P4797

Novel prognostic biomarkers identified by proximity extension assay are associated with major bleeding in patients with atrial fibrillation on oral anticoagulation: insights from the ARISTOTLE trial

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Background: Treatment of patients with atrial fibrillation (AF) with oral anticoagulants is essential to prevent thromboembolic events, mainly stroke, and mortality. However, this therapy is also associated with significant risk of major bleeding events. Biomarkers have recently been recognized to provide improved risk prediction models in AF populations.
Purpose: To further improve the assessment of bleeding risk and understand the pathophysiological mechanisms for bleeding events in patients with AF. The multiplex analytical technology Proximity Extension Assay (PEA) was utilized to screen hundreds of plasma biomarkers simultaneously in small amounts of plasma.
Method: In an unstratified case-control cohort of the ARISTOTLE trial a total of 204 cases with ISTH major bleeding were identified and a random sample of 3,996 controls were followed for a median of 1.7 years. Plasma samples obtained at randomization were analysed by conventional immunoassays or using PEA panels for cardiovascular disease and inflammation, which measured 255 protein biomarkers in multiplex. The association of biomarkers and outcome was evaluated simultaneously by Random Forest and individually by Cox-regression analyses adjusted for clinical characteristics and renal function. The significance level was adjusted for multiple testing.
Results: Six biomarkers were identified as most strongly associated with major bleeding according to both Random Forest and the adjusted Cox-regression analyses. The hazard ratio (95% confidence intervals) per interquartile range was 1.18 (1.04–1.33) for Ephrin type-B receptor 4 (EPHB4), 1.31 (1.14–1.52) for Fibroblast growth factor 23 (FGF-23), 1.35 (1.09–1.68) for Growth differentiation factor 15 (GDF-15), 1.55 (1.27–1.90) for Osteopontin (OPN), 1.45 (1.12–1.87) for Tumor necrosis factor receptor 1 (TNF-R1), 1.36 (1.15–1.60) for Trefoil factor 3 (TFF3).
Conclusions: In patients with AF treated with oral anticoagulants, out of a large number of biomarkers, Osteopontin and Fibroblast growth factor 23 were the strongest predictors of major bleeding events. The association of these biomarkers with bleeding events in this setting is novel and the pathophysiological mechanisms behind these findings warrant validation and further in-depth studies.
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P4798

Safety of short-term anticoagulation for watchman implantation in patients with prior intracranial hemorrhage

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Background: The Watchman device is increasingly used for left atrial appendage occlusion (LAAO) for stroke prevention in atrial fibrillation (AF). Patients with AF and prior intracranial hemorrhage (ICH) were excluded from clinical trials due to perceived risks of recurrent bleeding with post implant anticoagulation.
Purpose: To assess the efficacy and safety of Watchman implantation in patients with AF and prior ICH.
Methods: In a multidisciplinary AF stroke prevention clinic, all 34 consecutive patients with AF and prior ICH who were referred for Watchman implantation at our program underwent the implant procedures. Patients were enrolled in a prospectively maintained data registry. All procedures were performed without interruption of therapeutic anticoagulation.
Results: Patients mean age was 73 years and 17 (50%) were males. CHADSVASC was 4.9±1.2 and HASBLED 4.1±1.0. Prior ICH events were intracerebral in the majority (61%), followed by subdural (26%) and subarachnoid bleeds (11%). The event to implantation time was 641 days (quartiles 120–700, minimum 60). Watchman was implanted in all patients with no procedural complications. All patients completed 45 days of anticoagulation: 21 (61%) with warfarin, 12 (35%) with apixaban and 1 (2%) with dabigatran. Transesophageal echocardiograms at 45 days showed no peridevice leak or device related thrombi. While on anticoagulation, none of the patients developed intracranial bleeds. Minor bleeding occurred in 1 patient and consisted of trauma related lower extremity hematoma at 19 days. Upon 13.3 months (quartiles 7–19) of follow-up, there were no strokes, intracranial bleeds or deaths.
Conclusion: With proper multidisciplinary assessment, all AF patients with prior ICH tolerated short-term anticoagulation for the purpose of Watchman implantation. LAA closure with attendant short term anticoagulation appears to be both safe and effective in this patient population.

P4799

When are atrial fibrillation patients at risk to discontinue anticoagulation treatment? Results from the GLORIA-AF Registry

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Background: Oral anticoagulation (OAC) discontinuation has posed a barrier to achieving optimal outcomes in atrial fibrillation (AF) patients, most notably in the era when vitamin K antagonists (VKA) were the principle OAC in use.
Objectives: The objective of this investigation was to evaluate when newly diagnosed AF patients initiating dabigatran etexilate (DE) treatment are most prone to discontinue oral anticoagulation, and to describe reasons for discontinuation.
Methods: Patients with newly diagnosed AF (CHA2DS2VASc$\geq$1) were consecutively enrolled in a prospective global registry (GLORIA-AF). Enrollment began once DE was available in respective countries (from 2011–2014) and those prescribed DE were followed for 2 years. Treatment start and stop dates were recorded; discontinuation was defined as switch to another treatment or index treatment stop for $>$30 days. Kaplan Meier probabilities of remaining on treatment (persistence) were calculated. Reasons for discontinuation are presented as % of total patients.
Results: Of 4,873 eligible patients prescribed DE (mean age 70.2±10.4 years; 44.4% female), 4,859 took at least 1 dose (99.7%). Mean index DE therapy duration for the first treatment regimen was 18.0±9.4 months; probability of DE persistence at 2 years was 70.4% (95% CI 0.69–0.72). After the 2 year visit, 1305 patients (26.9%) were identified as having stopped DE (n=684, 14.1%) or switched to another OAC (n=621, 12.8%) at any point during the follow-up. Overall probability of persistence for the first 6 months was 83.5% (95% CI 82.4–0.84.6%), and for subsequent cohorts who remained on treatment at 12, 18 and 24 months, probability of persistence (95% CI) was numerically higher in each consecutive 6 month period: 92.3% (91.3–93.1%), 94.9% (94.1–95.6%) and 96.1% (95.4–96.8%) at 12, 18 and 24 months respectively. Patients who discontinued due to adverse events (AE) represent $<$10% of patients, the majority of which were observed in the first 6 months. The most frequently reported reason for discontinuation was "other" reason not further specified.

% of overall reasons for discontinuation	0-6 months n=756		6-12 months n=290		12-18 months n=145		18-24 months n=114		Total n=1305	
	N	%	N	%	N	%	N	%	N	%
Adverse Events*	282	5.8%	95	2.0%	45	0.9%	35	0.7%	457	9.4%
Other**	474	9.8%	195	4.0%	100	2.1%	79	1.6%	848	17.5%
Total	756	15.6%	290	6.0%	145	3.0%	114	2.3%	1305	
*includes bruising, bleeding, dyspepsia and hypersensitivity reactions										
**includes other reasons not specified, dementia, cost, start of bridging and social reasons such as excessive alcohol intake										

Conclusions: Overall probability of 2 year persistence in DE patients at $>$70% is higher than previously noted for VKA. Risk for treatment discontinuation in AF patients is highest in the early period following therapy initiation. Most reasons for discontinuation are not related to AEs, and the first 6 months following treatment initiation is the period when physicians should monitor patients and consider interventions to improve persistence.
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P4800

Why do clinicians prescribe oral anticoagulation in patients with atrial fibrillation despite a low CHA2DS2-VASc score?

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Background: Oral anticoagulant (OAC) therapy is prescribed in approximately 40% of patients with atrial fibrillation (AF) and low thromboembolic risk (CHA2DS2-VASc score 0 [male] or 1 [female]). Guidelines recommend against OAC therapy in such patients because the annual thromboembolic risk ($<$1%) is outweighed by bleeding.

Purpose: To identify patient characteristics and reasons for clinicians to prescribe OAC therapy in AF despite a low thromboembolic risk.
Methods: Patient characteristics associated with OAC prescription were assessed in the subgroup with a low CHA2DS2-VASc score from the GARFIELD-AF registry. All-cause mortality, ischemic stroke or systemic embolism, and major bleeding were compared according to OAC status. Next, a diverse group of clinicians involved in AF care were questioned through a web-based survey. Items included factors, not included in the CHA2DS2-VASc score, that may influence prescription of OAC therapy in AF.
Results: In the GARFIELD-AF registry (n=52,014), 2,123 patients had a low CHA2DS2-VASc score. OAC therapy was prescribed in 950 (45%). Permanent [OR (95%) = 2.32 (1.52–3.56)] or persistent AF [OR (95%) = 3.08 (2.17–4.38)] and increasing age <65 years [OR (95%) = 1.34 (1.20–1.50)] demonstrated a significant increase in odds for OAC use, while concomitant antiplatelet therapy [OR (95%) = 0.083 (0.065–0.105)] and female gender [OR (95%) = 0.714 (0.561–0.907)] showed a significant decrease in odds. Crude event rates were low for those with as well as without OAC therapy: all-cause mortality (14 versus 20), ischemic stroke or systemic embolism (6 versus 5), and major bleeding (4 versus 3). When clinicians (n=229) were questioned about decision-making regarding OAC therapy for AF patients with low thromboembolic risk, an enlarged left atrium or spontaneous echo contrast was the most frequently cited reason (reach: 59.8%). Adding cardioversion or ablation procedures, rheumatic heart disease, and subjective fear of stroke by the patient increased the reach to 83.8% (Table 1).

Table 1

Risk factor combinations	Reach, n (%)
Enlarged left atrium or spontaneous echo contrast	137 (59.8)
Previous + cardioversion or ablation procedures	165 (72.1)
Previous + rheumatic heart disease	183 (79.9)
Previous + subjective fear of stroke by the patient	192 (83.8)

Reach is the number (percentage) of respondents reporting some or strong preference to prescribe oral anticoagulation therapy when the risk factor combination is present.

Conclusions: There is a discrepancy between patient characteristics predicting OAC use in AF patients with a low CHA2DS2-VASc score and factors reported by clinicians influencing their decision-making.
Funding Acknowledgements: The Thrombosis Academy for Learning Education and Networking Training (TALENT) programme is organized and sponsored by Bayer Healthcare

ATRIAL FIBRILLATION – STROKE PREVENTION 2

P4801
Antithrombotic management in patients with atrial fibrillation and acute coronary syndromes

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Introduction: Antithrombotic therapy in patients with atrial fibrillation (AF) who present with an acute coronary syndrome (ACS) present a challenge given the need for combining antiplatelet (oftentimes dual therapy) with anticoagulation therapy. Triple antithrombotic therapy (TAT) increases the risk of bleeding and therefore remains a much-debated issue. Based on a large national registry we investigated antithrombotic practices and its prognostic value in patients with ACS accompanied by AF.
Methods: The PL-ACS registry is an ongoing, nationwide, multicenter, prospective, observational study of consecutively hospitalized patients with the whole spectrum of ACS in Poland. The current analysis pertains to the 677,591 patients hospitalized with a diagnosis of ACS between 2003 and 2017.
Results: 44,741 of 677,591 patients (6.6%) had AF, including 5.7% in the unstable angina (UA), 8.8% in the non-ST elevation myocardial infarction (NSTEMI), and 5.3% in ST-elevation myocardial infarction (STEMI). Patients with AF less frequently underwent percutaneous coronary intervention (PCI) in comparison to non-AF patients: 52.9% vs 54.1% P<0.05 in UA, 58.3% vs 69.3% P<0.05 in NSTEMI, and 88.1% vs 92.7% P<0.05 in STEMI. Interestingly, as many as 63.8% of patients received dual antiplatelet therapy (DAPT) without oral anticoagulant (OAC). 29.6% of patients received TAT (DAPT+OAC), and 1.8% of patients received dual antithrombotic therapy (single antiplatelet agent + OAC). 12-month follow-up revealed a higher rate of mortality, myocardial infarction and stroke and lower rates of hemorrhagic stroke (Figure 1).
Conclusions: Triple antithrombotic therapy in AF patients presenting with ACS is associated with a decline of major adverse cardiovascular (ischemic) events and is linked to a better prognosis. However, it is hampered by an elevated risk of hemorrhagic stroke. The relatively low rate of prescribing triple antithrombotic therapy probably reflects the changing guidelines and practices throughout the study period (2003–2017).

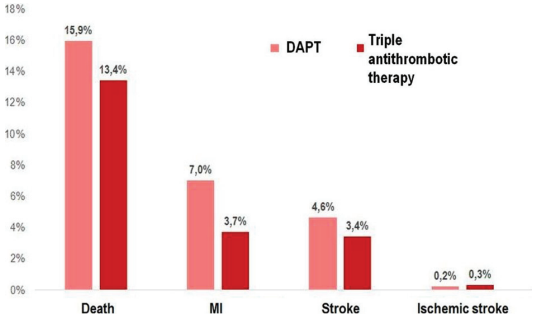

Figure 1

P4802
Advantage of novel oral anticoagulants compared to vitamin-K antagonist in atrial fibrillation. Data from real world

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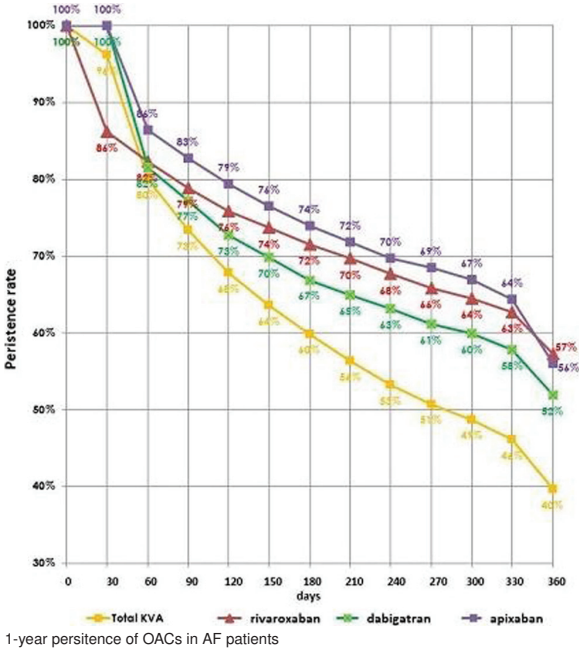
Introduction: Patient adherence to chronic drug treatment has a great importance to avoid adverse events. Oral anticoagulant therapy decrease significantly the risk of stroke in atrial fibrillation (AF).
Aim: Our aim was to investigate the one year persistence of the newly started vitamin K antagonist (VKA) and novel oral anticoagulnts (NOACs) therapy in patients suffered from AF.
Patients and methods: We analysed the database of National Health Insurance Found in Hungary on pharmacy-claims
The study included data for patients who newly started (not administered oral anticoagulants [OACs] therapy before one year) VKA therapy (acenocumarol or warfarin) or NOACs tharapy (apixaban, dabigatran or rivaroxaban) in last quarter of year 2015. To model the persistence, the apparatus of survival analysis was used, where "survival" was the time to abandon the medication. As it was available to month precision, discrete time survival analysis was applied: a generalized linear model was estimated with complementary log-log link function with the kind of drug being the only explanatory variable. Treatment discontinuation was defined as a 60-day gap (grace period) with no medication coverage.
Results: 19,059 AF patients started oral anticoagulants therapy in this period (KVAs n=13,144, dabigatran n=1,651, apixaban n=1,557 and rivaroxaban n=3,008). Six month persistence rate were with KVAs 60%, with dabigatran 67%, with rivaroxaban 72% and with apixaban 74%. 1-year persistence rate was lower in every treatment groups. AF patients with KVAs were 40%, with dabigatran was 52%, with apixaban was 56% and rivaroxaban was 57%. KVAs persistence rate was significantly lower compared to NOACs (p<0.001).



1-year persitence of OACs in AF patients

Conclusions: Results from our nationwide cohort study showed high non-