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Fifty years of research on antithrombotic therapy: Achievements and disappointments

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ABSTRACT

The achievements with antithrombotic therapy over the past 50 years have been monumental and the disappointments relatively few. In this review, we will discuss, chronologically, the major developments of the two recognized classes of antithrombotics - anticoagulants and antiplatelet agents.

1. Introduction

The achievements with antithrombotic therapy over the past 50 years have been monumental (Table 1) and the disappointments relatively few. In this review, we will discuss, chronologically, the major developments of the two recognized classes of antithrombotics - anticoagulants and anti-platelet agents (Fig. 1). In doing so, we will concentrate on drugs or combinations of drugs that have transformed clinical practice or provided important mechanistic insights. For the sake of convenience, we will review anticoagulants, antiplatelet drugs and combinations of antithrombotic agents in separate sections. We will not review fibrinolytic agents as a class.

Among antithrombotic drugs in current use, the first three were introduced into clinical practice before their mechanism of action was discovered and before their benefits and risks were properly evaluated. Heparin was discovered in 1916 and administered to patients in the 1930's [1]. Dicoumarol was isolated in 1939 and approved for medical use in 1954 [1,2]. Acetyl salicylic acid (aspirin) was reported to inhibit platelet aggregation in 1967 [3,4]. It was then evaluated in several small clinical trials before its effectiveness and exact mechanism of action as an anti-platelet agent was elucidated. All three antithrombotics were used in clinical practice before they were formally approved by regulatory agencies.

2. Anticoagulants

For the first 30 years of their clinical use, the dosing, and laboratory monitoring of heparin and the vitamin K antagonists (VKAs) were haphazard and their true efficacy and safety unknown [5–10]. Then in the 1970s and 1980s antithrombotic therapy was transformed by the introduction of the principles of clinical epidemiology [11]. Anecdotal reports and descriptive studies were replaced by randomized controlled trials (RCTs) and changes in clinical practice demanded definitive evidence from appropriately designed and analyzed studies.

The first clinical trials of antithrombotic therapy that provided definite results were in the prevention and treatment of venous thromboembolism (VTE) and their results changed patient care [12–14].

In the 1960s, the need for prophylaxis in patients at high risk for VTE was not widely appreciated. The situation changed when in 1975, it was shown, definitively, in one of the first large scale randomized trials ever performed, that low-dose unfractionated heparin (UFH) prophylaxis reduced the incidence of fatal pulmonary embolism by about 70% in high risk surgical patients [13,14].

In the late 1970s and 1980s, a series of RCTs were performed in the treatment of VTE [15–21]. The results of these trials taught us that patients with VTE needed to be treated promptly with loading doses of UFH and that the effectiveness of anticoagulant treatment was blunted if the loading dose of heparin was omitted or was too low. They also taught us that most patients with VTE require anticoagulant treatment for at least 3 months [22–25].

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Table 1
Achievements with antithrombotic therapy.

Achievements		References
Venous thromboembolism		
1960	Anticoagulation saves lives in patients with PE	[12]
1975	Low dose UFH effectively and safely prevents VTE in high risk surgical patients	[13,129]
1980s	Demonstration that in many parts of the world, patients are being overdosed with warfarin, a finding that leads to the recommendation that a target INR of 2.0 to 3.0 should be used for most indications.	[15,28,29,130]
1990s	LMWHs replace UFH for VTE treatment and make outpatient VTE management possible	[33,34]
1990–2000s	The results of a series of RCTs inform on the optimal duration of anticoagulant therapy in patients with provoked and unprovoked VTE	[22,24,25,131]
1990–2000s	Aspirin is effective for the prevention of VTE in high risk orthopedic patients	[80,81]
2010s	Aspirin is effective for secondary VTE prevention	[82]
2010s	DOACs simplify oral anticoagulant therapy for VTE treatment and prevention	[88,132–149]
Atrial Fibrillation		
1990s	The acceptance of a less intense targeted INR (2.0 to 3.0) opens the way to multiple RCTs in atrial fibrillation which demonstrates that VKAs prevent stroke (by two-thirds) and saves lives in patients with AF	[31]
2010s	DOACs simplify oral anticoagulant therapy and are safer than VKAs and are much more effective than aspirin	[87,150–153]
Atherosclerosis and Thrombotic complications		
1980s	Aspirin prevents stroke and myocardial infarction and saves lives in patients with symptomatic atherosclerosis	[70,71,74]
1990–2000s	Dual antiplatelet therapy is more effective than aspirin alone in patients with ACS or those undergoing PCI	[103]
1980–2000s	Short term use of UFH, LMWH, or fondaparinux on top of aspirin in patients with ACS reduces the risk of myocardial infarction or death by at least half	[37,38,48]
2017	Long term use of the combination of aspirin and low dose rivaroxaban reduces mortality in patients with chronic CAD or PAD and demonstrated evidence of clear net clinical benefit	[110]
2018	Dual antithrombotic therapy with a DOAC and single antiplatelet therapy reduces bleeding in patients with concomitant AF and CAD requiring PCI and appears to be as effective as triple therapy (VKA + DAPT).	[115–118]

The clinical trials comparing two levels of intensity of oral anticoagulant therapy transformed clinical practice, not only for patients with VTE, but also for those with atrial fibrillation (AF) and prosthetic heart valves [8,26–29]. The results of these trials showed that the standard intensity of warfarin anticoagulation used in North America was associated with an unnecessarily high rate of bleeding and that reducing the targeted intensity of oral anticoagulation reduced bleeding without compromising efficacy. These trials also highlighted the urgent need to standardize the laboratory monitoring of the anticoagulant effect of vitamin K antagonists (VKA) such as warfarin [30]. This latter need was fulfilled by the introduction of the International Normalized Ratio (INR) by the World Health Organization. These changes opened the way to the safer use of oral anticoagulants and set the stage for multiple RCTs in AF, the impact of which was monumental: VKAs reduced stroke rates in AF by about two-thirds and mortality by about one-quarter [31].

The next major event that changed clinical practice was the replacement of UFH with low molecular weight heparin (LMWH) for most indications [32]. Capitalizing on the more predictable pharmacodynamic response of LMWH (compared to UFH) and its longer half-life, two randomized trials reported, in the early 1990s, that LMWH administered predominantly out of hospital was as safe an effective as UFH given in hospital [33,34]. The results of these two studies were transformative, since they moved the location of initial VTE treatment from the in-patient to out-patient setting, thereby increasing convenience for patients and reducing the cost of treatment.

The aforementioned anticoagulants were also evaluated in patients with coronary heart disease. UFH and LMWH was shown to be effective in acute coronary syndromes (ACS) and became part of the standard of care [35–38]. VKAs were also shown to be effective in the post-MI setting, but their benefits were outweighed by their bleeding side effects [39].

The modern era of anticoagulant therapy was started in the 1980s with the introduction of argatroban, fondaparinux and bilavirudin [40–45]; and was consolidated over the next three decades with the discovery of the direct oral anticoagulants (DOACs) [46]. These developments were made possible by technological advances that allowed the production of new drugs that bound specifically and with high affinity to key targets.

Fondaparinux, a pentasaccharide, which binds specifically to the heparin binding site on antithrombin, proved to be at least as effective and safe as LMWH and UFH [47]. Although the impact of fondaparinux on clinical care has been less than expected, the results of its head to head comparison with enoxaparin, a LMWH, in patients with ACS provided an important insight on the impact of non-fatal bleeding on patients' survival [48]. In the OASIS 5 study, patients with ACS were randomly allocated to receive either the standard dose of enoxaparin (1 mg/kg twice-daily) or a low dose of fondaparinux (2.5 mg once-daily). A low dose of fondaparinux was selected because it appeared to be as effective and safer than higher doses in three phase 2 studies [49–51]. In the phase 3 study, patients assigned to fondaparinux had similar rates of ischemic events as those assigned to enoxaparin, but a lower 30-and 180-day mortality [48]. The lower mortality was strongly associated with, and likely caused by a lower incidence of non-fatal bleeding [52,53]. These findings, which have been reproduced in other studies and with other drugs highlighted (1) the importance of non-fatal bleeding in studies evaluating antithrombotic agents [54], and (2) the importance of identifying the lowest effective dose of an antithrombotic agent [55].

The development of the direct oral anticoagulants (DOACs) occurred in two stages [46]. The first was the synthesis of small molecules that bound tightly to the active site of thrombin and factor Xa. These new agents were administered parenterally because they had poor oral bioavailability. The second development was to increase the oral bioavailability of these small molecules. The first orally active specific inhibitor, ximelagatran, was devitalized from melagatran to form a prodrug that was bio-activated to melagatran during absorption in the small bowel [56]. Like all subsequent DOACs, ximelagatran was administered in fixed doses without the need for laboratory monitoring. It therefore had the potential to replace VKAs and its introduction was met with much excitement because it fulfilled an important clinical need.

Ximelagatran underwent extensive clinical evaluation for various indications, including venous thrombosis, AF, and post-myocardial infarction (MI) [57–62]. Although it was shown to be effective, it was not approved by the US Food and Drug Administration (FDA) because of hepatotoxicity and was subsequently withdrawn from other markets [63]. Although its failure to gain regulatory approval was a major setback, the results of the ximelagatran trials provided proof of concept that fixed dose DOACs had the potential to be effective and safe (from

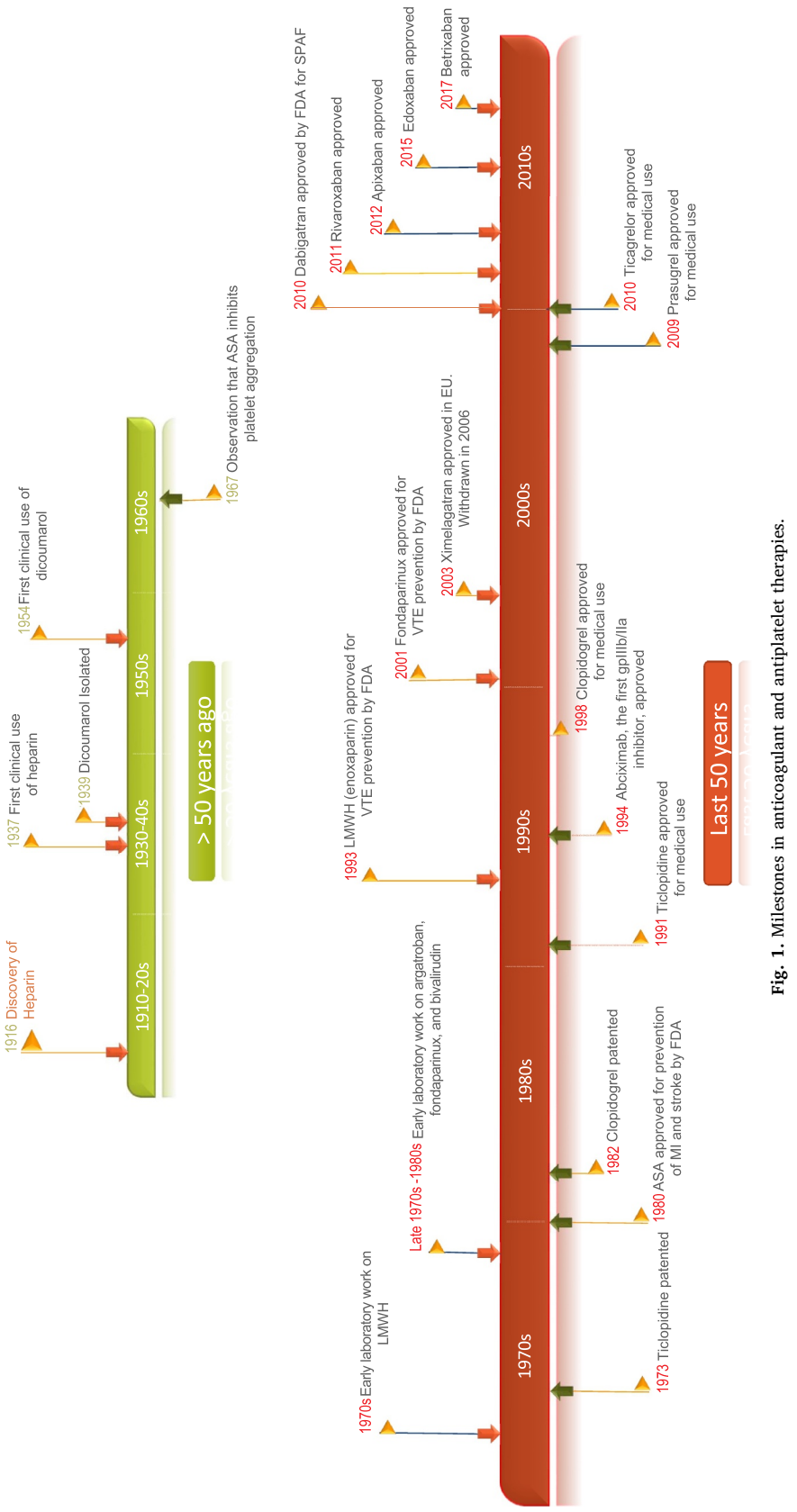

Fig. 1. Milestones in anticoagulant and antiplatelet therapies.

the standpoint of bleeding) and so opened the way for the development of other DOACs to replace VKAs. Of the five currently approved DOACs, dabigatran inhibits thrombin whereas rivaroxaban, apixaban, edoxaban and betrixaban inhibit factor (F) Xa [64]. In large phase III trials that included over 150,000 patients, fixed dosing regimens of these DOACs were shown to be at least as effective and safe as VKAs for stroke prevention in AF and as heparin or LMWH followed by VKAs for VTE prevention and treatment [64]. Since DOACs are more convenient to administer than VKAs or LMWHs, they are now replacing VKAs and LMWHs for stroke prevention in AF and for the prevention and treatment of VTE. To further enhance the safety of DOACs, antidotes have been developed and are now available to rapidly reverse the anticoagulant effect of dabigatran and the direct oral FXa inhibitors [65–67].

3. Antiplatelet therapy

For 20 years, ASA was the only antiplatelet drug in common use [68]. Dipyridamole was also available, but evidence of its efficacy was uncertain [69]. The initial trials with aspirin were underpowered and their results were inconclusive. This changed when in 1978, the Canadian Cooperative Study Group published the findings of the first appropriately powered clinical trial, which established the effectiveness of aspirin in preventing major stroke in patients with minor stroke [70]. Soon after, aspirin was shown to be effective in two RCTs in patients with unstable angina (about 50% reduction in death or MI) [71,72], and in the ISIS-2 trial in AMI (20% reduction in cardiovascular death) [73].

In 1988, reliable estimates of the efficacy and safety of aspirin in the secondary prevention of major cardiovascular events were provided by a meta-analysis of trials evaluating the efficacy of aspirin (alone or in combination) in patients with stroke (9 trials) and in those with unstable angina or myocardial infarction (10 trials) [74]. In this pooled analysis, aspirin reduced major cardiovascular events by about 25% and mortality by 10% without significantly increasing intracranial bleeding [74]. At that time, anticoagulants had also been shown to be effective for long term management of patients with coronary artery disease but with its better safety, aspirin became the standard of care for the secondary prevention of cardiovascular events [68].

Based on results in early trials of primary prevention and its success in the secondary prevention of coronary and cerebrovascular disease aspirin was also recommended for the primary prevention of vascular events in high risk patients. Recently, however, the role of aspirin for primary prevention has been called into question by the results of three trials involving a combined total of more than 45,000 subjects deemed at high risk of an atherothrombotic event [75–78]. An updated meta-analysis, that included these three studies, provided no evidence of net benefit, because the 11% reduction in cardiovascular events was offset by a 44% increase in bleeding, and there was no mortality benefit [75].

For years the dogma was that platelets only played a minimal role in the genesis of the stasis thrombi which characterized venous and intra-atrial thrombi [79]. This dogma was challenged in 1994 by the results of a meta-analysis performed by the Antiplatelet Collaborative Trialists', which reported that aspirin reduced the risk of postoperative pulmonary embolism by 64%, and DVT by 39% [80]. Subsequent RCTs confirmed the effectiveness of aspirin in the prevention and long-term treatment of VTE, and in the prevention of stroke in patients with AF [81–85]. However, aspirin is less effective than anticoagulants for these three indications [86–88]. Thus, compared to anticoagulants which reduce the thromboembolic event rates by 65–80%, aspirin reduces the rates of thromboembolic event by 20–35%. In general, anticoagulants cause more bleeding than aspirin, but based on their superior efficacy, oral anticoagulants are recommended for the prevention of stroke in AF and for the long-term treatment of VTE. However, either anticoagulants or aspirin are now recommended for the prevention of VTE in high risk orthopedic patients because the rates of symptomatic VTE and fatal PE are very low with either treatment [83,84,89–92].

Like ASA, the anti-platelet effect of the first ADP receptor antagonist, ticlopidine, was identified by chance while the thienopyridine was being developed as an anti-inflammatory agent [93]. Ticlopidine was effective in stroke and in coronary artery disease, but it sometimes caused life-threatening neutropenia and was soon replaced by clopidogrel [93]. This second generation thienopyridine did not cause neutropenia and was shown to be marginally more effective than aspirin in patients with symptomatic chronic atherosclerosis [94]. When clopidogrel was used in standard doses, about 30% of patents showed blunted inhibition of ADP induced aggregation [95,96], a potential shortcoming that was not shared by the more recently approved ADP receptor antagonists, prasugrel and ticagrelor [97]. Other platelet receptor antagonists have also been developed but are now infrequently used [98,99]. Thus, inhibitors of glycoprotein (gp) IIb/IIIa were approved for use in the late 1990s [99–101]. After initially being widely used in patients undergoing coronary interventions, their clinical use has been superseded by combinations of aspirin and ADP antagonists.

4. Combined antithrombotic therapy

Since aspirin and the ADP receptor antagonists inhibit different pathways of platelet activation, it was logical to evaluate their use in combination. Dual antiplatelet therapy with aspirin and clopidogrel was shown to be more effective than aspirin in patients with unstable angina or acute myocardial infarction and in those who had coronary artery stents inserted and became the standard of care for these indications [102,103]. Subsequently, the more potent ADP receptor antagonists, prasugrel and ticagrelor, were evaluated and shown to be more effective than clopidogrel but at the cost of more bleeding [104–106]. Accordingly, guidelines suggest that prasugrel and ticagrelor are preferred to clopidogrel only in patients at the highest risk of cardiovascular events [107].

In patients with chronic coronary artery disease treated with aspirin only, the addition of an ADP receptor antagonist or a VKA provides modest incremental benefit for prevention of non-fatal events but increases bleeding and is not associated with significant mortality benefits. Consequently, aspirin or clopidogrel monotherapy remained the recommended long term treatment for the majority of patients with atherothrombosis [68]. Attempts were made to maintain efficacy but reduce bleeding by combining a low dose of a VKA with aspirin, but these attempts proved to be unsuccessful [108,109]. The introduction of DOACs provided an opportunity to re-evaluate efficacy and net clinical benefit of the combination of aspirin and a low dose of an anticoagulant in patients with chronic atherosclerosis. This concept was tested in the COMPASS trial in which patients with chronic coronary or peripheral artery disease were randomly assigned to receive aspirin only or either the combination of low dose rivaroxaban 2.5 mg twice daily and aspirin, or rivaroxaban 5 mg bid only [110]. Dose selection was informed by the findings of the ATLAS-TIMI trial, which showed promising results with the combination of rivaroxaban 2.5 mg or 5 mg bid and aspirin [111].

The COMPASS trial demonstrated that compared with aspirin alone, the combination of rivaroxaban (2.5 mg twice daily) and aspirin not only reduced the risk of non-fatal cardiovascular events (by 24%) but also reduced mortality (by 18%). In contrast, rivaroxaban monotherapy (5 mg twice daily) had a more modest effect on cardiovascular events and no effect on mortality [110].

No other studies evaluating combination therapy in patients with symptomatic atherosclerosis showed a mortality benefit, although aspirin plus clopidogrel and aspirin plus low dose ticagrelor showed encouraging trends [112]. The findings of COMPASS support the notion that modulating more than one pathway in the thrombotic process is beneficial and highlight the importance of careful selection of antithrombotic drugs and their doses in combination therapy to ensure that any increase in bleeding does not vitiate the beneficial antithrombotic effect.

The importance of selecting the right combination of antithrombotic drugs is well exemplified by the experience in patients with AF and concomitant coronary artery disease requiring percutaneous coronary interventions (PCI). For some time, the combination of a vitamin K antagonist (VKA) and dual antiplatelet therapy with aspirin and clopidogrel (so called triple therapy) was the standard of care for these patients. Triple therapy was effective, but caused high rates of major bleeding [113,114], which were markedly reduced without mitigating efficacy by substituting VKAs with a DOAC and dual antiplatelet therapy with monotherapy [115–118].

5. Disappointments

Unlike the successes in patients with coronary artery disease, progress has been slow in the management of non-cardioembolic stroke and in patients with peripheral artery disease. The non-approval of ximelagatran by the FDA because of its hepatotoxicity was a disappointment to the thrombosis community [63]. However, it was soon forgotten after the success of the next generation of DOACs. There have also been two other major disappointments with DOACs, each of which taught us important lessons.

The first disappointment was in patients with mechanical heart valves (MHVs). In the RE-ALIGN trial, dabigatran was compared with warfarin in patients with MHVs [119]. The study was terminated early because of a trend for a higher stroke rate and a significant increase in major bleeding with dabigatran. It has been proposed that the failure of dabigatran in MHVs reflects the fact that thrombosis on MHVs is triggered by activation of the contact pathway which in turn leads to the downstream amplification of thrombin generation in concentrations that overwhelm the inhibitory effect of dabigatran, a stoichiometric inhibitor [120]. If this hypothesis is correct, then the newly developed inhibitors of FXIIa or FXIa might be effective in patients with MHVs [55].

The second major disappointment was in patients with embolic stroke of undetermined source (ESUS) [121–123]. Patients with ESUS constitute about 20% of all strokes. The conventional wisdom is that patients with ESUS should be responsive to anticoagulants because it is caused by artery to artery thromboembolism or occult embolism from the heart. The validity of this hypothesis was tested in two RCTs which compared DOACs with aspirin in patients with ESUS, but in both trials, DOACs were no more effective than aspirin and caused more bleeding [122,123].

6. Future perspectives

While enormous advances have been made over the past 50 years, important challenges remain. In patients treated with antithrombotic agents, bleeding has emerged as a powerful predictor of subsequent thromboembolic events [53]. Therefore, novel treatments that do not increase the risk of bleeding have an added potential to reduce thromboembolic events. Mechanical approaches are playing an increasingly important role in the prevention and treatment of thrombosis and with further refinements could become even more important adjuncts to antithrombotic drug therapy [124–126]. Two other novel approaches with no or low bleeding risk are being evaluated clinically. Thus, based on the established role of inflammation in the pathogenesis of atherosclerosis, anti-inflammatory therapy might be effective in preventing arterial thrombosis [127,128]. There is also recent evidence that inhibitors of the contact activation pathway prevent thrombosis with less bleeding complications than conventional anticoagulants [55]. Inhibiting contact activation might be particularly useful for preventing thrombosis on artificial surfaces, for which there is an important clinical need.

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