Stroke Prevention: Little-Known and Neglected Aspects

M. Reza Azarpazhooh^a Chrysi Bogiatzi^b J. David Spence^c

^aDivision of Neurology and Department of Epidemiology & Biostatistics, Western University, London, ON, Canada;

^bDepartment of Neurology, McMaster University, Hamilton, ON, Canada; ^cStroke Prevention & Atherosclerosis Research Center, Robarts Research Institute, Western University, London, ON, Canada

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Abstract

Combining available therapies has the potential to reduce the risk of stroke by 80% or more. A comprehensive review of all aspects of stroke prevention would be very lengthy; in this narrative review, we focus on some aspects of stroke prevention that are little-known and/or neglected. These include the following: (1) implementation of a Mediterranean diet; (2) B vitamins to lower homocysteine; (3) coordinated approaches to smoking cessation; (4) intensive lipid-lowering therapy; (5) lipid lowering in the elderly; (6) physiologically individualized therapy for hypertension based on renin/aldosterone phenotyping; (7) avoiding excessive blood pressure reduction in patients with stiff arteries; (8) treatment of insulin resistance with pioglitazone in stroke patients with prediabetes and diabetes; (9) impaired activation of clopidogrel in patients with variants of CYP2C19; (10) aspirin pseudoresistance due to enteric coating; (11) rationale for anticoagulation in patients with embolic stroke of unknown source; (12) pharmacologic properties of direct-act-

ing oral anticoagulants that should be considered when choosing among them; (13) the identification of which patients with asymptomatic carotid stenosis are at a high enough risk to benefit from carotid endarterectomy or stenting; and (14) the importance of age in choosing between endarterectomy and stenting. Stroke prevention could be improved by better recognition of these issues and by implementation of the principles derived from them.

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Introduction

It is likely that 80% or more of strokes could be prevented by a combination [1] of lifestyle modification, effective blood pressure control, antiplatelet or anticoagulant therapy as appropriate, lipid lowering, B vitamins to lower homocysteine, and judicious intervention with endarterectomy or stenting. A comprehensive review of all those topics would be very lengthy; in this narrative review, we focus on some aspects of stroke prevention that are less well known than they ought to be and often neglected. These include selected issues in lifestyle modification, nutrition, blood pressure control, lipid-lowering therapy, hypertension, diabetes, antiplatelet therapy, anticoagulation, and intervention for carotid stenosis. We

have not emphasized a distinction between primary and secondary prevention because any intervention is more effective (i.e., the number needed to treat [NNT] is lower) in patients at higher risk. An intervention that reduces stroke in primary prevention would be expected to have an even greater effect in secondary prevention.

Lifestyle

Lifestyle is far more important than most physicians suppose and tends to be neglected in comparison to a focus on medical and surgical management. In a study of health professionals who were healthy at baseline, among 43,685 men and 71,243 women, half of stroke was attributable to an unhealthy lifestyle [2]. Participants who achieved all 5 health lifestyle attributes (not smoking, moderate alcohol intake, a body mass index <25, daily exercise for 30 min and a diet in the top 40% of a healthy diet score) had an 80% reduction of ischemic stroke compared to the group with the worst lifestyle attributes. Similarly, myocardial infarction among men was markedly reduced by a healthy lifestyle [3]. Among Swedish women, those with all 5 healthy lifestyle factors had a reduction of ischemic stroke by 62% compared to no healthy factors [4]. Among Swedish men with hypertension and hyperlipidemia, those with all 5 healthy lifestyle attributes had an 86% reduction in myocardial infarction versus those with none [5].

Nutrition

Diet

Although it is possible that vegetarian or pesco-vegetarian diets [6] may be even better, the best evidence for stroke prevention is with the Cretan Mediterranean diet [7]. It is high in whole grains, fruits, vegetables, legumes, nuts, and olive oil or Canola oil and low in meat and dairy products. Keys, the leader of the 7 countries study in which the benefits of the diet were discovered, described it as a “mainly vegetarian” diet [8]. It is a high-fat diet, with 40% of calories from fat, but it is plant-derived fat, with 1/15th the coronary risk of the diet in Finland, in which 38% of calories were from fat, mainly animal fat, accompanied by its evil companion, cholesterol [9]. As a high-fat diet, the Mediterranean diet is a low-glycemic diet; in an Israeli study, it was clearly better for diabetes than either a low-fat diet or a low-carbohydrate diet [10]. Probably the benefits of the Mediterranean diet relate to substitution of olive oil for animal fat and a high intake of fiber, bioflavonoids, and antioxidants.

In secondary prevention, in the Lyon Diet Heart study, a Mediterranean diet reduced stroke and recurrent myocardial infarction by >60% in 4 years compared to a “prudent Western diet” resembling a low-fat diet [11]. This was twice the effect of simvastatin in the contemporaneous Scandinavian Simvastatin Survival Study, which reported a 40% reduction of recurrent myocardial infarction over 6 years [12]. In primary prevention, among participants with risk factors for vascular disease, the Mediterranean diet fortified with nuts reduced stroke by 46% in 5 years, compared to a low-fat diet [13].

Consumption of cholesterol and eggs increases cardiovascular risk in a dose-dependent manner [14]. Besides the high cholesterol content of eggs and meat, an important advance has been the understanding that toxic metabolic products of the intestinal microbiome are important in cardiovascular disease. Trimethylamine-N-oxide, produced largely from egg yolk and red meat, increases cardiovascular risk [15]. Other toxic metabolites, such as *p*-cresylsulfate, indoxyl sulfate, hippuric acid, *p*-cresyl glucuronide, phenyl acetyl glutamine, and phenyl sulfate are produced from amino acids in dietary protein. Both trimethylamine-N-oxide and *p*-cresylsulfate were independent predictors of carotid plaque burden in linear regression [16], and plasma levels of all 7 toxic metabolites measured in that study were significantly elevated by even moderate impairment of renal function, an estimated glomerular filtration rate <66 mL/min/1.73 m² [17]. That level of renal function is average for vascular patients aged >75 years [18]. Patients with impaired renal function, including the elderly, should avoid egg yolk and red meat and limit meat intake. Those issues were recently reviewed [19].

Patients at risk of stroke should be encouraged to follow a Mediterranean diet, avoiding egg yolk and red meat and limiting meat intake. They should be provided with resources to help them succeed in that effort. The diet recommended to patients at the Stroke Prevention & Atherosclerosis Research Center in London, Canada, is shown in Table 1. The recipe booklet provided to patients to help them with this approach can be downloaded from <http://www.robarts.ca/SPARC/>.

B Vitamins to Lower Homocysteine

Despite widespread belief to the contrary, it is now evident that using B vitamins to lower homocysteine reduces the risk of stroke. The benefit of B vitamins was obscured in early studies by harm from cyanocobalamin among participants with impaired renal function. This was evident in a meta-analysis stratified by renal function and dose of cyanocobalamin [20]. In a study of patients

Table 1. Diet recommended for stroke prevention

High intake of whole grains, fruits, vegetables, nuts, lentils, beans, olive oil/canola oil

Limit intake of animal flesh to a serving the size of the palm every other day (or half that daily), or less, mainly fish and chicken, seldom red meat

No egg yolks: use egg white-based substitutes instead to make tasty omelets, frittatas, and egg salad sandwiches

The recipe booklet provided to patient attending the Stroke Prevention & Atherosclerosis Research Center in London, Canada, can be downloaded from <http://www.robarts.ca/SPARC/>.

with diabetic nephropathy, B vitamins including 1,000 µg daily of cyanocobalamin accelerated the decline of renal function and nearly doubled the risk of a composite of myocardial infarction, stroke, revascularization, and all-cause mortality [21]. In contrast, stroke was reduced by 43% in the French Su.Fol.OM3 study, with the best renal function and the lowest dose of cyanocobalamin among trials that included cyanocobalamin (only 20 µg daily vs. 400–1,000 µg daily in the earlier studies). In the China Stroke Primary Prevention Trial, folic acid significantly reduced stroke in patients with hypertension; the reduction was greater among those with higher risk; ischemic stroke was reduced by 36% over 5 years among participants with LDL-C >2 mmol/L [22]. Folic acid was beneficial among participants with impaired renal function [23]. The history of this complex issue was reviewed in 2019 [24]. Two more recent meta-analyses have confirmed that folic acid and B vitamin combinations reduce the risk of stroke [25, 26]. Metabolic B12 deficiency with hyperhomocysteinemia is very common and easily treated [27]; the ongoing neglect of this opportunity to reduce the risk of stroke should not be permitted to persist.

Smoking Cessation

Smoking increases the risk of stroke 6-fold, and even passive smoking nearly doubles the risk of stroke [28]. All patients at risk of stroke should be strongly and repeatedly advised to quit smoking, with counseling, advised to use nicotine replacement therapy, and prescribed medications such as varenicline and bupropion. Patients should be advised that they must quit smoking and stop thinking of smoking cessation as something optional. The “parable of the cold lake,” an approach borrowed from a Lancet article on diet, can be helpful: “If you are walking along the shore of a cold lake and your grand-

child falls in, it doesn’t take willpower to go into the lake; it simply must be done.” A coordinated approach such as the Ottawa Model [29] is more successful than half-hearted approaches. In the Insulin Resistance Intervention after Stroke (IRIS) trial, participants who quit smoking had a 34% reduction in the 5-year risk of stroke, MI, or death compared to those who continued to smoke [30].

Lipid Lowering

It is now clear that lipid lowering is an important aspect of stroke prevention. Unfortunately, it is all too often not implemented or implemented only in a half-hearted way. A little bit of statin is not enough. Too often, high-dose statins are avoided because of misplaced concern about adverse effects or omitted in the elderly because early trials did not include patients above the age of 80. The only true causal adverse effects of statins are myopathy and a slight increase in the risk of diabetes. Statins do not cause cognitive impairment, renal impairment, cataracts, hepatotoxicity, intracerebral hemorrhage, or other adverse effects commonly attributed to them [24, 31]. Lipid lowering should be intensive, should include as high a dose of statin as tolerated, and should probably routinely include addition of ezetimibe. In some patients, therapies based on blocking PCSK9 should be considered, though cost is a limitation.

Intensive Lipid Lowering

The benefit of statins was underestimated in the Stroke Prevention by Aggressive Reduction in Cholesterol Level (SPARCL) trial, in part because many patients did not have large-artery disease and because many patients randomized to statin stopped it, and 25% of those randomized to placebo crossed over to statin. Among patients in SPARCL who had a 50% reduction of LDL-C (meaning they actually took the statin), there was a 33% reduction of stroke, a 37% reduction of MI, and no increase in intracerebral hemorrhage [32]. Amarenco et al. [32] recently reported that among patients with a prior TIA or stroke, treating to a target LDL-C <1.8 versus 2.3–2.8 mmol/L reduced ischemic stroke by 33%. In the SPARCL trial, lower LDL-C at 3 months was associated with a reduction of recurrent events; total events were prevented by atorvastatin twice as much as first events [33].

Lipid Lowering in the Elderly and Ezetimibe

Historical therapeutic nihilism regarding lipid lowering in old patients has now been debunked. It is now clear

that older patients benefit from lipid lowering even more than younger patients because they have a higher risk and therefore a greater absolute risk reduction, resulting in lower NNT to prevent stroke [34].

In a trial of ezetimibe added to simvastatin, the NNT was only 11 for patients above age 75, versus 115 below age 75. In a Japanese trial of ezetimibe versus placebo added to diet, in patients with a mean age of 80 years at baseline and followed up for 4 years, there was a 34% reduction of the composite outcome of sudden cardiac death, myocardial infarction, coronary revascularization, or stroke [35].

It is an important error to equate lipid lowering with statins alone; ezetimibe should be used routinely for stroke prevention. Whereas statins block the synthesis of cholesterol, ezetimibe blocks the absorption of cholesterol and other sterols. By blocking 2 mechanisms, the combination of ezetimibe with statin is synergistic; 10 mg of ezetimibe with 40 mg of atorvastatin lowers LDL by almost as much as 80 mg of atorvastatin. By combining ezetimibe with statin, lower doses of statin can be used, thereby minimizing adverse effects. In a trial in which ezetimibe or placebo was added to simvastatin, ezetimibe reduced stroke by 21% overall, but as discussed above, the effect was greater in older patients [36]. The European guideline on dyslipidemia now recommends addition of ezetimibe in patients who do not achieve lipid targets with statin alone [37].

Hypertension

Hypertension is probably the most important risk factor for stroke, and it is poorly treated. Controlling blood pressure well reduces the risk of stroke by half and virtually eliminates intracranial hemorrhage. After the Department of Family Medicine at Western University in London, ON, Canada, implemented in 1978 a large program to improve blood pressure control in the community [38], the detection and treatment of hypertension improved markedly. In that era, the “rule of halves” prevailed in North America: only half of hypertension was detected, of that only half (25%) was being treated, and of that, only half (12.5%) of the patients were controlled. By 1983, in Middlesex County, which surrounds the city, 94% of hypertension was detected, 92% of hypertensive patients were being treated, and 72% had their blood pressure controlled [39]. The result of that was a 50% reduction of stroke [40]. In part, that success was related to the establishment in 1977 of a hypertension clinic that

based therapy for resistant hypertension on measurement of stimulated renin [41], as discussed below. The stroke subtypes that were preferentially reduced were those due to hypertensive small-vessel disease: lacunar infarctions and intracerebral hemorrhages [40]. In the North American Carotid Endarterectomy Trial, strenuous efforts were made to achieve benchmark blood pressures. A stiff letter was sent to the site investigator every time a patient attended clinic with a blood pressure above target if anti-hypertensive therapy was not intensified. The result of this was that at a time when ~20% of strokes were due to intracranial bleeding, intracranial bleeds in the medical arm of the North American Carotid Endarterectomy Trial were reduced to 0.5%. That total included subarachnoid and lobar hemorrhages; that is, hypertensive intracerebral hemorrhages were virtually eliminated.

Resistant Hypertension

A population-based study in Sweden reported that among persons being treated for hypertension, 90% of strokes occurred in patients with uncontrolled hypertension [42]. It was estimated that strokes could have been reduced by 45% by controlling blood pressure. The causes of resistant hypertension include noncompliance, consumption of substances that aggravate hypertension (salt, licorice, nonsteroidal anti-inflammatory agents other than sulindac, decongestants, and excess alcohol), therapeutic inertia (failure to intensify therapy when blood pressure is not controlled), and diagnostic inertia (failure to investigate the cause of the hypertension so that appropriate therapy can be identified). Approximately half of non-compliant patients will admit it if questioned in a nonjudgemental way [43], and pharmacy records and sometimes blood levels of drugs can be checked to detect noncompliance [44]. Salt intake should be reduced to 2–3 g/day [45], sulindac should replace other NSAIDs [46], decongestants can be replaced, and alcohol intake should be moderate. Perhaps the most important missed opportunity is diagnostic inertia.

Physiologically Individualized Therapy for Resistant Hypertension

Blood pressure control can be markedly improved by physiologically individualized therapy based on renin/aldosterone phenotyping (PhysRx). There are 3 key phenotypes: low renin/high aldosterone (inappropriate aldosterone secretion), low renin/low aldosterone (a Liddle phenotype, due to overactivity of the renal epithelial sodium channel, ENaC), and high renin/high aldosterone (secondary aldosteronism, due to excess renin production re-

Table 2. Physiologically individualized therapy for control of resistant hypertension^a

	Primary hyperaldosteronism	Liddle's syndrome and variants (mutations affecting the renal Na ⁺ channel or its function)	Renal/renovascular
Renin	Low ^b	Low	High
Aldosterone	High ^b	Low	High
Primary treatment	Aldosterone antagonist (spironolactone or eplerenone) Amiloride for men where eplerenone is not available (rarely surgery)	Amiloride	Angiotensin receptor blocker ^c or renin inhibitor (rarely revascularization)

Reproduced by permission of Oxford University Press from Akintunde A, Nondi J, Gogo K, Jones ESW, Rayner BL, Hackam DG, and Spence JD. Physiological phenotyping for personalized therapy of uncontrolled hypertension in Africa. *Am J Hypertens*. 2017; 30(9):923–30. ^a It should be stressed that this approach is suitable for tailoring medical therapy in resistant hypertensives; further investigation would be required to justify adrenalectomy or renal revascularization. ^b Levels of plasma, renin, and aldosterone must be interpreted in the light of the medication the patient is taking at the time of sampling. In a patient taking an angiotensin receptor blocker (which would elevate renin and lower aldosterone), a plasma renin that is in the low normal range for that laboratory, with a plasma aldosterone in a high normal range, probably represents primary hyperaldosteronism, for the purposes of adjusting medical therapy. ^c Angiotensin receptor antagonists are less effective because of the aldosterone escape via non-ACE pathways, such as chymase and cathepsin; renin inhibitors are seldom used.

sulting from renal disease such as cysts, renal artery stenosis, obstruction, or hypertensive nephrosclerosis). Some patients whose hypertension begins with a low-renin phenotype may develop secondary hyperaldosteronism as a result of hypertensive nephrosclerosis, renal artery stenosis, or polycystic kidneys, but most patients with resistant hypertension can have their blood pressure control markedly improved by PhysRx.

Suppressed renin due to salt and water retention is more common in black patients. There are 2 streams of low-renin hypertension: inappropriate aldosterone secretion (low renin/high aldosterone), for which aldosterone antagonists are the best treatment, and the Liddle phenotype (low renin/low aldosterone), for which amiloride is the best therapy. There are variants of at least 6 genes that cause inappropriate aldosterone secretion (CYP11B2, KCNJ5, ATP1A1, ATP2B3, CACNA1D, and ARMC5) and variants of at least 6 genes that cause the Liddle phenotype (SCNN1B, true Liddle syndrome, as well as GRK, NEDD4L, CYP4A11, NPPA, and UMOD) [47]; probably others are yet to be discovered. Variants of those genes were very common in patients with uncontrolled hypertension in the African study described below [48].

The algorithm for selection of therapy based on PhysRx is shown in Table 2. In a study in Africa [49], patients with uncontrolled hypertension were allocated to usual care

versus PhysRx. The strategy was not successful at the site in Kenya, where amiloride was not available, patients attended the clinic less often, and the cost of medication was prohibitive. At the Nigerian site, where care more closely resembled that in developed nations, and patients were randomized to the 2 treatment strategies, “systolic control was obtained in 15% of usual care versus 85% of PhysRx ($p = 0.0001$), diastolic control in 45 versus 75% ($p = 0.11$), and control of both systolic and diastolic pressure in 15 versus 75% ($p < 0.0001$) even though the renal function was worse at that site.” This strategy has the potential to markedly improve control of hypertension and lessen the stroke disparity among African Americans; it should be used routinely in resistant hypertension [50]. Our Neurology colleagues may demur, saying that they leave control of hypertension to the internist or the family physician. The unfortunate consequence of that approach is that it does not happen. A recent study documented that in the Veteran’s Administration hypertension clinics, diagnostic inertia was highly prevalent: only 1.6% of the patients with resistant hypertension were tested for primary aldosteronism [51], even though it accounts for 22% of resistant hypertension [52]. The most neglected cause of hypertension is the Liddle phenotype. Guidelines do not mention Liddle syndrome, and amiloride, the specific therapy for the Liddle phenotype, is mentioned only as an alternative to spironolactone for primary aldosteronism [53].

Risk of Diastolic Pressure <60 mm Hg with Pulse Pressure >60 mm Hg

Another neglected topic in hypertension is the relatively recent recognition that low systolic blood pressure targets <120 mm Hg which is not safe in a subgroup of elderly frail patients with stiff arteries. McEvoy et al. [54] reported that patients with diastolic pressure <60 mm Hg and a pulse pressure >60 mm Hg (DBP <60/PP >60) had a doubling of subclinical myocardial ischemia; Park and Ovbiagele [55] reported that such patients had a 5.85-fold increase in the risk of stroke. Reasons for this phenomenon were recently summarized [56]: (1) wide pulse pressures are due to stiff arteries; (2) patients with stiff arteries are more likely to have a large cuff artifact, with the cuff diastolic pressure measuring substantially higher than the true intra-arterial pressure; (3) virtually all of myocardial perfusion and more than half of cerebral perfusion occurs during the diastole; (4) there is a large pressure gradient in the brain: “When the pressure in the brachial artery is 117/75 mm Hg, it is 113/73 mm Hg in the lenticulostriate artery but only 59/39 mm Hg in small branches in the posterior parietal subcortex” [57].

Patients with DPB <60/PP >60 may have diastolic pressures that are below the critical perfusion pressure if their systolic pressure is lowered too far. Elderly patients with hypotensive symptoms at blood pressures that seem too high to explain them should be suspected of having a large cuff artifact (“pseudohypertension” [58]); blood pressure targets should be reconsidered, and if feasible, intra-arterial pressure should be measured to clarify the situation.

Diabetes

Diabetes is an important risk factor for stroke. In the Honolulu Heart Study, diabetes increased the 22-year risk of stroke 3.47-fold [59]. A report from the Nurses’ Health Study [60] indicated that type II diabetes preferentially increased lacunar and large-artery stroke, whereas type I diabetes was also associated with hemorrhagic stroke (it seems likely that hypertension due to diabetic nephrosclerosis explains that finding). Great advances have been made in the treatment of diabetes with new drug classes, such as gliptins, but treatment of insulin resistance with thiazolidinediones, particularly pioglitazone, has been a missed opportunity. Thiazolidinediones have been largely avoided, for reasons that do not stand up to scrutiny. Evidence for an increased risk of bladder cancer is weak, and if there is a risk, it is very low:

0.0066% per year, based on a meta-analysis that reported marked heterogeneity among studies [61]. Pantoni reviewed reasons for the mistaken reluctance to use them [62], and others have called for an end to this nihilism.

Pioglitazone

Insulin resistance is very common, particularly in obese patients and South Asians. It is associated with high triglycerides, low high-density lipoprotein cholesterol, coagulation, inflammation, and vascular reactivity. Weight loss and exercise improve sensitivity to insulin, and the most potent drug therapy for insulin resistance is with thiazolidinediones. Pioglitazone is a potent agonist of peroxisome proliferator-activated receptor- γ and a weak agonist of peroxisome proliferator-activated receptor- α . It has common adverse effects in the highest dose of 45 mg daily: in a study in prediabetics, fluid retention occurred in 29% of the patients taking it versus 22% of patients on placebo; and weight gain affected 29% of patients taking it versus 12% of the patients on placebo. For that reason, intention-to-treat analyses (ITT) are not appropriate for therapeutic decisions in individual patients [63].

An ITT analysis of the IRIS trial reported that in patients with a prior stroke and with insulin resistance defined by the homeostasis model, pioglitazone reduced new-onset diabetes by 52% and reduced nonfatal stroke and myocardial infarction (stroke/MI) by 24% [64]. An ITT analysis of pioglitazone for secondary stroke prevention in the PROspective pioglitAzone Clinical Trial In macroVascular Events (PROactive) trial reported a 47% reduction of stroke [65], and a meta-analysis conducted prior to the study described below reported a 32% reduction of recurrent stroke with pioglitazone [66].

In a subgroup analysis of IRIS participants with pre-diabetes [67], defined by hemoglobin A1c level of 5.7–6.4%, the primary analysis was an on-treatment analysis (defined by taking $\geq 80\%$ of the protocol dose of 45 mg). That analysis revealed an 82% reduction of new-onset diabetes and a 43% reduction of stroke/MI over 5 years. The NNT to prevent 1 case of diabetes was 12, the number to prevent 1 stroke/MI was 25, and the NNT to cause 1 serious fracture was 125 [67]. The results are shown in Figure 1. The ITT analysis gave similar results, but as expected, risk reduction and adverse effects were less significant. Low-dose pioglitazone minimizes adverse effects while retaining much of the benefit [68, 69]. Pioglitazone should be much more widely used for stroke prevention.

Stroke or myocardial infarction

No. at risk				
Pioglitazone	644	613	553	414
Placebo	810	752	660	470

a

Stroke

No. at risk				
Pioglitazone	644	615	555	415
Placebo	810	757	673	484

b

Acute coronary syndrome

No. at risk				
Pioglitazone	644	623	569	430
Placebo	810	772	682	492

c

Stroke/MI/HHF

No. at risk				
Pioglitazone	644	613	553	413
Placebo	810	752	660	470

d

Diabetes

No. at risk				
Pioglitazone	644	627	569	428
Placebo	810	760	662	461

e

(For legend see next page.)

Antiplatelet Therapy

Antiplatelet therapy has been standard for secondary stroke prevention in patients with large-artery disease since the Canadian aspirin/sulfinpyrazone study in 1980 [70]. However, aspirin reduces recurrent stroke by only ~25%, and other antiplatelet agents, or dual antiplatelet therapy, are not great deal breakers. Two important issues are neglected: the effect of variants of CYP2C19 that reduce efficacy of clopidogrel, and the effect of enteric coating on aspirin resistance. One curious issue in antiplatelet therapy is the nonuse of cilastazol outside of Asia; probably this deserves more attention.

CYP2C19 Variants

Clopidogrel is a prodrug that must be oxidized by CYP2C19 to be activated. Variants of that gene that result in clopidogrel being ineffective [71] are common, being present in ~30% of Europeans and >50% of Chinese [71]. Although such findings have led to calls for pharmacogenetic testing, it would be simpler to use ticagrelor or prasugrel instead. A recent study indicated that prasugrel was superior to ticagrelor in acute coronary syndrome [72].

Enteric-Coated Aspirin

Aspirin resistance is a complicated topic of dubious significance. However, it transpires that enteric coating accounts for “pseudoresistance” to aspirin among a high proportion of patients thought to be aspirin resistant [73, 74]. We should probably be using uncoated aspirin, instead of coated aspirin. The risk of gastrointestinal bleeding could be minimized by detecting and treating *helicobacter pylori*, or perhaps by proton pump inhibitors in selected patients with gastritis from aspirin.

One of the most common errors in stroke prevention is a knee-jerk reaction of switching to clopidogrel in patients who have TIA or stroke while taking aspirin. If aspirin has failed and antiplatelet therapy is indicated, it would probably be better to add a second antiplatelet agent. More importantly, if aspirin has failed, the need for anticoagulation should be suspected [75].

Fig. 1. Secondary stroke prevention with pioglitazone in patients with prediabetes. **a** Stroke or myocardial infarction (HR, 0.57; 95% CI, 0.39–0.84; $p = 0.004$). **b** Stroke (HR, 0.64; 95% CI, 0.42–0.99; $p = 0.04$). **c** Acute coronary syndrome (HR, 0.47; 95% CI, 0.26–0.85; $p = 0.01$). **d** Stroke/MI/HHR (HR, 0.61; 95% CI, 0.42–0.88; $p = 0.008$). **e** New-onset diabetes (HR, 0.18; 95% CI, 0.10–0.33; $p < 0.001$). (Permission requested of the American Heart Association

Anticoagulation

White Thrombus versus Red Thrombus

Antiplatelet agents prevent “white thrombus,” platelet aggregates that form in the setting of fast flow, usually on atherosclerotic plaques, and embolize distally (Fig. 2). That is what antiplatelet agents prevent; antiplatelet agents are not anticoagulants. Red thrombus, a mesh of fibrin polymer with entrapped red cells, forms in the setting of stasis [76, 77] (e.g., a deep vein thrombosis or an atrial appendage). Anticoagulants are needed to prevent red thrombus.

Anticoagulation for ESUS

Although in the past, when warfarin was the mainstay of anticoagulation, the paradigm was essentially “we

Fig. 2. White thrombus. White thrombus is shown in the retinal artery of a patient with amaurosis fugax. This phenomenon was described by C. Miller Fisher in a case presented at Grand Rounds at the Massachusetts General Hospital. JDS has seen this twice by ophthalmoscopy when he happened to be in the room with a patient who suddenly lost vision in one eye. The white thrombus oozes slowly through the retinal arteries, with vision returning as blood flow is restored; the vision may be restored in quadrants or a hemifield as branches of the retinal artery clear serially (reproduced by permission of Vanderbilt University Press from: Spence J.D; How to prevent your stroke; *Vanderbilt University Press* 2006).

to reproduce from Spence JD, Viscoli CM, Inzucchi SE, Dearborn-Tomazos J, Ford GA, Gorman M, et al. Pioglitazone therapy in patients with stroke and prediabetes: a post hoc analysis of the IRIS randomized clinical trial. *JAMA Neurol.* 2019; 76(5):526–35). HR, hazard ratio; CI, confidence; MI, myocardial infarction; HHR, hospitalization for heart failure; IRIS, insulin resistance intervention after stroke.

Table 3. Properties of DOACs

Property	Rivaroxaban	Dabigatran	Apixaban	Edoxaban
Clotting factor target	Factor Xa	Factor IIa	Factor Xa	Factor Xa
Requires metabolism for activation	No	Yes	No	No
Dosing frequency	Daily	Twice daily	Twice daily	Daily
Bioavailability	80–100%	6.5%	50%	62%
Half-life, h	5–13	12–14	8–15	10–14
Renal clearance	~33%	85%	~27%	~50%
Time to peak blood level, h	2–4	1–2	3–4	1–2
Drug interactions	Strong inhibitors of CYP3A4 and P-gp	P-gp inhibitors	Strong inhibitors of CYP3A4 and P-gp	P-gp inhibitors

Reproduced by permission of Wolters Kluwer Health from Spence JD, Azarpazhooh MR, Larsson SC, Bogiatzi C, and Hankey GJ. Stroke prevention in older adults: recent advances. *Stroke*. 2020; 51(12):3770–7. DOACs, direct-acting oral anticoagulants; CYP3A4, intestinal cytochrome; P-gp, P-glycoprotein.

would never anticoagulate a patient unless we identify a definite cardioembolic source, such as atrial fibrillation.” However, with the advent of direct-acting oral anticoagulants (DOACs), everything has changed. DOACs are not significantly more likely than warfarin to cause severe bleeding [78, 79], so in a patient in whom a cardioembolic source is strongly suspected, it is more prudent to prescribe DOACs than to persist with antiplatelet agents [80]. Although some might think that dual antiplatelet therapy would be a better alternative to anticoagulation for atrial fibrillation, it is not: adding clopidogrel to aspirin in patients with atrial fibrillation reduced stroke by only 0.67% [81]. Studies of antiplatelet agents versus DOACs have for the most part not shown benefit of DOACs in patients with ESUS; neither rivaroxaban [82] nor dabigatran [83] was significantly better than aspirin in unselected patients with ESUS. However, it is very likely that this result was due to misclassification of large-artery atherosclerosis as ESUS. The studies defined large-artery disease as a 50% stenosis, which misses 79% of cases due to large-artery disease defined by a high plaque burden, as in the Subtypes of Ischemic Stroke classification (SPARKLE) [84] and Chinese Ischemic Stroke Subtype (CISS) classifications [85]. In contrast, in the NAVIGATE-ESUS substudy, in participants with patent foramen ovale [86], a meta-analysis reports a significant benefit of anticoagulation versus aspirin; the odds ratio favored anticoagulation: 0.48 (95% CI 0.24–0.96).

Too often, anticoagulants are avoided in old patients, perhaps because of fear of falls. It has been calculated that it would take 295 falls to equal the risk of not anticoagulating a patient with atrial fibrillation [87]. The elderly benefit from anticoagulation for atrial fibrillation even more

than younger patients [88, 89]; more should be anticoagulated, but it should be with DOACs rather than warfarin.

Direct-Acting Oral Anticoagulants

There are important differences among DOACs that should be considered (Table 3). It has become clear that rivaroxaban (and probably edoxaban) should not be used as a once-daily drug; it is not longer acting than other DOACs. The problem is illustrated in Figure 3. Indeed, recent studies of rivaroxaban plus aspirin for peripheral vascular disease have used twice-daily dosing of rivaroxaban. Apixaban is the least renally eliminated of the DOACs; this is important in the elderly because renal function declines with age. Those 2 factors may explain why a large population-based study reported that apixaban was safer and more effective than rivaroxaban [90].

Dabigatran is problematic for several reasons: it causes heartburn in ~20% of the patients, it is the most renally eliminated of the DOACs and by far the least bioavailable (only 6%). The latter issue means that it is subject to very large changes in blood levels with changes in absorption or with drug interactions. There are reasons to consider that blood levels of dabigatran should be monitored, thus eliminating one of the main benefits of DOACs over warfarin [91].

Intervention for Carotid Stenosis

Carotid endarterectomy (CEA) or stenting are more beneficial for symptomatic than for asymptomatic carotid stenosis (ACS). With increasingly intensive medical therapy, the risk of stroke or death in patients with ACS is now

Fig. 3. Once-daily versus twice-daily dosing: difference between intake and predicted biological impact in general. Different patterns of nonadherence lead to different exposition to “risk” between once- and twice-daily drugs. These graphs illustrate the theoretical pharmacokinetic profiles of QD and BID for a drug with a half-life of about 12 h and a $T_{\max}$ of 3 h. **a** The peak-to-trough ratio is much smaller for the BID than the QD dosing. **b** The concentration after a single missed BID dose (red dot) is similar to the expected trough concentration of QD dosing, suggesting that missing a single dose of a twice-daily dosing regimen should not be therapeutically critical. **c** The pharmacological equivalent of missing a single dose in a once-daily regimen (blue dot) is missing 3 consecutive doses (red dots) of a twice-daily dosing regimen. **d** Taking an extra dose results in a much higher peak for the QD than for the BID dosing regimen (Reproduced by permission of Oxford University Press from Heidbuchel H and Vrijens B. Nonvitamin K antagonist oral anticoagulants: considerations on once- vs. twice-daily regimens and their potential impact on medication adherence. *EP Europace*. 2015; 17:1317–131824.). QD, dose X administered once daily; BID, dose X/2 administered twice daily.

below the risk of either CEA or carotid artery stenting (CAS); the annual risk of stroke is ~0.5% with intensive medical therapy [92, 93], whereas the 30-day risk of stroke or death even in highly regulated clinical trials was 2.5–2.9% for CAS and 1.4–1.7% for CEA. In the real world, risks of intervention are higher. This means that CEA or CAS should not be performed routinely for ACS; only selected patients who can be identified as having a high enough risk to benefit should be subjected to these procedures. Rothwell et al. reported in 2021 that percent stenosis predicted higher risk in participants in the Oxford Vascular Study [94]. However, the study participants did not have true ACS; they were imaged because of TIA or stroke and found to have an asymptomatic carotid artery, so the reported risk may be an overestimate [95].

Identifying which Patients with Asymptomatic Could Benefit from Intervention

Ways to identify high-risk patients with ACS were reviewed in 2018 [96]. They include microemboli on tran-

scranial Doppler, intraplaque hemorrhage on MRI, ulceration, echolucency (particularly juxtaluminal black plaque), and reduced cerebrovascular reserve. The 2017 European Society for Vascular Surgery carotid guidelines [97] endorsed these indications and some others.

Effect of Age on Risk of Stenting versus Endarterectomy

There are risks to shoving a catheter into a stiff craggy carotid artery. Microemboli are commonly dislodged while crossing the aortic arch, deploying the protection device, and deploying the stent. Almekhlafi documented that a substantial number of such microemboli were large, termed “malignant” microemboli [98]. They reported that 80% of the patients had new diffusion-weighted lesions which were seen in 80% of the patients after stenting, and the clinical condition of the patient declined in 6.7% of the patients after CAS. Older patients are more likely to have stiff, tortuous craggy arteries; it is probably for that reason that there is a much

Fig. 4. Estimated event rates for patients assigned to CEA (a) and CAS (b) by age stratum. The age-groups are shown by the color key. Events plotted during the first 120-day periprocedural period include stroke in either hemisphere plus deaths, whereas events during the postprocedural period include ipsilateral stroke only. Patients were censored at 6 years for the graphical presentation of

event rates. (Reproduced by permission of Elsevier from Howard G, Roubin GS, Jansen O, Hendrikse J, Halliday A, Fraedrich G, et al., Association between age and risk of stroke or death from carotid endarterectomy and carotid stenting: a meta-analysis of pooled patient data from 4 randomized trials. *Lancet* 2016;67:1305–1311). CAS, carotid artery stenting; CEA, carotid endarterectomy.

higher risk with CAS than with CEA above age 70 (Fig. 4). For most older patients, CEA would therefore be preferable to CAS. “Factors that would favor CAS could include younger age, specific anatomical features (such as a stenosis, i.e., in the very distal internal carotid artery), lack of tortuosity of the arteries leading to the stenosis, absence of or only minimal plaque calcification, presence of local tissue scarring due to previous surgery or radiation, and conditions conferring a high medical risk for surgery (such as congestive heart failure, myocardial ischemia, or severe pulmonary disease) [99].

Conclusion

There are a number of little-known/neglected aspects of stroke prevention that in our opinion, if better recognized and applied, could substantially reduce the risk of stroke. These include aspects of nutrition, lipid-lowering therapy, physiologically individualized therapy for hypertension, more rational use of antiplatelet agents and anticoagulants, and more judicious application of CEA and CAS.

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Conflict of Interest Statement

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Author Contributions

J.D.S. wrote the first and final drafts; C.B. and M.R.A. contributed to revisions.

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