Solving the mystery of excessive warfarin-induced bleeding: A personal historical perspective

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For the first four decades after their introduction in 1941, the clinical use of vitamin K antagonists (VKAs) was hampered by haphazard laboratory control, lack of rigorous evidence for efficacy, and bleeding complications. In this narrative historical perspective, I discuss my personal experience in providing evidence for their clinical efficacy and in making oral anticoagulation with VKAs safer. I was joined in my efforts by key members of the McMaster University Thrombosis Program.

Coumarins were first used clinically in 1941 (1, 2). For the next four decades, their laboratory control was haphazard, evidence for their efficacy was weak and physicians were reluctant to use them because of the fear of bleeding. Three advances have made vitamin K antagonists (VKAs) safer: lowering the intensity of their effect, introducing the international normalized ratio (INR), and improving anticoagulant monitoring.

I was first alerted to the problem by Russell Hull in 1977. At that time, our approach was to treat patients who had acute venous thrombosis with unfractionated heparin for about 10 days, start warfarin on day 5 and then discharge them on adjusted dose warfarin targeted to a prothrombin time (PT) ratio of 1.5 to 2.5. One of the senior physicians refused to allow Russell to prescribe warfarin for his patients because he said that warfarin caused his pa-

tients to bleed. Since low-dose heparin (5,000 U twice daily subcutaneously) was effective for primary prevention of venous thrombosis, we wondered if we could replace warfarin with low-dose heparin. To test this hypothesis, we performed a randomised controlled trial in which we compared our standard approach of adjusted dose warfarin with low-dose heparin. The results showed that patients in the warfarin arm had a high rate of bleeding (21%) and that low-dose heparin was ineffective (►Table 1) (3).

We presented the results to our colleagues in Hamilton who did not believe that warfarin adjusted to a PT ratio of 1.5 to 2.5 caused so much bleeding. We decided to perform a second clinical trial with an identical design, except that the maintenance dose of heparin given after discharge from hospital was adjusted to an activated partial thromboplastin time (APTT) ratio of 1.5 (4). Heparin and warfarin were both effective (recurrent thromboembolism rates of 3.8% and 1.9%, respectively), but as in the first study, warfarin was associated with a higher rate of bleeding than adjusted dose heparin (17% and 1.8%, respectively) (►Table 2). This second study convinced us that our warfarin regimen was associated with an unacceptably high risk of bleeding. Although adjusted-dose heparin was as effective as warfarin, and much safer, this heparin regimen was impractical for outpatient use.

In retrospect, we should have lowered the intensity of warfarin. It was not until I presented our results at a meeting in London in 1980, that the penny dropped. My presentation was attended by a knowledgeable audience that was vocal in their disbelief of our findings. Our high rates of bleeding just did not match their experience. The most vocal dissenter was Leon Poller, a pioneer in the field of PT reagent development and VKA monitoring. For over a decade, he had been promoting a national PT

reagent standard in the UK and by the early 1980s, his laboratory was distributing their human brain thromboplastin to clinical laboratories throughout the UK. We were using Simplastin, a PT reagent that was commonly used in North America.

I met with Leon after my presentation and we continued our debate over a drink. I asked him what PT ratio he targeted, and he said 2.0 to 3.0, which was slightly higher than ours. Further questioning revealed that the mean dose of warfarin used in his patients was 4 mg per day; ours was over 5 mg per day. Leon said that he had just finished a warfarin dosage survey in seven countries (UK, US, Canada, Sweden, Australia, Hong Kong, and Zimbabwe) and found that the average daily doses varied from a low of about 2 mg to a high of over 8 mg (5).

It was now clear that we needed to do a third clinical trial comparing Poller's warfarin regimen with ours. Leon was enthusiastic. In our third randomized trial, patients were assigned to our standard regimen, warfarin dose-adjusted to a mean PT ratio of 1.8 using the Simplastin reagent (which corresponded to a PT ratio of 3.2 with Poller's Manchester reagent), or a less intense regimen wherein the warfarin was dose-adjusted to a mean Simplastin PT ratio of 1.3, which corresponded to a mean PT ratio of 2.0 with the Manchester reagent (6). Two patients (4%) in the less intense group had haemorrhagic complications, compared with 11 (22%) in the more intensely anticoagulated group. The frequency of recurrent venous thromboembolism was 2% in both groups (►Table 3).

Subsequently, we performed a fourth trial in which we evaluated the less intense warfarin regimen in patients with bioprosthetic heart valves and showed that the less intense regimen was effective but safer than the higher intensity regimen (►Table 4) (7).

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Table 1: Adjusted warfarin vs fixed low-dose heparin maintenance in treatment of leg DVT.

Rates at 12 weeks	Adjusted Warfarin ($PTR_{Simplastin}$=1.5–2.0 x) n=33 patients	Fixed UFH sc 5,000 units BID n=35 patients
Recurrent VTE during treatment period	0 95% CI: 0–12%	9 (26%) 95% CI: 14%-42%
Total bleeding during treatment period	7 (21%) 95% CI: 10%-38%	0 95% CI:0–11%
Major bleeding during treatment period	4 (12%) 95% CI: 4–28%	0 95% CI:0–11%

Table adapted from reference 3. PTR: Prothrombin Time Ratio, UFH: Unfractionated heparin, VTE: Venous thromboembolism

Table 2: Adjusted warfarin vs adjusted heparin maintenance in treatment of proximal leg DVT.

Rates at 12 weeks	Adjusted Warfarin ($PTR_{Simplastin}$=1.5–2.0 x) n=53 patients	Adjusted UFH (aPTT=1.5xcontrol) n=53 patients
Recurrent VTE	1 (1.9%) 95% CI: 0.1%-10.1%	2 (3.8%) 95% CI: 0.5%-13%
Total bleeding	9 (17%) 95% CI: 0.9%-29%	1/53 (1.8%) 95% CI: 0%-10.8%)
Major bleeding	3 (5.7%) 95% CI:1.4%-15.9%	0 95% CI:0–6.7%

Table adapted from reference 4. aPTT: Activated partial thromboplastin time, PTR: Prothrombin Time Ratio, UFH: Unfractionated heparin, VTE: Venous thromboembolism.

Table 3: Adjusted warfarin based on $PT_{Simplastin}$ vs adjusted warfarin based on PT_{MCR} in treatment of proximal leg DVT.

Rates at 12 weeks	Standard warfarin (Simplastin reagent) n=49 patients	Less intensive warfarin (Manchester comparative reagent) n=47 patients
Mean warfarin dose	5.8 mg	4.9 mg
Mean $PT_{Simplastin}$	19.4 s	15 s
Mean PT_{MCR}	41 s	26.9 s
Recurrent VTE	1 (2.0%) 95% CI: 0.1%-10.9%	1 (2.1%) 95% CI: 0.1%-11.3%
Total bleeding	11 (22%) 95% CI: 12.9%-36.0%	2 (4%) 95% CI:3.8%-15.0%
Major bleeding	2 (4.1%) 95% CI: 3.5%-14.5%	0 95% CI: 0–9.0%

Table adapted from reference 6. Pooled plasma gave a mean PT of 11 s for Simplastin reagent, and 13 s for Manchester comparative reagent. MCR: Manchester Comparative Reagent (human brain thromboplastin), PT: Prothrombin Time, UFH: Unfractionated heparin, VTE: Venous thromboembolism.

I delved into the older literature to learn how the PT therapeutic range was decided. It is an interesting story. A recommendation of a PT ratio of 2.0 to 2.5 was made by the American Heart Association (AHA) in 1954 based on a subgroup analysis of a cohort study of patients with myocardial infarction who were treated with dicoumarol (8). The lead author was Dr Irving Wright from the New York Hospital and Dr Clarence Mersky from Einstein Hospital in the Bronx was the consulting haematologist. When I spoke to Mersky in 1982, he told me that laboratories in New York used his home made human brain thromboplastin. Consequently, the AHA recommendation of a PT ratio of 2.0 to 2.5 would have been equivalent to a PT ratio of 1.3 using our Simplastin reagent.

The confusion arose in the 1960s when the thromboplastin reagents used in the US and Canada shifted from sensitive in-house reagents to less sensitive commercial reagents derived from rabbit brain tissue. The targeted PT ratio range also crept up from 1.5 to 2.5 to 2.0 to 3.0. In contrast in the UK, Poller established the British Comparative Thromboplastin in 1969 as the reference standard (9). The change in thromboplastin reagents in the 1960s from the sensitive in-house reagents to the less sensitive commercial reagents in North America led to a systematic increase in warfarin dosage (10). This systematic increase in dose went unnoticed by treating physicians and increased the risk of bleeding without providing incremental benefit. In addition, because the various commercial reagents were not standardised and had different sensitivities to reductions in the levels of the vitamin K-dependent clotting factors, warfarin dosage control in outpatients on long term anticoagulant therapy was erratic. No wonder experienced physicians lamented their difficulties in adjusting the dose of long term warfarin therapy in their patients.

Experts in Europe were aware of the need for standardising PT reagents and the problem was tackled by the WHO, which formed a standardisation committee. They published reports in 1977 and 1983 and introduced the INR (11–13). Unfortunately, these WHO recommendations were ig-

nored by leading organisations in North America.

In 1984, I was in charge of the reference coagulation laboratory at McMaster University Medical Centre. After discussing the issue with the other haematologists in Hamilton, we agreed that we should adopt the INR. I made presentations at medical rounds advocating for the INR, but the topic of PT ratios, international sensitivity index (ISI) and INR was boring for the audiences. In 1985, we made a unilateral decision to report laboratory results as both a PT ratio and an INR. On the report, we provided a stamp indicating that the target for patients being treated with warfarin was 2.0 to 3.0. After six months, we stopped reporting the PT ratio and just reported the INR. Remarkably, no one stopped us. There were grumblings from physicians and I continued to make presentations in all of the McMaster University-affiliated hospitals to explain why we were doing this. Gradually the INR was accepted and became routine in the Hamilton hospitals. I was invited to speak about the INR in other hospitals in Ontario, and the INR was gradually adopted in Canada.

That same year, I gained access to a powerful vehicle for knowledge dissemination in the U.S.; the American College of Chest Physicians (ACCP) Anti-thrombotic Guidelines, which I co-chaired with Jim Dalen (14). At our first meeting, I presented the story of low-intensity warfarin, of erratic PT testing and its consequences, and of the INR. The ACCP became a strong supporter of the need for promoting the less intense regimen and the INR. Although the less intense warfarin regimen was rapidly accepted in North America, we encountered barriers to acceptance of the INR.

At the conclusion of our first ACCP meeting we identified important knowledge gaps. One of the most urgent was the role of anticoagulants in patients with atrial fibrillation (AF). It was at this meeting that David Sherman and Robert Hart conceived the Stroke Prevention in Atrial Fibrillation study (SPAF) (15, 16). They elected to a use a low-intensity warfarin regimen. In a recent communication from Robert Hart, he stated: „It was our interactions with you at the first ACCP conference in 1985 that led

Table 4: Adjusted warfarin based on PT$_{DCR}$ vs adjusted warfarin based on PT$_{MCR}$ after tissue valve replacement.

Rates at 3 months	Standard warfarin (Dade C reagent) (INR range=2.5–4.0) n=108 patients	Less intensive warfarin (Manchester comparative reagent) (INR range=2.0–2.25) n=102 patients
Mean warfarin dose	5.14 mg	4.28 mg
Mean PTDCR	19.0 s	16.5 s
Mean PTMCR	38.0 s	28.5 s
Major thromboembolism	2 (1.9%) 95% CI: 0.2%-6.5%	2 (2.0%) 95% CI: 0.2%-6.9%
Minor thromboembolism	11 (10.2%) 95% CI: 5.6%-17.5%	11 (10.8%) 95% CI: 6.0%-18.4%
Total bleeding	15 (13.9%) 95% CI: 8.0%-21.9%	6 (5.9%) 95% CI: 2.2%-12.4%
Major bleeding	5 (4.6%) 95% CI: 1.5%-10.5%	0 95% CI: 0%-3.4%

Table adapted from reference 7. Pooled plasma gave a mean PT of 11 s for Dade C reagent, and 13 s for Manchester comparative reagent. DCR: Dade C reagent (rabbit brain thromboplastin), MCR: Manchester Comparative Reagent (human brain thromboplastin), PT: Prothrombin Time, UFH: Unfractionated heparin, VTE: Venous thromboembolism.

to the choice of a PT ratio of 1.3–1.8. Others were pushing us to target a PT ratio of 2–4. What a disaster that would have been!"

In their subsequent studies evaluating anticoagulants, the SPAF investigators used the INR. To promote the INR in the US, Leon Poller and I wrote a special report in 1989 advocating the INR system (17). The American College of Pathologists and other US organizations opposed the use of the INR. They felt that we were encroaching on their turf and they were being encouraged to resist by industry, which would have to bear the cost of ISI testing of their reagents.

In 1992, I wrote a provocative article, in which I accused US physicians of endangering their patients treated with warfarin (18). Henry Bussey, a pharmacist from Texas, joined my crusade and wrote: "Warfarin therapy in the United States is managed inappropriately because most laboratories do not report INRs" noting that only 21% of US hospitals surveyed reported their PT results as an INR (19). Pressure was mounting. The 1992 edition of the ACCP Antithrombotic Guidelines promoted both the low intensity warfarin ap-

proach and the INR system of monitoring (20).

DuPont, who dominated the warfarin market in North America, had an active education department and arranged for me to make presentations at key hospitals throughout the U.S. Over the course of six months, I delivered a talk per week. In my presentations, the slide that convinced the audience was the one that showed the PT ratios of the same plasma sample varying from a low of 1.3 to a high a 4.0 when tested with different PT reagents, which when converted to INR had a result of 2.0. The clinicians were not only convinced but some were critical of their haematologists (who usually sat in the back row) for not adopting the INR. By 1995, most laboratories in the U.S. were using the INR system and vendors were required to provide the ISI values of their thromboplastin reagents.

The events in my story changed clinical practice and saved lives. It all happened because Russell Hull joined me as a Fellow and we had open minds and listened to the concerns about bleeding. I met with Leon Poller and instead of arguing about who was right, we stepped back and identified a

potential reason for our differences, which Russell and I then investigated in a clinical trial. Once I was convinced by the hard data on low-intensity warfarin and the INR, I was relentless in persistence until the innovations were accepted in North America and became routine practice. My story ended in the mid-1990s, but progress in making warfarin safer and more effective has continued, particularly in the areas of laboratory control and patient selection (21).

Conflicts of interest
None declared.

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