Fondaparinux for the Treatment of Superficial-Vein Thrombosis

Superficial-vein thrombosis (SVT) of the legs is a condition more common that deep-vein thrombosis. Patients with SVT are at risk for subsequent symptomatic venous thromboembolic complications. The treatment of this disease has not been well studied in randomized trials, and both treatment recommendations and clinical practices vary widely. No published studies have shown a clinically relevant benefit of any treatment compared with placebo. The Comparison of Arixtra in Lower Limb Superficial Vein Thrombosis with Placebo (CALISTO) study was designed to evaluate the efficacy and safety of fondaparinux in reducing either symptomatic venous thromboembolic complications or death from any cause in patients with acute, isolated superficial-vein thrombosis of the legs.

Hospitalized or non-hospitalized patients with acute, symptomatic lower-limb superficial-vein thrombosis of at least 5 cm long, confirmed with standardized compression ultrasonography, were eligible to undergo randomization. The trial was randomized, double-blind, placebo-controlled with patients assigned to fondaparinux 2.5 mg or a matching placebo, administered subcutaneously once daily for 45 days.

The primary efficacy outcome was the composite of death from any cause, symptomatic pulmonary embolism, symptomatic deep-vein thrombosis, symptomatic extension to the saphenofemoral junction, or symptomatic recurrence of superficial-vein thrombosis up to day 47.

A total of 3002 patients were enrolled in the study from 171 centers in various countries, with 1502 in the fondaparinux group and 1500 in the placebo group. Overall, 1481 patients in the fondaparinux group (98.6%) and 1467 in the placebo group (97.8%) completed the follow-up visit at day 75. The primary efficacy outcome occurred in 13 of the 1502 patients (0.9%) in the fondaparinux group and 88 of the 1500 patients (5.9%) in the placebo group, relative risk with fondaparinux of 0.15, [P < 0.001]. The incidence of each component of the primary efficacy outcome was significantly reduced in the fondaparinux group as compared with the placebo group, except for the incidence of death, which did not differ significantly between the two groups. The risk of the composite of deep vein thrombosis or pulmonary embolism was reduced by 85% with fondaparinux compared with placebo, [P < 0.001]. In addition, more patients in the placebo group than in the fondaparinux group underwent surgery for superficial-vein thrombosis, including ligation of the saphenofemoral junction by day 77. By day 47, major bleeding occurred in one patient in each group. The rates of relevant non-major, minor, and total bleeding, and arterial thromboembolic complications did not differ significantly between the two groups.

Patients with isolated, symptomatic superficial-vein thrombosis in the legs are at substantial risk for symptomatic thromboembolic complications. Fondaparinux administered once daily for 45 days is effective and widely applicable for the treatment of such patients.


Clopidogrel and Proton-Pump Inhibitor Drug Interaction Retrospective Study

The functional status of the cytochrome P450 (CYP 2C19) enzyme is important in the conversion of clopidogrel to its pharmacologically active metabolite. The function of this enzyme can be compromised through direct drug inhibition or via a dysfunctional genetic variant, either of which can lower enzyme activity and diminish the clinical effect of clopidogrel. Proton-pump inhibitors (PPIs) are established substrates and inhibitors of CYP2C19, and are frequently prescribed concurrently with clopidogrel to reduce the risk of gastrointestinal bleeding. Studies of this potential interaction have been equivocal, but have been observational, retrospective, or in-vitro. To further investigate this potential drug-drug interaction, a large, retrospective cohort study was done to compare the 12 month cardiovascular outcomes of patients taking clopidogrel alone or in combination with a PPI, after coronary stent placement.

This study used the Medco Health Solutions data base. Patients were eligible for inclusion if they had a hospitalization claim for a percutaneous coronary intervention (PCI) with a coronary stent placement between October 1, 2005 and September 30, 2006. Patients were also required to have started clopidogrel within 30 days of the index PCI-stent procedure. Clopidogrel-treated patients were segregated into two cohorts, one with no record of a PPI prescription claim, and a second with a record of at least one PPI prescription claim in the 12 month period. The primary end point was the occurrence of a major adverse cardiovascular event (MACE), defined as hospitalization for a stroke or transient ischemic attack, an acute coronary syndrome, cardiovascular death, or coronary revascularization (CABG or PCI) over the 12-month period after the PCI-stent procedure.

A total of 16,690 patients met the inclusion criteria, and had undergone PCI with stent placement within the time parameters of the study. A total of 6828 patients (40.9%) received concomitant
PPI during the 12-month study period. Bare-metal stents were used in 6738 (68.3%) and 4864 (71.2%) patients in the no PPI and PPI groups, respectively [P < 0.001]. Patients receiving PPIs were slightly older, more often female, and had higher proportions of cardiovascular comorbidities in addition to higher gastrointestinal comorbidities. The rate of hospitalization for upper gastrointestinal bleeding was low, with 0.08% in the no PPI group and 1.0% in the PPI group having an event [P < 0.001]. During the 12 month study, a MACE occurred in 17.9% of patients who received clopidogrel alone and in 25.0% of patients receiving both clopidogrel plus a PPI, an adjusted hazard ratio of 1.51, (95% CI: 1.39 – 1.64, [P < 0.0001]). Concomitant clopidogrel-PPI exposure was also associated with a significant increase in risk of the individual components of both the primary and secondary end points with the exception of cardiovascular death. Similar associations of increased risk were observed for each PPI studied.

This study suggests that concomitant use of a PPI with clopidogrel after coronary stent placement is associated with an increased risk of subsequent hospitalization for a MACE over 12 months. This risk is evident on pooled analysis of all PPIs, as well as for the individual agents.


**Clopidogrel and Omeprazole Drug Interaction-Prospective Trial**

Randomized controlled trials have shown that proton-pump inhibitors (PPIs) reduce the rate of recurrent gastrointestinal bleeding in high risk patients receiving non-steroidal anti-inflammatory drugs. Observational studies suggest that there may be an interaction between clopidogrel and PPIs that could be clinically significant. These observational studies are bolstered by results of in-vitro studies that have shown a decrease in the antiplatelet effect of clopidogrel by PPIs, most often omeprazole. In addition, a genetic mutation (CYP2C19 gene loss) has been identified that reduces the effect of clopidogrel. There are some observational studies that do not show an interaction between clopidogrel and PPIs. Since the available information is conflicting, a randomized, prospective study has been done. The Clopidogrel and the Optimization of Gastrointestinal Events Trial (COGENT) was designed to assess the efficacy and safety of concomitant administration of clopidogrel and PPIs in patients with coronary artery disease who are receiving clopidogrel plus aspirin.

The initial planned sample size for COGENT was 3200 patients, with an accrual period of one year and a maximum follow-up of two years. The target sample size was eventually increased to 5000 to ensure an adequate number of gastrointestinal events. However, the study was ended prematurely when Cogentus Pharmaceuticals, the study sponsor, went into bankruptcy. COGENT was a phase 3 study testing the efficacy and safety of CGT-2168, a fixed-dose combination of clopidogrel 75 mg and omeprazole 20 mg, as compared with clopidogrel alone. All patients were to receive aspirin at a dose of 75 to 325 mg daily. Patients were eligible if the use of clopidogrel and aspirin was anticipated for at least the next 12 months. The prespecified primary gastrointestinal efficacy end point was time from randomization to the first occurrence of a composite of upper gastrointestinal clinical events, such as overt bleeding of gastrointestinal origin, overt upper gastrointestinal bleeding of unknown origin, bleeding of presumed occult gastrointestinal origin with a drop in hemoglobin of 2 gm/dl or more, or a drop in the hematocrit of 10% or more from the baseline value. The prespecified primary cardiovascular safety end point was the composite of death from cardiovascular causes, nonfatal myocardial infarction, coronary revascularization, or ischemic stroke.

There were 3761 patients who underwent randomization, with 1876 in the omeprazole group and 1885 in the placebo group. The median duration of follow-up was 106 days, with a maximum of 341 days. The two study groups were well matched with respect to baseline characteristics. There were 55 adjudicated gastrointestinal events. The event rate for the primary gastrointestinal end point was reduced from 2.9% with placebo to 1.1% with omeprazole at 180 days [P< 0.001]. Significant differences were seen between the omeprazole group and the placebo group with regard to overt gastrointestinal bleeding [P< 0.001], and overt upper gastrointestinal bleeding of unknown origin [P < 0.03]. There were 109 adjudicated cardiovascular events, with 54 in the placebo group and 55 in the omeprazole group with no significant difference in the rate of the primary cardiovascular end point. The event rate at 180 days after randomization was 5.7% in the placebo group and 4.9% in the omeprazole group [P = 0.96]. The rates of the individual components of the primary end point were also not significantly different. The rate of serious adverse events did not differ significantly between the two groups, 10.1% in the omeprazole group and 9.4% in the placebo group, nor did the rate of overall adverse events. Diarrhea as reported in 3.0% of patients receiving omeprazole and 1.8% of those receiving placebo [P = 0.01].

This randomized, prospective assessment of PPIs versus placebo in patients with coronary artery disease who were receiving dual antiplatelet therapy provides reassurance that there is no clinically significant cardiovascular interaction between PPIs and clopidogrel. In addition, PPIs provide a significant reduction in gastrointestinal bleeding compared with placebo.


**COMMENT:** This prospective, randomized, placebo-controlled study (COGENT) shows the reason that these types of studies are considered the gold standard compared to retrospective or observations studies. While this study has some deficiencies, the Medco study is hampered by not being able to adjust for confounders or inequalities between the groups, in addition to not being able to adjust for CYP2C19 genotype, and other concomitant drug therapy, particularly over-the-counter drugs. However, there are some deficiencies in this study to consider. For one, it was terminated prematurely so its power is limited, owing to a smaller number of events than was expected. In addition, there was no
genotyping done in the patients to assess the effect of the CYP2C19 gene prevalence. Further, the single pill formulation used in the study differs from generic omeprazole in its release kinetics, but after a week this should be inconsequential. It is likely that the controversy relating to the concomitant treatment with clopidogrel plus a PPI will continue, and its use should be determined by individual patient characteristics.

### Early Treatment of Rheumatoid Arthritis with Adalimumab plus Methotrexate

In patients with aggressive rheumatoid arthritis (RA), joint erosions can occur as early as 6 months after disease onset. The progression of damage then occurs rapidly, especially during the first two years. It has been shown that early treatment of RA can reduce disease progression and loss of function. There are few studies that have prospectively evaluated the influence of early RA treatment on prevention of both radiological damage and clinical disease progression, especially over the long term. Many studies have shown that a combination of a tumor necrosis factor (TNF) antagonist plus methotrexate is superior to methotrexate alone in improving clinical signs and symptoms of RA and inhibiting radiographic progression. In addition, there can be an improvement in physical functioning and health-related quality of life. PREMIER was a 2-year, randomized double-blind study of patients with RA. The design included three treatment groups, a combination of adalimumab plus methotrexate, or monotherapy with either adalimumab, or methotrexate alone. At the end of year two, the combination led to significantly better clinical responses, physical functioning, and radiographic inhibition than either monotherapy regimen. At the end of year two of the blinded study, patients were allowed to enter into an open label extension with adalimumab therapy for an additional three years.

This report presents the data from patients who participated in the extension trial and represents five years of treatment. In the extension trial all patients received open-label adalimumab 40 mg subcutaneously every other week. Open-label methotrexate could be added (up to a maximum dose of 20 mg weekly) at any time, based on clinical judgment. The efficacy and safety measures were clinical signs and symptoms with a 70% and 90% improvement in the American College of Rheumatology (ACR) ACR70 and ACR90 responses, respectively, and the Disease Activity Score 28 (DAS28). Patients were considered to have achieved clinical remission if they had a DAS28 of less than 2.6. Measurement of radiologic progression was measured with a modified total Sharp score (mTSS).

There were 388 patients who completed five years of the study. Based on initial treatment regimen there were 135 in the adalimumab plus methotrexate group (ADA+MTX), 126 from the adalimumab (ADA) alone group and 127 from the methotrexate (MTX) alone group. During the open label period 42% of patients in the original ADA+MTX group, 50% of the original ADA group, and 38% of the original MTX group received at least 12 weeks of methotrexate. At year five, ACR70 response was achieved by 64% of the combination therapy group, 53% of the ADA group and 57% of the MTX group. A DAS28 remission was achieved by 61% of the combination therapy group, 52% of the ADA group, and 56% of the MTX group. Better inhibition of radiological progression occurred in the initial combination therapy group than in either monotherapy group. In 53% of the initial combination group there was no radiographic progression at year five, compared with 34% and 33% in the ADA monotherapy and MTX monotherapy groups, respectively. During the open-label period of 1335.2 patient-years, serious infections occurred at a rate of 3.3 events per 100 patient-years. There were one case of lymphoma and non-melanoma skin cancer, and 11 cases of solid tumors.

In summary, two years of combination therapy with adalimumab plus methotrexate led to better long-term outcomes than either adalimumab or methotrexate monotherapy over five years of treatment. More patients in the initial combination treatment group had clinical remission, inhibition of structural damage and normal function than in either monotherapy group.

Van der Heijde D, Breedveld FC, Kavanaugh A, et al. Disease activity, physical function, and radiologic progression after longterm therapy with adalimumab plus methotrexate: 5-year results of PREMIER.


### Micafungin versus Voriconazole for Chronic Pulmonary Aspergillosis

Chronic forms of pulmonary aspergillosis (CPA) are characterized as a slowly progressive inflammatory pulmonary syndrome due to *Aspergillus* spp. The common characteristics of CPA consist of underlying pulmonary disorders, low-grade immunosuppression, and less severe findings of tissue invasion on histopathology. The latest guidelines from the Infectious Diseases Society of America recommend oral azoles as primary treatment. The utility of parenteral antifungal agents has not been studied. This is the first prospective trial comparing intravenous micafungin with voriconazole as induction therapy for patients with CPA.

Patients were enrolled from April 1, 2006 to November 30, 2008, and were eligible if they had been given the diagnosis of CPA. Patients with CPA had to fulfill the following conditions: the existence of at least one of the symptoms of fever, weight loss, sputum production, cough, hemoptysis, fatigue and shortness of breath; new infiltrates, cavity formation or expansion of pre-existing cavities; at least one positive serological test; and positive findings of at least one inflammatory marker (elevated white blood cell count, C-reactive protein, erythrocyte sedimentation rate) and a lack of improvement in symptoms after at least three days of therapy with broad-spectrum antibiotics. The primary efficacy end point was response to treatment, which was classified as success or failure at the end of administration of antifungal agents. Four factors were scored in determining the response to therapy, including clinical, laboratory, radiological and mycological. A “success” with respect to clinical response at the end of treatment was defined as an improvement in at least two of the four groups of factors. Patients
were randomized to receive intravenous voriconazole 6 mg/kg every 12 hours for 24 hours, and then 4 mg/kg every 12 hours. The other group received intravenous micafungin at a dose of 150 to 300 mg per day. Patients received treatment for at least two weeks, with a maximum duration of four weeks.

A total of 107 patients were recruited into the study, with 53 in the micafungin group and 54 in the voriconazole group. There were no significant differences in the clinical characteristics of the patients in either group at baseline. The mean administration time was 23.6 days for the micafungin group and 20.6 days for the voriconazole group. The average dose of micafungin was 167.4 mg per day and for voriconazole 8 mg/kg/day. The differences in success rates between micafungin or voriconazole was not significant, either after two weeks [68.0% vs. 58.7%] or at the end of therapy [60.0% versus 53.2%]. None of these response rates were statistically significant, nor were there significant differences in the response rates among any of the individual factors between the two treatments. There were significantly fewer adverse events observed in the micafungin group at 26.4% compared to the voriconazole group at 61.1% [P = 0.0004]. Hepatic events were the most common adverse event in both treatment arms, 15.1% for micafungin versus 35.2% for voriconazole [P = 0.025]. Visual events (photophobia, abnormal vision, defective color vision, blurred vision or visual disturbances) occurred in 29.6% of patients receiving voriconazole, but in none of the micafungin treated patients.

In patients with CPA, micafungin and voriconazole showed good clinical effectiveness, but there were significantly fewer adverse events with micafungin.


Voriconazole Pharmacokinetics in Immunocompromized Children

Voriconazole is increasingly used in pediatric patients, but only a few studies have reported on the pharmacokinetics in this population. Important pharmacokinetic differences exist between adults and children receiving voriconazole, primarily a higher elimination capacity in pediatric patients, likely due to their greater ratio of liver mass to body mass than seen in adults. An open-label, parallel-group study of the pharmacokinetics and safety was done in immunocompromized children aged 2 to less than 12 years and adults.

Twelve children and 12 adults with hematological malignancies who required treatment for the prevention or therapy of systemic fungal infections were included in the study. Nine children received a voriconazole dose of 7 mg/kg intravenously every 12 hours over the entire study period. Twelve adults and three children received two loading doses of 6 mg/kg every 12 hours, followed by a maintenance dose of 5 mg/kg for the children or 4 mg/kg for the adults, both given every 12 hours.

The children had mean age of 7 years and the adults averaged 44 years of age. The plasma trough levels of voriconazole in children receiving 7 mg/kg were not significantly different from the values obtained in adults receiving a dose of 4 mg/kg intravenously. The children had significantly higher C max values, but other pharmacokinetic parameters were not significantly different from those of adults. Voriconazole exhibited nonlinear pharmacokinetics in the majority of children.

In children 2 to < 12 years old, the European Medicines Agency approved dose of 7 mg/kg every 12 hours of voriconazole intravenously provides exposure (area under the curve) comparable to that observed in adults with a dose of 4 mg/kg every 12 hours.


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