
History of Polycystic Kidney Disease	
Glomerulonephritis	
History of dementia	
Organ transplant	○ Platelet disorder;Essential thrombocytosis; Genetic haematological disorder; Aplastic anaemia; DVT; Cerebral haemorrhage; Menorrhagia; Polycythaemia Vera; Excessive bleeding; Myeloproliferative disorder; Anaemia; Neutropenia; Sub-Arachnoid haemorrhage; Subdural haemorrhage
Systolic BP < 130 mmHg	
Did not have prospect for medications to be increased as per sprint protocol e.g. to be included patients needed:	
130–180 mmHg on ≤1 medication	
130–170 mmHg on ≤2 medication	
130–160 mmHg on ≤3 medication	Peptic ulcerAny neurodegenerative diseaseAt increased risk of muscular toxicity:Diagnosis of myopathy; rhabdomyolysis; renal failure; or any other renal disease.
130–150 mmHg on ≤4 medication	

* Specific BP indicationsAlpha blockers: benign prostatic hyperplasia, vasospasm, ACE inhibitors: heart Failure, diabetic nephropathy, myocardial infarction, angiotensin II receptor blockers: heart failure, diabetic nephropathy, beta blockers: heart failure, myocardial infarction, angina, arrhythmias, supraventricular tachycardia, atrial fibrillation, thyrotoxicosis, anxiety/panic attacks, migraine prophylaxis, glaucoma, essential tremor, calcium channel blockers: angina, supraventricular tachycardia, raynaud's, migraines. Diuretics: heart failure, pulmonary oedema, nephrogenic diabetes insipidus, primary hyperaldosteronism, ascites/oedema in hepatic cirrhosis, malignant ascites, nephrotic syndrome. Nitrovasodilators: angina, left ventricular failure.

Table 2
Exclusion criteria for antiplatelet trials.

Aspirin exclusion criteria	Clopidogrel exclusion criteria
Pre-existing indication for aspirin:	Pre-existing indication for clopidogrel:
Myocardial Infarction	Peripheral arterial disease
Stroke/TIA	Myocardial infarction
Angina	Stroke/TIA
Atrial Fibrillation (which would be an indication for anticoagulation)	Angina
Peripheral arterial disease	Atrial Fibrillation(which is likely to be an indication for anticoagulation)
After bypass-surgery	
On any antiplatelet therapy or anticoagulation	On any antiplatelet therapy or anticoagulation
Caution for Aspirin:	Caution for Clopidogrel:
Heart failure/Pulmonary oedema	History of coagulation and haematological disorders*
Thyrotoxicosis	History of peptic ulcer
Uncontrolled hypertension	Renal failure
Hepatic failure	Hepatic Failure
History of peptic ulcers	History of bleeding events†
Renal failure	
History of coagulation and haematological disorders*	
History of bleeding events†	
Gout	
Asthma	
Co-prescribed Methotrexate	

* Coagulation and haematological disorders defined as one or more of: essential thrombocytosis, deep vein thrombosis, genetic haematological disorder, platelet disorder, aplastic anaemia, haemophilia, polycythaemia vera, myeloproliferative disorders, anaemia, neutropenia†Bleeding events defined as one or more of: cerebral haemorrhage, menorrhagia, excessive bleeding, subarachnoid haemorrhage, subdural haemorrhage.

Table 3
Comparison of baseline characteristics of eligible participants, by trial, to all patients with SVD.

Trial	Full SVD cohort	BP lowering	Lipid lowering	Aspirin	Clopidogrel
Total eligible	5794	3262	3368	4006	4710
Mean age (years)	68.65	68.85$p = 0.142$	67.6$p < 0.001$*	68.29$p = 0.006$*	68.22$p = 0.001$*
Males	3034 (52.4%)	1823 (55.9%)$p = 0.001$*	1657 (49.2%)$p < 0.001$*	1943 (48.5%)$p < 0.001$*	2319 (49.2%)$p = 0.001$*
Mean SBP/DBP (mmHg)	140.6/79.4	147.0/82.3$p < 0.001$*	140.3/79.7$p = 0.09/0.08$	140.6/79.5$p = 0.899/0.574$	140.7/79.6$p = 0.886/0.230$
Positive smoking history	2524 (43.6%)	1370 (42.0%)$p = 0.145$	1369 (40.6%)$p = <0.001$*	1632 (40.7%)$p = 0.005$*	1958 (41.6%)$p = 0.001$*
≥1 vascular condition	2150 (37.1%)	1159 (35.5%)$p = 0.134$	838 (24.8%)$p < 0.00.1$*	1169 (29.2%)$p < 0.001$*	1416 (30.1%)$p < 0.001$*
≥1 heart condition	517 (8.9%)	118 (3.6%)$p < 0.001$*	49 (1.4%) $p < 0.001$*	60 (1.5%)$p < 0.001$*	70 (1.5%)$p < 0.001$*

Means for age, SBP, and DBP compared using two-sample *t*-tests. Proportions of males, current/former smokers (Positive smoking history), participants with one or more vascular conditions, and one or more cardiac conditions compared using two-sample *z*-tests. *P*-values are given, and statistically significant differences to the full SVD cohort represented by (*).

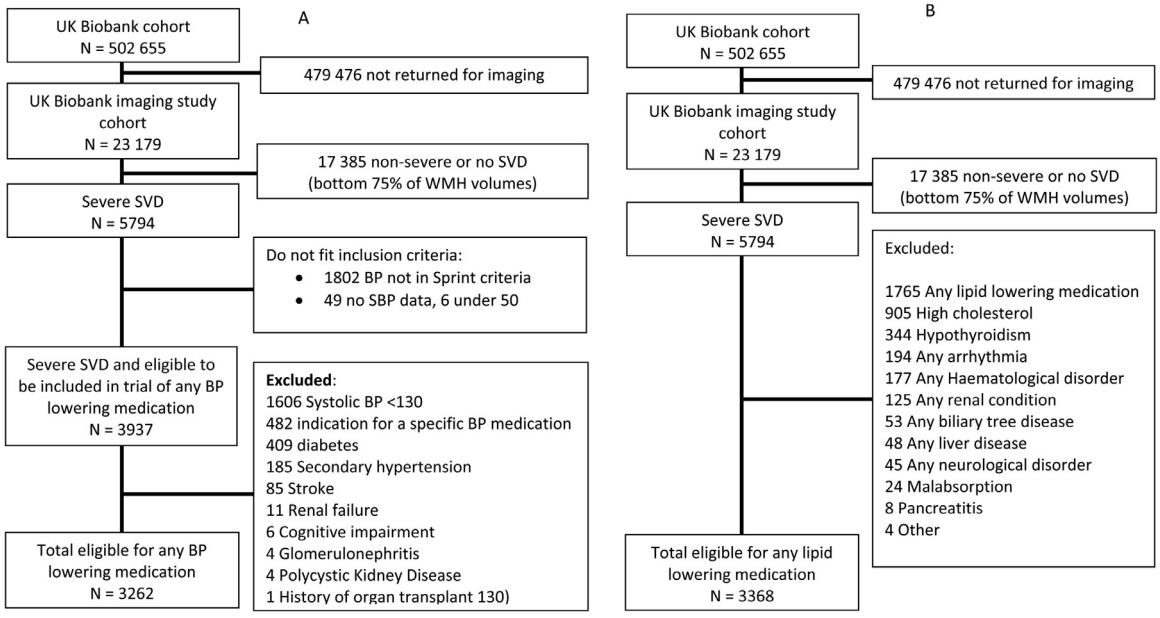

Fig. 1. Patients eligible for trials of (A) BP lowering and (B) statin medication. Participants may have been ineligible for multiple reasons.

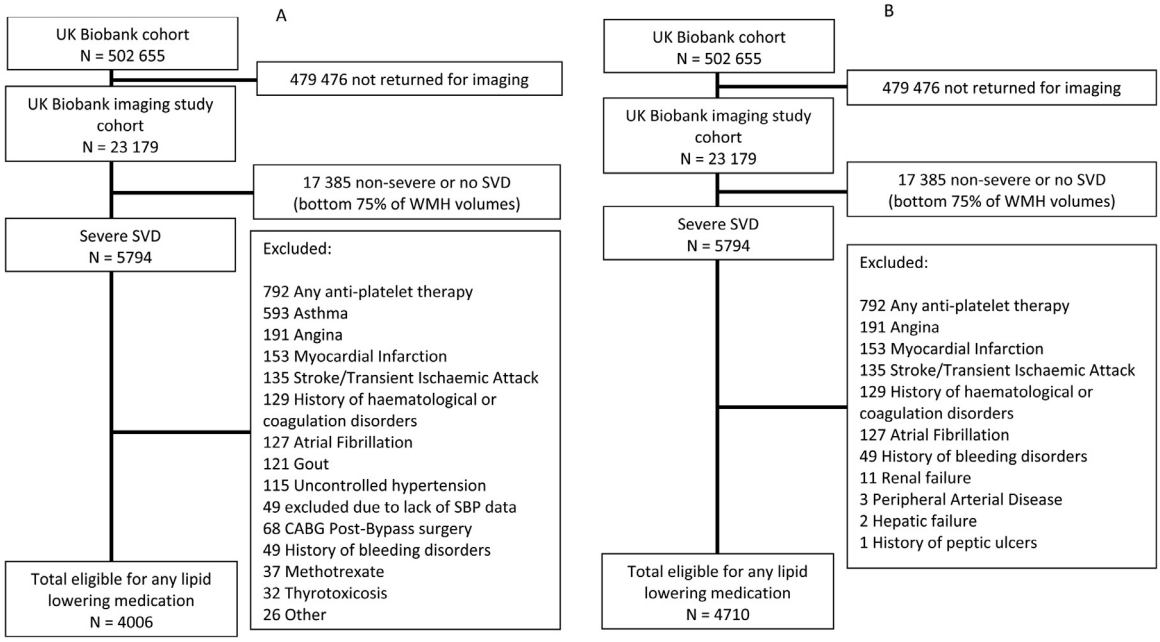

Fig. 2. Patients eligible for trials of (A) aspirin (B) clopidogrel medication. Participants may have been ineligible for multiple reasons.

3.3. Statins

3171/5794 (58%, 95% CI: 57–59%) of participants were eligible for treatment in a trial of a statin. 1765 would have been excluded because they were already taking a statin, and the remainder of the excluded group either had a contraindication or an existing indication.

As it was possible that the population of patients with SVD eligible for a trial is skewed so that it is not representative of those with more severe SVD, we analysed a subgroup of participants with WMH over 20 mls. Of the 332/5794 patients who had WMH volume over 20 mls, 57% (190/332) could have joined a trial of BP lowering similar to SPRINT, 45% (148/332) could join a trial of a statin, 63% (210/332) could join a trial of aspirin, and 72% (240/332) could join a trial of clopidogrel. This was not significantly different to participants with SVD eligible for a trial.

4. Discussion

This project identified that a majority of UK Biobank participants, with MRI data and radiological SVD, could be theoretically recruited to trials that repurpose cardiovascular medication. The majority were neither already on the medication for another reason, nor had a contraindication to taking it. Therefore, 69% could be potentially be recruited to a trial of aspirin, 81% to a trial of clopidogrel, 58% to a trial of a statin, and 56% to a trial of BP-lowering medication.

The strengths of this work include a relatively large sample size, particularly for an imaging study, with access to the full medical history and details of medications. Whilst these participants may not be representative of the general population, it is likely they are more representative of patients who would be willing to take part in clinical research.

Drawbacks include that this data was largely relating to a group of healthy volunteers with early WMH (median 5.2 mls). It is recognised that the UK biobank participants are healthier than average for their age; [20] however, the associations between known risk factors and disease are similar to more representative cohorts indicating generalisable results [21]. The cohort's median WMH value was lower than that of studies using symptomatic patients such as the Leukoarosis and disability (LADIS) study of symptomatic SVD (20 ml), and older healthy volunteers [22] such as the Lothian birth cohort of healthy 73 year-olds (7.9 ml) [23]. However, it is similar to the WMH volume in the SPRINT – MIND study (3.2 ml), which recruited patients over 50 with vascular risk factors. Whilst, WMH volume is not exactly equivalent to semi-quantitative visual rating scales such as Fazekas Score [24], our median WMH volume was roughly equivalent to a Fazekas score of 1 [25]. Although there are a number of causes of WMH other than SVD such as infection and multiple sclerosis, the vast majority of WMH seen in the UK Biobank are due to vascular causes. Participants with acute cerebral infections are unlikely to be well enough to volunteer for an imaging study, only 0.3% of participants had a diagnosis of multiple sclerosis [26], and WMH in UK Biobank were strongly associated with vascular risk factors [27].

It is possible that as this population is skewed so that it is not representative of those with more severe SVD; however, the subgroup analysis of participants with WMH of 20 mls or more, did not produce significantly different findings.

It is likely that these figures are an overestimation of the proportion of patients who would enter a clinical trial: there will also be other contraindications or cautions not apparent from the UK Biobank data. For the most part, recruitment into clinical trials is less than estimated, with only 56% of clinical trials funded by the UK Health Technology Assessment program reaching their recruitment target, the majority with an extension [28]. The SPRINT trial randomised 60% of screened patients. In practice, between 5 and 20% of the eligible population are recruited into clinical trials for a variety of reasons. Indeed only 6% of eligible participants were recruited to UK Biobank [21]. The data on medical history and medications may also be incomplete as it relies on participants' self-reports, whereas in a clinical trial the investigators would carefully check both a patient's self-report and medical records.

As SVD is a progressive condition, patients who have early features of SVD on imaging are most likely to benefit from treatment intended to prevent the progression of the disease. Despite the drawbacks, we have useful evidence that a trial of antiplatelet medication, antihypertensives or statins would not struggle to recruit participants due to patients already taking the target medication.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.cccb.2021.100015.

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