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### ► **To cite this version:**

Martina Teichert, Charlotte Van Noord, Andre Uitterlinden, Albert Hofman, Peter Buhre, et al.. Proton pump inhibitors and the risk of overanticoagulation during acenocoumarol maintenance treatment. *British Journal of Haematology*, 2011, 153 (3), pp.379. <10.1111/j.1365-2141.2011.08633.x>. <hal-00625171>

**HAL Id: hal-00625171**

**<https://hal.science/hal-00625171v1>**

Submitted on 21 Sep 2011

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**Proton pump inhibitors and the risk of overanticoagulation during acenocoumarol maintenance treatment**



Journal:	<i>British Journal of Haematology</i>
Manuscript ID:	BJH-2010-01831.R1
Manuscript Type:	Ordinary Papers
Date Submitted by the Author:	30-Jan-2011
Complete List of Authors:	Teichert, Martina; Erasmus Medical Center, Epidemiology Noord, Charlotte; Erasmus Medical Center, Epidemiology Uitterlinden, Andre; Erasmus Medical Center, Internal Medicine; Erasmus Medical Center, Epidemiology; Erasmus Medical Center, Clinical Chemistry Hofman, Albert; Erasmus Medical Center, Epidemiology; Erasmus Medical Center, Medical Informatics Buhre, Peter; Star Medical Diagnostic Center, Anticoagulation clinic Smet, Peter; UMC St Radboud, Clinical Pharmacy Straus, Sabine; Evaluation Board, Dutch Medicines; Erasmus Medical Center, Medical Informatics Stricker, Bruno; Inspectorate for Health Care, Drug Safety Unit; Erasmus Medical Center, Epidemiology; Erasmus Medical Center, Medical Informatics; Erasmus Medical Center, Internal Medicine Visser, Loes; Erasmus MC, Epidemiology & Biostatistics
Key Words:	ANTICOAGULANTS, BLEEDING DISORDERS, DRUGS, GENES, EPIDEMIOLOGY

# Proton pump inhibitors and the risk of overanticoagulation during acenocoumarol maintenance treatment

Short title: Interaction between proton pump inhibitors and acenocoumarol

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Word count for abstract: words from maximum of 150: 168

Word count for manuscript excluding abstract, tables, references: (max 4000): 3409

Number of references: (max 50): 41

Number of figures and tables (max 7) 3 tables

1  
2  
3 Key words: acenocoumarol, proton pump inhibitors, omeprazole, rabeprazole, pantoprazole,  
4 lansoprazole, esomeprazole  
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For Peer Review

## Abstract

### Background

In the Netherlands, several reports described a potentiation of acenocoumarol-induced anticoagulation by co-medication of (es)omeprazole.

### Objective

To investigate the effects of co-medication with PPIs on overanticoagulation during acenocoumarol maintenance treatment.

### Methods

All **2,755** subjects from the Rotterdam Study who received acenocoumarol maintenance treatment between April 1<sup>st</sup>, 1991 and September 9<sup>th</sup>, 2009 were followed for events of an international normalized ratio (INR)  $\geq 6$ , until death, end of treatment, or end of the study period. With the Andersen-Gill extension of the Cox proportional hazards model, risks for repeated events of overanticoagulation in relation to concomitant PPI use were calculated.

### Results

The risk for overanticoagulation was most pronounced for esomeprazole (HR 1.99, 95% CI 1.55 – 2.55) and lansoprazole (HR 1.49, 95% CI 1.05 – 2.10). There was also a lower and non-significant risk increase for the other PPIs. **We did not detect a modification of these results by *CYP2C19*\*2 genotype.**

### Conclusion

Caution should be paid to co-medication with esomeprazole and lansoprazole during acenocoumarol treatment and possibly also with the other PPIs.

## Introduction

Coumarin anticoagulants are first choice in treatment and prevention of arterial or venous thrombosis.(Ansell, *et al* 2004) Warfarin, acenocoumarol and phenprocoumon act as vitamin-K antagonists by inhibiting the synthesis of coagulation factor II, VII, IX and X. Due to a particularly narrow therapeutic range, patients treated with these drugs have to be closely monitored by regular assessments of the international normalized ratio (INR) to warrant anticoagulation without serious bleedings. Individual dosing schemes differ widely between patients, mainly due to genetic variation in the vitamin K epoxide reductase complex subunit 1 (*VKORC1*) and cytochrome P450 2C9 (*CYP2C9*) genes. In addition, age, sex and body mass index (BMI) are important determining factors.(Aquilante, *et al* 2006, Carlquist, *et al* 2006, D'Andrea, *et al* 2005, Geisen, *et al* 2005, Oldenburg, *et al* 2007, Qazim, *et al* 2009, Sconce, *et al* 2005, Teichert, *et al* 2009) Therefore, coumarin dosage is carefully titrated during an initiation period by reference to the INR to achieve a stable individual maintenance dosage. However, also within the maintenance period, effects of coumarins can vary due to interactions with co-medication, development of co-morbidity or changes in lifestyle. In the Netherlands, acenocoumarol and phenprocoumon are most frequently used whereas warfarin is only given on rare occasions. Although management of coumarin use in the Netherlands is constantly monitored in anticoagulation clinics by regular INR-measurements to obtain optimal INR-levels, bleeding associated with coumarins is among the leading causes of drug-induced hospital admissions.(Leendertse, *et al* 2008, van der Hooft, *et al* 2008) Over the years, different drugs were reported to increase the anticoagulation effect of coumarins.(Blume, *et al* 2006, Wells, *et al* 1994) Until April 2009, the Netherlands' national pharmacovigilance center (LAREB) received nine reports about an increase of the anticoagulant effect of acenocoumarol within eleven days after start of treatment with omeprazole and seven reports in combination with esomeprazole.(Lareb Dutch National

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3 Pharmacovigilance Center 2009) Cases of coumarin potentiation by other PPIs have not been  
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5 reported. In four of these reports, the INR rose above six. INR measurements rising above  
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7 four are increasingly associated with overanticoagulation, and above six the chance of serious  
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9 bleedings strongly increases.(Cannegieter, *et al* 1995) Competitive inhibition of CYP2C19  
10  
11 has been suggested as a possible mechanism for interactions of PPIs with other drugs.(Blume,  
12  
13 *et al* 2006) Although earlier studies did not show changes in acenocoumarol pharmacokinetics  
14  
15 or pharmacodynamics(Hoorn de, *et al* 1997) or a need of acenocoumarol dosage adjustment  
16  
17 (Vreeburg, *et al* 1997), the Dutch Federation of Anticoagulation Clinics added esomeprazole  
18  
19 and omeprazole to the list of drugs potentially interacting with coumarins as of January  
20  
21 2010.(Federatie van Nederlandse Trombosediensten visited 28th September 2010) Before that  
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23 date, Dutch computerized medication surveillance systems of GPs and pharmacists did not  
24  
25 flag interactions between acenocoumarol and PPIs.  
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33 In a large prospective population-based cohort study, we investigated whether co-  
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35 medication with the PPIs omeprazole, pantoprazole, lansoprazole, rabeprazole or  
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37 esomeprazole was associated with an increased risk of overanticoagulation during  
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39 acenocoumarol maintenance treatment and whether an effect was modified by *CYP2C19*  
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41 variant alleles.  
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## 51 **Results**

52 Of the 14,926 subjects in the Rotterdam cohorts, 2,755 had used acenocoumarol during the  
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54 study period for longer than 42 days continuously as maintenance therapy. In 887 subjects an  
55  
56 INR  $\geq 6$  was measured at least once and in total 2146 INR  $\geq 6$  occurred, between 1 and 22  
57  
58 events per subject at a median of 2 per person. Baseline characteristics of patients with an  
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INR  $\geq 6$  and the total cohort are shown in table 1. 43% subjects with acenocoumarol

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3 maintenance therapy were male, mean age at study entry was 69 years and mean BMI 27.2  
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5 kg/m<sup>2</sup>. BMI values had to be imputed in 280 subjects (10.9%). Increasing age and higher INR  
6  
7 target levels significantly increased the risk to develop an INR<sub>≥</sub>6. Higher BMI measures were  
8  
9 associated with a decreased risk of overanticoagulation. From the 2,059 subjects successfully  
10  
11 genotyped for *CYP2C19*\*2, 1,464 (71.1%) were homozygous for the *CYP2C19*\*2 *G*-allele  
12  
13 and 545 (28.9%) had a variant genotype with **at least** an A-allele. The frequency of the  
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15 *CYP2C19*\*2 variant allele A was 15.7% and alleles were in Hardy-Weinberg equilibrium  
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17 (HWE, p-value=0.93). Subjects homozygous with the variant A-allele of *CYP2C19*\*2 had a  
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19 decreased risk on overanticoagulation during acenocoumarol treatment (HR 0.54; 95% CI  
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21 0.36-0.83). As this group was quite small (2.4%), we pooled subjects homozygous and  
22  
23 heterozygous for the variant A-allele. Any variant A-allele was then no longer associated with  
24  
25 the risk of overanticoagulation (HR 0.99; 95% CI 0.89-1.11).  
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32 In our cohort in total 457 (16.6%) subjects used omeprazole, 160 (5.8%) pantoprazole,  
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34 102 (3.7%) lansoprazole, 286 (10.4%) rabeprazole and 149 (5.4%) esomeprazole (table 2). In  
35  
36 223 events of an INR <sub>≥</sub>6 a PPI (10.4% of all events) was used on the index date for at least  
37  
38 three days. Co-medication during acenocoumarol maintenance treatment with esomeprazole  
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40 was associated with a doubled risk of an INR <sub>≥</sub>6 (HR 1.99; 95% CI 1.55 – 2.55) and co-  
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42 medication with lansoprazole increased the risk by 49 percent (HR 1.49; 95% CI 1.05 – 2.10,  
43  
44 table 2). The other PPIs also increased the risk of overanticoagulation less pronounced  
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46 between 1.12 and 1.23 times, but associations were just below the significance threshold after  
47  
48 adjustment for co-medication with NSAIDs. Co-medication with ranitidine, used by 229  
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50 subjects (10.5%), showed no association with overanticoagulation (HR 1.06, 95% CI 0.83 –  
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52 1.35).  
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57 For esomeprazole and lansoprazole we investigated whether the *CYP2C19* genotype  
58  
59 modified the interaction with acenocoumarol (table 3). We did not find a multiplicative  
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3 interaction between the drugs separately or grouped for use of either of the drugs and at least  
4 one *CYP2C19*\*2 variant allele. To investigate presence of an additive effect modification we  
5 formed 4 groups for the combinations of drug use yes and no with absence and presence of  
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10 *CYP2C19*\*2 variant alleles. No additive effect modification was detected **with this dominant**  
11 **model by genetic variation in the *CYP2C19* gene as the risk for overanticoagulation for**  
12 **esomeprazole- or lansoprazole did not differ significantly between subjects within strata**  
13 **of *CYP2C19*\*2 genotypes (p-value = 0.11 for the Synergie Index for additive**  
14 **effectmodification, SI= 1.67 (95% CI 0.78 – 3.57) (Hosmer and Lemeshow 1992)). In our**  
15 **population there were no users of esomeprazole or lansoprazole with the *CYP2C19*\*2 AA**  
16 **genotype and therefore it was not possible to investigate additive effect modification by**  
17 **genetic variation in the *CYP2C19* gene with a recessive model.**  
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### 33 **Discussion**

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36 In our study population, all PPIs tended to increase the risk of overanticoagulation during  
37 acenocoumarol maintenance treatment. This was most pronounced for esomeprazole,  
38 doubling the risk of overanticoagulation and for lansoprazole with a risk increase of 49%.  
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41 Risk increases for omeprazole, pantoprazole and rabeprazole were between 12 and 23% and  
42 just failed to reach significance after adjustment for NSAID co-medication. PPIs have been  
43 mentioned occasionally as potential risk factors for overanticoagulation during treatment with  
44 vitamin K antagonist in case reports, however case control studies and trials concluded no  
45 effects of clinical relevance.(Ehrlich, *et al* 1996, Hoorn de, *et al* 1997, Sutfin, *et al* 1989,  
46 Unge, *et al* 1992, Vreeburg, *et al* 1997) However, the trials were only short term trials with  
47 small numbers of subjects and the case control study took dosage change as an outcome  
48 without regard to INR measurements. The highest number of case reports and  
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3 pharmacokinetic studies are available for omeprazole in combination with coumarins. Two  
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5 case reports described an INR increase in users of phenprocoumon after initiation of  
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7 omeprazole and return to normal after its cessation.(Enderle 2001) In one study for co-  
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9 medication with lansoprazole or rabeprazole in patients after open heart surgery,(Hata, *et al*  
10  
11 2008) lansoprazole enhanced the anticoagulation effects of warfarin whereas rabeprazole  
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13 could be used concomitantly without increasing the risk of overanticoagulation. We are not  
14  
15 aware of a clinical study on the effect of esomeprazole on coumarins to support our findings.  
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20 **Our results show a more pronounced association for esomeprazole than for**  
21  
22 **omeprazole. Omeprazole is a racemic composition of its two optical isomers, (S-**  
23  
24 **)omeprazole (esomeprazole) and (R-)omeprazole.(Andersson, *et al* 2001) The clearance**  
25  
26 **of the two enantiomeric omeprazole-forms by CYP2C19 is stereo-selective. In vivo,**  
27  
28 **CYP2C19 was responsible for 90% of the metabolism of (R-)omeprazole and 70% of (S-**  
29  
30 **) omeprazole.(Aebeloe, *et al* 2000) In our study population, omeprazole and**  
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32 **esomeprazole were used in similar defined daily doses (DDD), omeprazole at a mean**  
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34 **DDD of 1.35 (range 0.21 – 4.50) and esomeprazole at a mean DDD of 1.23 (range 0.33 –**  
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36 **4.00). However, these DDDs do not represent equipotent dosages as 1 DDD omeprazole**  
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38 **equals 20 mg and 1 DDD esomeprazole 30 mg. Consequently in our study population,**  
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40 **esomeprazole was used in a much higher pharmacological dosage than omeprazole and**  
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42 **this may explain a higher influence on acenocoumarol effectiveness.**  
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50 As a possible mechanism a competitive inhibition of CYP2C19 by PPIs on coumarin  
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52 clearance has been mentioned as both drug groups are metabolized by this enzyme and the  
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54 INR increases in the case reports were reported within 11 days after start of the PPI.(Blume,  
55  
56 *et al* 2006, Gerson and Triadafiopoulos 2001, McCarthy, *et al* 2003) (S-)acenocoumarol, the  
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58 enantiomeric form being mainly responsible for the drug effect, is for about 20% metabolized  
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60 via CYP2C19. For the five PPIs, in vitro studies showed that all five PPIs were able to

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3 competitively inhibit CYP2C19, but to a different extent. Lansoprazole had the highest  
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5 inhibitory potency of CYP2C19 in vitro.(Li, *et al* 2004) Rabeprazole had a relatively lower in  
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7 vitro inhibition of CYP2C19 than the other PPIs, possibly as it is metabolized mainly via a  
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9 non-enzymatic reaction to a thioether compound with only minor CYP2C19  
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11 involvement.(Gerson and Triadafiopoulos 2001, Hata, *et al* 2008, Li, *et al* 2004) Omeprazole  
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13 and esomeprazole in vitro also reduced CYP2C19 activity (Li, *et al* 2004) and were more  
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15 potent than pantoprazole.(Simon 2003) Theoretically a competition for scarce CYP2C19  
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17 enzyme might prolong the effectiveness of the coumarins which would result in an increased  
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19 INR. In subjects with variant allele genotypes and decreased enzyme availability this effect  
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21 may be even more pronounced. However, from our analysis, no multiplicative or additive  
22  
23 effect modification of *CYP2C19*\*2 variant alleles on the association between esomeprazole or  
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25 lansoprazole and acenocoumarol was detected. **In our study population there were no**  
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27 **subjects with the *CYP2C19*\*2 AA genotype using esomeprazole or lansoprazole and this**  
28  
29 **limited our possibilities for stratification.** Possibly the effect of the variant allele on  
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31 acenocoumarol elimination was too small and more cases are needed to warrant enough  
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33 power for a genotype-stratified analysis.  
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42 Our study is the first observational cohort study of an increase of acenocoumarol  
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44 effectiveness by co-medication of all PPIs separately with a substantial number of subjects  
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46 during the whole period of acenocoumarol maintenance treatment within a subject. We  
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48 consider the chance of bias and confounding due to study design as negligible. First, the  
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50 Rotterdam Study is a prospective cohort study and the regional anticoagulation clinic covered  
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52 a complete area of more than one million inhabitants in the Rotterdam area. Consequently,  
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54 everyone who is treated with a coumarin anticoagulant as an outpatient will be registered as  
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56 such and selection bias is unlikely. Second, all medication use of all subjects was almost  
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58 completely covered by the pharmacy data we retrieved and during the study period PPIs were  
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3 only available on prescription via pharmacies. Any lack of compliance would move our  
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5 results into the direction of the null hypothesis, and would tend to make our results  
6  
7 conservative. During our study period, an association between PPI and acenocoumarol  
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9 overanticoagulation was not yet common knowledge. Third we followed the cohort members  
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11 during their whole period of acenocoumarol maintenance therapy and compared cases to all  
12  
13 other cohort members available at the index dates for PPI exposure. The analysis made use of  
14  
15 all data available and adjusted for time varying effects. However, in observational studies  
16  
17 there is always a risk of confounding by indication. We therefore performed the same analysis  
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19 for ranitidine, a H<sub>2</sub>-receptor antagonist used for the same indication but not known for  
20  
21 inhibitory potential of CYP2C19. We did not find an association for ranitidine with an  
22  
23 increased risk on achieving INR  $\geq 6$  during acenocoumarol treatment. As PPIs might have  
24  
25 been started to treat the symptoms of an increased INR, in our analysis use of PPIs – and also  
26  
27 ranitidine - had to be started for at least 3 days prior to the index date. We did not take  
28  
29 bleedings as an outcome because PPI s are likely to be started with complaints preceding  
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31 gastrointestinal bleeding. Associations found might be due to protopathic bias.  
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40 In conclusion, in this population-based cohort study among outpatients of an  
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42 anticoagulation clinic using acenocoumarol for maintenance treatment, esomeprazole doubled  
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44 the risk on an INR  $\geq 6$  and lansoprazole tended to increase this risk by approximately 50%.  
45  
46 For omeprazole, pantoprazole and rabeprazole, a risk increase was less pronounced and non-  
47  
48 significant. Our results suggest that extra monitoring during acenocoumarol treatment may be  
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50 warranted in patients on esomeprazole or lansoprazole and this perhaps applies to other PPIs  
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52 as well.  
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## Methods

### Setting

We selected all subjects from the three cohorts of the Rotterdam Study (RS-I , RS-II and RS-III). The rationale and design of the Rotterdam Study have been described elsewhere.(Hofman, *et al* 2009, Hofman, *et al* 2007, Hofman, *et al* 1991) In brief, the Rotterdam Study is a prospective population-based cohort study, designed to study neurological, cardiovascular, locomotor and ophthalmologic diseases in a population of people of 45 years and older. During different periods, eligible inhabitants of Ommoord, a suburb of Rotterdam, were invited to participate. The RS-I cohort consisted of 7,983 subjects (response rate 78%), the RS-II cohort of 3,011 participants (response rate 67%) and the RS-III cohort of 3,932 subjects (response rate 65%). The RS-I cohort had baseline examinations during 1990 – 1993 with completion of standardized questionnaires, blood sampling and DNA isolation. The RS-II was formed as an independent cohort in 1999 with baseline examinations between 2000 and 2001 and the RS-III cohort was examined between 2006 and 2008.

A regional anticoagulation clinic, Star Medical Diagnostic Center, monitors all inhabitants of Ommoord with an indication for anticoagulant therapy. This clinic covers the patients from all three RS cohorts. From this clinic, since 1984, all data on dosing, laboratory and clinical data, including data on bleeding complications are fully computerized. The patients own treating physician decides about the type of anticoagulant. Prothrombin times are monitored every 1-6 weeks, depending on the target level and stability of the INR. Coumarin doses are adjusted on the basis of computerized dose calculations. More than 99% of participants fill their drug prescriptions at seven regional pharmacies, which are fully computerised. Complete data on drug use from these pharmacies were available as of

January<sup>1st</sup>, 1991. The pharmacy data include the Anatomical Therapeutical Chemical (ATC)-

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3 code(World Health Organization Collaborating Centre for Drug Statistics Methodology  
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5 2004), the filling date, the total amount of drug units per prescription, the prescribed daily  
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7 number of units, and product name of the drugs. As PPIs we included omeprazole (selected  
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9 from pharmacy dispensing data by the ATC code of the WHO (World Health Organization  
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11 Collaborating Centre for Drug Statistics Methodology 2004), A02BC01), pantoprazole  
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13 (A02BC02), lansoprazole (A02BC03), rabeprazole (A02BC04) and esomeprazole  
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15 (A02BC05).  
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#### 24 Cohort and outcome definition

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27 Our study population consisted of all patients of the three RS cohorts who started with  
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29 acenocoumarol in the study period from April 1<sup>st</sup>, 1991 through September 9<sup>th</sup>, 2009 and used  
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31 it consecutively for at least 42 days. The start date of April 1<sup>st</sup> was chosen to ensure that at  
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33 least 3 months of medication history from the pharmacy was available for each cohort  
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35 member. We regarded the period starting 42 days after initiation with acenocoumarol as  
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37 maintenance period. In general, steady state of a drug is usually achieved within 5-7 half-lives  
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39 of drug elimination. For (R-)acenocoumarol, the enantiomeric form on which treatment  
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41 effects mainly depend, with a half-life of 8 hours, a period of 6 weeks taken as initiation  
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43 period was considered extensive enough to reach a steady state.(Flockhart, *et al* 2008) In  
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45 patients from the Rotterdam study using acenocoumarol during the maintenance period, we  
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47 took an event of an INR of 6 and greater after baseline study enrolment as an outcome. INR  
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49 levels  $\geq 6$  are associated with an extensively increased risk of bleedings.(Cannegieter, *et al*  
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51 1995) We excluded INR events of six and greater that happened within 21 days of an earlier  
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60 event.

### Cofactors

The following baseline patient characteristics were considered as potential confounders or effect modifiers: sex, age, BMI, and target INR level. BMI was defined as ( $\text{kg}/\text{m}^2$ ) and missing values were imputed with a linear regression model consisting of  $\text{INR} \geq 6$ , age, sex and target INR as variables. We further adjusted for oral non-steroidal anti-inflammatory drugs (NSAIDs) as co-medication (ATC code M01A), since PPIs might have been started because of treatment with an NSAID and NSAIDs have been shown earlier to increase acenocoumarol effectiveness.(Visser, *et al* 2005)

In a subanalysis we studied the association of acenocoumarol maintenance treatment with use of ranitidine (A02BA02). This drug is used for the same indication and not known to be dependent on biotransformation via CYP2C19. (Koninklijke Nederlandse Maatschappij ter bevordering der Pharmacie; The Hague 2008) In further subanalyses, we studied effect modification of the *CYP2C19*\*2 variant allele (rs4244285) on an  $\text{INR} \geq 6$  during use of acenocoumarol. To date, about 19 variant alleles of CYP2C19 have been identified.(Yang and Link 2010) The majority of individuals can be classified into three phenotype groups, homozygous and heterozygous extensive metabolizers and poor metabolizers. They are determined by the wild-type genotype and two mutated alleles, *CYP2C19*\*2 and *CYP2C19*\*3. The principal defect, *CYP2C19*\*2 (rs4244285) with a G-allele for normal function and an A-allele as variant with decreased efficiency, leads to a truncated protein and was genotyped in our population. *CYP2C19*\*3 is rare in Caucasians and was not genotyped in the Rotterdam Study.(Cannegieter, *et al* 1995)

## Genotyping

All RS participants with available DNA were genotyped using Illumina Infinium II HumanHap BeadChips at the Department of Internal Medicine, Erasmus Medical Center following manufacturer's protocols. **With this technology DNA is methylated and the assay can measure the methylation level at 14,495 genes.** (Hancock, *et al*).

**Suggestion to skip the following details and just to keep the reference of Hancock et al.**

RS-I participants (n=6,449) were genotyped with 550k (V.3) single and duo chips, while RS-II participants (n=2,516) were genotyped with 550k (V.3) duo and 610k Quad chips. RS-III (n=2,420) participants were genotyped with the Human 610 Quad Arrays of Illumina.

Genotype calling was performed in RS-I using BeadStudio software (version 0.3.10.14), GenomesStudio in RS-II and Bead Studio (v3.2.23) in RSIII. Participants with call rates <97.5%, excess autosomal heterozygosity, sex mismatch or outlying identity-by-state clustering estimates were excluded. After quality control, 5,974 RS-I participants, 2,157 RS-II and 2,078 RS-III participants remained with complete data on genotyping.(Hancock, *et al*)

For imputation, 512,349 autosomal SNPs in RS-I and 466,389 autosomal SNPs in RS-II and RS-III were used after exclusions for call rate < 98%, HWE  $P < 10^{-6}$ , and MAF < 1%, in MACH (version 1.00.15 for RS-I, 1.00.16 for RS-II and RS-III) with reference to the 2,543,886 SNPs of the HapMap CEU (release 22, build 36). (Hancock, *et al*).

**Skip until here.**

## Statistical analysis

Within a subject, an INR  $\geq 6$  could occur more than once and co-medication with PPIs could change during acenocoumarol treatment period. In order to include all information available for the whole study period, we used the Andersen-Gill extension of the Cox proportional

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3 hazards model. This model allows to study multiple events of an  $\text{INR} \geq 6$  within one subject  
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5 and in association with PPI use as a time-varying covariable. (Andersen and Gill 1982) All  
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7 subjects on acenocoumarol maintenance therapy were followed as of April 1<sup>st</sup>, 1991, from  
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9 their first INR assessment until the last INR assessment because of the end of their treatment,  
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11 last INR  $\geq 6$  event or the end of the study period, whichever came first. The date on which an  
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13 INR  $\geq 6$  occurred was taken as the index date. In order to exclude protopathic bias, patients  
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15 were only considered as exposed to PPIs at the index date if they had started PPI at least 3  
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17 days before that date. Each case was compared for PPI exposure to all subjects who were on  
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19 acenocoumarol maintenance treatment at the index date. (Stricker and Steijnen 2010) Thus  
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21 cases could serve as controls on other index dates when still being on acenocoumarol  
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23 treatment. We computed hazard ratios (HRs) and their 95% confidence intervals (CIs) for all  
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25 events of an  $\text{INR} \geq 6$ . Risk estimates were adjusted for age, sex, target INR, BMI and NSAID  
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27 co-medication. To study effect modification by *CYP2C19* genotype, patients were stratified  
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29 according to their genotype as *CYP2C19*\*2 homozygous G-alleles and variant type  
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31 (*CYP2C19*\*2 heterozygous G/A-alleles or *CYP2C19*\*2 homozygous A-alleles).  
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39 SPSS 15.0 was used for data management and SAS 9.20 for the Andersen-Gill analysis.  
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#### 46 Acknowledgements

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50 The Rotterdam Study is funded by Erasmus Medical Center and Erasmus University,  
51  
52 Rotterdam, Netherlands Organization for the Health Research and Development (ZonMw),  
53  
54 the Research Institute for Diseases in the Elderly (RIDE), the Ministry of Education, Culture  
55  
56 and Science, the Ministry for Health, Welfare and Sports, the European Commission (DG  
57  
58 XII), and the Municipality of Rotterdam.  
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3 The generation and management of GWAS genotype data for the Rotterdam Study is  
4 supported by the Netherlands Organisation of Scientific Research NWO Investments (nr.  
5 175.010.2005.011, 911-03-012). This study is funded by the Research Institute for Diseases in  
6 the Elderly (014-93-015; RIDE2) and the Netherlands Genomics Initiative (NGI)/Netherlands  
7 Organisation for Scientific Research (NWO) project nr. 050-060-810. We thank Pascal Arp,  
8 Mila Jhamai, Dr Michael Moorhouse, Marijn Verkerk and Sander Bervoets for their help in  
9 creating the GWAS database. The authors are grateful to the study participants, the staff from  
10 the Rotterdam Study and the participating general practitioners and pharmacists.  
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### 26 **Conflict of interest statement**

27 All authors state that they do not have any conflicts of interest to declare.  
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**Table 1 Characteristics of acenocoumarol users with INR $\geq$ 6.0 and total cohort**

	Patients with INR $\geq$ 6.0 (N=887)	Total cohort (N=2,755)	HR <sup>a</sup>	95% CI
Gender				
Male (%)	405 (45.7)	1,192 (43.3)	1.00	Reference
Female (%)	482 (54.3)	1,563 (56.7)	<b>1.25</b>	<b>(1.15 – 1.36)</b>
Start age (years)				
45 – 54	10 (1.1%)	114 (4.2%)	1.00	Reference
55 – 64	72 (8.1%)	383 (14.0%)	<b>2.89</b>	<b>1.75 – 4.78</b>
65 – 74	214 (24.1%)	907 (33.2%)	<b>2.74</b>	<b>1.69 – 4.45</b>
75 – 84	389 (43.9%)	998 (36.5%)	<b>4.14</b>	<b>2.56 – 6.68</b>
>85	202 (22.8%)	334 (12.2%)	<b>6.10</b>	<b>2.63 – 14.1</b>
BMI (kg/m <sup>2</sup> )				
15.0 – 20.0	17 (1.9)	45 (1.6)	1.00	Reference
20.1 – 25.0	228 (25.7)	718 (26.1)	<b>0.70</b>	<b>0.52 – 0.93</b>
25.1 – 30.0	492 (55.5)	1446 (52.6)	<b>0.68</b>	<b>0.51 – 0.91</b>
>30.0	150 (16.9)	539 (19.6)	<b>0.56</b>	<b>0.42 – 0.76</b>
Target level (INR)				
2.0 – 2.5	1 (0.1)	118 (4.3)	1.00	Reference
2.0 - 3.5	389 (43.9%)	1728 (62.7%)	<b>10.1</b>	<b>3.23 – 31.2</b>
3.0 - 4.0	482 (54.3%)	889 (32.3%)	<b>27.9</b>	<b>9.00 – 86.7</b>
3.5 - 4.5	15 (1.7%)	20 (0.7%)	<b>65.4</b>	<b>17.3 - 247</b>
Subjects with NSAID use	89 (10.0)	470 (17.0)	<b>1.31</b>	<b>1.15 – 1.50</b>
<i>CYP2C19</i> *2 genotypes <sup>b</sup>	N=648 (73.1% of all cases)	N=2059 (74.7% of the total group)		
GG	472 (72.8%)	1464 (71.1%)	1.00	Reference
GA and AA	176 (27.2%)	595 (28.9%)	0.99	0.89 – 1.11

Statistically significant values are printed in bold. a Univariate analysis of RR were performed with a n Andersen-Gill model. RRs cannot be calculated with the numbers in this table because controls may later become cases; significant values are printed in bold.

b For the *CYP2C19*\*2 genotype within total cohort, allelic frequency of the G-allele was 84.3%, of the A-allele 15.7%, and HWE was 0.93

Abbreviations: INR, international normalized ratio; HR, hazard ratio; CI, confidence interval; HWE, Hardy-Weinberg equilibrium.

**Table 2 Association between overanticoagulation (INR $\geq$ 6) under acenocoumarol maintenance treatment and PPIs**

PPI	Total cohort <sup>a</sup> (N=2,755) and use of a specific drug	Andersen-Gill analysis		
		Cases with use of a specific drug with at least one INR $\geq$ 6.0	HR <sup>b</sup> (95% CI)	HR <sup>c</sup> (95% CI)
Omeprazole	457	82	<b>1.18 (1.01 – 1.38)</b>	1.12 (0.96 – 1.32)
Pantoprazole	160	31	1.27 (0.97 – 1.67)	1.21 (0.92 – 1.59)
Lansoprazole	102	24	<b>1.50 (1.06 – 2.12)</b>	<b>1.49 (1.05 – 2.10)</b>
Rabeprazole	286	44	<b>1.30 (1.01 – 1.67)</b>	1.23 (0.95 – 1.58)
Esomeprazole	149	42	<b>2.08 (1.63 – 2.67)</b>	<b>1.99 (1.55 – 2.55)</b>
<i>Subanalysis</i>				
Ranitidine	290	44	1.08 (0.84 – 1.35)	1.06 (0.83 – 1.35)

Statistically significant values are printed in bold

a In this time-dependent analysis, exposure in case patient and in the rest of the cohort is assessed at the time of the outcome in each case patient (index date). As control patients can be used multiple times, the number of assessments in the reference group is much larger than the number of individuals. Hence, crude RRs cannot be calculated from the data in this table.

b adjusted for age, sex, BMI and target INR

c adjusted for age, sex, BMI, target INR and use of non-steroidal anti-inflammatory drugs, ATC-group M01A.

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For Peer Review

**Table 3 Association between overanticoagulation ( $INR \geq 6.0$ ), esomeprazole or lansoprazole, stratified by *CYP2C19\*2* genotype**

	HR <sup>a</sup> (95% CI)	P-value for interaction
P-value of multiplicative interaction between esomeprazole or lansoprazole and <i>CYP2C19*2</i> genotypes (wild type genotype / at least one variant A-allele)		0.73
P-value for an additive effect modification between esomeprazole or lansoprazole and <i>CYP2C19*2</i> genotypes (wild type genotype / at least one variant A-allele)		0.11
No use of esomeprazole or lansoprazole, <i>CYP2C19*2</i> homozygous G-allele	1.00 reference	
No use of esomeprazole or lansoprazole, <i>CYP2C19*2</i> at least one variant A allele	0.92 (0.83 – 1.03)	
Use of esomeprazole or lansoprazole, <i>CYP2C19*2</i> homozygous G-allele	<b>1.69 (1.31 – 2.19)</b>	
Use of esomeprazole or lansoprazole, <i>CYP2C19*2</i> at least one variant A allele	1.52 (0.93 – 2.50)	

Significant values are printed in bold.

a adjusted for age, sex, BMI, target INR and use of nonsteroidal anti-inflammatory drugs, ATC-group M01A.