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Version: Accepted Version

Article:
Parker, W.A.E., Gorog, D.A., Geisler, T. et al. (2020) Prevention of stroke in patients with chronic coronary syndromes or peripheral arterial disease. European Heart Journal Supplements, 22 (Supplement_M). M26-M34. ISSN: 1520-765X

https://doi.org/10.1093/eurheartj/suaa165

This is a pre-copyedited, author-produced version of an article accepted for publication in European Heart Journal Supplements following peer review. The version of record [William A E Parker, Diana A Gorog, Tobias Geisler, Gemma Vilahur, Dirk Sibbing, Bianca Rocca, Robert F Storey, Prevention of stroke in patients with chronic coronary syndromes or peripheral arterial disease, European Heart Journal Supplements, Volume 22, Issue Supplement_M, November 2020, Pages M26–M34] is available online at: https://academic.oup.com/eurheartjsupp/article/22/Supplement_M/M26/6024774

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Prevention of stroke in patients with chronic coronary syndromes or peripheral arterial disease

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ABSTRACT

Stroke is a common and devastating condition caused by atherothrombosis, thromboembolism or haemorrhage. Patients with chronic coronary syndromes (CCS) or peripheral artery disease (PAD) are at increased risk of stroke because of shared pathophysiological mechanisms and risk factor profiles. A range of pharmacological and non-pharmacological strategies can help to reduce stroke risk in these groups. Antithrombotic therapy reduces the risk of major adverse cardiovascular events, including ischaemic stroke, but increases the incidence of haemorrhagic stroke. Nevertheless, the net clinical benefits mean antithrombotic therapy is recommended in those with CCS or symptomatic PAD. Whilst single antiplatelet therapy is recommended as chronic treatment, dual antiplatelet therapy should be considered for those with CCS with prior MI at high ischaemic but low bleeding risk. Similarly, dual antithrombotic therapy with aspirin and very-low-dose rivaroxaban is an alternative in CCS, as well as in symptomatic PAD. Full-dose anticoagulation should always be considered in those with CCS/PAD and atrial fibrillation. Unless ischaemic risk is particularly high, antiplatelet therapy should not generally be added to full-dose anticoagulation. Optimisation of blood pressure, low-density lipoprotein levels, glycaemic control and lifestyle characteristics may also reduce stroke risk. Overall, a multifaceted approach is essential to best prevent stroke in patients with CCS/PAD.

INTRODUCTION

Significant mortality and morbidity arises from complications of either chronic coronary syndromes (CCS), encompassing symptomatic or asymptomatic coronary artery disease (CAD) with or without a history of acute coronary syndrome (ACS),[1] or peripheral artery disease (PAD), including lower extremity arterial disease (LEAD) and carotid artery stenosis (CAS).[2] Those with CCS/PAD are at increased risk of acute atherothrombotic events, including ACS, (myocardial infarction [MI] or unstable angina [UA]), acute limb ischaemia (ALI) and acute stroke.[1, 2]

There are three main mechanisms of stroke (Figure 1). Patients with CCS/PAD may be at particular risk of stroke because of shared underlying disease processes and risk-factor profiles (Figure 2). Pathological mechanisms of atherothrombotic stroke are shared with most ACS and ALI, involving atheromatous plaque formation, rupture and/or erosion, triggering thrombosis including activation of platelets and the coagulation cascade.[3] The processes and risk factors leading to cardioembolic stroke, on the other hand, have less in common with CCS and PAD. Compared to atherothrombotic stroke in which platelets and adhesive molecules are central, activation of the coagulation cascade primarily drives cardiac thromboembolism in a setting of stasis and inflammation, most notably from the left atrial appendage in patients with atrial fibrillation (AF), although there are other possible sources (Figure 1).[4]

In this review, we present pharmacological strategies to prevent stroke in patients with CCS/PAD. Similarities in pathogenetic mechanisms can provide insights into therapies, and we explore clinical data supporting or refuting these. Whilst focussing on ischaemic stroke, preventing haemorrhagic stroke is also important, particularly since some treatments of CCS, PAD and acute stroke may increase its incidence.

ANTITHROMBOTIC THERAPY

Antiplatelet therapy

As platelet activation is the central process in acute complications of CCS and PAD, there is clear rationale for the use of antiplatelet therapy (APT) in these groups. Similarly, those treated by coronary or peripheral artery stenting are at risk of platelet-mediated stent thrombosis.[2]

Use of single antiplatelet therapy

Numerous randomised controlled trials (RCTs) have established the benefits of APT in patients with CCS/PAD. Single antiplatelet therapy (SAPT) with aspirin, which inhibits platelet cyclooxygenase-1-mediated TXA_2 synthesis,[5] has proven efficacy in the prevention of major adverse cardiovascular events (MACE, defined as cardiovascular [CV] death, non-fatal MI or non-fatal stroke) in high-risk patients., A meta-analysis by the Antithrombotic Trialists' Collaboration, including individual data from 135,000 patients with pre-existing CV disease, showed clear benefit, mainly with aspirin alone, in reducing MACE by around 25% (relative-risk-reduction, RRR: those with prior-MI=21%, p<0.0001; other-CAD=37%, p<0.0001; PAD 23%, p=0.004).[6] This included a significant reduction in non-fatal ischaemic stroke (3.5% to 2.6%, RRR=25%). Increases in haemorrhagic stroke risk were offset by a non-significant reduction in total stroke risk of 21%. Similarly, a more recent meta-analysis has provided further insight, suggesting that aspirin significantly reduces the risk of large-artery atherothrombotic stroke (odds ratio=0.87, 95% CI 0.76-1.00, p=0.046), but not small vessel occlusion or cardioembolism.[7]

Platelet $P2Y_{12}$ receptor inhibitors have also been tested in CCS/PAD (Table 1, Table 2, Figure 3).[8] $P2Y_{12}$, its natural ligand being adenosine diphosphate, plays a central role in the amplification of platelet activation. Three orally-active $P2Y_{12}$ inhibitors have been marketed. The thienopyridines clopidogrel and prasugrel are pro-drugs whose active metabolites irreversibly inhibit $P2Y_{12}$.[3] Both require metabolic activation, which is predictably consistent and effective for prasugrel whereas, for clopidogrel, there is significant interindividual variability and around one-third of the population are poor responders.[3] The cyclopentyl-triazolopyrimidine ticagrelor is a directly-acting, reversibly-binding $P2Y_{12}$ inhibitor and inverse agonist. Ticagrelor and prasugrel are more potent than clopidogrel with less inter-individual variability.[3, 9]

In the Clopidogrel versus Aspirin in Patients at Risk of Ischaemic Events (CAPRIE) study, $P2Y_{12}$ inhibitor SAPT with clopidogrel 75 milligrams (mg) once-daily was compared with aspirin 325 mg once-daily in patients with CCS and PAD (Table 1, Table 2).[10] There was a modest RRR in MACE but

a suggestion of greater efficacy in PAD patients, leading to recommendations that, if SAPT is indicated in symptomatic PAD, clopidogrel may be preferred to aspirin.[2] There was no difference in rates between the two treatments for stroke, including in those with PAD. Current ESC guidelines recommend either aspirin or clopidogrel for patients with symptomatic PAD and/or those who have required revascularisation.[2] In patients with asymptomatic LEAD, there is no clear evidence that SAPT with aspirin prevents vascular events, including stroke, although studies have been small and underpowered (Online supplement).[2]

It has been hypothesised that more potent and consistent $P2Y_{12}$ inhibitors than clopidogrel might offer better protection against MACE. The Examining Use of tiCagreLor In peripheral artery Disease (EUCLID) trial randomised patients with symptomatic PAD to ticagrelor or clopidogrel (Table 2).[11] Over a median follow-up of 30 months, there was no significant difference in MACE, although there was a significant reduction in the secondary endpoint of ischaemic stroke with ticagrelor, meaning that, for stroke prevention in PAD, ticagrelor may offer some benefit over clopidogrel, although ticagrelor monotherapy is not approved in PAD.[6]

In The Acute Stroke or Transient Ischaemic Attack Treated with Aspirin or Ticagrelor and Patient Outcomes (SOCRATES) trial, ticagrelor monotherapy was not superior to aspirin monotherapy in 13,199 patients with non-severe ischemic stroke or high-risk transient ischemic attack, with similar bleeding profile.[12] Around 12% of the trial population had CAD or previous MI and similarly in these patients there was no superiority of ticagrelor vs. aspirin (p=0.89).

Use of dual antiplatelet therapy

In ACS, aspirin plus a $P2Y_{12}$ inhibitor (dual antiplatelet therapy, DAPT) has proven benefits over aspirin alone in preventing MACE.[13] When used in DAPT, ticagrelor, in all ACS, and prasugrel, in those treated with percutaneous coronary intervention (PCI), are superior to clopidogrel.[6] A recent open-label RCT, Intracoronary Stenting and Antithrombotic Regimen: Rapid Early Action for Coronary Treatment

(ISAR-REACT) 5, demonstrated lower MACE rates with aspirin and prasugrel versus aspirin and ticagrelor in those with ACS scheduled for invasive evaluation.[3] Similarly, in patients with CCS undergoing PCI, DAPT with aspirin and clopidogrel for ≥6 months reduces stent thrombosis risk vs. aspirin alone.[1] This regimen is also recommended for one month in patients undergoing carotid artery stenting and, with weaker evidence, in those undergoing percutaneous revascularisation for LEAD.[2]

After minor stroke or transient ischaemic attack (TIA), a short period of DAPT offers superior protection from major ischaemic events when compared to aspirin alone, including in patients with CCS or PAD, albeit at the expense of more bleeding.[14, 15]

Considering the longer-term use of DAPT vs. aspirin alone in patients with CCS/PAD, the Clopidogrel for High Atherothrombotic Risk and Ischaemic Stabilization, Management, and Avoidance (CHARISMA) study provided valuable initial data (Table 1, Table 2).[16] There was a non-significant reduction in the primary efficacy endpoint of MACE, although there was slightly greater reduction in the secondary efficacy endpoint (primary endpoint events/hospitalisation for UA, TIA, or revascularisation) (HR=0.92, 95% confidence interval [0.86-1.00] p=0.04). Most of the benefit appeared to be stroke-derived (e.g. non-fatal stroke HR=0.79 [0.64-0.98], p=0.03), with no significant effect on MI or CV death.

Subsequent RCTs have built an evidence base for long-term DAPT post-ACS. For those at high ischaemic but low bleeding risk who have tolerated ≥1 year of DAPT, continuation beyond 1 year after MI is a recommended option.[1] For example, post-MI patients with at least one additional risk-factor benefit from long-term aspirin and reduced-dose ticagrelor (60-mg twice-daily) vs. aspirin alone, although underlying bleeding risk should be carefully evaluated. The Prevention of Cardiovascular Events in Patients with Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin–TIMI 54 (PEGASUS-TIMI 54) study showed MACE reduction in those receiving DAPT vs.

SAPT (Table 1).[17] There was also a reduction in the risk of stroke. Although TIMI-major bleeding was significantly more frequent with ticagrelor; intracranial haemorrhage, haemorrhagic stroke or fatal bleeding were not.

Evidence for thienopyridines comes from the DAPT study, which showed 30 vs. 12 months of thienopyridine, alongside aspirin, significantly reduced MACE in prior-MI patients (Table 1).[18] Stroke was not significantly reduced, although there was signal of possible benefit in ischaemic stroke. Unlike MI, stroke did not occur significantly more frequently in those with a prior MI compared to those without (e.g. total stroke=0.73% vs. 0.85%, p=0.51). Current recommendations suggest long-term thienopyridine in prior-MI patients at moderate/high ischaemic risk.[1] Prasugrel in combination with aspirin in any situation is contraindicated in those with prior stroke, and aspirin with ticagrelor is similarly not recommended for long-term use in this group.

In patients with CCS but without prior MI, there is little evidence for long-term DAPT. THE effect of ticagrelor on health outcomes in diabetes Mellitus patients Intervention Study (THEMIS) randomised 19,220 aspirin-treated patients with T2DM and CCS, but no MI, to ticagrelor (90-mg reduced to 60-mg twice-daily during the course of the trial) or placebo, for a median of 40 months (Table 1).[19] Whilst there was lower MACE incidence in those receiving ticagrelor vs. placebo, there was a greater increase in TIMI-major bleeding including intracranial haemorrhage. Ischaemic stroke occurred less frequently when receiving DAPT, as did all stroke. Although meeting its primary endpoint, the net clinical benefit has not supported adoption in practice.

Ticagrelor monotherapy

Ticagrelor monotherapy has been investigated as an alternative to DAPT in CCS patients treated with PCI, though this is not yet endorsed in recommendations (Online supplement).

Anticoagulant therapy

Oral anticoagulants (OACs) include vitamin K antagonists (VKAs), e.g. warfarin, and non-VKA oral anticoagulants (NOACs), e.g. the factor Xa (FXa) inhibitors (apixaban, edoxaban and rivaroxaban) or the thrombin inhibitor dabigatran.[20]

Anticoagulants in CCS or PAD patients with atrial fibrillation

AF increases the risk of cardioembolism from the left atrium through disruption in flow and inflammation. Anticoagulation reduces stroke risk in AF by around 60%.[1] The CHA_2DS_2-VASc score is recommended for determining whether an OAC is warranted.[1] An OAC is recommended with a score ≥2, and should be considered if ≥1 (excluding females without other criteria)..[1, 2]

NOACs offer superior stroke protection vs. VKA, outside of situations such as moderate/severe mitral stenosis, metallic valve prosthesis, very poor renal function or non-compliance, groups in whom there are negative data or therapeutic drug monitoring is necessary. A meta-analysis including 71,6123 participants of four phase 3 RCTs (15% with prior MI) showed significantly lower rates of stroke or systemic embolism (HR=0.81 [0.73-0.91], p<0.0001) and haemorrhagic stroke (0.49, [0.38-0.64], p<0.0001) in those receiving a NOAC compared to VKA.[20] There were numerically fewer ischaemic strokes in those receiving a NOAC (0.92 [0.83-1.02], p=0.10). Different NOACs have never undergone head-to-head clinical outcome-driven RCTs, although observational studies have provided some insight (online supplement). The availability of selective antidotes to both FXa inhibitors (andaxenet alfa) and dabigatran (idarucizumab) has increased the safety of these drugs.

There are limited data regarding long-term use of OAC-APT combinations in patients with CCS/PAD and AF, but current recommendations generally advise OAC alone during long-term maintenance therapy.[1] Recently, evidence from the Atrial Fibrillation and Ischaemic Events with Rivaroxaban in Patients with Stable Coronary Artery Disease (AFIRE) trial has largely supported this recommendation (Online supplement).

Anticoagulation in patients with CCS or PAD in sinus rhythm

The WArfarin Re-Infarction Study (WARIS) provided the first RCT evidence that an OAC, with or without concurrent aspirin, may offer protection against MACE, including stroke, in CCS/PAD patients without AF, but at the expense of excessive bleeding.[21] In the NOAC-era, an evidence-based option for secondary prevention of MACE in high-risk patients with CCS or symptomatic PAD, but without AF, is very-low-dose rivaroxaban in combination with low-dose aspirin. In the Cardiovascular OutcoMes for People using Anticoagulation StrategieS (COMPASS) study, treatment with aspirin 100-mg once-daily plus rivaroxaban 2.5-mg twice-daily (low-dose dual antithrombotic therapy, DATT) led to a significant reduction in the primary endpoint of MACE after a mean follow-up of 23 months, when compared to aspirin 100-mg once-daily alone (Table 1, Table 2).[22] When compared with aspirin monotherapy, low-dose DATT appeared to have the strongest effect on cardioembolic stroke (HR=0.40 [0.20-0.78], p=0.005) or embolic stroke of undetermined source (0.30 [0.12-0.74], p=0.006). Benefits of low-dose DATT on stroke prevention appear present in subgroups with CAD or symptomatic PAD, including carotid disease. These data support use of low-dose DATT over aspirin alone in high-risk patients with CCS and/or symptomatic PAD, both in providing general anti-ischaemic protection but also specifically for stroke prevention. This is reflected in the current ESC CCS guidelines,[1] whereas the current PAD recommendations were last updated before the COMPASS results were known;[2] however, regional bodies such as the European Medicines Agency has approved low-dose DATT in symptomatic PAD as well as high-risk CCS. Recently, the Vascular Outcomes Study of Aspirin Along with Rivaroxaban in Endovascular or Surgical Limb Revascularization for PAD (VOYAGER-PAD) study has shown similar findings in a PAD population treated by revascularisation (Table 2).[23]

In patients with PFO and CCS/PAD who have no prior history of stroke, there is no clear evidence that stroke risk is reduced by intensifying antithrombotic therapy beyond that already indicated for the underlying atherothrombotic disease.[4]

OTHER PREVENTIVE THERAPIES

Beyond antithrombotic therapy, a wide range of therapies and lifestyle interventions should be incorporated into routine management of CCS and PAD patients for reducing the risk of stroke (Figure 2 and Online supplement).

CONCLUSIONS

Patients with CCS/PAD are at increased risk of a range of ischaemic events, including stroke, with significant overlap of risk-factors and pathological mechanisms (Figure 1, Figure 2). Interventions targeting these factors and mechanisms present common therapeutic targets and have been exploited with good results. Overall, a holistic approach to aggressively manage risk factors (Figure 2), including addressing lifestyle aspects, is central to the management of patients with CCS/PAD to prevent the devastating complication of stroke.

REFERENCES

1. Knuuti J, Wijns W, Saraste A, Capodanno D, Barbato E, Funck-Brentano C, Prescott E, Storey RF, Deaton C, Cuisset T, Agewall S, Dickstein K, Edvardsen T, Escaned J, Gersh BJ, Svitil P, Gilard M, Hasdai D, Hatala R, Mahfoud F, Masip J, Muneretto C, Valgimigli M, Achenbach S, Bax JJ. 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes. Eur Heart J 2019.

2. Aboyans V, Ricco JB, Bartelink MEL, Bjorck M, Brodmann M, Cohnert T, Collet JP, Czerny M, De Carlo M, Debus S, Espinola-Klein C, Kahan T, Kownator S, Mazzolai L, Naylor AR, Roffi M, Rother J, Sprynger M, Tendera M, Tepe G, Venermo M, Vlachopoulos C, Desormais I. 2017 ESC Guidelines on the Diagnosis and Treatment of Peripheral Arterial Diseases, in collaboration with the European Society for Vascular Surgery (ESVS): Document covering atherosclerotic disease of extracranial carotid and vertebral, mesenteric, renal, upper and lower extremity arteriesEndorsed by: the European Stroke Organization (ESO)The Task Force for the Diagnosis and Treatment of

Peripheral Arterial Diseases of the European Society of Cardiology (ESC) and of the European Society for Vascular Surgery (ESVS). Eur Heart J 2018;**39**(9):763-816.

3. Parker WAE, Storey RF. Novel approaches to P2Y12 inhibition and aspirin dosing. Platelets 2020:1-8.

4. Pristipino C, Sievert H, D'Ascenzo F, Louis Mas J, Meier B, Scacciatella P, Hildick-Smith D, Gaita F, Toni D, Kyrle P, Thomson J, Derumeaux G, Onorato E, Sibbing D, Germonpre P, Berti S, Chessa M, Bedogni F, Dudek D, Hornung M, Zamorano J. European position paper on the management of patients with patent foramen ovale. General approach and left circulation thromboembolism. Eur Heart J 2019;**40**(38):3182-3195.

5. Patrono C, Morais J, Baigent C, Collet JP, Fitzgerald D, Halvorsen S, Rocca B, Siegbahn A, Storey RF, Vilahur G. Antiplatelet Agents for the Treatment and Prevention of Coronary Atherothrombosis. J Am Coll Cardiol 2017;**70**(14):1760-1776.

6. Parker WA, Storey RF. Long-term antiplatelet therapy following myocardial infarction: implications of PEGASUS-TIMI 54. Heart 2016;**102**(10):783-9.

7. Rajkumar CA, Floyd CN, Ferro A. Antiplatelet therapy as a modulator of stroke aetiology: a meta-analysis. Br J Clin Pharmacol 2015;**80**(3):331-41.

8. Storey RF. Biology and pharmacology of the platelet P2Y12 receptor. Curr Pharm Des 2006;**12**(10):1255-9.

9. Parker WAE, Schulte C, Barwari T, Phoenix F, Pearson SM, Mayr M, Grant PJ, Storey RF, Ajjan RA. Aspirin, clopidogrel and prasugrel monotherapy in patients with type 2 diabetes mellitus: a double-blind randomised controlled trial of the effects on thrombotic markers and microRNA levels. Cardiovascular Diabetology 2020;**19**(1):3.

10. CAPRIE Steering Committee. A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). Lancet 1996;**348**(9038):1329-39.

11. Hiatt WR FF, Heizer G, Berger JS, Baumgartner I, Held P, Katona BG, Mahaffey KW, Norgren L, Jones WS, Blomster J, Millegård M, Reist C, Patel MR; EUCLID Trial Steering Committee and Investigators.. Ticagrelor versus Clopidogrel in Symptomatic Peripheral Artery Disease. N Engl J Med 2017;**376**:32-40.

12. Johnston SC, Amarenco P, Albers GW, Denison H, Easton JD, Evans SR, Held P, Jonasson J, Minematsu K, Molina CA, Wang Y, Wong KS. Ticagrelor versus Aspirin in Acute Stroke or Transient Ischemic Attack. N Engl J Med 2016;**375**(1):35-43.

13. The Clopidogrel in Unstable Angina to Prevent Recurrent Events Trial Investigators. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. N Engl J Med 2001;**345**:494-502.

14. Pan Y, Elm JJ, Li H, Easton JD, Wang Y, Farrant M, Meng X, Kim AS, Zhao X, Meurer WJ, Liu L, Dietrich D, Johnston SC. Outcomes Associated With Clopidogrel-Aspirin Use in Minor Stroke or Transient Ischemic Attack: A Pooled Analysis of Clopidogrel in High-Risk Patients With Acute Non-Disabling Cerebrovascular Events (CHANCE) and Platelet-Oriented Inhibition in New TIA and Minor Ischemic Stroke (POINT) Trials. JAMA Neurol 2019.

15. Johnston SC, Amarenco P, Denison H, Evans SR, Himmelmann A, James S, Knutsson M, Ladenvall P, Molina CA, Wang Y. Ticagrelor and Aspirin or Aspirin Alone in Acute Ischemic Stroke or TIA. New England Journal of Medicine 2020;**383**(3):207-217.

16. Bhatt DL, Fox KAA, Hacke W, Berger PB, Black HR, Boden WE, Cacoub P, Cohen EA, Creager MA, Easton JD, Flather MD, Haffner SM, Hamm CW, Hankey GJ, Johnston SC, Mak K-H, Mas J-L, Montalescot G, Pearson TA, Steg PG, Steinhubl SR, Weber MA, Brennan DM, Fabry-

Ribaudo L, Booth J, Topol EJ, the CI. Clopidogrel and Aspirin versus Aspirin Alone for the Prevention of Atherothrombotic Events. New England Journal of Medicine 2006;**354**(16):1706-1717.

17. Bonaca MP, Bhatt DL, Cohen M, Steg PG, Storey RF, Jensen EC, Magnani G, Bansilal S, Fish MP, Im K, Bengtsson O, Ophuis TO, Budaj A, Theroux P, Ruda M, Hamm C, Goto S, Spinar J, Nicolau JC, Kiss RG, Murphy SA, Wiviott SD, Held P, Braunwald E, Sabatine MS, PEGASUS-TIMI 54 Steering Committee and Investigators. Long-Term Use of Ticagrelor in Patients with Prior Myocardial Infarction. New Engl J Med 2015;**372**:1791-800.

18. Yeh RW, Kereiakes DJ, Steg PG, Windecker S, Rinaldi MJ, Gershlick AH, Cutlip DE, Cohen DJ, Tanguay JF, Jacobs A, Wiviott SD, Massaro JM, Iancu AC, Mauri L. Benefits and Risks of Extended Duration Dual Antiplatelet Therapy After PCI in Patients With and Without Acute Myocardial Infarction. J Am Coll Cardiol 2015;**65**(20):2211-21.

19. Steg PG, Bhatt DL, Simon T, Fox K, Mehta SR, Harrington RA, Held C, Andersson M, Himmelmann A, Ridderstrale W, Leonsson-Zachrisson M, Liu Y, Opolski G, Zateyshchikov D, Ge J, Nicolau JC, Corbalan R, Cornel JH, Widimsky P, Leiter LA. Ticagrelor in Patients with Stable Coronary Disease and Diabetes. N Engl J Med 2019;**381**(14):1309-1320.

20. Ruff CT, Giugliano RP, Braunwald E, Hoffman EB, Deenadayalu N, Ezekowitz MD, Camm AJ, Weitz JI, Lewis BS, Parkhomenko A, Yamashita T, Antman EM. Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials. Lancet 2014;**383**(9921):955-62.

21. Hurlen M, Abdelnoor M, Smith P, Erikssen J, Arnesen H. Warfarin, aspirin, or both after myocardial infarction. N Engl J Med 2002;**347**(13):969-74.

22. Eikelboom JW, Connolly SJ, Bosch J, Dagenais GR, Hart RG, Shestakovska O, Diaz R, Alings M, Lonn EM, Anand SS, Widimsky P, Hori M, Avezum A, Piegas LS, Branch KRH, Probstfield J, Bhatt DL, Zhu J, Liang Y, Maggioni AP, Lopez-Jaramillo P, O'Donnell M, Kakkar AK, Fox KAA,

Parkhomenko AN, Ertl G, Stork S, Keltai M, Ryden L, Pogosova N, Dans AL, Lanas F, Commerford PJ, Torp-Pedersen C, Guzik TJ, Verhamme PB, Vinereanu D, Kim JH, Tonkin AM, Lewis BS, Felix C, Yusoff K, Steg PG, Metsarinne KP, Cook Bruns N, Misselwitz F, Chen E, Leong D, Yusuf S. Rivaroxaban with or without Aspirin in Stable Cardiovascular Disease. N Engl J Med 2017;**377**(14):1319-1330.

23. Bonaca MP, Bauersachs RM, Anand SS, Debus ES, Nehler MR, Patel MR, Fanelli F, Capell WH, Diao L, Jaeger N, Hess CN, Pap AF, Kittelson JM, Gudz I, Mátyás L, Krievins DK, Diaz R, Brodmann M, Muehlhofer E, Haskell LP, Berkowitz SD, Hiatt WR. Rivaroxaban in Peripheral Artery Disease after Revascularization. New England Journal of Medicine 2020;**382**(21):1994-2004.

24. Mauri L, Kereiakes DJ, Yeh RW, Driscoll-Shempp P, Cutlip DE, Steg PG, Normand S-LT, Braunwald E, Wiviott SD, Cohen DJ, Holmes DR, Krucoff MW, Hermiller J, Dauerman HL, Simon DI, Kandzari DE, Garratt KN, Lee DP, Pow TK, Ver Lee P, Rinaldi MJ, Massaro JM. Twelve or 30 Months of Dual Antiplatelet Therapy after Drug-Eluting Stents. New England Journal of Medicine 2014;**371**(23):2155-2166.

FIGURES

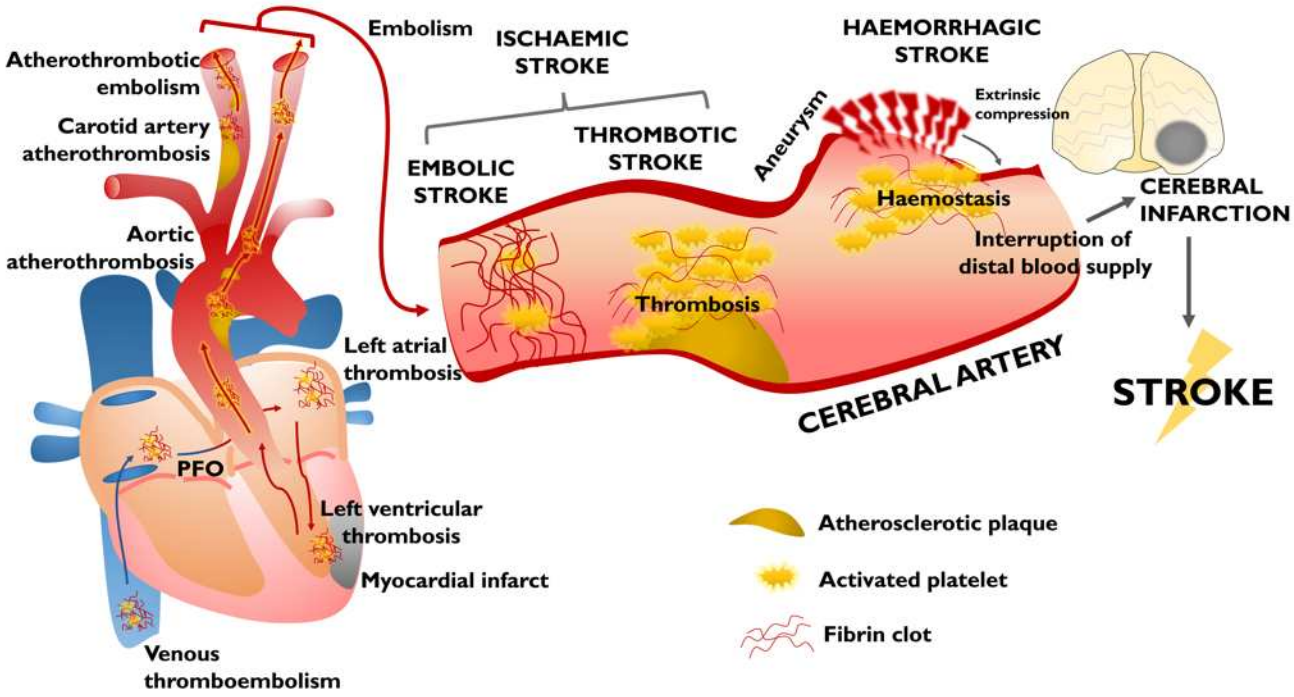

Figure 1 Mechanisms of stroke in patients with CCS/PAD. Stroke is caused by the interruption of blood supply to the brain. Ischaemic stroke may be due to atherothrombosis within a cerebral artery (thrombotic stroke) or from embolism of a thrombus formed at a distant site (embolic stroke), for example the left atrium, aortic arch or carotid arteries. Haemorrhagic stroke results from rupture of a cerebral artery aneurysm. Platelet activation and fibrin clot formation are the central processes in ischaemic stroke, whereas in haemorrhagic stroke these processes may limit its severity. PFO, patent foramen ovale.

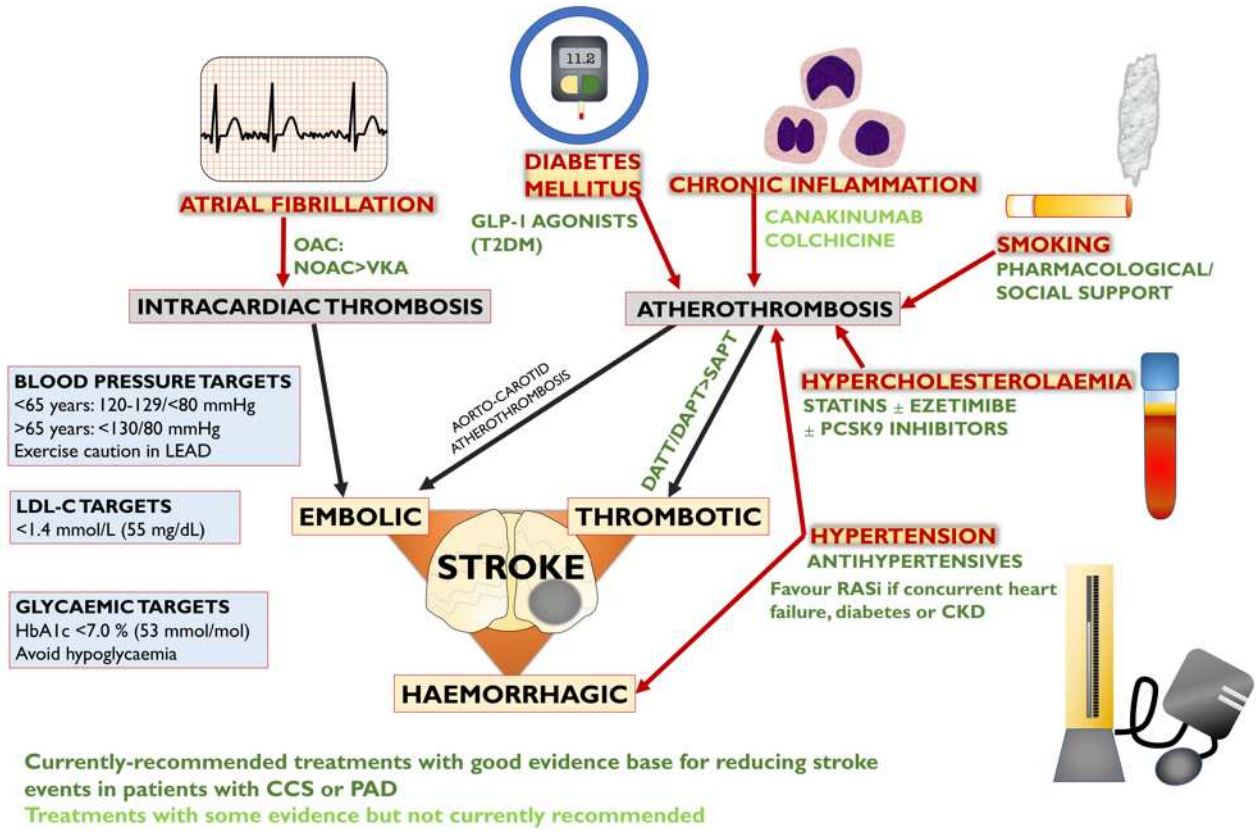

Figure 2 Modifiable risk factors for stroke in patients with CCS/PAD and evidence-based therapies to address these. CKD, chronic kidney disease; DAPT, dual antiplatelet therapy; DATT, dual antithrombotic therapy; GLP-1, glucagon-like peptide 1; HbA1c, glycated haemoglobin A1c; LDL-C, low-density lipoprotein cholesterol; LEAD, lower-extremity arterial disease; NOAC, non-vitamin-K antagonist OAC; OAC, oral anticoagulant; PCSK9, proprotein convertase subtilisin/kexin type 9; RASi, renin-angiotensin-system inhibitor; SAPT, single antiplatelet therapy; T2DM, type 2 diabetes mellitus; VKA, vitamin-K antagonist.

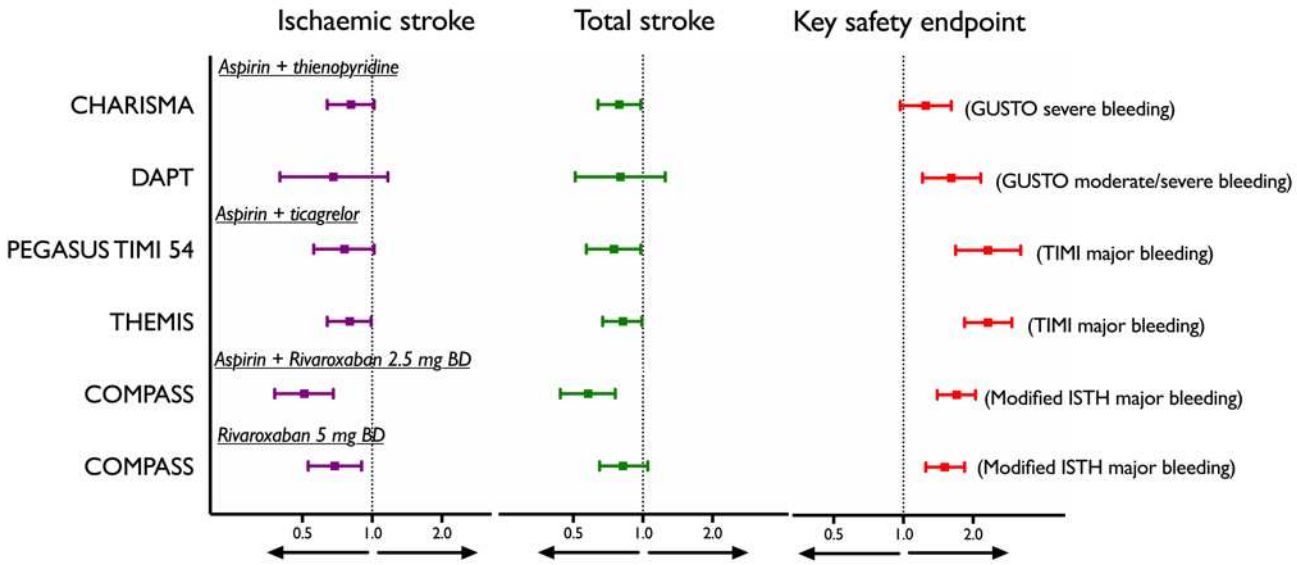

Figure 3 Forest plots showing HR ± 95% CI for ischaemic stroke, total stroke and the key safety endpoint in RCTs of antithrombotic regimens vs. aspirin monotherapy in patients with CCS/PAD (See table 1 for trial details).

GUSTO, Global Strategies for Opening Occluded Coronary Arteries; ISTH, International Society on Thrombosis and Haemostasis; TIMI, Thrombolysis In Myocardial Infarction.

Table 1. Primary and stroke outcomes of total study groups from key RCTs comparing regimens of $P2Y_{12}$ inhibitors or rivaroxaban with aspirin monotherapy in patients with CCS/PAD in sinus rhythm.

Short name (year published)	Population	Experimental group(s)	Comparator	Primary endpoint	Key safety endpoint	Ischaemic stroke	Haemorrhagic stroke	Total stroke
CAPRIE (1996)[10]	19,185 patients with atherosclerotic CV disease (including 6302 with prior MI, 6452 with PAD)	Clopidogrel 75-mg once-daily	Aspirin 325-mg once-daily	MI, ischaemic stroke or CV death: 5.32% vs. 5.83%, RRR 8.7% [0.3-16.5), p=0.043. Subgroup analysis: only significant difference in those with PAD	Severe bleeding: 1.38% vs 1.55% (p>=0.05)	NR	NR	438 events vs. 432
CHARISMA (2006)[16]	15,603 patients with clinically-evident CV disease or multiple risk factors (48% with CCS, 23% with symptomatic PAD)	Clopidogrel 75-mg once-daily + aspirin 75 to 162-mg once-daily	Aspirin 75 to 162-mg once-daily	CV death, MI or stroke: 6.8% vs. 7.3%, HR=0.93 [0.83-1.05], p=0.22	GUSTO severe bleeding: 1.7% vs. 1.3%, HR=1.25 [0.97-1.61], p=0.09	1.7% vs. 2.1%, HR=0.81 [0.64-1.02], p=0.07	NR	1.9% vs. 2.4%, HR=0.79 [0.64-0.98], p=0.03
PEGASUS TIMI 54 (2015)[17]	21,162 patients aged ≥50 years with a history of spontaneous MI 1–3 years prior to enrolment AND at least one additional atherothrombosis risk factor[@]	Ticagrelor 60-mg or 90-mg twice-daily* plus aspirin 75-150-mg once-daily	Aspirin 75-150-mg once-daily	CV death, MI or stroke: 7.77% vs. 9.04%, HR=0.84 [0.74-0.95], p=0.008	TIMI major bleeding: HR=2.32 [1.68-3.21], p<0.001	1.28% vs. 1.65%, HR=0.76 [0.56-1.02], p=0.06	0.19% vs. 0.19%, HR=0.97 [0.37 to 2.51], p=0.94	1.47% vs. 1.94% HR=0.75 [0.57-0.98], p=0.03
DAPT (2014)[24]	9961 patients 12 months post-PCI (26% for MI) followed up for a further 18 months	Aspirin 75 to 162-mg once-daily + continued thienopyridine (65% clopidogrel	Aspirin 75 to 162-mg once-daily	Stent thrombosis: 0.4% vs. 1.4%, HR	GUSTO Moderate or severe bleeding: 2.5% vs. 1.6%,	0.5% vs 0.7%, HR=0.68 [0.40-1.17], p=0.16	0.3% vs. 0.2%, HR=1.20 [0.50 to 2.91], p=0.68	0.8% vs. 0.9%, HR=0.80 [0.51-1.25], p=0.32

		75-mg once-daily, 35% prasugrel 5 or 10mg once-daily adjusted to weight)		0.29 [0.17-0.48], p<0.001; CV death, MI or stroke: 4.3% vs. 5.9%, HR=0.71 [0.59-0.85], p<0.001	HR=1.61 [1.21 to 2.16], p=0.001			
THEMIS (2019)[19]	19.220 patients with T2DM and CCS but no history of MI	Aspirin 75 to 150-mg once-daily + ticagrelor 60-mg twice-daily (reduced from 90-mg early in the trial)	Aspirin 75-mg to 150-mg once-daily	CV death, MI or stroke: 7.7% vs. 8.5%, HR=0.90 [0.81-0.99], p=0.04	TIMI major bleeding: 2.2% vs. 1.0%, HR=2.32 [1.82 to 2.94], p=0.005	1.6% vs. 2.0%, HR=0.80 [0.64 to 0.99]	NR	1.9% vs. 2.3%, HR=0.82 [0.67-0.99]
COMPASS (2017)[22]	27,395 with CCS (91%) + additional risk factors if <65 years old[#]) or symptomatic PAD (27%)	Aspirin 100-mg once-daily + rivaroxaban 2.5-mg twice-daily; or,	Aspirin 100-mg once-daily	CV death, MI or stroke: 4.1% vs. 5.4%, HR=0.76 [0.66-0.86], p<0.001;	Modified ISTH major bleeding: 3.1% vs. 1.9%, HR=1.70 [1.40 to 2.05], p<0.001;	0.7% vs. 1.4%, HR=0.51 [0.38 to 0.68], p<0.001;	0.2% vs. 0.1%, HR=1.49 [0.67 to 3.31], p=0.33	0.9% vs. 1.6%, HR=0.58 [0.44-0.76], p<0.001
		Rivaroxaban 5-mg twice-daily		4.9% vs. 5.4%, HR=0.90 [0.79-1.03], p=0.12	2.8% vs. 1.9%, HR=1.51 [1.25-1.84], p<0.001	1.0% vs. 1.4%, HR=0.69 [0.53-0.90], p=0.006	0.3% vs. 0.1%, HR=2.70 [1.31-5.58], p=0.005	1.3% vs. 1.6%, HR=0.82 [0.65-1.05], p=0.12

*Data shown is for ticagrelor 60-mg twice-daily vs. placebo: p value of <0.026 denotes statistical significance.
[@]Age ≥65 years, diabetes mellitus, second prior MI, multivessel CAD or chronic non-endstage renal disease.
[#]Documentation of atherosclerosis involving at least two vascular beds or to have at least two additional risk factors (current smoking, diabetes mellitus, an estimated glomerular filtration rate [GFR] <60 ml per minute, heart failure, or non-lacunar ischemic stroke ≥1 month earlier).
Values in square brackets represent 95% confidence intervals.

CCS, chronic coronary syndromes; CV, cardiovascular; GUSTO, Global Strategies for Opening Occluded Coronary Arteries; HR, hazard ratio; ISTH, International Society on Thrombosis and Haemostasis; MI, myocardial infarction; NR, not reported; PAD, peripheral artery disease; PCI, percutaneous coronary intervention; RRR, relative risk reduction; T2DM, type 2 diabetes mellitus, TIMI, Thrombolysis In Myocardial Infarction.

Table 2. Primary and stroke outcomes of key RCTs or subgroup analyses comparing regimens of antithrombotic therapy in patients with PAD in sinus rhythm

Short name (year published)	Population/subgroup	Experimental group(s)	Comparator	Primary endpoint	Key safety endpoint	Ischaemic stroke	Total stroke
CAPRIE (1996)[10]	Subgroup of 6452 with PAD	Clopidogrel 75-mg once-daily	Aspirin 325-mg once-daily	MI, ischaemic stroke or CV death: 3.71% vs. 4.86% per year, RRR=23.8% [8.9-36.2), p=0.028	NR	NR	81 events vs. 82 events
CHARISMA (2006)[16]	Subgroup of 3096 with PAD	Clopidogrel 75-mg once-daily + aspirin 75 to 162-mg once-daily	Aspirin 75 to 162-mg once-daily	CV death, MI or stroke: 8.2% vs. 6.8%, HR=1.25 [1.08-1.44], p=0.002	GUSTO severe bleeding: 1.7% vs. 1.7%, HR=0.97 [0.56-1.66], p=0.901	2.3% vs. 2.4%, HR=0.97 [0.75-1.25], p=0.782	2.6% vs. 2.9%, HR=0.94 [0.74-1.20], p=0.635
EUCLID (2017)[11]	13,885 patients with symptomatic PAD	Ticagrelor 90-mg twice-daily for 36 months	Clopidogrel 75-mg once-daily for 36 months	CV death, MI or ischaemic stroke: 10.8% vs. 10.6%, HR=1.02, [0.92-1.13], p=0.65	TIMI major bleeding: 1.6% vs. 1.6%, HR=1.10 [0.84-1.43], p=0.49	1.9% vs 2.4%, HR=0.78 [0.62-0.98]. p=0.03	NR
COMPASS (2017)[22]	Subgroup of 7470 patients with PAD	Aspirin 100-mg once-daily + rivaroxaban 2.5-mg twice-daily; or,	Aspirin 100-mg once-daily	CV death, MI or stroke: 5% vs. 7%, HR=0.72 [0.57-0.90], p=0.0047	Modified ISTH major bleeding: 3% vs. 2%, HR=1.61 [1.12-2.31], p<0.0089	NR	1% vs. 2%, HR=0.54 [0.33-0.87]
		Rivaroxaban 5-mg twice-daily		6% vs. 7%, HR=0.86 [0.69-1.08], p=0.19	3% vs. 2%, HR=1.68 [1.17-2.40], p<0.0043	NR	2% vs. 2%, HR=0.93 [0.61-1.40]
VOYAGER PAD (2020)[23]	6564 patients with PAD treated by revascularisation	Aspirin 100-mg once-daily + rivaroxaban 2.5-mg twice-daily	Aspirin 100-mg once-daily	ALI, major amputation, MI, ischaemic stroke, CV death: 17.3% vs.19.9%*, HR=0.85 [0.76-0.96], p=0.009	TIMI major bleeding: 2.65% vs 1.87%*, HR=1.43 [0.97-2.10], p=0.07)	2.7% vs. 3.0%*, HR=0.87 (0.63-1,19)	NR

CV, cardiovascular; GUSTO, Global Strategies for Opening Occluded Coronary Arteries; HR, hazard ratio; ISTH, International Society on Thrombosis and Haemostasis; MI, myocardial infarction; NR, not reported; PAD, peripheral artery disease; RRR, relative risk reduction; TIMI, Thrombolysis In Myocardial Infarction. *3-year Kaplan-Meier estimation.

SUPPLEMENTARY MATERIAL

A. Lack of evidence for antiplatelet therapy in patients with asymptomatic lower extremity arterial disease (LEAD)

A study of 3350 patients with asymptomatic LEAD there was neither a reduction in the primary endpoint, nor fatal stroke (0.4% [95% CI 0.2-0.9], vs. 0.7% [0.4-1.2]) or non-fatal stroke (2.2%, [1.6-3.0], vs. 2.3% [1.7-3.1]).[25] Similarly, in a higher risk population with asymptomatic LEAD and concurrent type 2 diabetes mellitus (T2DM), aspirin failed to offer benefit over placebo in preventing a primary composite endpoint of MI/stroke/above-knee amputation.[26] Whilst there were no significant effects on fatal (0.89, [0.34-2.30], p=0.80) or non-fatal stroke, numbers of the latter were lower in the aspirin group, but did not reach statistical significance (4.6 % vs. 6.4%, HR 0.71 [0.44-1.14], p=0.15).

Similarly, in a higher risk population with asymptomatic LEAD and concurrent T2DM, aspirin failed to offer benefit over placebo in preventing a primary composite endpoint of fatal or non-fatal myocardial infarction or stroke, or above-knee amputation (hazard ratio [HR] 0.98, 95% CI 0.76 to 1.26, p=0.86) in the Prevention Of Progression of Arterial Disease And Diabetes (POPADAD) study.[26] Whilst there were also no significant effects either on fatal (0.89, 0.34 to 2.30, p=0.80) or non-fatal stroke, numbers of the latter were lower in the group receiving aspirin, but did not reach statistical significance (4.6 % vs. 6.4%, HR 0.71, 95% CI 0.44 to 1.14, p=0.15).

B. Further discussion of ticagrelor monotherapy for stroke prevention

Given with aspirin, ticagrelor offers pharmacokinetic and pharmacodynamic advantages over clopidogrel of greater potency and reliability in chronic coronary syndrome (CCS) patients undergoing percutaneous coronary intervention (PCI), although there is no evidence this improves clinical outcomes.[27] It has been argued that aspirin adds little benefit when given with a potent $P2Y_{12}$

inhibitor,[28, 29] although the two remain additive in antiplatelet effect when assessed using gold-standard methods.[30, 31] Two recent RCTs have investigated ticagrelor monotherapy as an alternative to dual antiplatelet therapy (DAPT) after PCI, including in high-risk CCS patients. In particular, the Ticagrelor With Aspirin or Alone in High-Risk Patients after Coronary Intervention (TWILIGHT) study demonstrated significantly less bleeding (e.g. primary end point of Bleeding Academic Research Consortium (BARC) type 2, 3, or 5 bleeding HR, 0.56; [0.45-0.68; p<0.001) when receiving 12 months of ticagrelor monotherapy compared with aspirin and ticagrelor, in patients who already tolerated 3 months of DAPT post-PCI.[32] Acknowledging aspirin plus ticagrelor is not considered a standard-care regimen in many CCS patients (e.g. without prior MI), there appeared to be no increase in thrombotic risk (key ischaemic endpoint: all-cause death/non-fatal MI/stroke, 3.9% vs. 3.9%, non-inferiority-p<0.001). The overall thrombotic risk appeared non-inferior, although thrombosis was only a secondary endpoint of the trial based on an upper relative non-inferiority margin of 20% (1.6% over 8% incidence of MACE). However, there were numerically more ischaemic strokes in the ticagrelor monotherapy group (0.5% vs. 0.2%, HR 2.00 [0.86-4.67]), hence a detrimental effect of de-escalating antiplatelet therapy on stroke prevention cannot be ruled out. This is also supported by a randomised controlled trial (Acute Stroke or Transient Ischaemic Attack Treated with Aspirin or Ticagrelor and Patient Outcomes, SOCRATES) in non-severe acute stroke or high-risk transient ischaemic attack of single-APT (SAPT) with ticagrelor vs. aspirin.[12] A statistically-significant difference in the primary endpoint of stroke, MI or death (6.7% vs. 7.5%, HR 0.89 [0.78-1.01], p=0.07) was not demonstrated, but on exploratory analysis those that received both aspirin and ticagrelor in the peri-event period appeared to gain more benefit compared to those that did not (HR 0.76 [0.61-0.95], p=0.02; vs. 0.96 [0.82-1.12]). The hypothesis that, in acute stroke, aspirin plus ticagrelor is superior to SAPT in preventing recurrent ischaemic events, was tested in THe Acute stroke or transient ischaemic attack treated with ticagreLor and aspirin for prEvention of Stroke and death (THALES) trial, which demonstrated a significant reduction in the primary composite endpoint of stroke or death at 30 days (5.5% vs. 6.6%, HR 0.83 [0.71-0.96, p=0.02), but at the expense of more frequent Global Utilization of Streptokinase and Tissue

Plasminogen Activator for Occluded Coronary Arteries (GUSTO)-defined severe bleeding (0.5% vs. 0.1%, HR 3.99 [1.74-9.14], p=0.001.[15]

C. Relative safety and efficacy of different NOACs

Different NOACs have never undergone head-to-head clinical outcome-driven RCTs. However, some insight can be provided, for example, from a large retrospective observational study of 434,046 patients with non-valvular AF comparing treatment with apixaban, dabigatran, rivaroxaban and warfarin,[33] 40% with CAD and 20% PAD. All three NOACs performed well compared to warfarin. Between the NOACs, apixaban conferred a lower risk of stroke against both dabigatran (HR 0.72 [0.60-0.85]) and rivaroxaban (0.80 [0.73-0.89]), whilst also demonstrating a favourable effect on bleeding (major bleeding: vs. dabigatran 0.78 [0.70-0.87]; vs. rivaroxaban 0.80 [0.55-0.59]). A recent systemic review and meta-analysis, whilst similarly demonstrating benefits in bleeding risk of apixaban when compared to dabigatran, did not show any significant differences in stroke rates between apixaban, dabigatran and rivaroxaban but still suggested that apixaban might have the most favourable risk-benefit profile.[34] Prospective RCTs would clarify this issue more definitively.

D. Further discussion of evidence from the Atrial Fibrillation and Ischaemic Events with Rivaroxaban in Patients with Stable Coronary Artery Disease (AFIRE) study

2236 patients from a Japanese population with both atrial fibrillation (AF) and CCS (including 35% with prior MI, 71% with prior PCI) were randomised to receive either rivaroxaban alone, or in combination with SAPT (aspirin or clopidogrel).[35] Whilst the dose range of rivaroxaban (10 or 15 mg once-daily) was lower than that recommended for stroke prophylaxis in AF in European populations (20 mg once-daily), these dosing regimens have been validated for this purpose in Japanese patients. After a mean follow-up of 2 years, rivaroxaban alone offered both non-inferiority ($p<0.001$) and superiority (in a post-hoc analysis, $p=0.02$), in prevention of the (modified) primary endpoint of

composite of stroke, systemic embolism, MI, unstable angina requiring revascularisation, or death from any cause (HR 0.72 [0.55-0.95]), and superiority (pre-specified analysis, p=0.01) in the primary safety endpoint of International Society on Thrombosis and Haemostasis (ISTH) major bleeding (0.59 [0.39-0.89]). Examining stroke outcomes specifically, there was a neutral effect on ischaemic stroke (0.73 [0.42-1.29]), but a significant reduction in haemorrhagic stroke (0.30 [0.10-0.92]). Although this certainly supports NOAC monotherapy over NOAC-SAPT, some caution may arise from the fact that, although occurring in very small numbers, there were numerically more episodes of MI when receiving NOAC alone (0.59% vs. 0.37%, HR 1.60, [0.67-3.87]). This warrants the acknowledgement in the current guidelines it is a matter for case-by-case consideration and a combination of OAC-SAPT may sometimes be appropriate.[1]

E. Other preventive therapies

LIPID-LOWERING THERAPY

A key feature of atherogenesis is the accumulation of lipid-rich plaques within the arterial wall.[36] In particular, low-density lipoprotein cholesterol (LDL-C) is implicated in the process, and therefore lowering circulating levels of LDL-C is a rational strategy for preventing atherothrombotic complications.

In current European guidelines, patients with either CCS or PAD are judged ‘very-high-risk’ and, as such, the recommended target level of LDL-C is a reduction of at least 50% from baseline, with an LDL-C goal of <1.4 mmol/L, with consideration for an even lower goal of <1.0 mmol/L in patients who suffer two atherothrombotic events in two years.[37]

Statin therapy

Statins, the most commonly-prescribed lipid-lowering drugs, inhibit the enzyme 3-hydroxy-3-methyl-glutaryl-coenzyme A (HMG Co-A) reductase, responsible for converting HMG Co-A to mevalonic acid, a key step in hepatic synthesis of cholesterol.[38] Statins may offer superior stroke prevention to those with vs. without evidence of chronic inflammation.[39]

Individual statins have differing strength: rosuvastatin and atorvastatin are regarded as high-intensity (able to reduce LDL-C by >50%), whilst the remainder, including simvastatin and pravastatin, are only of moderate-intensity (reduce by 30-50%).[40]

Statins are currently recommended for all patients with CCS or PAD,[1, 2] based on strong evidence from RCTs. For example, a meta-analysis by the cholesterol treatment trialists' collaboration, including over 170,000 patients from 26 RCTs, suggested that intensive lowering of LDL-C convincingly reduced the incidence of major vascular events, including in those with a diagnosis of coronary heart disease (relative-risk, RR, 0.79; [0.76–0.82] per 1.0-mmol/L reduction in LDL-C) or non-coronary vascular disease (RR 0.81 [0.71-0.92]).[41] The reduction in events included ischaemic stroke (0.85 [0.8-0.9]), although this was more modest than for other outcomes, perhaps reflecting the multiple mechanisms involved in its aetiology, and statins less convincingly prevented fatal stroke (death from stroke of any type 0.96 [0.84-1.09]).

Ezetimibe

Whilst the brush-border absorption inhibitor ezetimibe lowers LDL-C in statin-treated patients, there is robust evidence only for its use in those with a recent ACS receiving simvastatin, of moderate-intensity in effect, from the IMProved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT).[42] Although study drug was started shortly after ACS, the patients were followed up for 7 years i.e. well into the CCS phase. Whilst the primary endpoint of CV death/major coronary event/non-fatal stroke was significantly less frequent when receiving ezetimibe, the effect was modest (HR 0.94 [0.89-0.99], p=0.016). There did appear to be a more pronounced reduction in ischaemic stroke (0.79 [0.67-0.94]), and possibly all stroke (0.86, [0.73-1.00]). However, there is currently no evidence that

ezetimibe prevents clinical events in patients treated with a high-intensity statin and current guidelines recommend it only if needed to meet lipid targets.[37]

Proprotein convertase subtilisin-kexin type 9 inhibitors

Recently the proprotein convertase subtilisin-kexin type 9 (PCSK9) inhibitors have become available. PCSK9 binds to the LDL receptor (LDLR), reducing its surface expression and activity.[43] By inhibiting PCSK9, LDLR activity increases and LDL is taken up from the extracellular fluid into cells, reducing circulating concentrations. The currently-available PCSK9 inhibitors are alirocumab and evolocumab.[44]

Early studies indicated that PCSK9 inhibitors have a powerful LDL-C-lowering effect, even in those already receiving high-intensity statins.[45] There are now robust clinical data supporting the use of either alirocumab or evolocumab in patients with cardiovascular disease.[46, 47] There is particularly valuable evidence for patients with CCS or PAD, such as from the Further cardiovascular OUtcomes Research with PCSK9 Inhibition in subjects with Elevated Risk (FOURIER) study, which randomised 27,564 such patients already receiving optimised lipid-lowering therapy but with a fasting LDL-C level of ≥1.8 mmol/L, or a non-high-density lipoprotein level of ≥2.6 mmol/L.[46] The primary end point of CV death, MI, stroke, hospitalisation for UA, or coronary revascularisation was significantly less frequent with evolocumab compared to placebo (HR 0.85 [0.79-0.92], p<0.001), and this included a significant reduction in ischaemic stroke (0.75 [0.62-0.92]) and total stroke (0.79 [0.66-0.95], p=0.01).

Although currently limited by their high financial cost, current European guidelines recommend PCSK9 inhibitors in patients with a history of CCS or PAD who cannot achieve their lipid targets with high-intensity statin and ezetimibe treatment, where tolerated.[37]

ANTI-HYPERTENSIVE THERAPY

Hypertension is a strong independent risk factor for atherothrombotic disease, including stroke. Furthermore, both ischaemic and haemorrhagic stroke risk is increased by hypertension, making it a powerful target for preventing stroke, including in patients with CCS or PAD.[48, 49]

Blood pressure targets

European guidelines have previously suggested a target systolic blood pressure (SBP) of <140 mmHg (or 140-150 in older people) and diastolic blood pressure (DBP) of <90 mmHg (<85 mmHg if diabetic).[50] More recent evidence has shown that a lower target may be beneficial. The Systolic blood PRessure Intervention Trial (SPRINT) randomised 9361 patients with hypertension and an additional risk factor to an SBP target of <120-mmHg or <140-mmHg, monitored using periodic 24-hour readings.[51] After 3 years of follow-up, those with the intensive target had lower rates of endpoints including the primary endpoint of MI/other ACS/stroke/heart failure/CV death (HR 0.75 [0.64 -0.89], p<0.001) and all-cause mortality (0.73 [0.60-0.90], p=0.003). Whilst stroke, when considered separately, was numerically lower in the intensive group and appeared more modest in magnitude (0.41%/yr vs. 0.47%/yr, HR 0.89 [0.63-1.25], p=0.50).

Current European guidelines have been updated to recommend a target of <140/90 mmHg in all patients, including those with atherothrombotic disease, falling to <130/80 mmHg in most patients if initial treatment is well-tolerated. An SBP target of 120-129-mmHg should be routinely aimed for in those <65 years old, and DBP should be kept <80-mmHg in all hypertensive patients.[50]

Over-aggressive BP control may be counterproductive in patients with LEAD, however, with the lowest rate of MACE in those with SBP 135-145-mmHg and DBP 60-90-mmHg, with increases in event-rates both above and below.[52] Relative caution should be exercised in this group, particularly if symptoms of LEAD worsen with BP reduction BP.[2]

Choice of antihypertensive agents

Certain antihypertensive drugs (AHDs) may be associated with better clinical-outcomes over and above effects on BP. For example, angiotensin-converting enzyme inhibitors (ACEi) reduce MACE in patients with CCS or PAD, including when compared with other AHDs, but only with reduced left ventricular ejection fraction (LVEF), chronic kidney disease (CKD) or T2DM. ACEi should therefore be

considered in all patients with these co-morbidities, regardless of BP.[1] Similarly, in heart failure, the neprilysin inhibitor-angiotensin receptor blocker sacubitril-valsartan reduced CV death/hospitalization.[53] Patients with CCS may benefit in a similar fashion to the study population as a whole, but there does not appear to be an effect on stroke (HR 0.99 [0.76-1.29], p=0.92).[54]

In patients without these co-morbidities, there is no clear evidence that renin-angiotensin-system inhibitors (RASi) are more beneficial than other AHDs, such as amlodipine or thiazide-diuretics, in preventing MACE.[55] In a meta-analysis of 24 trials including 198,275 patient-years, RASi were associated with a reduced risk of stroke when compared with placebo (HR 0.79 [0.70-0.89]) but not active comparators (1.10 [0.93-1.31]).[56]

Hence, in patients with CCS or PAD without reduced LVEF, diabetes or CKD, BP targets appear more important than the choice of agent.

OPTIMISING STROKE PREVENTION IN THE MANAGEMENT OF PATIENTS WITH TYPE 2 DIABETES AND CCS OR PAD

T2DM is an independent risk factor for a range of ischaemic events, including stroke.[57] Patients with CCS/PAD and T2DM have a higher risk of stroke than those with T2DM but without atherosclerotic disease.[58] In T2DM, a 1% reduction in glycated-haemoglobin-A1c (HbA1c) results in a 12% RRR in stroke.[59] However, over-intensive glycaemic control may be counterproductive, increasing mortality without reducing stroke.[60] Current recommendations suggest a target HbA1c of <7% (53-mmol/mol) to reduce the risk of vascular events, including stroke, although this should be individualised.[61]

Specific anti-diabetic agents may be associated with particular benefits in cardiovascular protection. For example, glucagon-like peptide-1 receptor agonists (GLP1-RA), such as liraglutide, semaglutide or dulaglutide, reduce the risk of MACE, and these are now recommended in European guidelines for patients with T2DM and CV disease, including CCS or PAD.[61] Although significant reductions in stroke risk have not been convincingly demonstrated in individual RCTs of GLP1-RA, pooling these has suggested a modest effect vs. placebo (HR 0.87, [0.78-0.98], p=0.021).[62]

Similarly, the sodium-glucose cotransporter 2 (SGLT2) inhibitors canagliflozin, dapagliflozin and empagliflozin reduce risk of MACE in patients with T2DM and established atherothrombotic disease, including CCS or PAD,[63] and are currently recommended for this purpose in this population.[61] In contrast to GLP1-RA, however, meta-analysis showed a neutral effect on stroke (HR 1.00 [0.88 to 1.13]).[64]

LIFESTYLE INTERVENTIONS

Smoking cessation

Smoking is a major risk-factor for the development of both CCS and PAD, also increasing the risk of acute events.[65] Similarly, stroke is more common in those who smoke, including in patients with CCS or PAD.[66]

Cessation offers a large benefit to patients, such as a 36% reduction in mortality.[67] Structured programmes incorporating pharmacological and non-pharmacological support are likely to be most successful.[1]

Alcohol intake

The relationship between alcohol intake and stroke risk has been contentious, often due to debates over possible benefits of low-level but not high-level drinking. Recent observational studies have suggested, for example, low- or moderate-level alcohol intake is associated with a reduction in stroke risk in a Scandinavian retrospective study of 78,546 individuals,[68] whereas, in a prospective study of a Chinese population of 500,000, any amount of alcohol was associated with increased risk.[69] Universally, recommendations advise avoidance of at least high-level drinking; for example, current ESC CCS guidelines suggest limiting to 100-g (12.5-units) per week or 15-g (1.9-units) per day.[1]

Exercise

Regular exercise may convey a wide range of health benefits including reducing obesity, BP, heart rate, insulin resistance and circulating LDL-C levels, as well as improving feelings of wellbeing.[70] Whilst baseline exercise habits may not be an independent predictor of stroke risk,[71] higher peak aerobic capacity, which can be increased with exercise, independently predicts survival of patients with CAD.[72] The effects of regular exercise on other parameters known to be strong risk factors mean exercise is an important component of stroke prevention, including in patients with CCS or PAD. Current CCS guidelines recommend 30-60 minutes of moderate-intensity aerobic activity at least 5 days per week, for example.[1]

Pollution

Environmental air, light and noise pollution have been linked to increased cardiovascular risk, and awareness of these as risk factors in a range of diseases is rapidly-increasing.[73-75] Interventions to combat these at personal and population levels may lead to a wide range of health benefits, including reduction in stroke risk.

TARGETING INFLAMMATION – A FUTURE DIRECTION?

Inflammation drives atherogenesis and thrombosis, so is an obvious target to reduce MACE, including stroke.[36]

Drug therapy to target inflammation

Several approaches have now been explored in outcome-driven RCTs of CAD patients. For example, in the Canakinumab Anti-inflammatory Thrombosis Outcome Study (CANTOS), canakinumab, a monoclonal antibody against interleukin (IL)-1ß, significantly reduced the incidence of MACE in patients with prior MI and ongoing inflammation (e.g. 150-mg canakinumab vs. placebo HR 0.85 [0.74 -0.98], p=0.021), which included a numerical reduction in all-stroke risk (0.80 [0.57-1.13], p=0.2).[76] Benefits were offset, however, by an increased risk of fatal infections (HR 0.31 vs. 0.18 per 100 person-

yrs, p=0.02), reflecting the benefit-risk balance of this approach limiting its overall efficacy. Nevertheless, CANTOS has affirmed the value of targeting inflammation in patients with CCS, benefits that are also likely relevant in PAD.

Similarly, the recent results of the Colchicine Cardiovascular Outcomes Trial (COLCOT) have demonstrated the value of anti-inflammatory therapy with colchicine if commenced within 30 days of an ACS event and continued for 42 months.[77] Particularly impressive was the reduction in stroke: even though numbers were small, the upper limit of the 95% CI for the HR was well below 1 (0.2% vs. 0.8%, HR 0.26 [0.10 to 0.70]). As well as notorious gastrointestinal side-effects, there was significantly increased risk of pneumonia. It remains to be seen, particularly given there was no benefit on CV death, whether colchicine, an already widely-available drug, will be recommended for routine use in this population. More insight may come from the ongoing factorial-RCT of colchicine and spironolactone in patients with acute ST-elevation MI (Colchicine and Spironolactone in Patients with STEMI / SYNERGY Stent Registry, CLEAR-SYNERGY, NCT03048825) aiming to enrol around 4000 patients.

Not all anti-inflammatory therapies may offer vascular protection, however. Notably, the use of the anti-folate drug methotrexate in a high-risk CAD population offered no reduction in MACE, including stroke, in the Cardiovascular Inflammation Reduction Trial (CIRT).[78] There were no reductions in inflammatory markers relevant to atherothrombosis, such as C-reactive protein, IL-1ß or IL-6, and it may be that more pathway-specific strategies are required.

Other measures to reduce chronic inflammation

Any source of chronic inflammation leading to increased circulating pro-inflammatory cytokines may hypothetically accelerate atherothrombosis. In particular, a large burden may arise from periodontitis, estimated to affect around half of adults in Western countries.[79] Periodontitis has been linked not only with detectable increases in platelet activation,[80] circulating IL-6 and hs-CRP,[81] but is also an

independent factor for CAD[82] and ischaemic stroke.[83] Intensive treatment is associated with, for example, a reduction in circulating IL-6 and hsCRP,[81] and improvements in endothelial function.[84] There is limited retrospective evidence that treatment also reduces MACE, including stroke, in high-risk groups such as those with previous stroke or T2DM.[85, 86]

REFERENCES

1. Knuuti J, Wijns W, Saraste A, Capodanno D, Barbato E, Funck-Brentano C, Prescott E, Storey RF, Deaton C, Cuisset T, Agewall S, Dickstein K, Edvardsen T, Escaned J, Gersh BJ, Svitil P, Gilard M, Hasdai D, Hatala R, Mahfoud F, Masip J, Muneretto C, Valgimigli M, Achenbach S, Bax JJ. 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes. Eur Heart J 2019.

2. Aboyans V, Ricco JB, Bartelink MEL, Bjorck M, Brodmann M, Cohnert T, Collet JP, Czerny M, De Carlo M, Debus S, Espinola-Klein C, Kahan T, Kownator S, Mazzolai L, Naylor AR, Roffi M, Rother J, Sprynger M, Tendera M, Tepe G, Venermo M, Vlachopoulos C, Desormais I. 2017 ESC Guidelines on the Diagnosis and Treatment of Peripheral Arterial Diseases, in collaboration with the European Society for Vascular Surgery (ESVS): Document covering atherosclerotic disease of extracranial carotid and vertebral, mesenteric, renal, upper and lower extremity arteriesEndorsed by: the European Stroke Organization (ESO)The Task Force for the Diagnosis and Treatment of Peripheral Arterial Diseases of the European Society of Cardiology (ESC) and of the European Society for Vascular Surgery (ESVS). Eur Heart J 2018;**39**(9):763-816.

3. Parker WAE, Storey RF. Novel approaches to P2Y12 inhibition and aspirin dosing. Platelets 2020:1-8.

4. Pristipino C, Sievert H, D'Ascenzo F, Louis Mas J, Meier B, Scacciatella P, Hildick-Smith D, Gaita F, Toni D, Kyrle P, Thomson J, Derumeaux G, Onorato E, Sibbing D, Germonpre P, Berti S, Chessa M, Bedogni F, Dudek D, Hornung M, Zamorano J. European position paper on the management of patients with patent foramen ovale. General approach and left circulation thromboembolism. Eur Heart J 2019;**40**(38):3182-3195.

5. Patrono C, Morais J, Baigent C, Collet JP, Fitzgerald D, Halvorsen S, Rocca B, Siegbahn A, Storey RF, Vilahur G. Antiplatelet Agents for the Treatment and Prevention of Coronary Atherothrombosis. J Am Coll Cardiol 2017;**70**(14):1760-1776.

6. Parker WA, Storey RF. Long-term antiplatelet therapy following myocardial infarction: implications of PEGASUS-TIMI 54. Heart 2016;**102**(10):783-9.

7. Rajkumar CA, Floyd CN, Ferro A. Antiplatelet therapy as a modulator of stroke aetiology: a meta-analysis. Br J Clin Pharmacol 2015;**80**(3):331-41.

8. Storey RF. Biology and pharmacology of the platelet P2Y12 receptor. Curr Pharm Des 2006;**12**(10):1255-9.

9. Parker WAE, Schulte C, Barwari T, Phoenix F, Pearson SM, Mayr M, Grant PJ, Storey RF, Ajjan RA. Aspirin, clopidogrel and prasugrel monotherapy in patients with type 2 diabetes mellitus: a double-blind randomised controlled trial of the effects on thrombotic markers and microRNA levels. Cardiovascular Diabetology 2020;**19**(1):3.

10. CAPRIE Steering Committee. A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). Lancet 1996;**348**(9038):1329-39.

11. Hiatt WR, Fowkes FG, Heizer G, Berger JS, Baumgartner I, Held P, Katona BG, Mahaffey KW, Norgren L, Jones WS, Blomster J, Millegård M, Reist C, Patel MR. Ticagrelor versus Clopidogrel in Symptomatic Peripheral Artery Disease. N Engl J Med 2017;**376**:32-40.

12. Johnston SC, Amarenco P, Albers GW, Denison H, Easton JD, Evans SR, Held P, Jonasson J, Minematsu K, Molina CA, Wang Y, Wong KS. Ticagrelor versus Aspirin in Acute Stroke or Transient Ischemic Attack. N Engl J Med 2016;**375**(1):35-43.

13. The Clopidogrel in Unstable Angina to Prevent Recurrent Events Trial Investigators. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. N Engl J Med 2001;**345**:494-502.

14. Pan Y, Elm JJ, Li H, Easton JD, Wang Y, Farrant M, Meng X, Kim AS, Zhao X, Meurer WJ, Liu L, Dietrich D, Johnston SC. Outcomes Associated With Clopidogrel-Aspirin Use in Minor Stroke

or Transient Ischemic Attack: A Pooled Analysis of Clopidogrel in High-Risk Patients With Acute Non-Disabling Cerebrovascular Events (CHANCE) and Platelet-Oriented Inhibition in New TIA and Minor Ischemic Stroke (POINT) Trials. JAMA Neurol 2019.

15. Johnston SC, Amarenco P, Denison H, Evans SR, Himmelmann A, James S, Knutsson M, Ladenvall P, Molina CA, Wang Y. Ticagrelor and Aspirin or Aspirin Alone in Acute Ischemic Stroke or TIA. New Eng J Med 2020;**383**(3):207-217.

16. Bhatt DL, Fox KAA, Hacke W, Berger PB, Black HR, Boden WE, Cacoub P, Cohen EA, Creager MA, Easton JD, Flather MD, Haffner SM, Hamm CW, Hankey GJ, Johnston SC, Mak K-H, Mas J-L, Montalescot G, Pearson TA, Steg PG, Steinhubl SR, Weber MA, Brennan DM, Fabry-Ribaudo L, Booth J, Topol EJ, the CI. Clopidogrel and Aspirin versus Aspirin Alone for the Prevention of Atherothrombotic Events. New Eng J Med 2006;**354**(16):1706-1717.

17. Bonaca MP, Bhatt DL, Cohen M, Steg PG, Storey RF, Jensen EC, Magnani G, Bansilal S, Fish MP, Im K, Bengtsson O, Ophuis TO, Budaj A, Theroux P, Ruda M, Hamm C, Goto S, Spinar J, Nicolau JC, Kiss RG, Murphy SA, Wiviott SD, Held P, Braunwald E, Sabatine MS. Long-Term Use of Ticagrelor in Patients with Prior Myocardial Infarction. New Engl J Med 2015;**372**:1791-800.

18. Yeh RW, Kereiakes DJ, Steg PG, Windecker S, Rinaldi MJ, Gershlick AH, Cutlip DE, Cohen DJ, Tanguay JF, Jacobs A, Wiviott SD, Massaro JM, Iancu AC, Mauri L. Benefits and Risks of Extended Duration Dual Antiplatelet Therapy After PCI in Patients With and Without Acute Myocardial Infarction. J Am Coll Cardiol 2015;**65**(20):2211-21.

19. Steg PG, Bhatt DL, Simon T, Fox K, Mehta SR, Harrington RA, Held C, Andersson M, Himmelmann A, Ridderstrale W, Leonsson-Zachrisson M, Liu Y, Opolski G, Zateyshchikov D, Ge J, Nicolau JC, Corbalan R, Cornel JH, Widimsky P, Leiter LA. Ticagrelor in Patients with Stable Coronary Disease and Diabetes. N Engl J Med 2019;**381**(14):1309-1320.

20. Ruff CT, Giugliano RP, Braunwald E, Hoffman EB, Deenadayalu N, Ezekowitz MD, Camm AJ, Weitz JI, Lewis BS, Parkhomenko A, Yamashita T, Antman EM. Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials. Lancet 2014;**383**(9921):955-62.

21. Hurlen M, Abdelnoor M, Smith P, Erikssen J, Arnesen H. Warfarin, aspirin, or both after myocardial infarction. N Engl J Med 2002;**347**(13):969-74.

22. Eikelboom JW, Connolly SJ, Bosch J, Dagenais GR, Hart RG, Shestakovska O, Diaz R, Alings M, Lonn EM, Anand SS, Widimsky P, Hori M, Avezum A, Piegas LS, Branch KRH, Probstfield J, Bhatt DL, Zhu J, Liang Y, Maggioni AP, Lopez-Jaramillo P, O'Donnell M, Kakkar AK, Fox KAA, Parkhomenko AN, Ertl G, Stork S, Keltai M, Ryden L, Pogosova N, Dans AL, Lanas F, Commerford PJ, Torp-Pedersen C, Guzik TJ, Verhamme PB, Vinereanu D, Kim JH, Tonkin AM, Lewis BS, Felix C, Yusoff K, Steg PG, Metsarinne KP, Cook Bruns N, Misselwitz F, Chen E, Leong D, Yusuf S. Rivaroxaban with or without Aspirin in Stable Cardiovascular Disease. N Engl J Med 2017;**377**(14):1319-1330.

23. Bonaca MP, Bauersachs RM, Anand SS, Debus ES, Nehler MR, Patel MR, Fanelli F, Capell WH, Diao L, Jaeger N, Hess CN, Pap AF, Kittelson JM, Gudz I, Mátyás L, Krievins DK, Diaz R, Brodmann M, Muehlhofer E, Haskell LP, Berkowitz SD, Hiatt WR. Rivaroxaban in Peripheral Artery Disease after Revascularization. New England Journal of Medicine 2020;**382**(21):1994-2004.

24. Mauri L, Kereiakes DJ, Yeh RW, Driscoll-Shempp P, Cutlip DE, Steg PG, Normand S-LT, Braunwald E, Wiviott SD, Cohen DJ, Holmes DR, Krucoff MW, Hermiller J, Dauerman HL, Simon DI, Kandzari DE, Garratt KN, Lee DP, Pow TK, Ver Lee P, Rinaldi MJ, Massaro JM. Twelve or 30 Months of Dual Antiplatelet Therapy after Drug-Eluting Stents. New England Journal of Medicine 2014;**371**(23):2155-2166.

25. Fowkes FG, Price JF, Stewart MC, Butcher I, Leng GC, Pell AC, Sandercock PA, Fox KA, Lowe GD, Murray GD. Aspirin for prevention of cardiovascular events in a general population screened for a low ankle brachial index: a randomized controlled trial. JAMA 2010;**303**(9):841-8.

26. Belch J, MacCuish A, Campbell I, Cobbe S, Taylor R, Prescott R, Lee R, Bancroft J, MacEwan S, Shepherd J, Macfarlane P, Morris A, Jung R, Kelly C, Connacher A, Peden N, Jamieson A, Matthews D, Leese G, McKnight J, O'Brien I, Semple C, Petrie J, Gordon D, Pringle S, MacWalter R. The prevention of progression of arterial disease and diabetes (POPADAD) trial: factorial randomised placebo controlled trial of aspirin and antioxidants in patients with diabetes and asymptomatic peripheral arterial disease. BMJ 2008;**337**.

27. Orme RC, Parker WAE, Thomas MR, Judge HM, Baster K, Sumaya W, Morgan KP, McMellon HC, Richardson JD, Grech ED, Wheeldon NM, Hall IR, Iqbal J, Barmby D, Gunn JP, Storey RF. Study of Two Dose Regimens of Ticagrelor Compared with Clopidogrel in Patients Undergoing Percutaneous Coronary Intervention for Stable Coronary Artery Disease (STEEL-PCI). Circulation 2018;**138**:1290-1300.

28. Warner TD, Armstrong PC, Curzen NP, Mitchell JA. Dual antiplatelet therapy in cardiovascular disease: does aspirin increase clinical risk in the presence of potent P2Y12 receptor antagonists? Heart 2010;**96**(21):1693-4.

29. Armstrong PC, Leadbeater PD, Chan MV, Kirkby NS, Jakubowski JA, Mitchell JA, Warner TD. In the presence of strong P2Y12 receptor blockade, aspirin provides little additional inhibition of platelet aggregation. J Thromb Haemost 2011;**9**(3):552-61.

30. Teng R, Maya J, Butler K. Evaluation of the pharmacokinetics and pharmacodynamics of ticagrelor co-administered with aspirin in healthy volunteers. Platelets 2013;**24**(8):615-624.

31. Scavone M, Femia EA, Caroppo V, Cattaneo M. Inhibition of the platelet P2Y12 receptor for adenosine diphosphate does not impair the capacity of platelet to synthesize thromboxane A2. Eur Heart J 2016;**37**(44):3347-3356.

32. Mehran R, Baber U, Sharma SK, Cohen DJ, Angiolillo DJ, Briguori C, Cha JY, Collier T, Dangas G, Dudek D, Dzavik V, Escaned J, Gil R, Gurbel P, Hamm CW, Henry T, Huber K, Kastrati A, Kaul U, Kornowski R, Krucoff M, Kunadian V, Marx SO, Mehta SR, Moliterno D, Ohman EM, Oldroyd K, Sardella G, Sartori S, Shlofmitz R, Steg PG, Weisz G, Witzenbichler B, Han YL, Pocock S, Gibson CM. Ticagrelor with or without Aspirin in High-Risk Patients after PCI. N Engl J Med 2019;**381**(21):2032-2042.

33. Lip GYH, Keshishian A, Li X, Hamilton M, Masseria C, Gupta K, Luo X, Mardekian J, Friend K, Nadkarni A, Pan X, Baser O, Deitelzweig S. Effectiveness and Safety of Oral Anticoagulants Among Nonvalvular Atrial Fibrillation Patients. Stroke 2018;**49**(12):2933-2944.

34. Li G, Lip GYH, Holbrook A, Chang Y, Larsen TB, Sun X, Tang J, Mbuagbaw L, Witt DM, Crowther M, Thabane L, Levine MAH. Direct comparative effectiveness and safety between non-vitamin K antagonist oral anticoagulants for stroke prevention in nonvalvular atrial fibrillation: a systematic review and meta-analysis of observational studies. Eur J Epidemiol 2019;**34**(2):173-190.

35. Yasuda S, Kaikita K, Akao M, Ako J, Matoba T, Nakamura M, Miyauchi K, Hagiwara N, Kimura K, Hirayama A, Matsui K, Ogawa H. Antithrombotic Therapy for Atrial Fibrillation with Stable Coronary Disease. N Engl J Med 2019;**381**(12):1103-1113.

36. Libby P, Buring JE, Badimon L, Hansson GK, Deanfield J, Bittencourt MS, Tokgozoglu L, Lewis EF. Atherosclerosis. Nat Rev Dis Primers 2019;**5**(1):56.

37. Mach F, Baigent C, Catapano AL, Koskinas KC, Casula M, Badimon L, Chapman MJ, De Backer GG, Delgado V, Ference BA, Graham IM, Halliday A, Landmesser U, Mihaylova B, Pedersen TR, Riccardi G, Richter DJ, Sabatine MS, Taskinen MR, Tokgozoglu L, Wiklund O. 2019 ESC/EAS

Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. Eur Heart J 2020;**41**(1):111-188.

38. Stancu C, Sima A. Statins: mechanism of action and effects. J Cell Mol Med 2001;**5**(4):378-87.

39. Everett BM, Glynn RJ, MacFadyen JG, Ridker PM. Rosuvastatin in the prevention of stroke among men and women with elevated levels of C-reactive protein: justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER). Circulation 2010;**121**(1):143-50.

40. Stone NJ, Robinson JG, Lichtenstein AH, Bairey Merz CN, Blum CB, Eckel RH, Goldberg AC, Gordon D, Levy D, Lloyd-Jones DM, McBride P, Schwartz JS, Shero ST, Smith SC, Jr., Watson K, Wilson PW. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2014;**63**(25 Pt B):2889-934.

41. Baigent C, Blackwell L, Emberson J, Holland LE, Reith C, Bhala N, Peto R, Barnes EH, Keech A, Simes J, Collins R. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials. Lancet 2010;**376**(9753):1670-81.

42. Cannon CP, Blazing MA, Giugliano RP, McCagg A, White JA, Theroux P, Darius H, Lewis BS, Ophuis TO, Jukema JW, De Ferrari GM, Ruzyllo W, De Lucca P, Im K, Bohula EA, Reist C, Wiviott SD, Tershakovec AM, Musliner TA, Braunwald E, Califf RM. Ezetimibe Added to Statin Therapy after Acute Coronary Syndromes. N Engl J Med 2015;**372**(25):2387-97.

43. Peterson AS, Fong LG, Young SG. PCSK9 function and physiology*1. J Lipid Res 2008;**49**(6):1152-6.

44. Pasta A, Cremonini AL, Pisciotta L, Buscaglia A, Porto I, Barra F, Ferrero S, Brunelli C, Rosa GM. PCSK9 inhibitors for treating hypercholesterolemia. Expert Opin Pharmacother 2020:1-11.

45. Giugliano RP, Desai NR, Kohli P, Rogers WJ, Somaratne R, Huang F, Liu T, Mohanavelu S, Hoffman EB, McDonald ST, Abrahamsen TE, Wasserman SM, Scott R, Sabatine MS. Efficacy, safety, and tolerability of a monoclonal antibody to proprotein convertase subtilisin/kexin type 9 in combination with a statin in patients with hypercholesterolaemia (LAPLACE-TIMI 57): a randomised, placebo-controlled, dose-ranging, phase 2 study. Lancet 2012;**380**(9858):2007-17.

46. Sabatine MS, Giugliano RP, Keech AC, Honarpour N, Wiviott SD, Murphy SA, Kuder JF, Wang H, Liu T, Wasserman SM, Sever PS, Pedersen TR. Evolocumab and Clinical Outcomes in Patients with Cardiovascular Disease. N Engl J Med 2017;**376**(18):1713-1722.

47. Schwartz GG, Steg PG, Szarek M, Bhatt DL, Bittner VA, Diaz R, Edelberg JM, Goodman SG, Hanotin C, Harrington RA, Jukema JW, Lecorps G, Mahaffey KW, Moryusef A, Pordy R, Quintero K, Roe MT, Sasiela WJ, Tamby JF, Tricoci P, White HD, Zeiher AM. Alirocumab and Cardiovascular Outcomes after Acute Coronary Syndrome. N Engl J Med 2018;**379**(22):2097-2107.

48. Staessen JA, Gasowski J, Wang JG, Thijs L, Den Hond E, Boissel JP, Coope J, Ekbom T, Gueyffier F, Liu L, Kerlikowske K, Pocock S, Fagard RH. Risks of untreated and treated isolated systolic hypertension in the elderly: meta-analysis of outcome trials. Lancet 2000;**355**(9207):865-72.

49. Kannel WB, Wolf PA, McGee DL, Dawber TR, McNamara P, Castelli WP. Systolic blood pressure, arterial rigidity, and risk of stroke. The Framingham study. Jama 1981;**245**(12):1225-9.

50. Mancia G, Fagard R, Narkiewicz K, Redon J, Zanchetti A, Bohm M, Christiaens T, Cifkova R, De Backer G, Dominiczak A, Galderisi M, Grobbee DE, Jaarsma T, Kirchhof P, Kjeldsen SE, Laurent S, Manolis AJ, Nilsson PM, Ruilope LM, Schmieder RE, Sirnes PA, Sleight P, Viigimaa M, Waeber B, Zannad F. 2013 ESH/ESC Guidelines for the management of arterial hypertension: the

Task Force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). J Hypertens 2013;**31**(7):1281-357.

51. Wright JT, Jr., Williamson JD, Whelton PK, Snyder JK, Sink KM, Rocco MV, Reboussin DM, Rahman M, Oparil S, Lewis CE, Kimmel PL, Johnson KC, Goff DC, Jr., Fine LJ, Cutler JA, Cushman WC, Cheung AK, Ambrosius WT. A Randomized Trial of Intensive versus Standard Blood-Pressure Control. N Engl J Med 2015;**373**(22):2103-16.

52. Bavry AA, Anderson RD, Gong Y, Denardo SJ, Cooper-Dehoff RM, Handberg EM, Pepine CJ. Outcomes Among hypertensive patients with concomitant peripheral and coronary artery disease: findings from the INternational VErapamil-SR/Trandolapril STudy. Hypertension 2010;**55**(1):48-53.

53. McMurray JJ, Packer M, Desai AS, Gong J, Lefkowitz MP, Rizkala AR, Rouleau JL, Shi VC, Solomon SD, Swedberg K, Zile MR. Angiotensin-neprilysin inhibition versus enalapril in heart failure. N Engl J Med 2014;**371**(11):993-1004.

54. Mogensen UM, Kober L, Kristensen SL, Jhund PS, Gong J, Lefkowitz MP, Rizkala AR, Rouleau JL, Shi VC, Swedberg K, Zile MR, Solomon SD, Packer M, McMurray JJV. The effects of sacubitril/valsartan on coronary outcomes in PARADIGM-HF. Am Heart J 2017;**188**:35-41.

55. Williams B, Mancia G, Spiering W, Agabiti Rosei E, Azizi M, Burnier M, Clement DL, Coca A, de Simone G, Dominiczak A, Kahan T, Mahfoud F, Redon J, Ruilope L, Zanchetti A, Kerins M, Kjeldsen SE, Kreutz R, Laurent S, Lip GYH, McManus R, Narkiewicz K, Ruschitzka F, Schmieder RE, Shlyakhto E, Tsioufis C, Aboyans V, Desormais I. 2018 ESC/ESH Guidelines for the management of arterial hypertension. Eur Heart J 2018;**39**(33):3021-3104.

56. Bangalore S, Fakheri R, Wandel S, Toklu B, Wandel J, Messerli FH. Renin angiotensin system inhibitors for patients with stable coronary artery disease without heart failure: systematic review and meta-analysis of randomized trials. Bmj 2017;**356**:j4.

57. Chen R, Ovbiagele B, Feng W. Diabetes and Stroke: Epidemiology, Pathophysiology, Pharmaceuticals and Outcomes. Am J Med Sci 2016;**351**(4):380-6.

58. Cavender MA, Steg PG, Smith SC, Jr., Eagle K, Ohman EM, Goto S, Kuder J, Im K, Wilson PW, Bhatt DL. Impact of Diabetes Mellitus on Hospitalization for Heart Failure, Cardiovascular Events, and Death: Outcomes at 4 Years From the Reduction of Atherothrombosis for Continued Health (REACH) Registry. Circulation 2015;**132**(10):923-31.

59. Stratton IM, Adler AI, Neil HA, Matthews DR, Manley SE, Cull CA, Hadden D, Turner RC, Holman RR. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. Bmj 2000;**321**(7258):405-12.

60. Gerstein HC, Miller ME, Byington RP, Goff DC, Jr., Bigger JT, Buse JB, Cushman WC, Genuth S, Ismail-Beigi F, Grimm RH, Jr., Probstfield JL, Simons-Morton DG, Friedewald WT. Effects of intensive glucose lowering in type 2 diabetes. N Engl J Med 2008;**358**(24):2545-59.

61. Cosentino F, Grant PJ, Aboyans V, Bailey CJ, Ceriello A, Delgado V, Federici M, Filippatos G, Grobbee DE, Hansen TB, Huikuri HV, Johansson I, Juni P, Lettino M, Marx N, Mellbin LG, Ostgren CJ, Rocca B, Roffi M, Sattar N, Seferovic PM, Sousa-Uva M, Valensi P, Wheeler DC. 2019 ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD. Eur Heart J 2020;**41**(2):255-323.

62. Barkas F, Elisaf M, Milionis H. Protection against stroke with glucagon-like peptide 1 receptor agonists: a systematic review and meta-analysis. Eur J Neurol 2019;**26**(4):559-565.

63. Zelniker TA, Wiviott SD, Raz I, Im K, Goodrich EL, Bonaca MP, Mosenzon O, Kato ET, Cahn A, Furtado RHM, Bhatt DL, Leiter LA, McGuire DK, Wilding JPH, Sabatine MS. SGLT2 inhibitors for primary and secondary prevention of cardiovascular and renal outcomes in type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials. Lancet 2019;**393**(10166):31-39.

64. Ahn CH, Lim S. Effects of Thiazolidinedione and New Antidiabetic Agents on Stroke. J Stroke 2019;**21**(2):139-150.

65. Messner B, Bernhard D. Smoking and cardiovascular disease: mechanisms of endothelial dysfunction and early atherogenesis. Arterioscler Thromb Vasc Biol 2014;**34**(3):509-15.

66. Shah RS, Cole JW. Smoking and stroke: the more you smoke the more you stroke. Expert Rev Cardiovasc Ther 2010;**8**(7):917-32.

67. Critchley JA, Capewell S. Mortality risk reduction associated with smoking cessation in patients with coronary heart disease: a systematic review. Jama 2003;**290**(1):86-97.

68. Christensen AI, Nordestgaard BG, Tolstrup JS. Alcohol Intake and Risk of Ischemic and Haemorrhagic Stroke: Results from a Mendelian Randomisation Study. J Stroke 2018;**20**(2):218-227.

69. Millwood IY, Walters RG, Mei XW, Guo Y, Yang L, Bian Z, Bennett DA, Chen Y, Dong C, Hu R, Zhou G, Yu B, Jia W, Parish S, Clarke R, Davey Smith G, Collins R, Holmes MV, Li L, Peto R, Chen Z. Conventional and genetic evidence on alcohol and vascular disease aetiology: a prospective study of 500 000 men and women in China. Lancet 2019;**393**(10183):1831-1842.

70. Pinckard K, Baskin KK, Stanford KI. Effects of Exercise to Improve Cardiovascular Health. Front Cardiovasc Med 2019;**6**:69.

71. Lee IM, Hennekens CH, Berger K, Buring JE, Manson JE. Exercise and risk of stroke in male physicians. Stroke 1999;**30**(1):1-6.

72. Keteyian SJ, Brawner CA, Savage PD, Ehrman JK, Schairer J, Divine G, Aldred H, Ophaug K, Ades PA. Peak aerobic capacity predicts prognosis in patients with coronary heart disease. Am Heart J 2008;**156**(2):292-300.

73. Newby DE, Mannucci PM, Tell GS, Baccarelli AA, Brook RD, Donaldson K, Forastiere F, Franchini M, Franco OH, Graham I, Hoek G, Hoffmann B, Hoylaerts MF, Künzli N, Mills N,

Pekkanen J, Peters A, Piepoli MF, Rajagopalan S, Storey RF. *Expert position paper on air pollution and cardiovascular disease*; 2015.

74. Chepesiuk R. Missing the dark: health effects of light pollution. Environ Health Perspect 2009;**117**(1):A20-7.

75. Munzel T, Gori T, Babisch W, Basner M. Cardiovascular effects of environmental noise exposure. Eur Heart J 2014;**35**(13):829-36.

76. Ridker PM, Everett BM, Thuren T, MacFadyen JG, Chang WH, Ballantyne C, Fonseca F, Nicolau J, Koenig W, Anker SD, Kastelein JJP, Cornel JH, Pais P, Pella D, Genest J, Cifkova R, Lorenzatti A, Forster T, Kobalava Z, Vida-Simiti L, Flather M, Shimokawa H, Ogawa H, Dellborg M, Rossi PRF, Troquay RPT, Libby P, Glynn RJ. Antiinflammatory Therapy with Canakinumab for Atherosclerotic Disease. N Engl J Med 2017;**377**(12):1119-1131.

77. Tardif JC, Kouz S, Waters DD, Bertrand OF, Diaz R, Maggioni AP, Pinto FJ, Ibrahim R, Gamra H, Kiwan GS, Berry C, Lopez-Sendon J, Ostadal P, Koenig W, Angoulvant D, Gregoire JC, Lavoie MA, Dube MP, Rhainds D, Provencher M, Blondeau L, Orfanos A, L'Allier PL, Guertin MC, Roubille F. Efficacy and Safety of Low-Dose Colchicine after Myocardial Infarction. N Engl J Med 2019;**381**(26):2497-2505.

78. Ridker PM, Everett BM, Pradhan A, MacFadyen JG, Solomon DH, Zaharris E, Mam V, Hasan A, Rosenberg Y, Iturriaga E, Gupta M, Tsigoulis M, Verma S, Clearfield M, Libby P, Goldhaber SZ, Seagle R, Ofori C, Saklayen M, Butman S, Singh N, Le May M, Bertrand O, Johnston J, Paynter NP, Glynn RJ. Low-Dose Methotrexate for the Prevention of Atherosclerotic Events. N Engl J Med 2019;**380**(8):752-762.

79. Eke PI, Dye BA, Wei L, Thornton-Evans GO, Genco RJ. Prevalence of periodontitis in adults in the United States: 2009 and 2010. J Dent Res 2012;**91**(10):914-20.

80. Papapanagiotou D, Nicu EA, Bizzarro S, Gerdes VEA, Meijers JC, Nieuwland R, van der Velden U, Loos BG. Periodontitis is associated with platelet activation. Atherosclerosis 2009;**202**(2):605-611.

81. Marcaccini AM, Meschiari CA, Sorgi CA, Saraiva MC, de Souza AM, Faccioli LH, Tanus-Santos JE, Novaes AB, Gerlach RF. Circulating interleukin-6 and high-sensitivity C-reactive protein decrease after periodontal therapy in otherwise healthy subjects. J Periodontol 2009;**80**(4):594-602.

82. Humphrey LL, Fu R, Buckley DI, Freeman M, Helfand M. Periodontal disease and coronary heart disease incidence: a systematic review and meta-analysis. J Gen Intern Med 2008;**23**(12):2079-86.

83. Grau AJ, Becher H, Ziegler CM, Lichy C, Buggle F, Kaiser C, Lutz R, Bultmann S, Preusch M, Dorfer CE. Periodontal disease as a risk factor for ischemic stroke. Stroke 2004;**35**(2):496-501.

84. Tonetti MS, D'Aiuto F, Nibali L, Donald A, Storry C, Parkar M, Suvan J, Hingorani AD, Vallance P, Deanfield J. Treatment of periodontitis and endothelial function. N Engl J Med 2007;**356**(9):911-20.

85. Peng CH, Yang YS, Chan KC, Kornelius E, Chiou JY, Huang CN. Periodontal Treatment and the Risks of Cardiovascular Disease in Patients with Type 2 Diabetes: A Retrospective Cohort Study. Intern Med 2017;**56**(9):1015-1021.

86. Lin HW, Chen CM, Yeh YC, Chen YY, Guo RY, Lin YP, Li YC. Dental treatment procedures for periodontal disease and the subsequent risk of ischaemic stroke: A retrospective population-based cohort study. J Clin Periodontol 2019;**46**(6):642-649.