Pro: "The novel oral anticoagulants should be used as 1st choice for secondary prevention in patients with atrial fibrillation."

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Introduction

Patients with atrial fibrillation (AF) are at a high risk of stroke. Stroke risk is doubled if patients have already suffered a transient ischaemic attack (TIA) or an ischaemic stroke (1). Oral anticoagulation with adjusted-dose vitamin-K antagonists (VKA, warfarin) is effective for the prevention of stroke in these patients (2). Treatment with warfarin has many limitations including a narrow therapeutic window, interaction with food and many drugs and the need for regular coagulation monitoring. Novel anticoagulants (NOACs) like apixaban, dabigatran or rivaroxaban are given in a fixed-oral daily dose irrespective of age, gender or body weight, do not require coagulation monitoring and have no interaction with food and only few interactions with other drugs. The NOACs were compared with warfarin in patients with AF in three trials (ARISTOTLE, RE-LY and ROCKET-AF) whereas the AVERROES trial studied AF patients not suitable for treatment with warfarin and compared apixaban with aspirin. All four studies had subgroups of patients with prior TIA or ischaemic stroke. The results for these subgroups are summarised here. The primary endpoint was identical in all trials namely stroke or systemic embolism. Stroke included ischaemic stroke (which needs to be prevented) and cerebral haemorrhage (a complication of anticoagulation).

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Baseline characteristics

Patients in the four randomised trials had a very similar risk profile. They were on average 71 years old, had a high rate of hypertension and diabetes and a high $CHADS_2$ score. Between 30 – 40% of patients were treated with aspirin and between 44 – 61% with VKA at baseline.

Vascular outcomes

In the ARISTOTLE trial the rate of stroke or systemic embolism was significantly higher in patients in secondary prevention (hazard ratio [HR] 2.52). The rate of stroke or systemic embolism in the subgroup of patients with previous stroke or TIA was 2.46 per 100 patient-years of follow-up in the apixaban group and 3.24 in the warfarin group (HR 0.76) (3). The absolute reduction in the rate of stroke and systemic embolism with apixaban vs warfarin was 0.77 per 100 patient-years of follow-up in patients with previous stroke or TIA (►Table 1). Numerically all other vascular events shown in ►Table 1 were less frequent on apixaban compared to warfarin.

In the AVERROES trial in patients with previous stroke or TIA, 10 events of stroke or systemic embolism occurred in the apixaban group (2.39%/year) compared with 33 in the aspirin group (9.16%/year; HR 0.29) (4). In those without previous stroke or TIA the rate of stroke and systemic embolism was lower (1.68%/year for apixaban, 3.06%/year for aspirin). Numerically all other vascular events shown in ►Table 1 were less frequent on apixaban compared to aspirin.

In the RE-LY trial, within the subgroup of patients with previous stroke or TIA, stroke or systemic embolism occurred in 65 patients (2.78%/year) on warfarin compared with 55 (2.32%/year) on 110 mg dabigatran (relative risk [RR] 0.84) and 51 (2.07%/year) on 150 mg dabigatran (RR 0.75). The rate of stroke was higher in patients with prior TIA or stroke compared to patients without. The effects of both doses of dabigatran compared with warfarin were not significantly different between patients with previous stroke or transient ischaemic attack and those without for any of the outcomes.

In ROCKET-AF the number of events per 100 person-years for the primary endpoint (stroke and systemic embolism) in patients treated with rivaroxaban compared with warfarin was consistent among patients with previous stroke or TIA (2.79% rivaroxaban vs 2.96% warfarin; HR 0.94) and those without (1.44% vs 1.88%; HR 0.77).

For the other vascular endpoints, no differences between NOACs and warfarin were observed. In all trials the risk of stroke was higher in patients who already had a TIA or stroke compared to those in primary prevention.

Bleeding complications

►Table 2 shows the numbers of bleeding complications in the four trials. In the ARISTOTLE trial in patients with TIA or stroke the difference in major bleeding with apixaban compared to warfarin was 2.84 per 100 patient years and 3.91 per 100 patient years (0.54-1.32) favouring apixaban. In AVERROES major bleeding was more frequent in patients with history of stroke or TIA than in patients without (HR 2.88), but the risk of major bleeding did not differ between apixaban and aspirin. In the RE-LY trial the rate of major bleeding was significantly lower in patients on 110 mg dabigatran (RR 0.66) and similar in patients on 150 mg dabigatran (RR 1.01) compared

See also ►Contra Article by Stöllberger and Finsterer. Thromb Haemost 2013; 110: 496-500.

Table 1: Vascular outcomes of AF patients with prior TIA or stroke in the randomised trials.

	ARISTOTLE		AVERROES		RE-LY			ROCKET AF	
	Apixaban	Warfarin	Apixaban	Aspirin	Dabi 110	Dabi 150	Warfarin	Rivaroxaban	Warfarin
N	1694	1742	390	374	1195	1233	1195	3754	3714
Stroke/SE	73	98	10	33	55	51	65	179	187
Stroke	67	96	10	30	53	47	59	171	172
Ischaemic stroke	57	68	9	27	52	43	41	151	144
Death	129	150	22	27	77	108	107	288	294
CV death	72	76	16	20	45	73	70	192	194
MI	17	26	6	4	18	25	15	65	57

Dabi = dabigatran; 110 = 2 x 100 mg; 150 = 2 x150 mg.

Table 2: Major bleeding complications of AF patients with prior TIA or stroke in the randomised trials. The definition of major bleed was different in the different trials.

	ARISTOTLE		AVERROES		RE-LY			ROCKET AF	
	Apixaban	Warfarin	Apixaban	Aspirin	Dabi 110	Dabi 150	Warfarin	Rivaroxaban	Warfarin
N	1694	1742	390	374	1195	1233	1195	3754	3714
Major bleeding	77	106	14	11	65	102	97	178	183
Haemorrhagic stroke	28	47	1	4	2	5	18	26	31
Intracranial bleed	37	81	4	5	6	13	30	34	46
Major GI bleed	87	97	4	5	33	57	33	NA	NA

Dabi = dabigatran; 110 = 2 x 100 mg; 150 = 2 x150 mg; NA = data not available.

with those on warfarin. In the ROCKET-AF trial the number of major bleeding events per 100 person-years in patients treated with rivaroxaban compared with warfarin was consistent among patients with previous stroke or TIA (3.13% rivaroxaban vs 3.22% warfarin; HR 0.6) and those without (4.10% vs 3.69%; HR 1.10).

The most important result in the three trials comparing NOACS with warfarin was the impressive reduction in the risk of cerebral haemorrhage and other intracranial bleeds. This is highly clinically relevant since the mortality of anticoagulation associated cerebral haemorrhage is around 40% (5).

Meta-analyses in secondary stroke prevention

Most of the differences in outcomes in the trials on secondary stroke prevention did not achieve statistical significance. This was due to small patient numbers and the low statistical power. The trials were powered for the overall populations. The meta-analysis of Ntaios et al. (6) included 14,527 patients in secondary stroke prevention. NOACs were associated with a significant reduction of stroke or systemic embolism (odds ratio [OR] 0.85; relative risk reduction, 14%; absolute risk reduction, 0.7%; number needed to treat, 134 over 1.8–2.0 years) compared with warfarin. NOACS were also associated with a significant reduction of major bleeding compared with warfarin (OR 0.86; relative risk reduction, 13%; absolute risk reduction, 0.8%; number needed to treat, 125). This bleeding reduction was driven by the significant reduction of hemorrhagic stroke (OR, 0.44 relative risk reduction, 57.9%; absolute risk reduction, 0.7%; number needed to treat, 139). The meta-analysis of Rasmussen et al. (7) concluded that for secondary prevention, apixaban, rivaroxaban and dabigatran had broadly similar efficacy for the main endpoints. The endpoints of haemorrhagic stroke, vascular death, major bleeding and intracranial bleeding were less common with dabigatran 110 mg bid than with rivaroxaban.

Conclusions

The novel anticoagulants are a major breakthrough for stroke prevention in patients with AF who had a prior TIA or stroke. These patients are at higher risk of a recurrent stroke that is reduced significantly by the NOACS but also at higher risk of bleeding complication on warfarin that is also reduced by NOACS. In addition NOACs have a fast onset of action that is important in enabling early discharge of patients from stroke units. Unfortunately all patients with very recent TIA or ischaemic stroke were excluded from the randomised trials. Therefore we have no

data on efficacy and safety in early secondary stroke prevention in patients with AF.

The largest absolute benefits of the NOACs over warfarin in reducing risk of ischaemic stroke are for secondary prevention in AF patients, i.e. those with prior stroke/TIA. The relative risk reductions by NOACs vs warfarin are not different for primary vs secondary prevention (i.e. there is no interaction with treatment effects), but absolute benefits are larger because the stroke rates are higher among those with prior stroke/TIA. Therefore the NOACS are the preferred choice in secondary stroke prevention in patients with AF.

Conflicts of interest

HCD received honoraria for participation in clinical trials, contribution to advisory boards or oral presentations from: Abbott, Allergan, AstraZeneca, Bayer Vital, BMS, Boehringer Ingelheim, CoAxia, Corimmun, Covidien, Daichii-Sankyo, D-Pharm, EV3, Fresenius, GlaxoSmithKline, Janssen Cilag, Knoll, MSD, Medtronic, MindFrame, Neurobiological Technologies, Novartis, Novo-Nordisk, Paion, Parke-Davis, Pfizer, Sanofi-Aventis, Schering-Plough, Servier, Solvay, Thrombogenics, Wyeth and Yamanouchi. Financial support for research projects was provided by Astra/Zeneca, GSK, Boehringer Ingelheim, Lundbeck, Novartis, Janssen-Cilag, Sanofi-Aventis, Syngis and Talecris. The Department of Neurology at the University Duisburg-Essen received research grants from the German Research Council (DFG), German Ministry of Education and Research (BMBF), European Union, NIH, Bertelsmann Foundation and Heinz-Nixdorf Foundation. H.C. Diener has no ownership interest and does not own stocks of any pharmaceutical company.

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