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Investigators of studies of n = 1: Pioneers or kamikazes?

Reflections on "Les histoires de chasse"

Nicole R. Bonetti[a], *Jürg H. Beer*[a, b]

[a] Department of Medicine, Cantonal Hospital Baden AG, Switzerland

[b] Laboratory for Platelet Research, Molecular Cardiology, University Hospital of Zürich, Switzerland

Case reports are always fascinating and lively, they tell stories – *"les histoires de chasse"*, as the French call it – much appreciated by clinically working physicians. All experienced doctors carry a wealth of them, they remind us of our own personal experiences, successes and failures, of "blood, sweat and tears" and of decision making, where guidelines are in conflict with each other and we rely on opinions, eminence and instincts.

More often than not, these tough decisions concern difficult and under-studied patient populations, which are systematically and carefully excluded from controlled clinical trials and current guidelines.

Case reports are therefore of particular value in teaching and research, since they often inspire a discussion on how to handle certain diseases and on how to generate new hypotheses. They are valued for illustrating clinical decision making at its best. We might call them the "icebreakers of modern medicine" and, in accordance with this view, Laura Massobrio and colleagues [1] have to be congratulated on breaking new ground.

The downside is the potential risk, which our patient (and not the "pioneer doctor"!) has to take with these new icebreaker routes. Therefore, it is our obligation to perform particularly careful risk assessment and decision making, in the spirit of "primum nihil nocere" (Hypocrates) and "the least autistic thinking" [2].

In the case of Massobrio, the reader essentially partakes in three difficult decisions with new oral anticoagulants (NOACs). The case follows up a 79-year-old woman with atrial fibrillation, who suffered from a chronic sub-dural haematoma (cSDH) while on warfarin; after the evacuation she was on low molecular weight heparin (LMWH) for 1 month, after "local reactions/intolerance to all LMWHs and fondaparinux" (which occurs rarely, and it is unknown to the reader whether this was a prophylactic or therapeutic regimen). She was then

(a) put on a reduced dose of apixaban (2 x 2.5 mg);

(b) after 1 month, she underwent electroconversion, and eventually

(c) electrophysiological ablation and pacemaker implantation with typical bridging (48 h pre- and 12 h post-) without further complications.

She is doing well 7 months after the initial observation.

This case is instructive for three general reasons and it is paradigmatic for decision making:

(1.) *Lack of baseline information* of the case, which is important for an adequate decision. For example, the reader would like to know whether the cSDH was spontaneous or traumatic, because this has prognostic implications [3–6]. We know neither the kidney function nor her weight (<60 kg?). Which LMWHs were tested in which dose? Was there any other bleeding history? What were the significant laboratory findings (platelet count, haemoglobin)? She was on warfarin before, how was her time in therapeutic range (TTR)? Was she bleeding with an INR >4 or while in the therapeutic range? The patient did not fulfil any of the three criteria for the lower dosing regimen of 2 x 2.5 mg apixaban, but it was still chosen. This decision may expose her to the therapeutic bleeding risk, potentially without protection from thromboembolic events.

(2.) *Critical review and implementation of the literature*. The ARISTOTLE study found an encouraging reduction of intracranial bleeds in the apixaban group and this was found with all NOACs compared with VKA [8]. Can this finding be applied to patients after ICB/SDH and if yes, after what time period? Would it be 30 days, as in this case? With or without the challenge with LMWH? In prophylactic or therapeutic dosing? Or sequentially prophylactic and then therapeutic? Should such cases be monitored by trough plasma levels [8]? Would a well-controlled VKA therapy (INR 2–2.5) at a TTR >80% be equivalent? These are all questions that are not studied and may never be studied adequately in the future. However by approximation, we do know that this patient was at high risk for thromboembolism and stroke with a CHA_2DS_2Vasc score of 8,

which translates into a risk rate of between 6.4% [9] and 23.3% [10] of strokes and systemic embolisations annually. The highly variable range of roughly 10%–20% again indicates the insecurity. On the other hand, SDH presents a major challenge and recurrence rates of approximately 30% [11–13] are reported, even higher in women than in men [14]. In addition, non-traumatic SDHs tend to recur twice as frequently as the traumatic ones [4]. The recent and most relevant CHIRONE trial [4] sets an interesting and helpful point of comparison: 267 patients with ICB that were well controlled and re-exposed with anticoagulant therapy (VKA) did bleed again in 7.5%, in comparison the warfarin arm in ROCKET for example was at 1.2% annually (i.e.: sevenfold) [15]. The old age, gender and the spontaneous (?) SDH puts our patient instead in the above cited range of 20%–30% [11] than 7.5% [4]. On the other hand and as discussed in the case report, extrapolation (but not proof!) from reduced ICB rates with NOACs (compared to VKA) may reduce it to approximately 15%, which is still more than double of the extrapolation for thromboembolism reported by Lip [9] but somewhat lower than the one reported by Olesen [10]. Our calculation underlines the need for a critical handling of the HAS BLED score. Previous ICB/SDH as in this case should not lead us to over-optimistic assumptions. The HAS BLED score of 4, suggesting a severe bleeding rate of 9.5% [9], is based on particularly thin ice, since only 241 patients had this score (23 of whom bled), presenting the currently best possible data base, for clinicians to rely upon. In summary, the risk of bleeding may be at least as high as, and potentially substantially higher than, the one of TE and we would seriously consider the option “no anticoagulation” in this case. The other two decisions appear reasonable and well taken (bridging for the intervention and electroconversion after TEE, also supported by 743 cardioversions in 540 pts (ref. [5] in the paper)), although they are based on a retrospective analysis and are underpowered, as with the other NOACs [16–20].

(3.) *Taking a rational conclusion based on the clinical reasoning* above, one would likely prefer not to anticoagulate this elderly woman. Whether or not the low ICB incidence with apixaban, similar to aspirin in the AVERROES trial [21], will (hopefully) translate from the low to the high risk population, will only be answered by well-designed studies and registries. Many decisions like these are being made daily and it is of utmost importance to have well documented registries of these high-risk patients and their follow-up. High turnover cardiology and neurology centres, as well as the anticoagulant drug companies, are responsible and are invited to study adequately our ever increasing high-risk population who never fit into the typical study criteria. We are thankful to Laura Massobrio and colleagues because they shared their experience and, by doing so, took a step in the right direction.

Correspondence: *Professor Jürg H. Beer, M.D., F.A.C.P., Head of the Department of Medicine, Kantonsspital Baden AG, CH-5404 Baden, Switzerland, hansjuerg.beer[at]ksb.ch*

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Figures (large format)

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