

Editorial Focus

Bleeding risks with combination of oral anticoagulation plus antiplatelet therapy: Is clopidogrel any safer than aspirin when combined with warfarin?

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Many patients are taking oral anticoagulation therapy (OAC) for various reasons, for example, prosthetic heart valve, atrial fibrillation (AF), venous thromboembolism, intracardiac thrombus or recurrent strokes. The numbers of patients on OAC are increasing with ageing of the general population. Indeed, out-patient prescriptions for warfarin rose from 21 million in 1998 to over 30 million in 2004 in the United States (1).

Given the increasing prevalence and incidence of probably the most common indication for OAC, AF, it is no surprise that even more patients – including elderly subjects and those with vascular disease, who have AF – will be anticoagulated, especially in the setting of risk factors for stroke and thromboembolism, whether the AF is paroxysmal or not (2, 3).

Many OAC users have concomitant coronary artery disease and/or peripheral arterial disease (PAD). Some of patients also require percutaneous coronary intervention (PCI) following presentation with acute coronary syndrome (ACS), or even peripheral vascular interventions for PAD. Hence, the addition of dual- or mono- antiplatelet therapy to their existing anticoagulated regime is common in everyday clinical practice (4). For example, in a study by Johnson et al. (5) of approximately 5,000 of their commercially insured population managed by an anticoagulation service, 40% were on combined warfarin and antiplatelet therapy.

Nonetheless, the use of the combination of OAC and antiplatelet agents leads to an increased risk of bleeding (4). In one retrospective registry analysis involving 10,093 patients, there was a three-fold increase in risk of intracranial haemorrhage (odds ratio 2.95, 95% confidence interval [CI] 1.58–5.51) and a rise in major bleeding rates from 2.0% for the warfarin monotherapy group to 2.8% for the combined therapy group at 180 days (6).

Clinicians tend to add antiplatelet therapy to existing OAC in patients with AF if they have associated vascular disease, on the presumption that OAC ‘acts’ on stroke and thromboembolism

prevention for AF, whilst the antiplatelet drugs ‘acts’ on the vascular disease. What is the evidence of stroke and thromboembolism prevention by combination OAC plus aspirin therapy in this context? One small prospective randomised controlled trial (7) assessed the use of aspirin and OAC (international normalised ratio [INR] of 2–3) compared to anticoagulation arm alone in patients with AF but this was stopped following poor recruitment (157 patients in less than a year) as well as a trend towards a higher risk of arterial thromboembolism and substantial increase in major bleeding risk (odds ratio [OR] 3.29, 95% CI 0.33–32.3). A post-hoc retrospective analysis of two contemporary large randomized clinical trials of anticoagulation for AF also demonstrated substantial bleeding risk with combination therapy of aspirin and OAC (major bleeding 3.9% per year; $p < 0.01$), with no beneficial effect of combination OAC plus aspirin therapy on stroke and myocardial infarction (8). Thus, aspirin should not be added to patients receiving oral anticoagulation therapy for stable coronary (or peripheral) artery disease given the relatively limited evidence for benefit and the potential for significant harm from bleeding (9).

A particular management problem arises in relation to adding OAC to antiplatelet therapy occurs in relation to anticoagulated patients presenting with ACS or those who need PCI with coronary stenting (4). The joint American College of Cardiology/ American Heart Association/European Society of Cardiology 2006 Guidelines on the management of AF recommend that following PCI or revascularization surgery in patients with AF, low-dose aspirin (less than 100 mg/day) and/or clopidogrel (75 mg/day) may be given concurrently with anticoagulation to prevent myocardial ischaemic events, but acknowledge that these strategies have not been thoroughly evaluated and are associated with an increased risk of bleeding (10). The guidelines also suggest that clopidogrel should be given for a minimum of one month after implantation of a bare metal stent, at least three months for a sirolimus-eluting stent, at least six months for a paclitaxel-eluting stent, and 12 months or longer in selected pa-

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tients, following which warfarin may be continued as monotherapy in the absence of a subsequent coronary event (10). These guidelines do not address the issue of a presentation with an ACS (where PCI is often performed) and bleeding risk.

Given the need to balance stroke prevention, recurrent cardiac ischaemia and/or stent thrombosis, versus bleeding, more recent consensus guidelines (11, 12) provide more detailed guidance, by advocating initial triple therapy (with OAC, aspirin and clopidogrel) in patients with high risk for the initial period (depending on clinical presentation and type of stent, although bare metal stents are advocated) and swapping over to OAC plus clopidogrel thereafter. The published data – as reviewed by Rubboli et al. (11) – suggest that the prevalence of major bleeding with triple therapy use is 2.6–4.6% at 30 days, which increases to 13.9% at six months and 7.4–10.3% at 12 months.

In the current issue of *Thrombosis and Haemostasis*, the study by Schalekamp et al. (13) evaluates the bleeding risk of concomitant use of antiplatelet therapy (aspirin, clopidogrel and dipyridamole) among new users of OAC (acenocoumarol or phenprocoumon). In this study, 1,848 cases were compared against 5,818 controls via the PHARMO record linkage system (<http://www.pharmo.nl>) in the Netherlands. The daily dose of aspirin used was between 30–100 mg, and for clopidogrel, 75 mg and dipyridamole, 150–450 mg. Their results show that all antiplatelet drugs increased the risk of major bleeding when used in combination with OAC, although the greatest bleeding risk was seen with clopidogrel (OR 2.9, 95% CI 1.2–6.9, p=0.018) followed by aspirin (OR 1.6, 95% CI 1.3–1.9, p<0.001) and dipyridamole (OR 1.5, 95% CI 1.0–2.3, p=0.078), even after adjustment for use of non-steroidal anti-inflammatory drugs, antibiotics usage, steroids and gastroprotective agents. One third of bleeding events arose from the gastrointestinal tract whilst two-third were non-gastrointestinal (approximately 20% intracranial). Even for gastrointestinal bleeding per se, clopidogrel increased bleeding risk much more than that seen with dipyridamole and aspirin: adjusted OR 3.6 (95% CI 0.9–13.5, p=0.062)

versus 2.2 (95% CI 1.1–4.6, p=0.043) versus 2.1 (95% CI 1.5–3.1, p<0.001), respectively.

Hence, these results from Schalekamp et al. (13) suggest that the use of OAC plus clopidogrel may not be any safer than OAC plus aspirin. Indeed, the potential of harm from bleeding by the addition of antiplatelet drugs (whether clopidogrel, aspirin or dipyridamole) to existing OAC may outweigh the perceived benefits.

Nonetheless, the study by Schalekamp et al. (13) is a retrospective analysis of registry data, and limitations are evident. Clearly, such registry analyses are limited by the quality of the data and validation. Indeed, statistical adjustments cannot account for all biological variables, and pathophysiological processes. Bleeding is multifactorial and careful considerations ought to be taken into account prior to initiation of OAC or combining potent antithrombotic drugs in any patient. A previous history of bleeding, ischaemic heart disease and polypharmacy are risk factors associated with OAC-related bleeding (6, 14, 15). Advanced age (especially 80 and older) is a risk factor for major bleeding (i.e. intracranial haemorrhage) regardless of whether or not the subject is taking OAC, even after adjusting for prior stroke, gastrointestinal bleeding, anaemia and renal impairment (16). The systematic review undertaken as part of the United Kingdom National Institute for Health and Clinical Excellence (NICE) guidelines for AF management found that a history of myocardial infarction, anaemia, diabetes, previous history of bleeding and polypharmacy (especially with aspirin and non-steroidal anti-inflammatory drugs) were risk factors for anticoagulation-related bleeding (17).

Since OAC is often prescribed to elderly patients with diverse co-morbidities (i.e. falls, impaired cognitive function), the consequences from major bleeding events could potentially be devastating – especially intracranial haemorrhage – when compared to extracranial haemorrhage complications (primarily gastrointestinal bleeding) which are largely reversible. Of note, 90% of deaths from warfarin-associated haemorrhage stem from intra-

	Low	Moderate	High	Risk factors for score calculation
Kuijjer et al. [20]	0	1–3	>3	Risk score = [1.6x age] + [1.3x sex] + [2.2x malignancy] with 1 point for ≥60, female or presence of malignancy in each factor and 0 if not any of those.
Beyth et al. [21]	0	1–2	≥3	Aged ≥65, GI bleed in last 2 weeks, previous stroke, comorbidities (≥1 of the following: recent MI, haematocrit <30%, diabetes mellitus or creatinine >1.5 mg/dl) with 1 point for presence of each condition and 0 if absent.
Gage et al. [22]	0–1	2–3	≥4	HEMORR ₂ HAGES: Hepatic / renal disease, ethanol abuse, malignancy, older (age >75), ↓ platelet count or function, re-bleeding risk, uncontrolled hypertension, anaemia, genetic factors (CYP 2 C9 single nucleotide polymorphisms), excessive fall risk & stroke, with 1 point for each risk factor present, with the exception of 2 points for a previous bleed.
Shireman et al. [23]	≤	>1.07 to <2.19	≥2.19	Risk score = (0.49 x aged >70) + (0.32 x female) + (0.58 x remote bleed) + (0.62 x recent bleed) + (0.71 x alcohol/drug abuse) + (0.27 x diabetes) + (0.86 x anaemia) + (0.32 x antiplatelet drug use) with 1 point for presence of each condition and 0 if absent.

Table 1: Published bleeding risk scores.

cranial haemorrhage in patients on warfarin for AF (18). Even if they survive these events, intracranial haemorrhage is still associated with major functional disability.

Perhaps an assessment of bleeding risk may help management, in the same way that numerous stroke risk stratification scores have been developed. There are four published bleeding risk scores which have been validated for bleeding risk in patients on OAC (see Table 1) (20–23). All four have different modalities in evaluating bleeding risks and categorization into low-, moderate- and high-risk strata. Age (at least from 60 years old onwards) is collectively taken into account by all four schema, whilst two (21, 22) do not consider female gender as significant risk factor to be included in the bleeding risk model. Anaemia is regarded as important risk factor in three schema (21–23), whilst recent myocardial infarction is only listed in the schema by Beyth et al. (21). The remaining bleeding risk factors included in the four bleeding risk scoring systems include diverse factors

such as diabetes mellitus, malignancy, previous stroke, liver/renal disease, recent bleed, concurrent antiplatelet drug usage and excessive falls. As with stroke risk stratification, the lack of consensus and varying predictive value (as well as clinical applicability) limits their widespread application.

In conclusion, all antiplatelet drugs increase the risks of bleeding in patients who are already taking OAC. The important findings by Schalekamp et al. (13) requires thoughtful re-examination of the recommendations provided in consensus guidelines (10–12) that OAC plus clopidogrel may be preferred to OAC plus aspirin. Newer drugs with less bleeding risks but of similar efficacy to the current OAC (largely the vitamin K antagonists, such as warfarin) are clearly needed. Bleeding risk assessment should also be part of clinical assessment for stroke and thromboembolism, to allow a useful balanced review of the risk-benefit ratio of OAC treatment in everyday clinical practice.

References

1. Wysowski DK, Nourjah P, Swartz L. Bleeding complications with warfarin use: a prevalent adverse effect resulting in regulatory action. *Arch Intern Med* 2007; 167: 1414–1419.
2. Lip GY. Paroxysmal atrial fibrillation, stroke risk and thromboprophylaxis. *Thromb Haemost* 2008; 100: 11–13.
3. McBane RD, Hodge DO, Wysokinski WE. Clinical and echocardiographic measures governing thromboembolism destination in atrial fibrillation. *Thromb Haemost* 2008; 99: 951–955.
4. May AE, Geisler T, Gawaz M. Individualized anti-thrombotic therapy in high risk patients after coronary stenting. A double-edged sword between thrombosis and bleeding. *Thromb Haemost* 2008; 99: 487–493.
5. Johnson SG, Witt DM, Eddy TR, et al. Warfarin and antiplatelet combination use among commercially insured patients enrolled in an anticoagulation management service. *Chest* 2007; 131: 1500–1507.
6. Shireman TI, Howard PA, Kresowik TF, et al. Combined anticoagulation-antiplatelet use and major bleeding events in elderly atrial fibrillation patients. *Stroke* 2004; 35: 2362–2367.
7. Lechat P, Lardoux H, Mallet A, et al. Anticoagulant (fluidione)-aspirin combination in patients with high-risk atrial fibrillation: a randomized trial (Fluindione, Fibrillation, Auriculaire, Aspirin et Contraste Spontane; FFAACS). *Cerebrovasc Dis* 2001; 12: 245–252.
8. Flaker GC, Gruber M, Connolly SJ, et al. Risks and benefits of combining aspirin with anticoagulant therapy in patients with atrial fibrillation: an exploratory analysis of stroke prevention using an oral thrombin inhibitor in atrial fibrillation (SPORTIF) trials. *Am Heart J* 2006; 152: 967–973.
9. Lip GYH. Don't add aspirin for associated stable vascular disease in a patient with atrial fibrillation receiving anticoagulation. *Br Med J* 2008; 336: 614–615.
10. Fuster V, Ryden LE, Cannom Ds, et al.; ACC/AHA/ESC 2006 guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Revise the 2001 Guidelines for the Management of patients with Atrial Fibrillation). *Circulation* 2006; 114: 257–354.
11. Rubboli A, Halperin JL, Juhani Airaksinen KE, et al. Antithrombotic therapy in patients treated with oral anticoagulation undergoing coronary artery stenting. An expert consensus document with focus on atrial fibrillation. *Ann Med* 2008; 40: 428–436.
12. Lip GYH, Karpha M. Anticoagulant and antiplatelet therapy use in patients with atrial fibrillation undergoing percutaneous coronary intervention: The need for consensus and a management guideline. *Chest* 2006; 130: 1823–1827.
13. Schalekamp T, Klungel O, Souverein P, et al. Effect of oral antiplatelet agents on major bleeding in users of coumarins. *Thromb Haemost* 2008; 100: 1076–1083.
14. Abdelhafiz AH, Wheeldon NM. Results of an open-label, prospective study of anticoagulant therapy for atrial fibrillation in an outpatient anticoagulation clinic. *Clin Therap* 2004; 26: 1470–1478.
15. Wehinger C, Stöllberger C, Länger T, et al. Evaluation of risk factors for stroke/embolism and of complications due to anticoagulant therapy in atrial fibrillation. *Stroke* 2001; 32: 2246–2252.
16. Fang MC, Go AS, Hylek EM, et al. Age and the risk of warfarin associated-haemorrhage: The anticoagulation and risk factors in atrial fibrillation study. *J Am Geriatr Soc* 2006; 54: 1231–1236.
17. Hughes M, Lip GYH; Guideline Development Group for the NICE national clinical guideline for management of atrial fibrillation in primary and secondary care. Risk factors for anticoagulation-related bleeding complications in patients with atrial fibrillation: a systematic review. *QJM* 2007; 100: 599–607.
18. Fang MC, Go AS, Chang Y, et al. Death and disability from warfarin-associated intracranial and extracranial haemorrhages. *Am J Med* 2007; 120: 700–705.
19. Kuijjer PMM, Hutten BA, Prins MH, et al. Prediction of the risk of bleeding during anticoagulant treatment for venous thromboembolism. *Arch Intern Med* 1999; 159: 457–460.
20. Beyth RJ, Quinn LM, Landefeld CS. Prospective evaluation of an index for predicting the risk of major bleeding in outpatients treated with warfarin. *Am J Med* 1998; 105: 91–99.
21. Gage BF, Yan Y, Milligan PE, et al. Clinical classification schemes for predicting haemorrhage: Results from the National Registry of Atrial Fibrillation (NRAF). *Am Heart J* 2006; 151: 713–719.
22. Shireman TI, Mahnken JD, Howard PA, et al. Development of a contemporary bleeding risk model for elderly warfarin recipients. *Chest* 2006; 130: 1390–1396.