

**REVIEW**

## New Oral Antithrombotic Drugs

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**ABSTRACT**

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New oral antithrombotic drugs are currently used for several indications, but mostly for the long-term treatment or prevention of thromboembolic disease in situations such as high-risk orthopedic surgery, deep vein thrombosis and myocardial infarction. They are also used in atrial fibrillation for the prevention of stroke. This family of drugs includes anti-platelet agents, eg. ticlopidine and clopidogrel, antithrombin agents, eg. ximelagatran and several others with various mechanisms of action. Oral intake has to fulfill certain conditions regarding absorption, efficacy and safety.

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Orally administered antithrombotic agents are the most appropriate and, therefore, the most commonly recommended drugs used for long-term treatment and prophylaxis against both venous and arterial thrombotic events.

The expansion of indications for antithrombotic agents is the result of an ever-growing population of patients in need of treatment or prevention against thromboembolic disease.

Venous thrombosis, and, in particular, its commonest presentation, deep vein thrombosis (DVT), usually develops during conditions favoring venous blood stasis, usually in the legs. The pathogenetic mechanism is triggered by vascular endothelial injury and activation of the coagulation cascade followed by thrombin generation, which in turn leads to platelet adhesion and aggregation. Among the risk factors associated with venous thrombosis are extended periods of bed-confinement, trauma, fractures, obesity, malignancy, old age, surgical procedures such as high risk abdominal surgery, gynecological, cardiovascular, and, in particular, orthopedic procedures such as hip and/or knee replacements, which are most commonly associated with DVT and pulmonary embolism.

Arterial thrombosis is usually triggered by an already damaged arterial endothelium mostly due to atheromatous changes which become the focus of thrombogenesis in a high-shear environment. The initial event attracts at first platelets with subsequent mobilization of the coagulation cascade which in turn results in thrombin generation and, finally, fibrin formation. Among the pathological conditions associated with arterial thrombosis are hypertension, diabetes and hyperlipidemia. Arterial thrombosis is usually manifested as coronary, cerebral or peripheral ischemic vascular events. In both venous and arterial thrombosis, congenital thrombophilia or acquired hypercoagulable states may also be the causative or the aggravating factors for abnormal thrombogenesis.

The problem is serious and its magnitude is impressive if one considers that in the USA DVT is responsible for 250,000/year hospitalizations and pulmonary embolism is the cause of 12% of hospital deaths [1]. Other statistical data confirm that,

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among Caucasians, 1/1000/year experience their first DVT [2], 1.3-4.1/1000/year have their first cerebral episode [3] and 5/1000/year suffer their first myocardial infarction. The risk of thromboembolic disease increases with age; it increases by 3 to 5 times in individuals aged 70 years or more, whereas atrial fibrillation, a condition closely related to old age, not only maintains a prominent position among the conditions requiring antithrombotic treatment, but it is also undertreated due to poor judgment and non-compliance with established guidelines, both on the patients' part as well as on the part of the physicians [4].

It is obvious that antithrombotic treatment is needed not only during the acute phase of thrombotic events but also for long-term prevention. It is this particular factor, i.e. time, that, in some cases, makes the use of oral antithrombotic substances indispensable.

At present, 0.7% of the "western" population is under oral antithrombotic treatment [5]. In table 1 are listed the most common antithrombotic agents currently in use, with their main sites of action and routes of administration. They may belong to the groups of anti-platelet or anti-thrombin agents, whereas a group labeled "miscellaneous" includes agents exercising their action in other less commonly considered sites. They can also have a direct or indirect mechanism of action and they can be administered through the oral or parenteral route.

The present article will present a brief account of the recently developed, orally administered antithrombotic agents.

## 1. ANTI-PLATELET AGENTS

For several decades, nearly a century, aspirin has been holding a strong position as an oral antiplatelet drug. It has also been serving as a reference drug to which many other newly developed agents (not only antiplatelet drugs) are compared. Its mechanism of action is based on its interference with arachidonic acid metabolism, i.e. the inactivation of cyclooxygenase (COX) activity, thus affecting prostaglandin synthesis [6]. It blocks the generation of thromboxane (TXA<sub>2</sub>), [a prostaglandin, antagonistic to its relative, prostacyclin (PGI<sub>2</sub>)], which enhances platelet aggregation and vasoconstriction [7]. It is not a new but an old and everlasting antiplatelet agent, inexpensive, easily available, not requiring laboratory monitoring [except for "aspirin resistance" cases [8,9]] and with a usually dose-dependent antithrombotic effect and dose-dependent adverse effects as well.

The newly developed, oral anti-platelet drugs, ticlopidine and clopidogrel, are both thienopyridines, exercising their antiplatelet action through the ADP receptors of the platelets, inhibiting ADP-induced platelet aggregation, with no direct effect on arachidonic acid metabolism

TABLE 1. Available antithrombotic agents

Name	Site of action	Route of administration
<b>A. ANTIPLATELET AGENTS</b>		
• Aspirin	COX	oral
• Dipyridamol	COX	oral
• Ticlopidine	ADP-Receptors	oral
• Clopidogrel	ADP-Receptors	oral
• GPII $\beta$ /IIIa Inhibitors	GPII $\beta$ /IIIa Receptors	parenteral (oral?)
<b>B. ANTITHROMBIN AGENTS</b>		
• Heparin (Ind)	} Ila, Xa, IXa	parenteral
• LMWHs (Ind)		parenteral
• Danaparoid (Ind)		parenteral
• Hirudin (Dir)	Ila	parenteral
• Argatroban (Dir)	Ila	parenteral
• Melagatran (Dir)	Ila	parenteral
• Ximelagatran (Dir)	Ila	oral
• AVK agents	II-VII-IX-X etc	oral
<b>C. MISCELLANEOUS</b>		
• Anti-TF/VIIa	TF/VIIa	} parenteral
• TFPI	TF/VIIa	
• NaPc2	TF/VIIa	
• Danaparoid	Xa	
• Fondaparinux (Ind)	Xa	
• Idraparinux (Ind)	Xa	

[10,11]. It seems, especially in the case of clopidogrel, that the crucial point in their mechanism of action is the irreversible reduction of the number of ADP-binding sites on the platelet surface [12], with a dose- and time-dependent accumulative effect [13].

Ticlopidine, orally administered, in the usual dose of 250 mg/day, has a satisfactory absorption of approximately 90% and a peak plasma concentration of 1-3 hours after intake. Repeated dosage causes an accumulation of the substance, thus tripling its plasma concentration at the end of a 3-week bid treatment. However, 98% of the drug is bound to plasma proteins [13]. Its T<sub>2</sub> varies from 24 to 36 hours after a simple oral dose to 96 hours after a 2-week repeated administration, usually of 250 mg bid and its delayed effect is a negative feature when rapid antiplatelet action is required [14].

The drug has been evaluated (STIMS, CATS, TASS studies) in patients with stroke, transient cerebral ischemia, unstable angina, myocardial infarction and intermittent claudication, as well as in cases of aortocoronary bypass surgery [15-19]. It is more effective than aspirin, even though marginally; the initial indications referred to patients not tolerating aspirin [14]. The combination of ticlopidine and aspirin proved to be superior to aspirin alone or to aspirin and warfarin combined, particularly for the prevention of thrombotic complications after coronary artery stent placement [20]. However, its high cost combined with its slow onset and slow action decrease, and, mainly, its toxic effect on bone marrow resulting in leukopenia and thrombocytopenia, led to the practical withdrawal of the drug, particularly after the detection of the occurrence of thrombotic thrombocytopenic purpura (TTP) in some cases. TTP, although rare (0,02%), is associated with a high mortality rate (20%) [21], and was the triggering factor for the gradual abandonment of the substance in favor of clopidogrel [22].

Clopidogrel, an agent inactive *in vitro*, when orally administered, is transformed in the liver into its active metabolite (SR 26334) with a T/2 of approximately 8 hours [23]. The impact of a possible liver function impairment on clopidogrel metabolism and effectiveness has not been evaluated yet. However, there is an obvious interindividual variability in its metabolic activation leading to the hypothesis that the P450 isoenzymes CYP3A4 and -3A5 metabolize the drug much faster than other similar isoenzymes do, and that these are the ones probably responsible for the metabolism of some statins as well, namely atorvastatin [24]. In fact, it seems that the simultaneous administration of clopidogrel and atorvastatin (but not pravastatin) alters the efficacy of the drug, causing a "clopidogrel resistance" effect, although the phenomenon has been questioned by some [25-28].

ADP-induced platelet aggregation is inhibited by clopidogrel in a usual pattern of a daily dose of 100-200 mg, whereas a loading dose of 300-600 mg is recommended by some to be taken orally immediately before the performance of percutaneous coronary intervention (PCI) [29].

Clopidogrel was tested in limited phase II studies and in an extensive phase III trial. The CAPRIE study [30] included 6400 patients in total with an increased risk of recurrent ischemic events. 75 mg/day of clopidogrel versus 325 mg/day of aspirin were compared. The patients suffering from symptomatic peripheral arterial disease were the ones that benefited the most from clopidogrel, even though the overall conclusion showed a marginally superior effectiveness of the drug over aspirin. Hemorrhagic complications were similar (~9,3%) in both groups and no bone marrow toxicity from clopidogrel was detected. The

drug has been, therefore, judged to be appropriate for use in symptomatic patients with peripheral atherosclerotic disease.

The complementary inhibitory activities of clopidogrel and aspirin on the platelets were evaluated in the CURE trial [31,32]. In it, more than 12,000 patients suffering from acute (less than 24 hour-duration) coronary syndromes with no ST-elevation were included. They received an initial loading dose (300 mg) of clopidogrel followed by a combination of aspirin (doses varied: 75-325 mg/day) and clopidogrel (75 mg/day) or aspirin and placebo for a period of 3-12 months. Clopidogrel combined with aspirin had a superiority in effectiveness, lasting even after the first month of its administration, while bleeding complications were increased in that group (3,7% versus 2,7%) and were related to the higher doses of aspirin [33]. Finally, the cost-effectiveness of such an approach of long duration has been investigated [34].

It has also been shown that long-term intervals (one year) of treatment with clopidogrel reduced the risk of post-PCI vascular events and established the combination of aspirin and clopidogrel as a standard post-coronary-stent-placement treatment for a period of one month [35].

In the CREDO study [36], it was observed that a longer interval before the clopidogrel loading dose (300 mg 3 hrs and, preferably 6 hours pre-PCI) reduced the post-PCI thrombotic events.

In the CLARITY and CLARITY-TIMI-28 trials it was shown that clopidogrel was both effective and cost-effective in acute coronary syndromes and in patients with ST-segment elevation myocardial infarction, but probably also as part of the reperfusion regimen in patients with myocardial infarction undergoing thrombolysis [37-39].

The accumulated evidence of the benefits from the addition of aspirin to clopidogrel in the secondary prevention of ischemic stroke on one hand and of the increased bleeding risk on the other, led to the MATCH study [37]. It is a randomized, double-blind, placebo-controlled trial comparing aspirin combined with clopidogrel and clopidogrel alone in patients with a recent ischemic stroke or cerebral attack in high risk patients. 7599 individuals were included in the study, which lasted for 18 months, and the final conclusion was that the difference in reducing major vascular events by the addition of aspirin to clopidogrel was non-significant, whereas the risk of life-threatening major bleeding events was increased [40-42].

Even so, the last word in this field has not been pronounced yet, since the inhibition target of the two drugs, ticlopidine and clopidogrel, is only one of the three known platelet ADP receptors, the P<sub>2</sub>Y receptor (the other two being P<sub>2</sub>Y<sub>A</sub> and P<sub>2</sub>Y<sub>AC</sub>). Even through this limited inhibition, their superiority over aspirin is evident [43,44]. It is, therefore, reasonable to expect in the future a further

development of more potent similar agents.

A parallel development may be expected from the group of substances against platelet thrombin receptors, namely the PAR-1 receptor (there are three more: PAR-2, PAR-3 and PAR-4). Experiments on animals are not yet completed and the possibility of such an agent being effective through the oral route cannot be excluded [45,46].

Finally, the integrin IIb $\beta$ 3/GPIIb/IIIa antagonists, at present, are in use only parenterally. They belong to various categories such as monoclonal antibodies (abciximab), natural inhibitors (RGD-disintegrins) with the Lys-Gly-Asp peptide sequence, or synthetic ones (KGD) such as eptifibatid and tirofiban with the Arg-Gly-Asp peptide sequence. These RGD sequences are responsible for fibrinogen, von Willebrand factor or fibronectin-binding [47].

The indications for the use of these agents are mainly unstable angina and PCI [48]. Attempts have been made for their structural alteration into non-peptide forms that could be easily absorbed through the gastrointestinal tract. However, in spite of the initial optimism regarding their efficacy superiority over aspirin and the hope to overcome the need for laboratory monitoring, the outcome of clinical studies was disappointing. The results of the trials on orbofiban (OPUS), sibrafiban (SYMPHONY), xemifiban (EXCITE) and lotrafiban (BRAVO), which included more than 40.000 patients with acute coronary events, could not be adequately evaluated [49-52]. In fact, a meta-analysis of these trials showed that, when taken orally, these agents were not indeed more effective than aspirin, nor superior to a placebo when combined with aspirin. Their efficacy proved to be dependent on high doses, which also caused a high frequency of bleeding as well [53].

A very serious outcome, in addition to the above, was an alarmingly increased mortality rate observed in some cases [54]. This was an unexpected unfortunate event and its magnitude could not be neglected (31%), therefore an explanation was sought. Among the several possible mechanisms examined were the unexpected, in some individuals, activation of platelets or excessive fibrinogen binding by those ligands initially designed to block them. It also seems that the limited extent of phase II trials proved insufficient to provide the data necessary, in phase III trials, for the establishment of a dose-dependent response, a correlation with bleeding complications and a disengagement from laboratory monitoring [49-58].

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## 2. ANTITHROMBIN AGENTS

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This large group (table 1) includes substances that inhibit thrombin only, or thrombin primarily, in addition to other coagulation factors (eg: fIX, fX etc). They exercise their action indirectly, mainly through ATIII, like the heparins (UFH,

LMWHs) or directly, like hirudin and related substances. As to their route of administration, it can be oral or parenteral.

Our interest will be focused on new oral antithrombins.

As a general rule, the polypeptidic nature of many antithrombotic agents does not allow their satisfactory use through the oral route. Therefore, ways have been looked for to make them easily absorbable and subsequently efficient. Some of them are: molecule size reduction (eg: argatroban, napsa-gatran, inegatran, melagatran etc), and molecular synthesis alterations. In fact, some properties that seem to be needed in order to make a substance suitable for oral antithrombotic use are discussed, as illustrated by the 5 points of the Lipinski rule [59,60]. Among them are a low molecular weight, preferably below 500 D, an oligopeptide molecular synthesis (tripeptides are preferable to pentapeptides), a specific amino acid sequence (eg: D-Phe-Pro-Arg-Chloromethyl-Ket) etc. The above appear to contribute to the high bioavailability and efficacy of a substance once it has successfully crossed the GI tract barrier into the blood circulation.

A good example of the use of a "carrier" or "delivery" molecule helping the active substance to be actually carried towards its target is the UFH/ SNAC complex. Heparin, when combined with SNAC (N-8-2-sodium-hydroxybenzoyl-amino-carzylate) as a delivery substance, since it facilitates translipid transport of UFH through gastric mucosa [61], is easily absorbed when taken orally, and can thus reach therapeutic plasma levels. The first steps of this agent's trials have been made. In a comparative study [62], UFH (5000 U subcut) versus UFH/SNAC in two scales of oral dosages (60.000 U/1,5 gr or 90.000 U/2,25 gr, tid) administered post-operatively in 123 patients submitted to hip- or knee-arthroplasty, proved encouraging. Although aPTT was in fact prolonged, anti-Xa activity was preferably used for laboratory monitoring. Multi-center studies then followed: in 124 centers worldwide, a total of 2,264 patients submitted to knee arthroplasty were given the complex. It was administered every 4-6 hours for 27-30 days postoperatively, and was compared to a LMWH under no laboratory monitoring [63].

Further data on UFH/SNAC are pending at present.

The need for pharmaceutical substances with an effective antithrombotic action, in no need of laboratory monitoring, free of adverse effects, easily obtainable and easily administered through the oral route, in summary, appropriate for long-term antithrombotic treatment / prevention, has long generated research activities, stimulating both clinicians and basic scientists. So far, the properties of such an "ideal" agent have been found only in part. The already existing substances in use have only partly satisfied the above mentioned expectations, since, in addition to the efficacy of the classical, long-time used antithrombotic agents, a series of limitations has emerged stimulating the search for such novel agents.

These limitations are listed in tables 2 and 3 and refer to the main antithrombotic agents used at present, both orally

**TABLE 2.** Limitations of heparin

• Indirect action (ATIII)
• Protein binding
• Limited bioavailability
• PF4 binding
• Non predictable dose-effect relation
• Narrow therapeutic range
• Laboratory monitoring

**TABLE 3.** Limitations of AVK

• Slow onset/end of action
• Food/drug interference
• Genetic particularities in metabolism
• Non predictable dose-effect relation
• Narrow therapeutic range
• Laboratory monitoring

(warfarin) and parenterally (UFH, LMWH).

Vitamin K antagonists (VKA), such as warfarin, have been in use for more than 60 years. They are administered orally and their antithrombotic action lies on their inhibition of the vitamin K-dependent coagulation factors (II, VII, IX, X) which is dose- and time-dependent. The need for laboratory monitoring, targeting to an INR of 2-3, and their narrow therapeutic range, as well as the dietary and pharmaceutical interference with their action, along with their adverse effects, triggered a need for the development of new similar drugs free of the above restrictions while exhibiting the desired qualities of VKA's and heparins.

Such a new drug is ximelagatran. It is a novel, orally administered antithrombotic substance, in fact a pro-drug, the inactive form of melagatran, the active direct antithrombin inhibitor [64]. Since melagatran is not absorbed through the GI tract, via a slight modification of its molecule, ximelagatran has been developed. Its absorption is quick, about 20 minutes, and its metabolism lies in the liver and is not affected by age or gender nor by simultaneous consumption of food or other drugs. Among ximelagatran's metabolites (eg: ethyl-melagatran, OH-melagatran) rapidly excreted is melagatran (20%), an at least 100 times more potent agent, which directly inhibits plasma thrombin as well as thrombin trapped by the thrombus [65,66].

The T/2 of unmetabolized ximelagatran is 0,34 hrs and, when transformed to melagatran, 3-4 hrs. Its peak action is manifested in 2 hours, this being much superior to the one of hirudin [67-70]. Other actions include inhibition of

the thrombin/thrombomodulin complex, interference with fibrinogen, protein C, platelets and fibrinolysis [71,72]. It is excreted through the kidneys and its activity reflects, to a certain degree, the renal function, an important factor in elderly patients [73]. In cases of renal impairment its dosage needs to be readjusted [74]. The substance has a satisfactory bioavailability since only 15% of it is bound to plasma proteins. Its dose-effect relation is predictable and its administration does not depend on laboratory monitoring even though it affects aPTT and ECT (ecarin clotting time) according to a predictable linear pattern [75,76].

Ximelagatran has been extensively tried through several grand scale clinical studies including a total of about 35.000 individuals. The initial studies were directed toward thromboprophylaxis of patients undergoing orthopedic surgery, such as knee and/or hip replacement (METHRO, EXPRESS) in which ximelagatran was given orally either alone or following parenteral melagatran, and its use was compared to warfarin or LMWHs [77-80].

These were followed by studies in DVT cases with or without pulmonary embolism [THRIVE,81,82], myocardial infarction [ESTEEM, 83] and atrial fibrillation (AF) for the prevention of stroke [84].

Of particular interest is the indication for ximelagatran in cases of non-valvular AF. It affects mostly elderly people, under conditions of diminished compliance and increased risk for stroke or cerebral hemorrhage if antithrombotic treatment is not achieved. Its prevalence magnitude is also impressive [85] since only in the USA it affects 22 million adults and more than 46.000 new cases/year are diagnosed in the UK. Independent risk factors are those, already mentioned, associated with arterial thrombosis and, in particular, male sex, hypertension, valvular heart disease and advanced age. Age is a determinant factor since, after the age of 50, each additional decade doubles AF prevalence, whereas rheumatic valvular disease increases the risk of stroke 18-fold. Preventive antithrombotic treatment is considered mandatory in elderly patients (over 75 years) and especially those with at least one additional risk factor. It has to be ardent (so far with warfarin and not just aspirin) and carefully monitored [86].

There has been a series of clinical studies, at least five, with ximelagatran for AF. Of these, the combined results of SPORTIF III and SPORTIF V allow us to draw the final conclusions on the treatment profile of the drug: it seems that there is no significant efficacy between ximelagatran and well monitored warfarin for AF (0.03% difference of stroke incidence). However, if hemorrhagic events and the presence or absence of laboratory monitoring are taken into account, effectiveness and safety of ximelagatran, in the absence of laboratory monitoring, as compared to warfarin, is evident [85-87]. The usual dose is 36 mg bid for a period of 4-6 weeks, sometimes even for one to two years [84].

A possible limitation of the drug is the occurrence, in 4-10% of patients taking it for 6 weeks to 4 months, of a transient, reversible and asymptomatic increase in alanine aminotransferase (ALT) levels. Even so, more information is needed to investigate the phenomenon, benign as it seems to be [83].

Recently it was reconfirmed [88] that elevation of ALT levels occurring within the first 6 months of treatment, affects the 7,9% of patients and is mainly asymptomatic. However, a close follow-up of these patients according to a recently developed algorithm helps to ensure that the probable hepatic risk is minimal.

Another new oral direct anti-thrombin agent is being currently evaluated. Dabigatran etexolate (BIBR 1048) is being investigated in a multicenter, parallel-group, double blind study of 1,973 patients undergoing hip- or knee-replacement surgery [the BISTRO trial, 88]. Its dosage and treatment escalation have been compared to LMWHs for the prevention of DVT in orthopedic surgery. Further information on the use of this new drug is needed.

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### 3. MISCELLANEOUS ANTITHROMBOTIC AGENTS ACTING IN VARIOUS SITES

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There are certainly other antithrombotic agents acting in several other sites of the thrombogenesis process, which could possibly be administered orally.

Some are already known for their parenteral use, such as the TF/f.VIIa complex [89], TFPI, NaPC<sub>2</sub>, inhibitors of factors IX or X, such as fondaparinux and idraparinix are already being studied for a possible oral use [90], and also inhibitors of the intrinsic pathway, or interfering with protein C pathway or fibrinolysis [91].

Of these, the interest is focused predominantly on the f. Xa inhibitors. The aim has been to develop short-molecule direct anti-Xa substances easy to administer. Idraparinux and fondaparinux are such agents and the AMADEUS and Van Gogh PE, Van Gogh DVT and Van Gogh Ext phase III studies focus on patients with atrial fibrillation, pulmonary embolism and deep vein thrombosis [92]. Simultaneously, such orally administered, drugs are being developed either by molecular ligand modifications [93] through the use of a "prodrug" strategy [94] or dealing with non-peptide agents [95].

Potentially promising results are expected on the oral use of a novel direct f. Xa inhibitor, BAY 59-7939, which seems to express an enormous affinity for f. Xa rather than for other serine proteases and will be tried in venous and arterial thromboses [96].

The research area is certainly bursting with activity, indicating that the desired target, the use of an oral, effective, safe, easy to take antithrombotic agent will soon be achieved.

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