Non-vitamin K antagonist oral anticoagulants (NOACs): No longer new or novel

Steen Husted1; Raffaele de Caterina2; Felicita Andreotti3; Harald Arnesen4; Fedor Bachmann5; Kurt Huber6; Jørgen Jespersen7; Steen Dalby Kristensen8; Gregory Y. H. Lip9; Joao Morais10; Lars H. Rasmussen11; Agneta Siegbahn12; Robert F. Storey13; Jeffrey I. Weitz14; on behalf of the ESC Working Group on Thrombosis Task Force on Anticoagulants in Heart Disease

1Medical Department, Hospital Unit West, Denmark; 2Institute of Cardiology & Center of Excellence on Aging, G. d’Annunzio University, Chieti, Italy; 3Department of Cardiovascular Science, Catholic University, Rome, Italy; 4Center for Clinical Heart Research, Department of Cardiology, Oslo University Hospital, Ullevål, Oslo, Norway; 5University of Lausanne, Switzerland; 63rd Department of Medicine, Wilhelminenspital, Vienna, Austria; 7Unit for Thrombosis Research, Institute of Public Health, University of Southern Denmark, Denmark; 8Department of Cardiology, Aarhus University Hospital, Aarhus, Denmark; 9University of Birmingham Centre for Cardiovascular Sciences, City Hospital, Birmingham, United Kingdom; 10Cardiology Division, Santo Andre’s Hospital, Leiria, Portugal; 11Thrombosis Research Centre, Department of Clinical Medicine, Faculty of Medicine, Aalborg University, Denmark and Department of Cardiology, Aalborg University Hospital, Denmark; 12Department of Medical Sciences and Uppsala Clinical Research Center, Uppsala University, Uppsala, Sweden; 13Department of Cardiovascular Science, University of Sheffield, Sheffield, United Kingdom; 14Thrombosis and Atherosclerosis Research Institute, McMaster University, Hamilton, Canada McMaster University, Hamilton, Canada

For long-term treatment and prevention of arterial and venous thromboembolic diseases, oral vitamin K antagonists (VKAs) have been the only oral anticoagulant option for more than half a century. Under optimal conditions, VKA treatment is effective and safe provided that a stable level of anticoagulation can be achieved, as reflected by good compliance and a high time in therapeutic range (1). This may, however, be problematic since various foods, numerous drugs and comorbidity, such as renal impairment or liver disease, may alter the pharmacokinetics and/or pharmacodynamics of these drugs (2). Poor anticoagulant control is common with VKAs and is associated with an increased risk of thromboembolic events with under-treatment or an increased risk of bleeding, including intracranial haemorrhage, with over-treatment (2, 3). These issues contribute to the general underuse of VKAs despite guideline documented indications (4, 5).

In recent years, several new oral drugs with a direct and reversible inhibitory effect on the enzymatic activity of thrombin or factor Xa have been developed (6, 7). These agents are effective alternatives to VKAs for the treatment and prevention of venous thromboembolism and for stroke prevention in atrial fibrillation and have been tested against placebo for the prevention of recurrent ischaemic events after acute coronary syndrome.

The new oral anticoagulants include dabigatran etexilate, which inhibits thrombin, and rivaroxaban, apixaban, and edoxaban, which inhibit factor Xa (6, 7). These agents have been compared with warfarin, the most commonly used VKA, for VTE treatment and for stroke prevention in atrial fibrillation in major phase 3 clinical trials. In these trials, in many reviews, and in several guidelines these drugs have been designated as “new oral anticoagulants” or “novel oral anticoagulants”, which is abbreviated as NOACs (6, 8). The NOAC term can eventually be used to refer to other direct inhibitors of specific pathways, such as inhibitors of Factor IX and Factor XII, which are in development (7).

NOACs have some characteristics that distinguish them from the VKAs. The NOACs target specific coagulation enzymes, either thrombin or factor Xa, whereas VKAs lower the levels of multiple coagulation factors, notably factors II, VII, IX and X (6, 7). At this point in time, there are no specific antidotes available for the NOACs, which can complicate the management of life-threatening bleeding; however, some specific antidotes are in early development (9). The NOACs have variable effects on commonly available routine tests of coagulation, which can sometimes complicate assessment of their anticoagulant activity (10).

Although the NOACs are relatively novel and new at present, they will not remain so forever. Consequently, several alternative names have been proposed for these drugs, as follows (12): Target-Specific Oral antiCoagulants (TSOCs), Direct Oral AntiCoagulants (DOACs), Oral Direct Inhibitors (ODIs), Non-monitored Oral AntiCoagulants (NOACs), Non-warfarin Oral AntiCoagulants (NOACs), Non-vitamin K antagonist Oral AntiCoagulants (NOACs), etc.

To avoid confusion when describing trials evaluating these drugs in meetings or lectures, or when preparing future publications (as well as reviews or guidelines) as well to aid in the identification of relevant studies in search engines such as MEDLINE, PubMed, EMBASE or Google Scholar, consensus on terminology is important. A recent appeal for consensus has recently been made (11), and the European Society of Cardiology (ESC) Working Group on Thrombosis Task Force on Anticoagulants in Heart Disease (which has recently issued position papers on the topic of anticoagulation [2, 6, 12]) felt that a consensus statement was urgently needed for these drugs.

Because the acronym NOAC has already well penetrated the literature in various papers, reviews and guidelines internationally, we support maintenance of this designation, in keeping with the appeal for
consensus (11). Rather than referring to new or novel oral anticoagulants, the NOAC acronym would now refer to “non-vitamin K antagonist oral anticoagulants”, which probably best describes this class of oral anticoagulants given that there are other VKAs besides warfarin (most notably acenocoumarol, phenprocoumon and fluindione).

In conclusion, the ESC Working Group on Thrombosis Task Force on Anticoagulants in Heart Disease recommends retaining the “NOACs” designation to denote “Non-vitamin K antagonist Oral Anticoagulants”, when referring to the current oral direct inhibitors of thrombin or factor Xa. Future lectures, meetings, publications and guidelines should continue to use this acronym (with its new definition), which would allow consistency with the NOAC acronym used in older literature.

Conflicts of interest
S. Husted has been a speaker and consultant for Pfizer, Boehringer Ingelheim, BMS, AstraZeneca and Bayer, and has received research grants from GSK and Pfizer. R. De Caterina receives consultant and speaker fees from AstraZeneca, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Daiichi Sankyo, and Lilly; and research grants from AstraZeneca and Boehringer-Ingelheim. F. Andreotti has served as consultant or speaker for Amgen, Bayer, BMS-Pfizer, Boehringer Ingelheim, Daiichi Sankyo and Eli Lilly. L. H. Rasmussen has been on the speaker bureaus for Bayer, BMS/Pfizer, Janssen Pharmaceuticals, Takeda, Roche Diagnostics and Boehringer Ingelheim (< 10.000 Euro). J. Weitz was a consultant for and received honoraria from Boehringer Ingelheim, Bayer, BMS, Pfizer, Daiichi Sankyo, Merck and Janssen. G. Y. H. Lip has served as a consultant for Bayer, Astellas, Merck, AstraZeneca, Sanofi, BMS/Pfizer, Daiichi-Sankyo, Medtronic, Biotronik and Boehringer Ingelheim, and has been on the speaker bureaus for Bayer, BMS/Pfizer, Boehringer Ingelheim, Daiichi-Sankyo, Medtronic and Sanofi. S. D. Kristensen has received lecture fees from Bayer, Boehringer-Ingelheim, BMS and Pfizer. A. Siegbahn has received institutional research grants from AstraZeneca and Boehringer Ingelheim. R. F. Storey has received institutional grants, honoraria and/or consultancy fees from AstraZeneca, Accumetrics, Eli Lilly, Daiichi Sankyo, Merck, Roche, Regeneron and Sanofi Aventis. J. Morais has received speakers fees from Boehringer Ingelheim, Pfizer and AsztaZeneca, has served on the advisory board for Bayer Healthcare and is on the steering committees for ATLAS ACS 2 and ENGAGE. J. Jespersen, F. Bachmann and H. Arnesen declare no conflicts of interest.

References