SCREENING FOR VASCULAR RISK FACTORS IN GLAUCOMA: THE GVRF STUDY

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ABSTRACT[1]

Purpose: To determine the prevalence of vascular risk factors (VRF) in patients with primary open-angle glaucoma (POAG), normal tension glaucoma (NTG), and ocular hypertension (OH), and to evaluate their influence in the progression of the disease.

Methods: 269 Belgian ophthalmologists were invited to participate in this cross-sectional prevalence study. Using a questionnaire the following parameters were analyzed in patients with POAG, NTG, and OH: age, intraocular pressure, refraction, visual field defect, vertical cup/disc ratio, medical therapy, and vascular risk factors. Progression of visual field was based on subjective analysis of minimum three reliable automated perimetries over a period of minimum three years.

Results: 4920 patients were enrolled in the study. 75% had POAG, 8% had NTG, and 17% had OH. The mean age was 67 years (40-99 y.). Fifty-three percent were female. There was a significant difference in the prevalence of no VRF vs. >1 VRF between the patients with OH and the patients with POAG/NTG ($p<0.01$). Visual field progression was found in 34% of the patients with POAG and 46% of the patients with NTG. In the group with POAG the presence of at least 2 and at least 3 VRF increased the risk for visual field progression with respectively 16% and 42% compared to patients without VRF (p = respectively 0.03 and 0.002).

Conclusions: The prevalence of VRF is significantly higher in patients with POAG/NTG compared to patients with OH. The presence of VRF might increase the risk for progression of glaucomatous visual field defects.

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* *On behalf of the Belgian Glaucoma Society*

received: 13.06.05
accepted: 09.11.05

RÉSUMÉ

Objectif: Déterminer la prévalence des facteurs de risque vasculaire (FRV) chez des patients atteints de glaucome primitif à angle ouvert (GPAO), de glaucome à pression normale (GPN), et d'hypertonie oculaire simple (HOS), afin d'évaluer leur influence sur la progression de la maladie.

Méthodes: 269 ophtalmologues belges ont été invités à participer à cette étude transversale de prévalence. A l'aide d'un questionnaire les paramètres suivants ont été analysés chez des patients ayant un GPAO, un GPN ou une HOS: âge, pression intraoculaire, réfraction, déficits du champ visuel, ratio cup/disc vertical, traitement médicamenteux et facteurs de risque vasculaire. La progression du champ visuel est basée sur l'analyse subjective de minimum trois périmétries fiables et automatisées sur une période de trois ans minimum.

Résultats: 4920 patients ont été inclus dans l'étude. 75% ont un GPAO, 8% un GPN, et 17% une HOS. L'âge moyen est de 67 ans (49-99 ans). Cinquante-trois pour cent sont de sexe féminin. On observe une différence significative quant à la prévalence des FRV (aucun FRV vs. >1 FRV) entre les patients ayant une HOS et les patients ayant un GPAO ou un GPN ($p<0.01$). Une progression du champ visuel a été observée chez 34% des patients ayant un GPAO et 46% des patients ayant un GPN. Dans le groupe atteint de GPAO, la présence d'au moins 2 ou au moins 3 FRV a augmenté le risque de progression du champ visuel de 16% et de 42% en comparaison avec les patients sans FRV (p = respectivement 0.03 et 0.002).

Conclusions: La prévalence de FRV est significativement plus importante chez des patients atteints de GPAO et GPN en comparaison avec les patients ayant une HOS. La présence de FRV peut représenter un facteur de risque pour la progression des déficits glaucomateux du champ visuel.

KEY WORDS

Glaucoma, ocular hypertension, vascular risk factors, intraocular pressure, epidemiology.

MOTS-CLÉS

glaucome, hypertonie oculaire, facteurs de risque vasculaire, pression intra-oculaire, épidémiologie.

INTRODUCTION

Glaucoma is a progressive optic neuropathy with a multifactorial etiology. Although elevated intraocular pressure is the most important risk factor, blood flow deficits may also contribute to the initiation and progression of the disease, more particularly in normal tension glaucoma (1-4, 6-9, 11-13, 19, 22). Many techniques have been used to evaluate the vascular role in the pathogenesis of glaucomatous damage. Among them pulsatile ocular blood flow measurement (POBF), scanning laser angiography of the peripapillary choroid (SLAPPC), scanning laser angiography of the retinal circulation (SLARC), scanning laser Doppler flowmetry (SLDF), and color Doppler imaging (9). The purpose of our study was to evaluate the impact of vascular risk factors (VRF) in glaucoma using a questionnaire. To the best of our knowledge no other study has been published using a questionnaire to evaluate the impact of VRF in glaucoma.

MATERIAL AND METHODS

269 Belgian ophthalmologists were invited to participate in this cross-sectional prevalence study. Using a questionnaire, the following parameters were analyzed in patients with POAG, NTG, and OH: age, gender, intraocular pressure (IOP), refraction, visual field (VF) defect, vertical cup/disc ratio, medical therapy, and vascular risk factors. Participating ophthalmologists were instructed during preparatory meetings on uniform interpretation of the questionnaire.

Patients with POAG, NTG, and OH were included at the discretion of the ophthalmologist after having given their informed consent. The IOP was measured with the Goldmann applanation tonometer. The subjective refraction at distance was documented as a spherical equivalent. VF defects were based on the last reliable standard white on white automated perimetry available, and were categorized for the most affected eye as being normal (MD<2 dB), mild (MD between 2 and <6 dB), moderate (MD between 6 and < 12 dB), and advanced (MD > 12 dB). Progression of VF was based on subjective analysis of minimum three reli-

Table 1. *Risk factors*

General	Cardio-vascular	Neurological
Familial history of glaucoma	Treated hypertension	Syncope
Treated diabetes	Nocturnal hypotension	Alzheimer disease
Myopia	Coronary disease	Tinnitus
Smoking habits	Intermittent claudication	Migraine
	Cold hands and feet	

Table 2. *Patient's demographics*

	TOTAL	POAG	NTG	OH
N	4917	3700	383	834
Age (y.) (range)	67 (40-99)	68.6 (40-99)	68.2 (40-90)	62.7 (40-90)
Gender (F/M)	53/47	54/46	60/40	48/52
IOP (mm Hg)	17.6 ± 3.5	17.8 ± 3.5	14.7 ± 2.6	18.4± 3.1*

* 90% of the patients with OH were treated

able automated perimetries over a period of minimum three years. The vertical cup to disc ratio was recorded for the most affected eye and categorized as follows: <0.3, 0.3-0.5, 0.6-0.8, and >0.8. It was also noted if the optic disc diameter appeared to be small, normal, or large. The medical therapy and any change in therapy at the time of the visit were documented.
Risk factors were classified as: general, cardiovascular, and neurological (table 1).
Fisher's exact test and Wilcoxon rank sum test were used to compare proportions. Wald test within logistic regression was used for the calculation of odds ratios. P values of < 0.05 were considered statistically significant. No adjustment for age was done when comparing the group with POAG and NTG.

RESULTS

6442 patients were screened in 269 centers between April and September 2003. 1525 patients were excluded for the following reasons: age < 40 y. (304), missing diagnosis (39), POAG with normal visual field and optic disc (265), and OH with abnormal visual field or optic disc (917). 4917 patients were included in the study. Patient demographics are shown in table 2. The alteration of the VF and of the optic disc for the patients with POAG and NTG is shown in figures 1-4. Surprisingly 13% of the patients with NTG had a normal achromatic automated perimetry.

The prevalence of VRF in the total group of patients is shown in figure 5. There was a significant difference in the prevalence of no VRF vs. > 1 VRF between the patients with OH and the patients with POAG/NTG (p<0.01, Fisher's exact test). The prevalence of arterial hypertension was significantly higher in patients with POAG than in those with NTG (p=0.02, Fisher's exact test). The prevalence of migraine and syncope was significantly higher in patients with NTG than in those with POAG (p=0.04 and p=0.02 respectively, Fisher's exact test). Visual field progression was found in 34% of the patients with POAG and 46% of the patients with NTG. In the group with POAG, the mean number of VRF was significantly higher in patients with VF progression than in those with stable VF, 1.22 and 1.07 respectively (p=0.0004, Wilcoxon rank sum test). In the group with POAG, the presence of at least 2 and at least 3 VRF increased the risk for visual field progression with respectively 16% and 42% compared to patients without VRF (p=0.03 and p=0.0002 respectively, Fisher's exact test). In the groups with POAG and NTG, the mean IOP was higher in patients with VF progression than in those with stable VF, respectively 17.9 and 17.4 mmHg in POAG, and 15 and 14 mmHg in NTG (p=0.04 and p=0.003 respectively, Wilcoxon rank sum test).
In the group with POAG, the odds for progression are significantly higher in the presence of diabetes and coronary disease, respectively

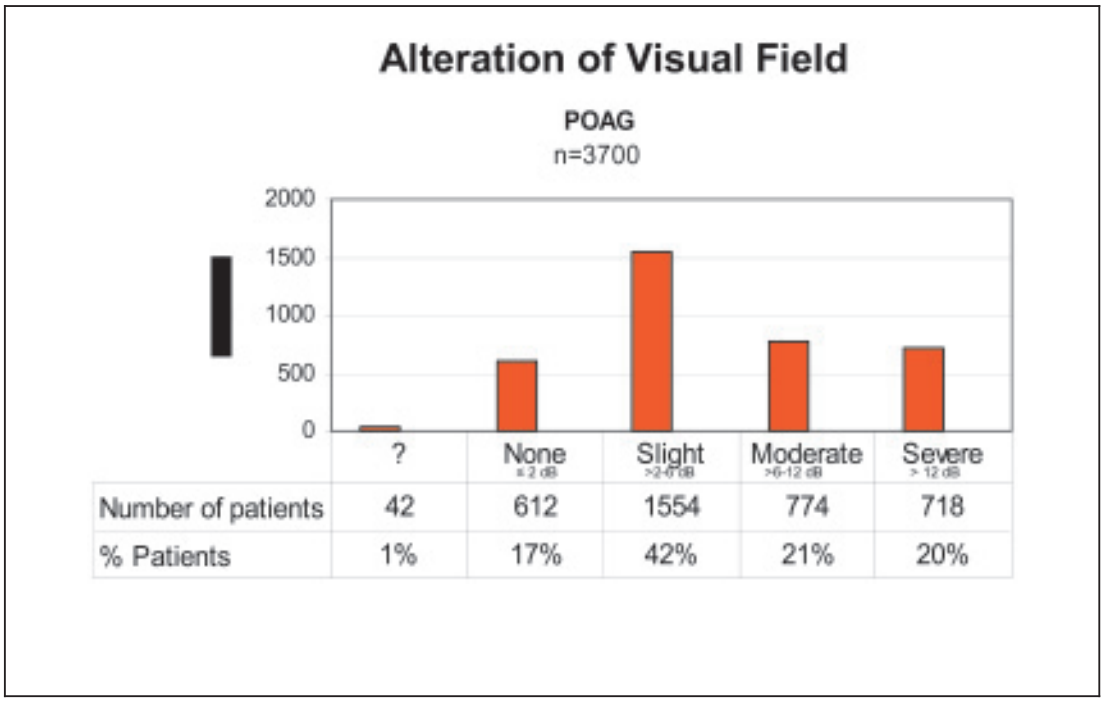


Figure 1. Alteration of the visual field in the most affected eye of patients with POAG.

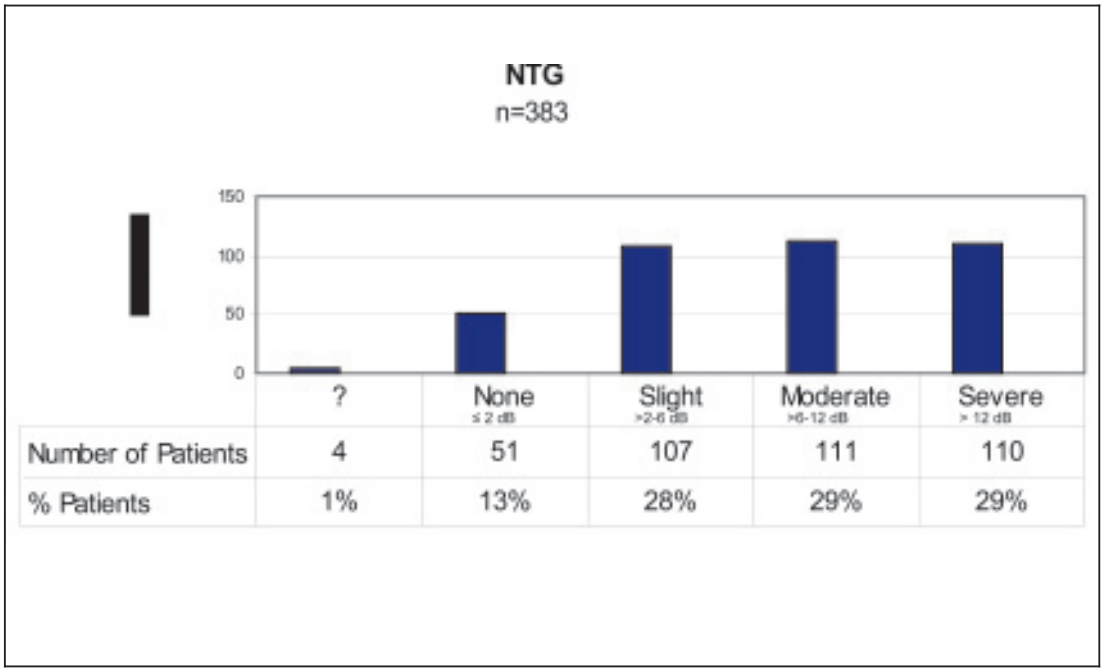


Figure 2. Alteration of the visual field in the most affected eye of patients with NTG.

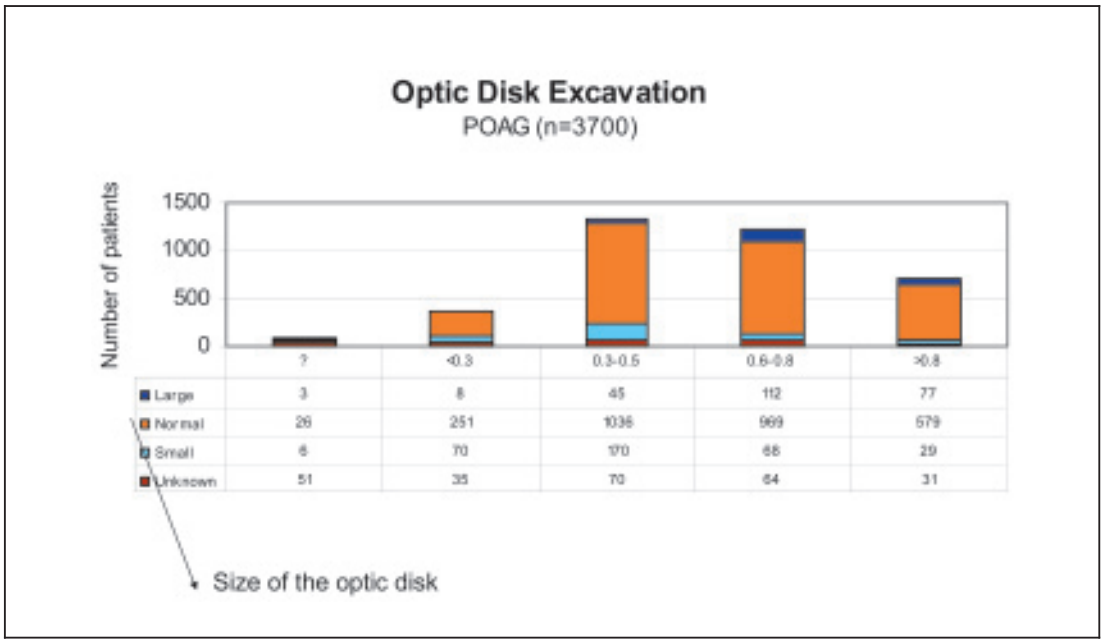


Figure 3. Alteration of the optic disc in the most affected eye of patients with POAG.

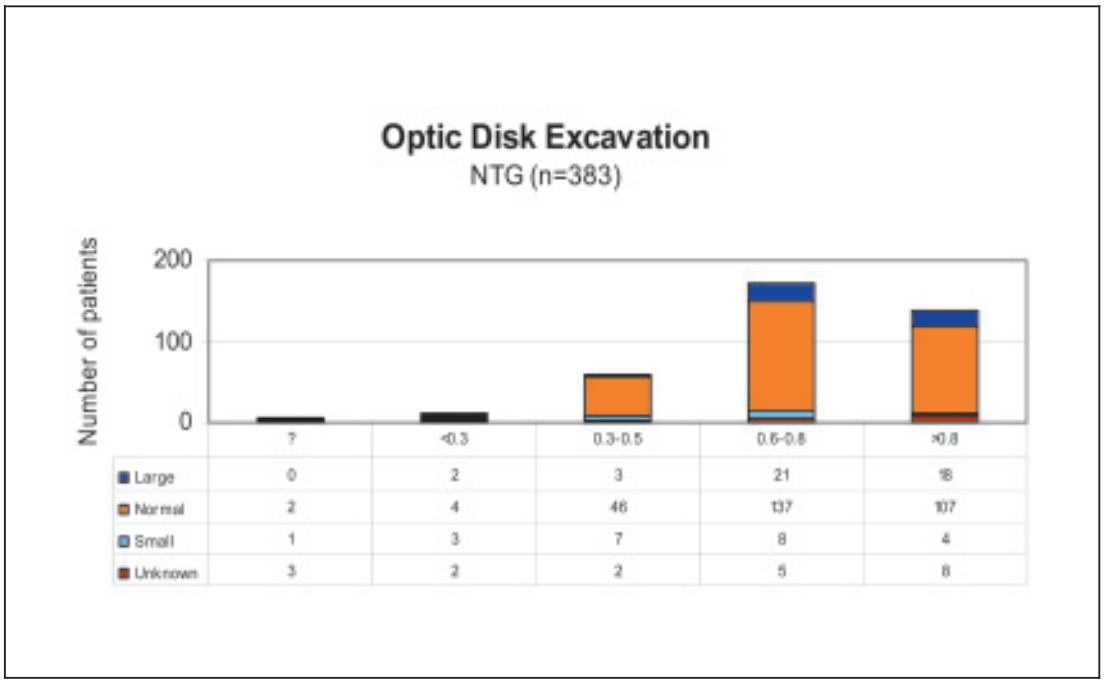


Figure 4. Alteration of the optic disc in the most affected eye of patients with NTG.

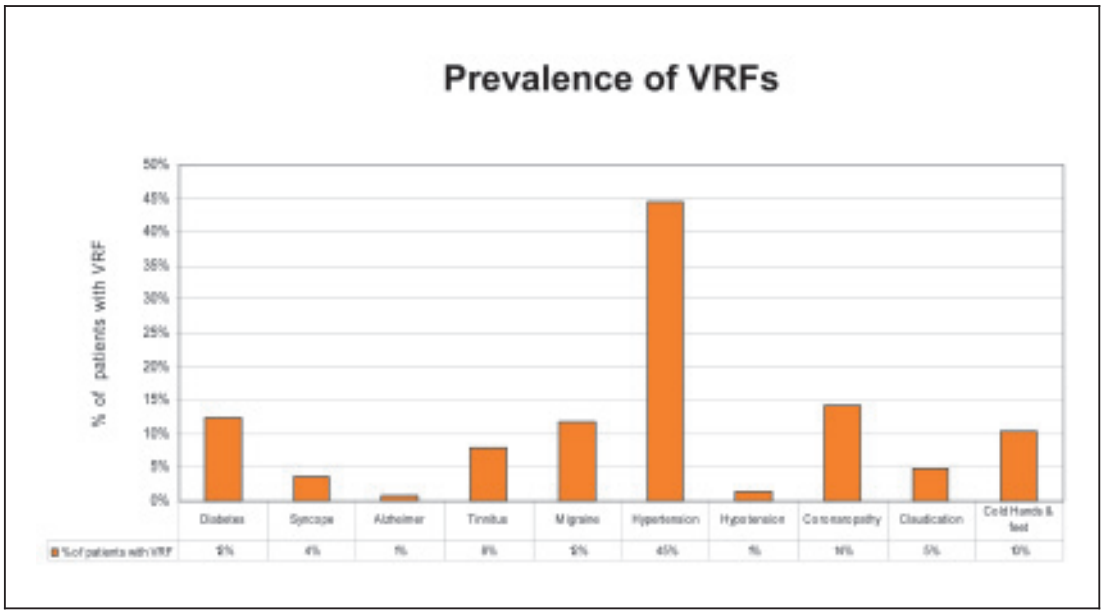


Figure 5. Prevalence of Vascular Risk Factors (VRF) in the total group of patients.

1.384 (CI 1.109-1.722) and 1.398 (CI 1.135-1.718). No VRF on its own was significant in predicting VF progression in patients with NTG.

DISCUSSION

The etiology of glaucoma remains unclear. Although elevated intraocular pressure remains the main risk factor, VRF also play a role in the initiation and progression of both primary open-angle and normal tension glaucoma (3,9,11-13,19,20,24). The above mentioned studies were based on qualitative clinical observations (peripapillary atrophy, disc hemorrhages, and myopia) or on quantitative measurements of ocular blood flow. To the best of our knowledge no other published study assessed the impact of VRF in patients with OH and glaucoma using a questionnaire.

We found a significant difference in the prevalence of no VRF vs. > 1 VRF between the patients with OH and the patients with POAG/NTG. A similar result was found by Orzalesi et al., who also used a questionnaire to investigate the cardiovascular risk factors in glaucoma (17). Further, these findings corroborate those of Cohen et al., who used the arteriolar pressure attenuation index to predict ocular hypertension progression to open-angle glaucoma (4). Landers et al., on the other hand, did not find systemic hypertension, diabetes, Raynaud's phenomenon, or migraine to be risk factors for converting from OH to POAG (14). The Ocular Hypertension Treatment Study (OHTS) could only detect heart disease to be a VRF predicting the onset of primary open-angle glaucoma (10). In the same study, diabetes even appeared to be significantly protective for developing POAG! This finding however is probably biased by the fact that diabetes patients are more often examined by an ophthalmologist.

In our study, the mean number of VRF was significantly higher in POAG patients with VF progression than in patients with stable VF. Likewise, in the same group of patients the presence of at least 2 and at least 3 VRF increased the risk for visual field progression by respectively 16% and 42%, compared to patients without VRF. This is in agreement with the above mentioned studies that were based on qualitative clinical observations and quantitative measurements of ocular blood flow (3,9,11-13,19,20,24). Most of those studies also

showed that VRF play a similar role in the progression of patients with NTG (3, 9, 11, 18, 23, 24). Surprisingly, in our study, what was found for patients with POAG could not be confirmed for patients with NTG. A possible explanation is that the impact of a single VRF, as assessed by a questionnaire, on the progression of NTG is weak, and could therefore not be detected in the number of patients examined. Another explanation is the limitation of the methodology used to detect progression, namely the subjective analysis of VF progression by more than 200 ophthalmologists.

This same limitation probably also explains the relatively high number of patients who progressed. Indeed in our study visual field progression was found in 34% of the patients with POAG and 46% of the patients with NTG after at least 3 years. This is much higher than in the big randomized clinical trials that were recently published. In the Collaborative Initial Glaucoma Trial (CIGTS) the incidence of VF progression on medically treated patients with POAG was 11% after 5 years, and in the Early Manifest Glaucoma Trial (EMGT) the incidence was 45% after 6 years (15, 16). In the Advanced Glaucoma Intervention Study (AGIS) the incidence was 14% after 5 years for patients having an IOP < 18 mmHg at each visit (21). In the Normal Tension Glaucoma Study (NTGS) the incidence of VF progression in treated patients was 10% after 7 years (5). On the other hand the shortcomings of our methodology, also reflected in the relative high number of exclusions, can be compensated, at least to a certain extent, by the large number of patients included.

Finally, another potential bias in this observational study is that the patients were included at the discretion of the ophthalmologist instead of consecutively or at random. However this is often the case when a questionnaire is used because of time constraints of both the ophthalmologist and the patient. It is therefore unlikely that any intentional inclusion bias would have happened.

CONCLUSIONS

Using a questionnaire to evaluate the impact of VRF in glaucoma, we conclude that the prevalence of VRF is significantly higher in patients with POAG/NTG compared to patients with OH. Despite the limitations to this study, we also conclude that the presence of VRF might increase the risk for progression of glaucomatous visual field defects.

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This multicenter, cross-sectional prevalence study was carried out under the auspices of the Belgian Glaucoma Society and sponsored by Merck Sharp & Dohme Belgium