

Review Article

The 2018 Stockport Vascular Neuro Cognitive Disorder Investigation, Treatment and Annual Review Guidelines (Including the Spectrum from Mild Vascular Cognitive Impairment to Vascular Dementia) Supporting Primary and Secondary Care Physicians

Sally Gilmour^{1*}, Peter Ngoma^{2*}, Rachel Price¹

¹The Meadows Hospital, Stockport, Pennine Care NHS Foundation Trust, United Kingdom

²Stepping Hill Hospital, Stroke Consultant, Stockport NHS Foundation Trust, United Kingdom

***Corresponding author:** Sally Gilmour, The Meadows Hospital, Stockport, Pennine Care NHS Foundation Trust, United Kingdom. Tel: +44-01617164532; Fax: +44-01617164566; Email: s.gilmour@nhs.net; Peter Ngoma, Stepping Hill Hospital, Stroke Consultant, Stockport NHS Foundation Trust, United Kingdom. Tel: +44-01614831010; Fax: +44-01614194213; Email: Peter.Ngoma@stockport.nhs.uk

Citation: Gilmour S, Ngoma P, Price R (2018) The 2018 Stockport Vascular Neuro Cognitive Disorder Investigation, Treatment and Annual Review Guidelines (Including the Spectrum from Mild Vascular Cognitive Impairment to Vascular Dementia) Supporting Primary and Secondary Care Physicians. J Aging Neuro Psychol: JANP-111. DOI: 10.29011/JANP-111.100011

Received Date: 18 May, 2018; **Accepted Date:** 22 October, 2018; **Published Date:** 09 November, 2018

Abstract

This guideline ensures we do not miss an opportunity to optimise existing cardiovascular medication for previously diagnosed cardiovascular disease such as myocardial infarction when new Target Organ damage is detected as with Vascular Neurocognitive disorder [1,2]. A minority of patients are not already receiving secondary cardiovascular prevention as Vascular Neurocognitive Disorder DSM-5(5th edition) [3] is their first diagnosis of cardiovascular system disease. Many of these newly diagnosed patients may not subsequently receive secondary cardiovascular risk prevention due to lack of guidelines. There is no research evidence to treat Cerebrovascular disease which is proportional to that expected for the patient age on MRI or CT brain.

The MRI Fazekas score should reflect the clinical indication of Brain Target Organ Vascular Disease more so than expected age-related change to indicate treatment for vascular neurocognitive disorder [4]. Gradient Echo assesses micro haemorrhage which may mean anti-platelets or anticoagulants are contra-indicated.

Although there is no consensus from research evidence that treating blood pressure, cholesterol and using antiplatelets or anticoagulation will reduce cognitive decline in vascular Neurocognitive Disorder, there is evidence for secondary cardiovascular prevention once there is diagnosis of Target Organ damage to the brain with vascular pathological Brain Target Damage [5,6].

The guidelines allow consideration of risk affecting patients and carers, patient treatment advice leaflets assist informed shared decisions, SIGNPOST to support groups and healthy lifestyle leaflets examples include '4ME' [7].

The Guideline helps seize opportunities to prevent progression of cardiovascular disease from mild Neuro vascular disease /mild vascular cognitive impairment to sudden severe stroke, heart attack or peripheral vascular disease.

Keywords: Annual Review; Investigation; Treatment; Vascular Dementia

Introduction

There are few specific vascular neurocognitive disorder guidelines existing at the time of Publication include Passmore BMJ July 2017 [8], Australia Alzheimer's Dementia, Yates [9] A minority of patients are not already receiving secondary cardiovascular prevention as Vascular Neurocognitive Disorder is their first diagnosis of cardiovascular system disease. Many of these newly diagnosed patients may not subsequently receive secondary cardiovascular risk prevention perhaps especially with sub cortical vascular dementia and associated gradual reduction in activities of daily living and change to personality, which is less obvious as a cardiovascular disease to patients, families and clinicians compared with sudden disabling stroke, cardiac disease, retinal artery thrombosis or painful intermittent claudication due to peripheral vascular disease.

The Stockport 2018 Guideline ensures we do not miss an opportunity to optimise existing cardiovascular medication for previously diagnosed disease such as myocardial infarction when new Target Organ damage is detected as with Vascular Neurocognitive disorder. This includes excluding patients from having recently acquired causative factors which may have occurred subsequent to a previous cardiology or stroke clinic assessment, months or years earlier particularly e.g. atrial fibrillation or new lifestyle factors e.g. smoking or alcohol intake increase.

There is no research evidence to treat Cerebrovascular disease which is proportional to that expected for the patient age on MRI or CT brain. Wiberg, et al. 2010. Cognitive function has been shown to predict the risk of stroke in elderly men [10]. The Guideline helps seize opportunities to prevent progression of cardiovascular disease from mild Neuro Vascular Disease /mild vascular cognitive impairment to sudden severe stroke, heart attack or peripheral vascular disease. Patient Treatment advice leaflets assist informed shared decisions.

The guidelines allow consideration of cognitive decline associated risks affecting patients and carers, SIGNPOST to support groups and healthy lifestyle advocated by Lancet 2017 Dementia Commission [11]. Vascular Neurocognitive Disorder Healthy Lifestyle published leaflets examples include '4ME', J. Keady and R. Price 2010 [7].

The Stockport 2018 Vascular Neuro Cognitive Disorder Investigation, Treatment and Annual Review Guideline was presented in poster form by S. Gilmour and P. Ngoma, at the February Paris 2018 International Vascular Dementia Conference [12] and an abstract of the poster published in the related Journal of Alzheimer's

Disease and Parkinsonism and met with positive response.

The memory investigations are based on routine practice in The Meadows memory assessment services STOCKPORT. Post diagnosis currently support for vascular neurocognitive disorder patients includes a patient leaflet based on the 4ME, published by Rachel Price and John Cready [7], as well as supportive monthly information group for vascular dementia patients and carers. There is also a vascular dementia advice post diagnostic health care professional in Stockport.

Secondary cardiovascular Investigation and treatment is also based on established practice for post stroke vascular dementia patients in Dr P. Ngoma's Stroke Clinic, Stepping Hill Hospital, Stockport. The Stroke Unit at Stepping Hill Hospital, Stockport was named by the Sentinel Stroke Audit, 1st out of 224 units in the United Kingdom in 2017. The RCP Stroke Guidelines 2016 [5], and the current supporting practice of the Greater Manchester Stroke Operational Delivery Network [6] website information also was extensively sourced. Recent Non-systematic Journal Review by Dr Sally Gilmour MRCGP affil RCPsych, affiliated member of the Royal College Psychiatry, former General Practitioner, now Specialty Doctor, Old Age Psychiatry of recent related seminal vascular dementia research papers. Previous author of Stockport CCG You Tube Dementia podcast [13] and contributor to the GMSODN Secondary Stroke Prevention Task and Finish Group.

It is a potential missed opportunity when active patients in the community, still driving, caring for grandchildren or even working; are diagnosed with mild vascular cognitive impairment, but perhaps are not considered for secondary cardiovascular investigations and treatment. Subsequently some develop a life changing stroke with hemiplegia or dysphasia and within a few months of mild vascular cognitive impairment diagnosis can find themselves bed bound in a nursing home with hemiplegia and dysarthria in the worst-case scenario.

These mild vascular cognitive impairment patients have potentially the most to benefit from timely secondary cardiovascular risk reduction including cardiovascular investigations to exclude cardiac causes, atrial fibrillation, hypercholesterolemia, diabetes, and hypertension. They are most likely to benefit from lifestyle changes, even though research shows, as outlined in the Lancet 2017 consensus paper, to prevent 35% of all dementia types; optimum blood pressure, hearing and obesity should be from middle age, whereas from later life it is still indicated that addressing diabetes, cholesterol, smoking cessation, exercise 150 minutes per week [11], sensible alcohol intake and depression is beneficial. Many clinicians are concerned that addressing lifestyle factors and targeting cardiovascular medicines optimization may be too late once someone is over 75, or has developed mild cognitive impairment or dementia.

However, when considering cut off points for action and benefit we have to consider that for one individual patient 40-50 years may be their 'middle age' but for a patient who will live to 105 years their 'middle age' may be 60-70 and that we are treating individuals depending on their potential future function and frailty and not their age, but the Lancet commission 2017 paper addresses the benefits statistically for the average population as a whole.

It is surely more beneficial to also address these risk factors at the point of diagnosis of mild vascular cognitive impairment, before development of dementia; rather than allow a stroke or other cardiovascular event to occur without attempted prior lifestyle modification at this mild vascular cognitive impairment stage or in early vascular dementia.

We need more research to look at whether we can delay cognitive decline from mild vascular cognitive impairment to vascular dementia, or deterioration in all dementia types, as there is divided opinion following a small number of research studies regarding the ability to delay cognitive decline once it has been diagnosed, with cardiovascular risk reduction, but we know that with diagnosed cardiovascular disease of all presentations including angina, myocardial infarction, peripheral vascular disease, retinal artery thrombosis, we should be addressing route cause with investigation, treatment and lifestyle modification to prevent further cardiovascular disease. Vascular neurocognitive disease is part of the cardiovascular disease 'family'.

All patients with TIA and Stroke should now receive extensive investigation and treatment for secondary cardiovascular prevention in the UK as per the Royal College of Physicians stroke guidelines updated 2016 [5], but we need to elevate to this standard for vascular neurocognitive disorder, with 'its shared risk factors', 'Subclinical brain MRI markers of vascular damage are risk factors shared between stroke and dementia and can be used for risk stratification and early intervention damage' Gardener, et al. [14]; which is also Target Organ Brain vascular disease; where appropriate for individual patients.

There is no research evidence to treat Cerebrovascular disease which is proportional to that expected for the patient age on MRI or CT brain scan which may represent the radiology signs expected with 'normal ageing' [15-17].

Patient Treatment advice in the Stockport Guidelines recommendations assist informed shared decisions to reduce risk of subsequent stroke, heart attack and other cardiovascular disease. Although there is no consensus from research evidence that treating blood pressure, cholesterol and using anti-platelets or anticoagulation will reduce cognitive decline in vascular Neurocognitive disorder; there is evidence for secondary cardiovascular prevention once there is diagnosis of vascular target

organ damage and this should be conveyed to patients to help them make informed decisions regarding acceptance of investigation, treatment and lifestyle change; 'Be Smart exercise your Heart' [18-22].

We need to make it clear to patients that until we reach consensus with further research evidence; we are treating to reduce further cardiovascular events. The Scandinavian multi infarct trial did show that Nimodipine may improve cognition in those with subcortical dementia [23]. The Prospect Perindopril Study did show a reduction in the development of white matter hyper intensities in patients with cerebrovascular disease on MRI scan; in those on an active blood pressure lowering regime compared to controls [24].

There is evidence for secondary cardiovascular prevention of heart attack, peripheral vascular disease or stroke, once there is diagnosis of target organ damage to the brain with vascular pathology. It ensures we treat diagnosed vascular neuro cognitive disorder whether mild or severe as we do all other cardiovascular disease with secondary prevention and offer further investigation, treatment and support as secondary cardiovascular risk prevention as appropriate for each individual patient.

We need to ensure patients whose mild cognitive impairment or vascular dementia is their first presentation of a cardiovascular disease has adequate investigation and secondary prevention. Also, patients with slowly progressing insidious sub cortical or multi infarct dementia have similar access to investigation, treatment and support as do the more dramatic sudden post stroke vascular dementia patients.

We should reassess those already on CVD treatment including excluding atrial fibrillation as 'Anticoagulants could cut the risk of dementia for patients with atrial fibrillation, researchers find, *The Pharmaceutical journal* 2017[online]' [25] ensure optimum Secondary Cardiovascular Risk Prevention with New Location Target Organ damage of the BRAIN.

There is no research evidence to treat Cerebrovascular disease which is proportional to that expected for the patient age on MRI or CT brain. The assessment should consider both MRI Brain Fazekas score [4] and clinical assessment of Cerebrovascular Disease to be more so than that expected for age to diagnose Neurovascular cognitive disorder and also to investigate and treat for secondary cardiovascular prevention.

Initial Investigation of Cognitive Impairment, Usually Including Referral to Secondary Care Memory Clinics

The initial guidelines section represents investigation of all

causes of cognitive decline [26,27] as currently usually occurs in secondary care older age psychiatry memory and stroke clinics. In Stockport we use the Addenbrooke's Cognitive Examination, but the Montreal Cognitive Assessment MOCA is alternatively used in other areas in conjunction with good history taking from patients and carers. Currently there is no cognitive assessment tool which aids differentiation of dementia type but clinical skill and training interpretation of cognitive tools adjacent to history and examination helps distinguish types.

Cognitive scores may be higher or lower than expected from clinical assessment and are a tool which should not be solely relied on, although usually we diagnose dementia with an Addenbrooke's cognitive examination score <82 and mild cognitive impairment score <88, particularly in vascular neurocognitive disease. We must keep in mind that expressive aphasia may lower the ACE <82 but the patient may be able to drive or complete other activities of daily living and we would not diagnose dementia, but post stroke expressive aphasia.

Similarly, patients, who have previously been excellent at crosswords, quizzes or even had high IQ in Mensa, may score over 90 on the ACE with good semantic memory but have reduced insight, personality change, and reduction in executive function which results in deterioration of activity of daily living and clinically have a dementia. Dementia should only be diagnosed with a history of at least 6 months of cognitive decline.

The specific cerebral location of vascular damage is more variable than the pattern of cerebral damage in Alzheimer's dementia and initially reflects the presentation. Post stroke vascular dementia develops suddenly or gradually in at least a third of patients following stroke within 3 years. Classically vascular dementia was always diagnosed after 'stepwise deterioration in cognition' [27-29] this would often represent multi-infarct dementia. Sub cortical vascular dementia is likely to cause a gradual insidious reduction in activities of daily living and slower reaction time.

Alzheimer's prodromal mild cognitive impairment patients are more likely to have targeted short-term memory decline due to temporal damage. Vascular neurocognitive disorder patients may have also had predominant short-term memory decline if the site of vascular damage affects the temporal lobe. However, there can be many manifestations of vascular neurocognitive disorder including frontal cognitive syndrome such as difficulty solving problems, apathy, disinhibition, slowed processing of information, poor attention and retrieval memory deficits or delayed retrieval [8].

We include MRI brain with Gradient Echo 30 and Fazekas score 8 as well as the Medial Temporal Atrophy score as detailed later. In those patients where an MRI scan is contraindicated or not available a brain CT scan can be a second option.

Standard delirium/ Dementia screen bloods to rule out alternative causes of cognitive impairment includes Folate, Vitamin B12, Thyroid Function Test (TFT), Calcium, CRP (C Reactive Protein), Liver Function Test (LFT), Urea and Electrolytes (U&E), Full Blood Count (FBC), Hemoglobin A1C (HbA1c or alternatively blood glucose) [8,12] Individual secondary care clinicians can use clinical judgment regarding HIV, Wasserman Reaction and other tests which are not routinely necessary in the United Kingdom and not included, so as not to over complicate for the primary care physician.

Resting ECG helps exclude sustained atrial fibrillation and bradycardia which can impact on vascular neurocognitive disease or preclude treatment of acetyl cholinesterase inhibitors, indicating Memantine may be more suitable in mixed vascular and Alzheimer's dementia.

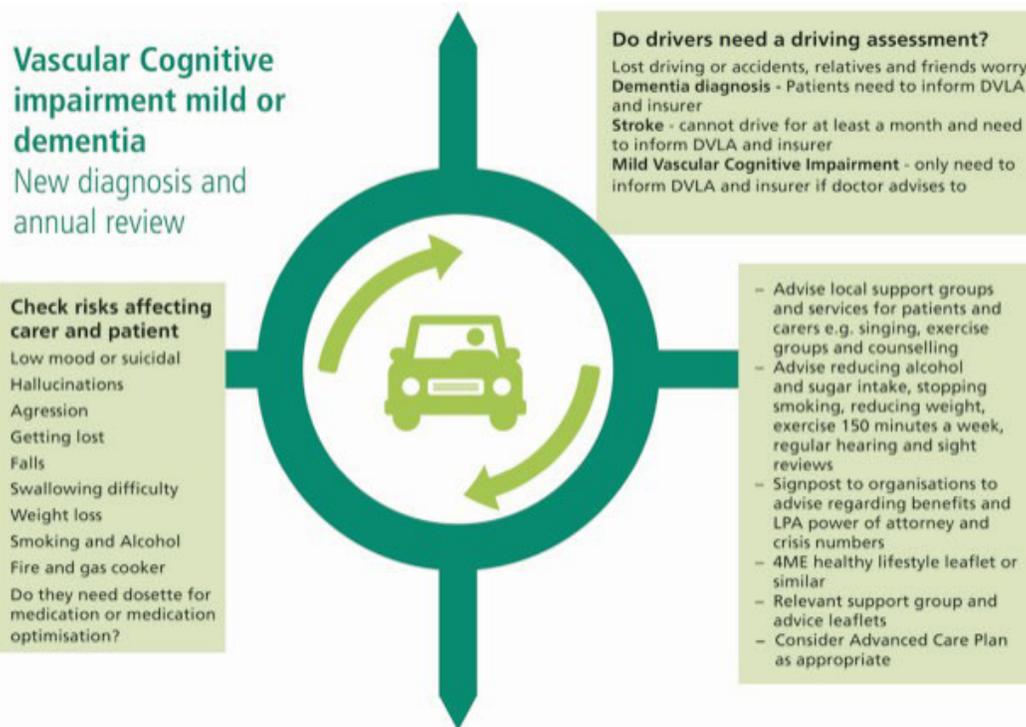
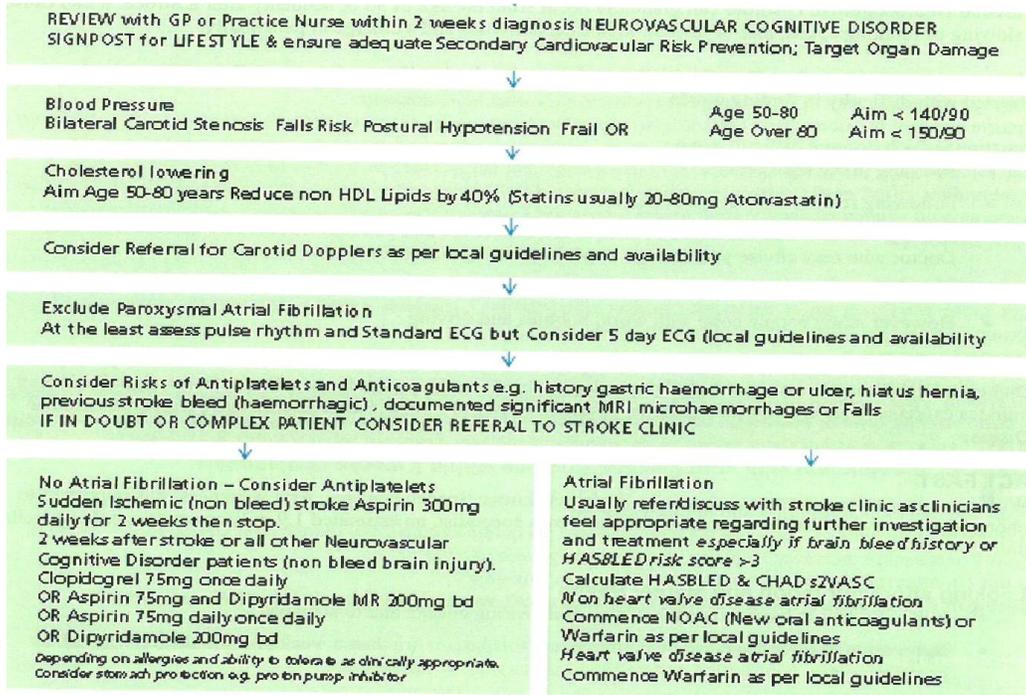
Physical examination includes neurological cranial and peripheral nerves to assess for signs of prior stroke, focal upper motor neurone signs e.g. hemi paresis, dysarthria and dysphasia. Parkinsonism due to vascular and non-vascular damage to the basal ganglia area or side effects of neuroleptic medication may reveal cogwheeling, shuffling gait, feet stuck to the floor and poor balance and frailty [8]. Cardiac examination assessment can include pulse rate, blood pressure, cholesterol overview and for cardiac murmur.

The MRI (or CT Brain result) can indicate unsuspected haemorrhagic stroke or acute ischaemic Stroke within 7 days both of which require urgent same day stroke team assessment. Drivers are advised to contact the DVLA and insurers and not drive for at least a month.

When the MRI (CT brain scan) supports prior clinical assessment, and reveals established cerebro-vascular disease with Fazekas score >2 in those over 75 years, then Neuro vascular cognitive disorder is diagnosed the treatment pathway below is commenced. [8,14] Under age 75 years a Fazekas score equal to 2 or more with supporting clinical assessment would enable diagnosis of vascular neurocognitive disease. Over 75 years a Fazekas score of 3 or more suggests a diagnosis of vascular neurocognitive disease which can equate to mild vascular cognitive impairment or vascular dementia clinically.

Mixed vascular and Alzheimer's dementia may occur in over 50% dementia [30] and must be considered using the MRI result and Medial Temporal Atrophy Score >2 Age over 75 years or equal to 2, Age less than 75 years. Patients with Alzheimer's pathology normally have a predominant memory loss on cognitive assessment. Normal MRI brain or CT brain appearance does not exclude early Alzheimer's or other dementia especially Lewy Body and Parkinson's Dementia. It is also imperative to consider that cognitive decline may be reversible and be due to Depression, Delirium or Medication particularly opiates and anticholinergic medication

Treatment and Investigation of Mild Vascular Cognitive Impairment or Vascular Dementia Usually in Primary Care



Treatment and Further Investigation and Annual Review following diagnosis of Vascular Cognitive Impairment Vascular Dementia

The Stockport Vascular Neurocognitive Disorder Guidelines gives a structured approach for primary or secondary care regarding follow up cardiovascular investigation and treatment involving patients in an informed decision process and cardiovascular risk review is advised within two weeks by the most appropriate primary or secondary care physician.

Hypertension in mid-life is particularly associated with an increased risk of developing dementia of all causes. There is significant association with blood pressure >160mmHg.”midlife hypertension increases the risk for vascular dementia by the same pathological mechanism as it increases the risk for lacunar infarcts. The Cornu Ammonus (CA1) sector of the hippocampus is extremely vulnerable to vascular damage compared to other areas of the brain. It is this region which is also vulnerable to Alzheimers Disease neurofibrillary degeneration and both may lead to anterograde amnesia.” SP Kennelly 2009. There are some trials supporting optimisation of blood pressure to reduce cognitive decline including Pantoni et al 2000. Scandinavian Multi Infarct Dementia Trial [23] a double-blind placebo controlled trial on nimodipine in multi infarct dementia revealed favourable effect on cognition in the subgroup of patients affected by sub cortical small vessel vascular dementia. The PROGRESS Trial Perindopril Protection against recurrent Stroke MRI sub study revealed a less noticeable progression of white matter change in patients with stroke [24,31].

The SPRINT MIND trial published by the American Alzheimers Association July 2018, was the first randomised clinical trial to demonstrate intensive blood pressure control ;systolic blood pressure <120mmhg ; reduces the risk of new cases of Mild Cognitive Impairment and combined risk of MCI plus all cause dementia.” The future of reducing MCI and dementia could be in treating the whole person with modifiable risk factor interventions as we do now in heart disease”. However, lowering blood pressure in diagnosed Vascular dementia intensively is not always advised particularly where there is bilateral carotid stenosis, falls risk, postural hypotension or frailty and as per stroke guidelines over the age of 80 it is sensible to aim for blood pressure <150/90 [32-35].

Treatment aim is as for stroke [5,6] guidelines secondary cardiovascular prevention, aiming for blood pressure < 140/90 in those below 80 years. However, clinicians use their clinical judgment as to whether a higher systolic blood pressure is necessary especially in those with bilateral carotid stenosis, falls risk, postural hypotension or frailty when as for those over 80 years Aiming for Blood pressure over 150/90 is more appropriate [32,36,37].

Cholesterol Lowering

Advice regarding varying clinical research findings is in the Stockport patient information leaflet, which also details that some studies especially K. Swiger following a systematic review and Meta-analysis of Short and Long Term effects looking at 23,443 patients; advise that statins reduce Dementia incidence by 29% in statin treated patients [38-42]; as well as the known reduction in stroke risk of 21% when reducing cholesterol by 1 mmol/l. Whereas other studies of intensive lipid intervention, O’keefe [38] and the FDA in the USA have not advocated statin use routinely to reduce decline in vascular dementia; concerned regarding a reduction in cognition and risks with statin use over 80 years of age including Altered Metabolism, Co morbidities, usually perform carotid dopplers within 7 days of an acute stroke and arrange carotid surgery within this time frame, but would not usually routinely arrange carotid dopplers in more chronic cerebrovascular disease [43-45]. Memory Assessment Centres such as the University Hospital of South Manchester where Professor Charles McCollum ‘s Manchester based research into carotid stenosis have been advocates of carotid dopplers in chronic cerebrovascular disease , reflecting there is no consensus currently nationally and stroke clinics carotid doppler resources will affect this. ‘Carotid stenosis >70% is generally thought to be significant but lower grade stenosis (50 to 70%) may be important if patient is symptomatic, especially if ulcerated plaques are present. In the absence of acute focal neurological symptoms, there is no value in doing a carotid Doppler Passmore 2017 [8]

Excluding Atrial Fibrillation

Excluding atrial fibrillation ideally is with a 5-day ECG as soon as practicable, but if resources are limited or it is not practical, some patients may have a resting ECG only or pulse examination which would exclude non-paroxysmal persistent atrial fibrillation at least. [5,6] 2015 Nogrady published ‘atrial fibrillation doubles silent infarct risk’ [46]

Edwards et al 2016 ‘atrial fibrillation is independently associated with brain atrophy and cognitive dysfunction [47] Ikram in Rotterdam -. ‘Participants with atrial fibrillation are 33% more likely to develop dementia than participants who don’t have atrial fibrillation’ [48] ‘arranging 5 day tapes as soon as possible should be common practice as resources allow’ [48] Tokatli, et al 2016, found ‘Paroxysmal atrial fibrillation and related thromboembolism may be a hidden factor in the development of dementia’ [49,50] Biesels Micro infarcts : Key to prevention of the vascular burden in dementia? 2015 [51] The pharmaceutical Journal, delaying anticoagulation treatment for atrial fibrillation increases dementia risk, study suggests [52] The guidelines are aligned with the NICE 2016 management of atrial fibrillation [53].

Vascular Neurocognitive disorder patients with a diagnosis of atrial fibrillation

If atrial fibrillation is newly diagnosed in vascular mild cognitive impairment or dementia; CHADs2Vasc and HAS BLED score regarding anticoagulant treatment should be used to determine treatment as per NICE guidelines for atrial fibrillation in addition to a brain MRI report if available detailing evidence of microhaemorrhages [5,53,54].

The Pharmaceutical journal 2017 ‘Delaying anticoagulation treatment for atrial fibrillation increases dementia risk’ [52] ‘When there is an available MRI Gradient echo report for patients we assess micro haemorrhage [54], these can especially be prevalent in Cerebral Amyloid Angiopathy [55], sub cortical hypertension related vascular dementia & mixed Vascular & Alzheimer’s pathology [54-59].

When there is significant radiological micro haemorrhage diagnosis it is likely an experienced Stroke Physician would need to advise regarding suitability of anti-platelets and anticoagulants and risk of associated intracerebral haemorrhage. Clinicians not feeling confident in prescribing anti-coagulants or unsure because of history including excessive falls, gastric bleed micro infarct or previous cerebral haemorrhage should refer to the local stroke clinic to be seen within 7 days or discuss on the telephone with on-call physicians. ‘This can include warfarin prophylaxis in valvular disease associated with atrial fibrillation or in non-valvular atrial fibrillation, Direct Oral Anticoagulants(DOACs), dabigatran, apixaban, rivaroxaban and edoxaban. If there are contraindications to warfarin or DOAC such as heightened bleeding risk the US government recommended aspirin alone or in combination with clopidogrel as it has some efficacy in prevention of stroke in people with atrial fibrillation (though the combination has heightened cerebral haemorrhage risk)’ [8].

Vascular Neurocognitive disorder patients where atrial fibrillation has been excluded

Many experts are of the view that there is still no good evidence that aspirin is effective in treating patients with vascular dementia to reduce a cognitive decline, there is a paucity of research related to this, partly due to ethical reasons, secondly that aspirin in a cheap generic drug which will not repay the costs of research to companies, but also subject standardisation criteria given variability of cognitive decline at each point of diagnosis and that cognitive decline is not purely a number but a functional effect on individuals. An important ongoing study is the Finnish Geriatric Intervention study to Prevent Cognitive Impairment and Disability FINGER [60] As well as Ballard Wales [61] Rostamian S, a Systematic Review and meta-analysis cognitive impairment and risk of stroke [30] Defries T 2009 Level and Change in Cognitive Test Scores

predict risk of first stroke *Journal of American Geriatrics Society* [62] However we know it is still useful as secondary prevention of cardiovascular disease (Passmore, Peter *BMJ* July 2017) [8].

‘The main options for preventing cardiovascular disease are anti platelet therapy for atherosclerotic disease, anticoagulation for cardio embolic disease, and carotid endarterectomy or carotid angioplasty and stenting for carotid stenosis’. American Heart Association Kernan WN Ovbiagele B Black HR, et al.’ [35] Evidence supports the use of aspirin, clopidogrel or combination treatment with aspirin/ dipyridamole for preventing further infarction in patients with stroke and transient ischaemic attack relating to atherosclerotic or small vessel disease. We can argue that stroke and TIA are the same disease family as vascular neurocognitive disorder so we should give patients the option of anti-platelets treatment as secondary cardiovascular prevention where there is no evidence of micro or macro haemorrhage; even though there is no consensus that cognition will be improved or decline in cognition managed.

Joanna Wardlaw University of Edinburgh 63 ‘Stroke and dementia what research tells us -Declining cognition is a warning of stroke, Stroke is a warning of declining cognition’. For now, in vascular dementia: Lower blood pressure, lower lipids, lifestyle advice, regarding smoking, salt reduction and exercise, use anti platelets drugs but not ASA and clopidogrel long term [63] Dr Bayer, Cardiff University, former president of Royal College of Physicians, Aspirin Foundation 2016 ‘Most specialists believe that aspirin should be offered to patients with cognitive impairment and dementia’ [64] Update on vascular dementia, Khan, C Ballard et al, *Journal of Geriatric Psychiatry and Neurology* 2016 ‘The Prevention and Treatment of Vascular Dementia covers a broad range of therapies including anti hypertensives, vasodilators’ [28] ‘A RCT of a daily dose of 325mg of aspirin conferred significant benefit in comparison to placebo, preventing cognitive decline in 50% of the participants although some irregularities in the randomisation procedures have been found. A recent systematic review concluded that there were no adequate studies of aspirin in people with vascular dementia. It would be impossible to ethically repeat the above-mentioned study as aspirin is now routinely used for the prophylaxis of stroke at a much lower dose. The question remains as to whether higher dose aspirin would be more effective and whether the tolerability would be acceptable in vascular dementia’ [28].

Aspirin was routinely advocated by many Older Age psychiatrists in vascular dementia however until the Rands Cochrane review March 2012 [65,66]. ‘There is still no good evidence that Aspirin is effective in treating patients with a diagnosis of vascular dementia’. There is increasing concern that low dose aspirin is associated with an increased risk of haemorrhages ‘Aspirin doubles the risk of GI bleed. It is possible aspirin causes small

cerebral haemorrhage that could stimulate the amyloid cascade possibly leading to Alzheimer's or death from brain haemorrhage' [66], Clopidogrel can also be used as per the clinician's decision and the Stroke Guidelines [5,67].

The MRI Gradient echo in this Guidelines allows assessment of micro haemorrhage prior to commencement of anti-platelets or antithrombotic and discussion with the patient regarding uncertainty regarding the risks of patients with microhaemorrhage and events of haemorrhagic stroke; who take antiplatelet as opposed to the risks to patients with micro-haemorrhages who do not take anti-platelets or micro-haemorrhage in secondary prevention. Primary and Secondary care physicians often evaluate risk and benefits of anti-platelets for secondary cardiovascular prevention following stroke, transient ischaemic attack, peripheral vascular disease or myocardial infarction, they can similarly assess potential risks of using anti-platelets and share for secondary cardiovascular prevention once mild vascular cognitive impairment or vascular dementia have been diagnosed.

Micro bleeds are associated with a higher risk of both ischaemic Stroke and haemorrhagic stroke, [68] standard practice is to give everybody with ischaemic stroke and micro bleeds standard anti- thrombotic therapy for secondary prevention. Dr Peter Ngoma at Stepping Hill Hospital Stroke clinic would always discuss with patients the uncertainty around micro bleeds when prescribing anti- platelets or anticoagulants medication if significant micro bleeds are detected.

Diabetes

Studies of intense control of diabetes are underway. Abnormal HbA1c, glucose result should be treated following detection during initial memory impairment investigation, whether vascular neurocognitive disorder is diagnosed or not.

Vascular Neurocognitive Disorder Stockport Patient Information (Includes Mild Vascular Cognitive Impairment and Vascular Dementia)

Information which can be discussed with patients and can be adapted for local information leaflets. Vascular Neurocognitive Disorder can gradually occur from the age of 50 or suddenly after a Stroke. It can cause a slowing of thinking speed, loss of interest in normal activities and a change in personality.

Memory may or may not be affected initially; such as remembering lists or directions. Speech may also be affected with difficulty in finding words.

Functions which become difficult can be:

- Dressing in the right order.
- Following recipes and using cookers.

- Driving can continue but if you or friends are concerned that you may be less safe discuss with your Doctor who may advise you to arrange a special Driving Assessment.
- Patients with a diagnosis of Vascular dementia or Stroke should inform the DVLA and their car insurer.
- However, many people cope with work, hobbies and driving.

The Main Risk Factors -The Lancet July 2017

Diabetes, High Blood Pressure, Alcohol dependence, Smoking, Hyperlipidaemia, Being Overweight, less than 30 minutes exercise twice weekly (150 minutes total per week advised in UK currently), Previous Stroke, Heart disease and Peripheral Vascular Disease.

Act Fast

With any new stroke symptoms, especially Facial weakness, Speech changes, Arm weakness, it is important to phone 999. For every minute a Stroke is untreated by a specialist, an estimated 1.9 million neurons or brain cells die.

Looking after your mood and Mental Health

- It is important to have 6 monthly hearing checks and yearly vision checks and to socialise.
- Depression or poor sleep can be common, and this lasts more than a week you should see your GP as exercise advise, counselling and antidepressants may be appropriate.
- Changes in life such as loss of a loved one, health problems or coping as a carer can cause Suicidal thoughts, contact your GP, NHS 111, Mind or the Samaritans 116123 as soon as you can.
- Occasionally a patient's personality may change with hallucinations, or carers may feel there are risks; medication and therapists may help - you should speak to your GP.

Healthy Lifestyle includes healthy diet, reducing alcohol, stopping smoking exercise

Your GP practice can advise you regarding Healthy Lifestyle. Being overweight increases your risk of Ischaemic Stroke by 22%. 150 minutes of exercise per week is recommended. Moderate exercise can reduce your risk of Stroke by up to 27% and can reduce isolation and improves Mood.

Make an appointment with your General Practice within 2 weeks of diagnosis

Every patient is different; your doctor needs to discuss the best treatment for secondary prevention of Cardiovascular disease

depending on your other medical conditions and your age. If left untreated and even with treatment, Mild Neuro Cognitive Disease can lead to Stroke, other cardiovascular disease and Vascular Dementia.

Blood Pressure

Blood Pressure should be maintained at or below 140/90: For those aged over 80 or suffering Postural Hypotension, Bilateral Carotid Stenosis, the usual aim is 150/90 (NICE hypertension guidelines November 2016).

Anti-platelets

These tablets help prevent clots in the blood. Patients with sudden Ischaemic (non-bleed) Stroke are given Aspirin 300mg daily for 2 weeks followed by Clopidogrel 75 mg daily, long term. Other alternatives can be advised by your Doctor who will consider if you can tolerate these medications to prevent Stroke and other cardiovascular disease as Secondary Prevention.

Some patients may not be able to tolerate these if they have suffered Duodenal or Gastric Ulceration, Hiatus Hernia and/or a previous Stroke due to Haemorrhage (brain bleed) or Micro haemorrhages found on MRI brain scan. Your doctor may give you extra medication to protect your stomach.

Reducing High Cholesterol

Cholesterol is a helpful fatty substance in the blood in moderate amounts, but too much can cause deposits on the artery walls and restrict blood flow. Reducing alcohol intake, saturated fat in the diet, stopping smoking, exercising 150 minutes per week, and taking Statins; reduce Cholesterol. Statins to reduce Cholesterol are advised for those aged 50-80. From midlife these reduce the risk of Stroke and Vascular Dementia once you have a cardiovascular disease. Reducing Cholesterol by 1mmol/L reduces Stroke risk by 21%.

The FDA in America issued a warning that patients should not take statins over 80 years of age; some research showed they reduced Cognition (understanding or memory), also potential risks when taken over 80 years include Altered Metabolism, Co morbidities, Polypharmacy (too many drugs causing ill affects together). Other research disagrees, and a project led by Swiger looking at 23,443 patients found 29% showed a reduction in Developing Dementia in Statin treated patients.

Benefits include Secondary Atherosclerotic Cardiovascular prevention, Stroke reduction, decreased morbidity (illness) and Heart attack reduction). Treatment should follow well informed shared decision between patients and doctors.

Anticoagulants to treat Atrial Fibrillation

Your doctor may detect Atrial Fibrillation on an ECG heart tracing. Atrial Fibrillation is a heartbeat which is irregular (not in predictable time), and it leads to 1 in 5 strokes in the UK. There may be half a million people in the UK with this condition undiagnosed before a Stroke, as sometimes it only occurs in bursts (Paroxysmal Atrial Fibrillation) and is not constantly present.

Blood thinning (Anticoagulant drugs) are recommended such as Warfarin or, in people without known heart valve disease, DOAC (newer types of anti-coagulants) can be prescribed. Usually Anti platelets such as Aspirin or Clopidogrel are stopped if starting an Anti-coagulant.

Healthy Life Style Advise

Healthy lifestyle is promoted including using the '4ME' leaflet published by Rachel Price and John Cready [7], and used at Pennine Care promoting smoking cessation, alcohol reduction, exercise vision and hearing annual checks. This also reflects the 2017 Lancet commission paper 'Dementia prevention, intervention, and care' and the recent paper Schwarzingler, et al. [69], advocating reduction from heavy drinking of alcohol related to dementia in the French Population. Exercise improves mood and prolongs functional ability to carry out Activities of Daily Living, it reduces obesity [70-75] even though it may not slow decline in cognition in dementia patients. Gebhard, et al. 2016 studied 'Promoting physical activity for people with dementia :a systematic review [70] In Greater Manchester GM moving, supported by Mayor Andy Burnham and Dementia United, aiming to create the world's first dementia friendly city; is working to enable access to activities throughout boroughs including Stockport with appropriate exercise groups which clinicians can prescribe or advise to patients .It is important this is addressed locally to ensure exercise provision is varied and supports types of exercise popular in a borough for the mild cognitive impairment, dementia and over 60 population to enjoy , to ensure continued participation whether in dance , walking football or swimming. Stockport has always had a strong Tennis and Lacrosse, football participation for the population, but in other boroughs dance and rugby may be more popular and help engage more people. The challenge is to engage those with limited finances who have not enjoyed sport participation previously and perhaps tended to smoke and more heavily use alcohol, with reduced access to open spaces and facilities to engage. In vascular dementia prevention this population has the highest risk factors to address and would potentially benefit the most from free tailored exercise, provision with dementia friendly transport support to attend, or provision perhaps of exercise in lounges at the foot of high rise buildings in social housing.

We should consider how groups which help reduce social isolation and improve mood and reduce cognitive decline such as ‘knit and natter’, book clubs, singing for the brain, dementia groups and can be encouraged to incorporate exercise into their groups even chair based exercise. We should encourage groups such as the Stockport Educate Intergenerational choir for dementia patients and school children, helping reduce social isolation and foster understanding between generations and of dementia.

As outlined in the Lancet Commission July 2017; Important non-medical risk prevention and treatment of Vascular mild cognitive impairment and Vascular Dementia and all Dementia to address (particularly targeting areas with highest cardiovascular disease rates) includes exercise (150 minutes per week advised in UK), advising alcohol reduction, smoking cessation, annual hearing and vision checks, obesity, education, depression, social isolation, diabetes by healthy eating. This is considered by Keady, et al; Neighborhoods and dementia in health and social context: a realist review of the literature and implications for UK policy development [76].

In summary; working on the message

‘What’s good for your heart is good for your Brain’

Box 1: Summary of daily, weekly, monthly and yearly activities

4ME – Vascular Dementia Cue Card What do I need to do?

TODAY

- Take my medication as prescribed.
- Try to eat a well balanced diet that is low in fat, salt and sugar and contains five portions of fruit and vegetables daily.
- Attempt mental activity.
- Give up or try to give up smoking.

THIS WEEK

- Complete 30 minutes of physical exercise on five different days this week.
- Make sure alcohol consumption is in moderation.
- Be aware of any changes to my mood and sleep pattern.

THIS MONTH

- Check my weight.
- Keep a note of regular appointments.

THIS YEAR

- Visit GP for an annual health check.
- Have a review of all my medication.
- Have an eye test and/or a hearing test.
- Have a ‘wellcheck’.

What do I need to do?

today

- Take your medication as prescribed.
- Try to eat a well balanced diet that is low in fat, salt and sugar and contains five portions of fruit and vegetables daily.
- Attempt mental activity.
- Give up or try to give up smoking.

What do I need to do?

this week

- Complete 30 minutes of physical exercise on five different days this week.
- Make sure alcohol consumption is in moderation.
- Be aware of any changes to your mood and sleep pattern.

What do I need to do?

this month

- Check my weight.
- Keep a note of regular appointments.

What do I need to do?

this year

- Visit GP for an annual health check.
- Have a review of all your medication.
- Have an eye test and/or a hearing test.
- Have a ‘wellcheck’.

Patient leaflet for lifestyle advice adapted from the 4ME cue card for vascular dementia 2010 Price, R and Keady, J risk assessment and annual review

Patients and carers need risk assessment and support both at diagnosis and annually and this is reflected in the ‘Roundabout, section of the pathway. Assessed are Risks to patients and carers both at diagnosis and annual review, including Low mood and suicidal thoughts, Driving, aggression, hallucinations, Alcohol and smoking, Risks in the home e.g. gas fires, stairs and falls. Consideration of medicine optimization to reduce polypharmacy and medication which can cause cognitive decline and falls (particularly anti cholinergic, opiate pain killers or Tramadol, sleeping tablets). The patient may need a dosette box if compliance is reduced or liquid or crushed medication if dysphagia is a problem. Annually there should be consideration of which medications are appropriate in the patients’ best interests.

The SIGNPOST also reflects the annual need to direct patients and carers to healthy lifestyle, planning for the future and support locally for patients & carers, reflected in 2014 Dementia revealed toolkit [77]. It is important to assess that there is no risk of

carer breakdown or suicide/low mood affecting carers or patients. Annual review also allows clinicians to discuss at the right opportunity future care needs including assessment of the need for future care plans, end of life planning and support. The discussion also often includes withdrawing some long term medication which may not be as beneficial on balance compared with when initially prescribed. This discussion is sensitive and may not be appropriate at the time of initial diagnosis, but perhaps a while after diagnosis with a professional who has time and empathy and ideally who knows the patient well.

It is important to check whether carers or friends are concerned about a patient driving and discuss safer times to drive, whether a driving assessment is necessary, alternative means of transport if needing to stop driving.

Patients in the United Kingdom diagnosed with vascular dementia are required by law to inform the DVLA and car insurance company but can continue driving if their doctor has no concerns.

Patients in the United Kingdom diagnosed with mild vascular cognitive impairment need only inform the DVLA if their doctor has concerns but individual's insurance company may differ as to whether they wish to be informed regarding mild cognitive impairment diagnosis.

Aims of Publication

We welcome views of readers and please email s.gilmour@nhs.net with correspondence.

Next year we will attempt to implement the pathway more widely in clinical practice including a consensus discussion at a Stockport Vascular Dementia Conference in January 2019. Where there is not a consensus among clinicians who read this paper I hope debate will lead to clarification, but our concern is that if we are to wait for further research to clarify the benefit of secondary cardiovascular prevention on cognition in vascular neurocognitive disorder we are denying patients cardiovascular investigation and treatment which is already proven in closely related stroke secondary cardiovascular prevention and indicated by many studies so far.

We should offer patients the choices based on previous papers and consider personally once having read evidence, which choices we would recommend to family members, friends or ourselves.

References

1. Hachinski V, Iadecola C, Petersen R, Breteler M, Nyenhuis D, et al. (2006) National Institute of Neurological Disorders and Stroke-Canadian Stroke Network Vascular Cognitive Impairment Harmonization Standards. *Stroke* 37: 2220-2241.
2. 2018 Major and Mild Neurocognitive Disorder (2013) *Psychiatric News* 48: 12.
3. Diagnostic and Statistical Manual of Mental Disorders: DSM-5 (5th edition) Washington, DC American Psychiatric Association 2013.
4. Fazekas F, Kleinert R, Offenbacher H, Schmidt R, Kleinert G, et al. (1993) Pathologic correlates of incidental MRI white matter signal hyperintensities. *Neurology* 43: 1683-1683.
5. Stroke guidelines released by Royal College of Physicians. (2000) *In-pharma Weekly* 3.
6. GMSODN Greater Manchester Stroke Operational Delivery Network (2018) Gmsodn.org.uk. ODN 2018.
7. Price R, Keady J (2010) Introducing the 4ME cue card for vascular dementia. *Journal of Dementia Care* 17: 88-101 4ME Vascular Dementia Cue Card What do I need to do? *Today This Week This Month This Year* 2010.
8. Passmore P (2017) *Vascular Dementia*. BMJ Best Practice 2017.
9. Yates, P. (2016). *Vascular Cognitive Impairment*. *Alzheimer's Australia* 1- 4.
10. Wiberg B, Lind L, Kilander L, Zethelius B, Sundelof J et al. (2010) Cognitive function and risk of stroke in elderly men. *Neurology*, 74:379-385.
11. Livingston G, Sommerlad A, Orgeta V, Costafreda S, Huntley J, et al. (2017) Dementia prevention, intervention, and care. *The Lancet*, 390:2673-2734.
12. Gilmour S, Ngoma P, Price R, Burns A (2018) The 2018 Stockport vascular neurocognitive disorder investigation, treatment and annual review guidelines (including the spectrum from mild vascular cognitive impairment to vascular dementia) supporting primary and secondary care physicians. In: 10th International Conference on Vascular Dementia. Paris: The journal of Alzheimer's disease and Parkinsonism, 8:54.
13. Gilmour S (2017) *Dementia Masterclass*.
14. Gardener H, Wright C, Rundek T, Sacco R (2015) Brain health and shared risk factors for dementia and stroke Sub clinical brain MRI markers of vascular damage are risk factors shared between stroke and dementia and can be used for risk stratification and early intervention damage. *Nature Reviews Neurology* 11:651-657.
15. DeBette S, Markus H (2010) The clinical importance of white matter hyperintensities on brain magnetic resonance imaging: systematic review and meta-analysis. *BMJ* 341:3666-3666.
16. Lechner H, Schmidt R, Fazekas F, Koch M, Offenbacher H, et al. (1994). White matter lesions on magnetic resonance imaging in a healthy elderly population: Correlations to vascular risk factors and carotid atherosclerosis. *Journal of Stroke and Cerebrovascular Diseases* 4:224-228.
17. Lazarus R, Prettyman R, Cherryman G (2005) White matter lesions on magnetic resonance imaging and their relationship with vascular risk factors in memory clinic attenders. *International Journal of Geriatric Psychiatry* 20:274-279.

18. Swarbrick C, Keady J, Deaton C, Reilly S, Price R, et al. (2012) Proposing a cardiac model for vascular dementia. *British Journal of Nursing* 21:1124-1124.
19. Elkins J, O'Meara E, Longstreth W, Carlson M, Manolio T et al. (2004) Stroke risk factors and loss of high cognitive function. *Neurology* 63: 793-799.
20. Price R, Keady J (2010) Systematic review: role of health promotion in vascular dementia. *Journal of Nursing and Healthcare of Chronic Illness* 2: 88-101.
21. Hillman C, Erickson K, Kramer A (2008) Be smart, exercise your heart: exercise effects on brain and cognition. *Nature Reviews Neuroscience* 9: 58-65
22. Yu F, Bronas U, Veith D (2014) Prescribing Aerobic Exercise To Older Adults With Alzheimer's Disease. *Alzheimer's & Dementia* 10: 607
23. Pantoni L, Bianchi C, Beneke M, Inzitari D, Wallin A et al. (2000) 22 The Scandinavian Multi-Infarct Dementia Trial: a double-blind, placebo-controlled trial on nimodipine in multi-infarct dementia. *Journal of the Neurological Sciences*, 175: 116-123.
24. Dufouil C, chalmers J, Coskun O, Besancon V, Bousser MG, et al. (2005) Effects of Blood Pressure Lowering on Cerebral White Matter Hyperintensities in Patients With Stroke: The PROGRESS (Perindopril Protection Against Recurrent Stroke Study) Magnetic Resonance Imaging Substudy. *Circulation* 112: 1644-1650.
25. Anticoagulants could cut the risk of dementia for patients with atrial fibrillation, researchers find. (2017) *The Pharmaceutical Journal* 2017.
26. Holmes C, Cairns N, Lantos P, Mann A (1999) Validity of current clinical criteria for Alzheimer's disease, vascular dementia and dementia with Lewy bodies. *British Journal of Psychiatry* 174: 45-50.
27. Burns A, Barrett E (2014) Dementia Revealed What Primary Care Needs to Know.UK: RCGP, p.ALL.
28. Khan A, Kalaria R, Corbett A, Ballard C (2016). Update on Vascular Dementia. *Journal of Geriatric Psychiatry and Neurology* 29: 281-301.
29. Black S (2011) Vascular cognitive impairment: epidemiology, subtypes, diagnosis and management. *Journal of the Royal College of Physicians of Edinburgh* 41: 49-56.
30. Rostamian S, Mahinrad S, Stijnen T, Sabayan B, de Craen A (2014) Cognitive Impairment and Risk of Stroke: A Systematic Review and Meta-Analysis of Prospective Cohort Studies. *Stroke* 45: 1342-1348.
31. Jellinger K, Attems J (2006) Prevalence and impact of cerebrovascular pathology in Alzheimer's disease and parkinsonism. *Acta Neurologica Scandinavica* 114: 38-46.
32. Tully P, Dartigues J, Debette S, Helmer C, Artero S, et al. (2016) Dementia risk with antihypertensive use and blood pressure variability. *Neurology* 87.
33. Shah K, Qureshi S, Johnson M, Parikh N, Schulz P, et al. (2009) Does use of antihypertensive drugs affect the incidence or progression of dementia? A systematic review. *The American Journal of Geriatric Pharmacotherapy* 7: 250-261.
34. Kennelly SP, Lawlor BA, Kenny RA (2009) Review blood pressure and dementia- a comprehensive review. *Therapeutic Advances in Neurological Disorders* 2009.
35. Kernan W, Ovbiagele B, Black H, Bravata D, Chimowitz M, et al. (2014) Guidelines for the Prevention of Stroke in Patients With Stroke and Transient Ischemic Attack: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association. *Stroke*, 45: 2160-2236.
36. Kjeldsen S, Narkiewicz K, Burnier M, Oparil S (2018) Intensive blood pressure lowering prevents mild cognitive impairment and possible dementia and slows development of white matter lesions in the brain: the SPRINT Memory and Cognition IN Decreased Hypertension (SPRINT MIND) study. *Blood Pressure* 27: 247-248.
37. Hanon O, Seux M, Lenoir H, Rigaud A, Forette F (2004) Prevention of dementia and cerebroprotection with antihypertensive drugs. *Current Hypertension Reports* 6: 201-207.
38. O'Keefe J, Bybee K, Lavie C (2008). Intensive Lipid Intervention in the Post- ENHANCE Era. *Mayo Clinic Proceedings* 83: 867-869.
39. Swiger K, Manalac R, Blumenthal R, Blaha M, Martin S (2013) Statins and Cognition: A Systematic Review and Meta-analysis of Short- and Long-term Cognitive Effects. *Mayo Clinic Proceedings* 88: 1213-1221.
40. Wilmot K, Khan A, Krishnan S, Krishnan S, Eapen D, Sperling L (2014) Statins in the Elderly: A Patient-Focused Approach. *Clinical Cardiology* 38: 56-61.
41. Thompson G (2011) Cardiovascular disease prevention and the rise in dementia. *QJM* 105: 93-97.
42. McGuinness B, Craig D, Bullock R, Passmore P (2016) Statins for the prevention of dementia. *Cochrane Database of Systematic Reviews* 2016.
43. Cramer C, Haan MN, Galea S, Langa KM, Kalbfleisch JD (2008) Use of statins and incidence of dementia and cognitive impairment without dementia in a cohort study. *Neurology*, 71: 344-350.
44. Suemoto C, Grinberg L, Ferretti R, Menezes P, Farfel J et al. (2010) Carotid artery atherosclerosis is associated with Alzheimer disease and vascular dementia: A postmortem study. *Alzheimer's & Dementia* 6: 466-467.
45. Suemoto C, Santos I, Bittencourt M, Pereira A, Goulart A, et al. (2015) Subclinical carotid artery atherosclerosis and performance on cognitive tests in middle-aged adults: Baseline results from the ELSA-Brasil. *Atherosclerosis* 243: 510-515.
46. Nogrady B (2015) Atrial Fibrillation Doubles Silent Cerebral Infarct Risk. *Caring for the Ages* 16: 2.
47. Edwards J, Ramirez J, Callahan B, Berezuk C, Gladstone D, et al. (2016) Atrial Fibrillation Is Independently Associated with Brain Atrophy And Cognitive Dysfunction. *Alzheimer's & Dementia* 12: 952.
48. Wolters F, de Bruijn R, Ikram M (2016) Potential Association Between Atrial Fibrillation and Dementia— Reply. *JAMA Neurology* 73: 607.
49. Tokatli A, Yiginer O, Ozmen N, Uzun M, Kilicaslan F (2016) Paroxysmal atrial fibrillation and related thromboembolism may be a hidden factor in the development of dementia. *Psychogeriatrics* 16: 382-383.
50. Purandare N, Burns A, Daly K (2006) Cerebral emboli as a potential cause of Alzheimer's disease and vascular dementia: Case-control study. *Journal of Vascular Surgery* 44: 1132.

51. Biessels G (2015) Microinfarcts: Key to prevention of the vascular burden in dementia?. *Alzheimer's & Dementia* 11: 216.
52. Delaying anticoagulation treatment for atrial fibrillation increases dementia risk, study suggests. (2017) *The Pharmaceutical Journal* 2017.
53. CG180 management of Atrial Fibrillation (2016) NICE.
54. Yaneva-Sirakova T, Tarnovska-Kadreva R, Traykov L (2013) Atrial fibrillation and mild cognitive impairment. *Alzheimer's & Dementia* 9: 771.
55. Werring D, Frazer DW, Coward LJ, Losseff NA, Watt H, et al. (2004) Cognitive dysfunction in patients with cerebral microbleeds on T2-weighted gradient-echo MRI. *Brain* 127: 2265-2275.
56. Lee SH, Kim SM, Kim N, Yoon BW, Roh JK (2007) Cortico-subcortical distribution of microbleeds is different between hypertension and cerebral amyloid angiopathy. *Journal of the Neurological Sciences* 258: 111-114.
57. Al-Shahi Salman R (2010) Brain MRI roulette. *Practical Neurology* 10: 188-190.
58. Copenhagen BR, Shin J, Warach S, Butman J, Saver JL, et al. (2009) Gradient echo MRI: Implementation of a training tutorial for intracranial hemorrhage diagnosis. *Neurology* 72: 1576-1581.
59. Johnston K, Marx W (2003) Microhemorrhages on gradient echo MRI. *Neurology* 60:518-518.
60. Kivipelto M, Solomon A, Ahtiluoto S, Ngandu T, Lehtisalo J, et al. (2013) The Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER): Study design and progress. *Alzheimer's & Dementia* 9: 657-665.
61. ALLARD WALES
62. DeFries T, Avendaño M, Glymour M (2009) Level and Change in Cognitive Test Scores Predict Risk of First Stroke. *Journal of the American Geriatrics Society* 57: 499-505.
63. Wardlaw J (2016) Stroke and dementia what research tells us Declining cognition is a warning of Stroke, Stroke is a warning of declining cognition. UK Stroke Assembly 2016.
64. Aspirin foundation (2016) Most specialists believe that aspirin should be offered to patients with cognitive impairment and dementia 2016.
65. Devine M, Rands G (2003) Does aspirin affect outcome in vascular dementia? A retrospective case-notes analysis Regular low dose aspirin increased life expectancy and reduced institutionalisation. *International Journal of Geriatric Psychiatry* 18: 425-431.
66. Rand (2012) Aspirin for vascular dementia There is still no good evidence that Aspirin is effective in treating patients with a diagnosis of vascular dementia. There is increasing concern that aspirin is associated with an increase in haemorrhages. It is possible that aspirin causes small cerebral haemorrhage that could stimulate the amyloid cascade possibly leading to Alzheimer's or death from brain haemorrhage. *Cochrane* 2012.
67. Seadon S, Lang E (2015) Clopidogrel with aspirin versus aspirin alone in prevention of stroke following transient ischemic attack or acute minor stroke. *CJEM* 17: 315-317.
68. Salman RAS, McGoohan K, Rodrigues M, Dichgans M (2016) Dementia after stroke due to intracerebral haemorrhage. *The Lancet Neurology* 15: 779-780.
69. Schwarzingner M, Pollock B, Hasan O, Dufouil C, Rehm J, et al. (2018) Contribution of alcohol use disorders to the burden of dementia in France 2008-13: a nationwide retrospective cohort study. *The Lancet Public Health* 2018.
70. Gebhard D (2016) Promoting physical activity for people with dementia: a systematic review. *European Journal of Public Health* 26.
71. Johnson D, Vidoni E, Burns J (2012) Trial of exercise on aging and memory (TEAM Study). *Alzheimer's & Dementia* 8: 583.
72. Aarsland D, Sardaheae F, Anderssen S, Ballard C, Alzheimer's Society Systematic (2010) Is physical activity a potential preventive factor for vascular dementia? A systematic review. *Aging & Mental Health* 14: 386-395.
73. White F (2016) Minds in Motion®: A Community-Based Physical And Social Recreation Program Promoting A Healthy Active Lifestyle For People With Dementia and Their Care Partners. *Alzheimer's & Dementia* 12:797-798.
74. Kramer A (2011) Exercise, Cognition and the Brain. *Alzheimer's & Dementia* 7: S87.
75. Beckett N, Pedditzi E, Peters R (2011) Dementia and the obesity paradox. *Alzheimer's & Dementia* 7:8.
76. Keady J, Campbell S, Barnes H, Ward R, Li X, et al. (2012). Neighbourhoods and dementia in the health and social care context: a realist review of the literature and implications for UK policy development. *Reviews in Clinical Gerontology* 22:150-163.
77. Alistair B (2014) Dementia revealed toolkit.