



## Possible Questions About the BRIDGE Study

### Questions about the Rationale and Justification of the Study

**Q. I've read recent studies that indicate patients with AF may have a low risk for stroke during interruption of warfarin for surgery/procedure and that such patients may not require bridging anticoagulation with LMWH or heparin. If this is the case, does it not make the BRIDGE study unnecessary?**

**A.** Two recent studies by Garcia et al. (Arch Intern Med) and Wysokinski et al. (Mayo Clin Proceed) studied patients with AF who had warfarin interruption prior to surgery/procedure. These studies reported that the risk for stroke appeared low (0.5–1%) when bridging was not given during warfarin interruption. However, these studies do not make BRIDGE study unnecessary based on these reasons:

- These studies were retrospective, meaning patient data and outcomes were collected after warfarin interruption and surgery. It is possible that outcomes (possibly stroke) were not reliably captured.
- Patients who did not receive bridging may have been a lower risk group and may have had a low risk for stroke. In fact, some patients in both studies did receive bridging and in the study by Wysokinski et al. a pre-specified sub-group of (presumed higher-risk) patients did in fact receive bridging.
- As the study authors mention, their studies are not a substitute for a well-designed clinical trial that will determine if bridging is needed.

**Q. What about all the other studies assessing bridging anticoagulation? Do they not inform best practice about whether 'to bridge or not to bridge'?**

**A.** There are over two dozen studies involving over 3,000 patients that have assessed bridging anticoagulation in patients with AF, mechanical heart valves, and venous thromboembolism. **All of these studies** are lacking clinical evidence in one important way: they do not compare a 'bridging anticoagulation' to 'no bridging anticoagulation' and do not inform best practice about the need for bridging.

These studies tell us 'how to bridge' but they do not tell us 'should we bridge' and, thereby, leaves the clinician in a quandary as to whether bridging is necessary or not, especially in moderate-to-higher risk patients with AF. This is where the BRIDGE study comes in. The BRIDGE study aims to provide definitive evidence about the pros and cons of bridging and will establish a standard-of-care.

**Q. Will emerging alternatives to warfarin make the BRIDGE study irrelevant?**

**A.** We believe the emergence of new oral anticoagulants such as direct thrombin inhibitors (dabigatran) and anti-Xa inhibitors (rivaroxaban, apixaban) will not have a negative impact on the BRIDGE study for the following reasons:

- If newer drugs are as effective and safe as warfarin to prevent stroke in AF they will be more expensive and it is likely that warfarin will continue to be widely used.
- Even if the cost of newer drugs is paid by a third-party (e.g., insurance company), many patients who have been comfortable using warfarin for many years may be reluctant to switch to a newer, perhaps 'less trusted' alternative.
- The question (addressed by the BRIDGE study) of whether to bridge or not to bridge will remain relevant because the half-life of new drugs such as dabigatran (approx. 14 hrs) will require them to be stopped 2–4 days before

surgery and bridging may be required in the period before and, possibly, after surgery.

### Questions about the Design of the Study

**Q. Will a placebo-controlled trial be acceptable to clinicians and patients?**

**A.** We agree that *any* placebo-controlled trial should be considered carefully because it involves having half of patients *not* receiving an active drug. For some patients and clinicians, receiving any treatment may appear better than not receiving it, even if it is unclear if the treatment works or is associated with possible harms. We believe that for patients who require temporary interruption of warfarin, a placebo-controlled trial will be acceptable based on these reasons:

- *The efficacy and safety of bridging is not established.* It is not known if bridging anticoagulation is effective to prevent stroke and other thromboembolic events and whether bridging exposes patients to an increased risk for important bleeding. In such instances, referred to as 'clinical equipoise', where there are good arguments both in favor and against bridging a placebo-controlled trial is best suited to resolve the uncertainty about the potential benefits and harms of a treatment.
- *There is no accepted standard of care.* In patients who require warfarin interruption, a 'bridging' approach may be as acceptable as a 'no bridging' approach and neither approach would violate a standard of patient care.
- *Expert guidelines are not definitive about best practice.* Influential guidelines like the American College of Chest Physician (ACCP) Guidelines on Antithrombotic Therapy (8<sup>th</sup> Edition, 2008) provide weak (Level 1C or 2C) recommendations regarding whether bridging therapy is needed for patients who will be studied in this study. The BRIDGE study will fill this void in knowledge and aims to provide strong, Level 1A evidence in regard to the need for bridging anticoagulation that will establish a standard-of-care.

## Questions about the Design of the Study (cont.)

### **Q. Why does the study design need to be double-blind? Is an open-label study not easier?**

**A.** In deciding whether to do a double-blind study (where patients and study personnel *do not know* whether they are receiving active drug or placebo) or an open-label study (where patients and study personnel *know* if they are receiving active drug or placebo), an important consideration is how this will affect reporting of outcome events (stroke, bleeding). We need to minimize the potential that these outcome events are not more likely to be reported because of prior knowledge of what treatment a patient is receiving, as would occur in an open-label study.

In a study such as BRIDGE, if the patient and physician know that the active study medication (low-molecular-weight heparin) is being given, they might have a greater tendency to report bleeding whereas if the patient and physician know they are not receiving an active medication, they may be more likely to report temporary weakness, blurred vision or other symptoms that might be a 'mini-stroke'. Either way, it is possible that prior knowledge of the study medication type a patient is receiving may bias the reporting of outcomes thereby making it difficult to reliably compare a bridging anticoagulation vs. no bridging approach. Furthermore, it is important that outcome events are reliably reported because we do not expect that there will be many of them (i.e., in approx. 5% of patients) in this study.

### **Q. After surgery, I do not fully understand why DVT prophylaxis is not allowed with LMWH or unfractionated heparin?**

**A.** After surgery, the use of LMWH or unfractionated heparin for DVT prophylaxis is not allowed in the BRIDGE trial because this will expose patients to additional anticoagulants, which are not part of the study design.

However, all patients will receive DVT prophylaxis after surgery in the form of warfarin. In the 2008 ACCP Antithrombotic Consensus Guidelines,

warfarin therapy (INR: 2.0 to 3.0) was given a Level 1A recommendation for DVT prophylaxis in high-risk patients such as those having hip or knee replacement surgery. It is likely, therefore, that warfarin will also be effective in preventing DVT in lower-risk patients who are participating in BRIDGE and are having other types of surgery.

The use of mechanical devices for DVT prevention such as anti-embolic stockings or intermittent pneumatic compression devices will be allowed as this will not impact on the primary study efficacy and safety outcomes (ATE, major bleeding).

### **Q. I do not fully understand why patients with other indications for warfarin (e.g., mechanical heart valve, DVT/PE) are not included in the BRIDGE trial?**

**A.** This is an important point. We agree it would be ideal to do a clinical trial of 'bridging vs. no bridging' in all patients assessed in everyday practice who require temporary interruption of warfarin. However, a clinical trial aims to answer a specific question (in this case, is bridging anticoagulation warranted during interruption of warfarin) and to do so requires that the study population is well-defined. If it were feasible and we were to include patients with mechanical heart valves and DVT/PE along with patients with AF, one study would be not be able to answer the question of 'bridging or no bridging' in any of these 3 patient groups because we would need 3 separate studies of roughly equal size, one for each group. In other words, if we were to allow inclusion of such patients in BRIDGE we would be no further ahead after the study was completed than we were before in providing a definitive answer to our question because we would not be able to make meaningful conclusions about bridging in any of the 3 groups. To provide a definitive answer, aimed at establishing a standard of care, we had to choose one of these patients groups to

study. We chose patients with AF for the following reasons:

- AF is the most common group who is receiving long-term warfarin and would require temporary interruption of warfarin before surgery
- a placebo-controlled trial is more acceptable in patients with AF group than in patients with a mechanical heart valve
- the issue of bridging is more important than in patients with DVT/PE in whom the objective is to prevent recurrent DVT/PE after surgery and in whom bridging anticoagulation before and after surgery is less important.

The logo for the BRIDGE trial. It features the word "BRIDGE" in a large, bold, black, sans-serif font. Above the letters "R", "I", "D", and "G" is a thick purple horizontal bar. The letters "B", "E", and "E" are positioned below the purple bar.

### **How can I learn more about participating?**

For more information, please contact Wanda Parker, RN, MSN, Project Leader, at (919) 668-8589 or email [parke010@dcri.duke.edu](mailto:parke010@dcri.duke.edu)