For the question “how long should heparin overlap with warfarin in VTE?”

It’s a guideline free area right now, since CHEST withdrew their recommendation to overlap “5 days or until the INR is ≥ 2.0 for at least 24 hours” (in the 2012 guidelines https://journal.chestnet.org/article/S0012-3692(12)60129-9/fulltext, but not in the Feb 2016 guidelines where they just say “overlapped” https://journal.chestnet.org/article/S0012-3692(15)00335-9/pdf) and no other society guideline since has addressed the issue. Experts at conventions familiar with the guideline writers have stated that this change was due to lack evidence for the exact timing of the overlap. I have not found new literature on PubMed that has tested and clarified (let me know if you have something!).

Evergreen’s policies do still specify the old overlap durations. https://www.lucidoc.com/cgi/doc-gw.pl?ref=everg5:10696, https://www.lucidoc.com/cgi/doc-gw.pl?ref=everg5:18525. I would consider these outdated to current guidelines and possible candidates for consideration of updating, keeping in mind that there is currently no guidance for a “right answer,” but as the de facto keeper of this rule CHEST did purposely withdraw it.

For those interested, my practice is 5 days as a general rule but approached on a case by case basis utilizing the reasoning described below. It often makes sense because warfarin is pro-thrombotic for the first few days of use. I.e if the INR increases rapidly (day 1: 1.2, day 2: 1.6, day 3: 2.1, day 4: 2.5) one could consider stopping the parenteral anticoagulant on either the evening of day 3 or the morning of day 4, likely the latter date if the clot was more severe. I personally do not think the “and INR > 2.0 for 24 hours” makes sense if I am confident INR is increasing.

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For review:

Early INR increase is mostly due to rapid depletion of factor VII, which alone is not sufficient for anticoagulation. That is, INR increases, but it is not meaningful. Protein C (also vitamin k dependent and provides negative feedback on coagulation) is also fairly rapidly depleted causing warfarin to be a procoagulant for the first 1-3 days of use. Direct and fast acting anticoagulants (i.e the heparins) should be used to protect from this effect. The longer-lived essential clotting factors II and X are adequately cleared after 5-7 days of warfarin, after which the INR is “true.” Even very intense warfarin will not cause these to wear out faster, only more thoroughly once they do. An excessive INR at the point when Factor X wears out suddenly switches indicating benign loss of Factor VII to an excess bleeding risk. Therefore the real goal is to continue the parenteral anticoagulant until a prudent judgement of the point in time when both that switch occurs and the INR is neither above or below the target range. For me that is, assuming treatment of serious VTE or other high risk indication and confidently upward trending INR > 2.0: longer than three days, but not longer than five days.

What a mess! In fact, an INR that only measures the essential clotting factors II and X – the “Fiix-prothrombin time” – was developed by a group in Iceland a few years back. It was even found to have preferable performance. Of course it will almost certainly never enter practice due to momentum of use of the traditional INR. https://www.ncbi.nlm.nih.gov/pubmed/26688233
The activity of various clotting proteins (logarithmic scale) is shown here as a function of time after ingestion of warfarin (10 mg/day PO for four consecutive days) by a normal subject. Factor VII activity, to which the prothrombin time is most sensitive, is the first to decrease. Full anticoagulation, however, does not occur until factors IX, X, and prothrombin are sufficiently reduced. Protein C activity falls quickly, and, in some patients, a transient hypercoagulable state may ensue (eg, coumarin necrosis).