From: Redacted (MED) BI-PT-L
Sent: Thursday, June 28, 2012 6:18 PM
To: Redacted ClinD&MedA) BIP-DE-I
Cc: (ClinD&MedA) BIP-DE-I
Subject: RE: Recent BJCP Paper: Optimising the dose of dabigatran etexilate

OK.

Redacted
Medical Manager – Medicine Department

Boehringer Ingelheim, Lda - Portugal
Redacted
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From: Redacted (ClinD&MedA) BIP-DE-I
Sent: quinta-feira, 28 de Junho de 2012 15:48
To: Redacted (MED) BI-PT-L
Cc: Redacted (ClinD&MedA) BIP-DE-I; zxLIS Redacted (MED) EXTERNAL; Redacted (MED) BI-PT-L
Subject: AW: Recent BJCP Paper: Optimising the dose of dabigatran etexilate

Dear Redacted

This needs a TelCon and we should NOT interact via e-mail on this. Be assured that this would not be underestimated, but we have no prospective data on this. More as said via TelCon. Jutta knows the details too.

Mit freundlichen Grüßen / Kind regards /此致 敬礼 / 敬具,
Redacted

Boehringer Ingelheim Pharma GmbH & Co. KG
TA Cardiology
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mailto Redacted @boehringer-ingelheim.com

Von: Redacted (MED) BI-PT-L
Gesendet: Donnerstag, 28. Juni 2012 12:18
An: Redacted (ClinD&MedA) BIP-DE-I
Cc: Redacted (ClinD&MedA) BIP-DE-I; Redacted EXTERNAL; Redacted (MED) BI-PT-L
Betreff: RE: Recent BJCP Paper: Optimising the dose of dabigatran etexilate

Dear Redacted and Redacted,

Thanks for your prompt answers.

RE-LY was designed to validate a NOAC with no monitoring, and it was successful for the vast majority of patients, but we should not ignore that in those over 80 Years old, even the 110 mg had a unfavourable trend compared to warfarin (major bleeding ≥ 80 years: HR 1.12 (95% CI 0.84, 1.49). In my opinion, any strategies that may improve dabigatran safety profile in the elderly, improving confidence, are of great value and should not be underestimated.

Redacted is not the only thinking that, in theory, there may be a role for 1 ou 2 dabigatran measurements when starting the treatment, in high risk patients, to exclude high exposure levels. As far as I remember, no published data validates this approach; however, there isn't also any published data saying that it is useless… From our local pharmacovigilance experience, most bleeding events are occurring in the first weekes after treatment start, and, when available, many times the aPTT is above the 80 secs threshold.

The fact that "there is no clear cut plasma level range that provides an optimal therapeutic level for all subgroups of patients" may be a very good reason for BI to validate this hypothesis with a trial in an high-risk AF population. If we don't do it, an independent IIS trial probably will. Eventually, it will show that the number of patients that we need to monitor to prevent a bleeding event is not cost-effective, but until we have that data, we cannot be sure.

I hope you see my comments as a positive contribution, expressing a perspective many hematologists have and that, in my opinion, should not be underestimated.

Thanks a lot again.

Regards,

Redacted
Medical Manager – Medicine Department

Boehringer Ingelheim, Lda - Portugal

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< OLE-Objekt: Picture (Device Independent Bitmap) >>

From: Redacted (ClinD&MedA) BIP-DE-I
Sent: quarta-feira, 27 de Junho de 2012 19:43
To: Redacted (MED) BI-PT-L
Cc: Redacted (MED) BI-PT-L; Redacted EXTERNAL; Redacted (ClinD&MedA) BIP-DE-I
Subject: AW: Recent BJCP Paper: Optimising the dose of dabigatran etexilate

Dear Redacted,

Who is the leading SCE cardiologist specialist – is it Redacted? If so he should be aware that the best dosing recommendation is given via the patient characteristics. Let me know it it is Redacted as I am writing a manuscript with him about this … so I would be surprised.

I have to support Redacted – that the measure of plasma level is NOT a clear predictor of bleedings (like INR is it not for warfarin treated patients). It only provides an estimate of risk, BUT there are e.g. you people which clearly have no issue, let´s say with 150 ng/ml exposure, but elderly which could have an issue. Best is the clinical observation of risk pateints – plasma levels are not really predictive.

It is like driving a car – 220 km/h does not mean that one would have for sure an accident ….

Mit freundlichen Grüßen / Kind regards /此致 敬礼 / 敬具,
Redacted

Boehringer Ingelheim Pharma GmbH & Co. KG
TA Cardiology
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Von: Redacted (ClinD&MedA) BIP-DE-I
Gesendet: Mittwoch, 27. Juni 2012 17:43
An: Redacted (MED) BI-PT-L
Cc: Redacted (MED) BI-PT-L; Redacted EXTERNAL; Redacted (ClinD&MedA) BIP-DE-I
Betreff: AW: Recent BJCP Paper: Optimising the dose of dabigatran etexilate

Dear Redacted
Tx for this interesting article. I will have to discuss here internally whether this deserves at least a letter to the editor.

I would like to answer your question as follows:

While stroke prevention and bleeding are related to dabigatran plasma concentrations, there is, however, no single ideal plasma concentration range for all patients and dosing decisions must be based upon individual patient characteristics and concomitant medication use.
There is large variability in the plasma concentrations achieved with any given dose, depending on absorption, renal function, and other patient factors . Additionally, other factors unrelated to dabigatran plasma concentrations also affect bleeding risk such as age, concomitant administration of ASA and/or other antiplatelet agents, SSRIs, etc. How much the risk of stroke or bleeding also varies across the concentration range as well as unrelated factors (age and concomitant medication use) has important implications for the benefit-risk ratio in individual patients. Multiple factors are known to impact bleeding and stroke risk, irrespective of dabigatran concentrations.
In conclusion, there is no clear cut plasma level range that provides an optimal therapeutic level for all subgroups of patients.

Moreover, while there are case reports of bleeding associated with extremely high dabigatran plasma concentrations, there are also cases known who did not have had bleeding events at high concentrations or who bled although the measured concentration was quite low.
This is quite comparable to the situation with warfarin, where despite a recommended rate of INR of 2-3 you nevertheless see strokes and/or bleedings. So, there is more to be considered than a plasma concentration.

It is correct that the Haemoclot is used in the REALIGN trial. This is a phase II study in an indication where mortality is very high if the wrong dose is chosen. Moreover, the characteristics of the patients is different from the AF population and therefor the monitoring applied here is a kind of safety ensurance for the patients. The phase III design is still under discussion.

Hope this helps.
Redacted

Von: Redacted (MED) BI-PT-L
Gesendet: Mittwoch, 27. Juni 2012 12:15
An: Redacted (ClinD&MedA) BIP-DE-I
Cc: Redacted (MED) BI-PT-L; Redacted EXTERNAL
Betreff: Recent BJCP Paper: Optimising the dose of dabigatran etexilate

Dear Redacted

< Datei: Optimising the dose of dabigatran etexilate.pdf >>

I've just read this paper, and I would like to know what's BI public reaction to what's advocated by the author: the use of the Hemoclot dTT in high bleeding risk patients, to optimize dabigatran dose. I'm expecting that some of our hemathology SCE will challenge us with this paper. Others (few), are already doing what Dr. Redacted recommends.

My personal opinion, and also the one of our leading SCE cadiologist in Portugal (and many hematologists), is that this approach makes sense in a subset of patients (the elderly and borderline renal function patients). Furthermore, we may have this approach in the near future in mechanical heart valves patients, if the clinical program succeeds.

However, we never say this in public, because it may confuse many physicians and the Hemoclot is not widely available yet.

I'd like to have your comment and guidance regarding this issue.

Thanks,

Redacted

Medical Manager – Medicine Department

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< OLE-Objekt: Picture (Device Independent Bitmap) >>