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ORIGINAL RESEARCH ARTICLE

Physician and Patient Knowledge of Safety and Safe Use Information for Aflibercept in Europe: Evaluation of Risk-Minimization Measures

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Abstract

Background As part of the risk-management plan for aflibercept in the European Union, materials have been developed to educate physicians and patients in Europe on the safe use of aflibercept.

Objectives The objectives of this study were to measure receipt of the educational materials and to evaluate understanding of key safety information for aflibercept.

Methods An observational cross-sectional study among physicians and patients with recent aflibercept experience in France, Germany, Italy, Spain, and the UK was conducted. Eligible physicians and patients completed a brief questionnaire regarding their knowledge of key safety information.

Results Among the 8424 physicians invited to participate in the survey, 428 physicians were eligible, completed the questionnaire, and were included in this analysis. Most physicians reported having received the aflibercept summary of product characteristics (87%) and prescriber guide (77%); approximately half reported receiving the injection procedure video (50%) and patient booklet (54%). Physician knowledge of the most important topics (i.e., side effects; preparing patients for aflibercept injection) was high. Physician knowledge of dosing was high for neovascular (wet) age-related macular degeneration and lower for less commonly prescribed indications. Most physicians knew the contraindications for aflibercept and recognized possible side effects. Among the 874 patients approached about participation in the study, 773 patients were eligible, completed the questionnaire, and were included in the analysis. Patients' reported receipt was relatively low for the aflibercept patient booklet (38%) and the audio CD (23%). Patient knowledge of the health conditions to discuss with a doctor prior to injection was generally high; knowledge about possible side effects varied. Most patients knew that they should speak to a physician immediately if they experienced a possible side effect of aflibercept.

Conclusion Most physicians reported receiving the summary of product characteristics, prescriber guide, and patient booklet; half reported receiving the intravitreal injection procedure video. Patient receipt of the educational material was variable. Observed patterns of knowledge indicated the greatest knowledge of the most important risks emphasized in the educational material and lower knowledge of more complex or less salient aspects of safe use.

1 Introduction

The anti-vascular endothelial growth factor (VEGF)-A therapy aflibercept (Eylea; Bayer AG), administered as an intravitreal injection, is approved by the European Medicines Agency in adults for the treatment of neovascular (wet) age-related macular degeneration (wAMD), visual impairment due to macular edema secondary to central retinal vein occlusion (CRVO), visual impairment due to macular edema secondary to branch retinal vein occlusion (BRVO), visual impairment due to diabetic macular edema (DME), and visual impairment due to myopic choroidal neovascularization [1].

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Key Points

European physicians' and patients' receipt of aflibercept educational materials and knowledge of key safety information for aflibercept were evaluated in a survey.

Physicians' reported receipt was relatively high for most educational materials (50–87%). Physician knowledge was high for side effects, contraindications, preparing patients for aflibercept injection, and dosing practices for neovascular (wet) age-related macular degeneration and was lower for less commonly prescribed indications.

Patients' reported receipt was relatively low for the educational materials (23–38%). Patient knowledge of the health conditions to discuss with a doctor prior to injection was generally high; knowledge about possible side effects varied. Most patients knew to consult a physician immediately when experiencing a possible side effect of aflibercept.

Observed patterns of knowledge among physicians and patients indicated the greatest knowledge of the most important risks emphasized in the educational material and lower knowledge of more complex aspects of safe use. Relatively high levels of patient knowledge despite low reported receipt of the educational materials suggests that patients were receiving information from other sources.

Intravitreal injections, including anti-VEGF therapies, have been associated with ocular complications including endophthalmitis, transient increases in intraocular pressure, traumatic cataract, and retinal and vitreous detachment. Less serious and more common complications include conjunctival hemorrhage, vitreous floaters, and eye pain [2, 3].

A risk-management plan is in place for aflibercept in the European Union [4]. As part of the risk-management plan, the manufacturer has developed materials to educate physicians and patients on the key safety information and safe use for aflibercept. The key content of the educational materials for physicians includes the importance of using the correct sterile injection technique and monitoring and managing potential injection-related adverse events. Key content for patients includes steps for preparing for treatment, monitoring for adverse events, and steps to take if they identify adverse events.

The objectives of this study were to investigate whether physicians and patients received the educational materials and to assess physicians' and patients' knowledge and understanding of key safety information therein. A similar study was conducted to evaluate physician knowledge of the key safety information for aflibercept in Canada [20].

2 Methods

2.1 Study Design and Sample

The study was an observational cross-sectional study of knowledge, understanding, and self-reported behavior among a sample of physicians and patients with recent aflibercept experience in France, Germany, Italy, Spain, and the UK. The five countries included were chosen to provide some diversity in practice patterns and patient treatment indication, and to observe differences in physician and patient knowledge in these settings. In addition, prescribing levels in these countries were such that there was a sufficient number of eligible physicians and patients with aflibercept experience to participate in the study. Design and implementation of the study followed best practices in pharmacoepidemiology and pharmacovigilance [5–8]. This study complied with the principles of the Declaration of Helsinki and all national and local regulatory and ethical requirements were fulfilled. The study was exempted from review by the Office of Research Protection and Ethics at RTI International. All participants provided informed consent.

Eligible physicians were licensed practicing ophthalmologists who had prescribed or administered aflibercept in the previous 6 months. Physicians were primarily recruited from an online physician panel comprising convenience samples of physicians derived from hospital books, medical directories, and peer referrals. Invitations to complete a self-administered web-based questionnaire were sent by e-mail and telephone. Because of the fact that the number of ophthalmologists on the panel was relatively limited, we invited all ophthalmologists on the panel in each country to participate to reach the target sample size for the study. A sample of 60–100 physicians per country was targeted, for a total of 300–500.

As is common in cross-sectional surveys, sample sizes were targeted based on the desire for reasonable statistical precision (e.g., confidence intervals) around percentage estimates of knowledge and understanding of the key safety information as well as feasibility. Two independent groups of physicians were selected to participate in the patient and physician assessments: those who only participated in the physician assessment as described above (non-recruiting physicians) and those who recruited patients for the patient assessment as described below (recruiting physicians) [see the Appendix in the Electronic Supplementary Material (ESM)]. Physicians provided informed consent and completed a screening question before completing the questionnaire.

Eligible patients had received an aflibercept injection within the previous 6 months. Patients were recruited from

46 participating sites. Eligible patients who were present for a scheduled visit were invited to participate by their physicians; those who wished to participate completed an interviewer-administered questionnaire after providing informed consent. To minimize a potential intervention effect, sites were trained not to discuss the study with patients before their visit, so that patients would not prepare for the survey beforehand. Further, sites were asked not to deviate from their customary patient counseling practices and were asked to administer the questionnaire to patients during the visit prior to any patient counseling. Site personnel were trained on the importance of and processes for conducting an objective interview. The questionnaire was administered without the aid of a patient booklet for referral, thus relying on patients' recall of the key messages for completion. Each site aimed to recruit at least one patient per indication. A sample of 150 patients per country was targeted, for a total of 750. Patients were not incentivized for their participation in the study, and the patient information sheet and informed consent form clearly stated that participation was voluntary.

Recruitment and data collection occurred in December 2015–September 2016. Data collection was initiated after the prescriber education packets had been distributed and physicians and patients had an opportunity to receive and use the information. Sites selected for the patient assessment were excluded from the primary physician assessment. However, participating physicians from the sites included in the patient assessment completed the physician questionnaire to allow additional exploratory analyses (see the ESM). Physicians were compensated for their time in completing the survey and in recruiting patients.

2.2 Questionnaire

The physician and patient questionnaires evaluated receipt and use of the aflibercept educational materials and knowledge and understanding of the key information therein (see the ESM). Before administration of the survey, the questionnaires were cognitively pretested among physicians and patients similar to the study population in each country and were modified based on interview feedback. Overall, nine interviews with physicians and 11 interviews with patients were first conducted in the UK to identify issues and optimize wording, after which the questionnaires were translated into French, German, Italian, and Spanish; each translated questionnaire was pretested with four physicians and four patients in each of the four remaining countries. The cognitive interviews revealed challenges in administering paper-based questionnaires to the target population; thus, an in-person interviewer-administered mode of administration was used for the patient assessment.

2.3 Statistical Methods

All analyses were performed using SAS 9.4 statistical software (SAS Institute, Inc., Cary, NC, USA). Data analyses were descriptive. Exact 95% confidence intervals around the percentage of participants who answered each knowledge question correctly were generated using the Clopper–Pearson method. No imputation of missing values was performed.

3 Results

3.1 Participant Characteristics

3.1.1 Physicians

Of the 8424 physicians invited to participate in the survey, 428 physicians were eligible, completed the questionnaire, and were included in this analysis. The overall response rate was 5.1%.

The most common ophthalmology specialties were retina (74%), general ophthalmology (54%), glaucoma (35%), or cataract (45%); 73% were male, and the duration of time in practice varied (Table 1). Per the study inclusion criteria, all physicians had prescribed (91%) and/or administered (83%) aflibercept in the previous 6 months for indications including wAMD (97%), DME (79%), CRVO (67%), and BRVO (58%) (Table 2).

3.1.2 Patients

Among the 874 patients approached about participation in the study, 773 patients were eligible, completed the questionnaire, and were included in the analysis. The overall response rate was 91%.

Overall, most patients (81%) were aged 66 years or older; 54% were female (Table 3). Most patients (82%) reported having no university-level education (Table 3). The most common indication for which aflibercept was prescribed to patients was wAMD (71%), followed by DME (19%), CRVO (5%), and BRVO (4%) (Table 4). Over half of patients (60%) had received their first injection of aflibercept within the previous year, and most (74%) had received one to six aflibercept injections in the prior 12 months.

3.2 Physician Assessment

3.2.1 Physician Receipt and Use of Educational Materials

Physicians participating in the study were asked to indicate whether they had received and reviewed aflibercept

Table 1 Physician characteristics

Question	Number of physicians (%)					
	France (*N* = 69)	Germany (*N* = 59)	Italy (*N* = 99)	Spain (*N* = 102)	UK (*N* = 99)	Overall (*N* = 428)
Focus within ophthalmology[a]						
Retina	50 (72)	45 (76)	67 (68)	79 (77)	77 (78)	318 (74)
General ophthalmology	36 (52)	43 (73)	50 (51)	48 (47)	52 (53)	229 (54)
Glaucoma	24 (35)	26 (44)	31 (31)	43 (42)	26 (26)	150 (35)
Cataract	30 (43)	32 (54)	36 (36)	50 (49)	46 (46)	194 (45)
Other	2 (3)	3 (5)	9 (9)	13 (13)	9 (9)	36 (8)
No answer	1 (1)	1 (2)	3 (3)	3 (3)	2 (2)	10 (2)
Years treating patients						
5 or fewer	8 (12)	0 (0)	19 (19)	9 (9)	9 (9)	45 (11)
6–10	19 (28)	12 (20)	32 (32)	29 (28)	31 (31)	123 (29)
11–15	14 (20)	15 (25)	11 (11)	21 (21)	21 (21)	82 (19)
16–20	17 (25)	12 (20)	15 (15)	27 (26)	15 (15)	86 (20)
21–25	5 (7)	10 (17)	6 (6)	7 (7)	12 (12)	40 (9)
More than 25	5 (7)	9 (15)	13 (13)	6 (6)	9 (9)	42 (10)
No answer	1 (1)	1 (2)	3 (3)	3 (3)	2 (2)	10 (2)
Sex						
Male	53 (77)	45 (76)	78 (79)	54 (53)	81 (82)	311 (73)
Female	15 (22)	13 (22)	18 (18)	45 (44)	16 (16)	107 (25)
No answer	1 (1)	1 (2)	3 (3)	3 (3)	2 (2)	10 (2)

[a]This was a "tick all that apply" question; thus, the sum of responses can be greater than 100%

Table 2 Physicians' experience with aflibercept

Question	Number of physicians (%)					
	France (*N* = 69)	Germany (*N* = 59)	Italy (*N* = 99)	Spain (*N* = 102)	UK (*N* = 99)	Overall (*N* = 428)
Prescribed and/or administered aflibercept in the past 6 months						
Prescribed aflibercept	66 (96)	54 (92)	84 (85)	93 (91)	93 (94)	390 (91)
Administered an aflibercept injection	62 (90)	48 (81)	67 (68)	93 (91)	85 (86)	355 (83)
Indications for which prescribed and/or administered aflibercept						
wAMD	67 (97)	58 (98)	94 (95)	100 (98)	97 (98)	416 (97)
CRVO	61 (88)	49 (83)	41 (41)	62 (61)	73 (74)	286 (67)
DME	64 (93)	51 (86)	63 (64)	90 (88)	72 (73)	340 (79)
BRVO	54 (78)	45 (76)	37 (37)	58 (57)	53 (54)	247 (58)
Other indication	4 (6)	6 (10)	2 (2)	16 (16)	3 (3)	31 (7)
Average monthly anti-VEGF intravitreal injections						
Less than 5	5 (7)	2 (3)	15 (15)	6 (6)	15 (15)	43 (10)
5–40	38 (55)	24 (41)	56 (57)	63 (62)	41 (41)	222 (52)
More than 40	23 (33)	31 (53)	20 (20)	29 (28)	40 (40)	143 (33)
I don't know	2 (3)	1 (2)	5 (5)	1 (1)	1 (1)	10 (2)
No answer	1 (1)	1 (2)	3 (3)	3 (3)	2 (2)	10 (2)
Last aflibercept injection administered						
Less than 1 month ago	61 (88)	53 (90)	71 (72)	83 (81)	69 (70)	337 (79)
1 to 6 months ago	4 (6)	3 (5)	18 (18)	16 (16)	23 (23)	64 (15)
I don't know	3 (4)	2 (3)	7 (7)	0 (0)	5 (5)	17 (4)
No answer	1 (1)	1 (2)	3 (3)	3 (3)	2 (2)	10 (2)

BRVO branch retinal vein occlusion, *CRVO* central retinal vein occlusion, *DME* diabetic macular edema, *VEGF* vascular endothelial growth factor, *wAMD* wet age-related macular degeneration

Table 3 Patient demographics

Question	Number of patients (%)					
	France ($N=114$)	Germany ($N=158$)	Italy ($N=168$)	Spain ($N=169$)	UK ($N=164$)	Overall ($N=773$)
Age (years)						
18–45	0 (0)	2 (2)	1 (1)	2 (2)	2 (1)	7 (1)
46–65	20 (18)	31 (19)	26 (16)	38 (23)	26 (16)	141 (18)
66–85	79 (69)	107 (67)	125 (74)	109 (65)	115 (70)	535 (69)
86 or older	15 (13)	18 (11)	16 (10)	20 (12)	21 (13)	90 (12)
Sex						
Female	69 (61)	85 (54)	86 (51)	86 (51)	91 (55)	417 (54)
Male	45 (39)	73 (46)	82 (49)	83 (49)	73 (45)	356 (46)
Education						
No university (primary school, secondary school, university, or professional preparation)	81 (71)	121 (77)	150 (89)	141 (83)	138 (84)	631 (82)
Undergraduate and/or post-graduate university	33 (29)	33 (21)	18 (11)	24 (14)	25 (15)	133 (17)
No answer	0 (0)	4 (3)	0 (0)	4 (2)	1 (1)	9 (1)

For patients with multiple responses for Question 11, only the highest indicated education level was used in this analysis

Table 4 Treatment characteristics

Question	Number of patients (%)					
	France ($N=114$)	Germany ($N=158$)	Italy ($N=168$)	Spain ($N=169$)	UK ($N=164$)	Overall ($N=773$)
Indication						
wAMD	84 (74)	95 (60)	136 (81)	116 (69)	118 (72)	549 (71)
DME	19 (17)	34 (22)	25 (15)	35 (21)	31 (19)	144 (19)
CRVO	5 (4)	11 (7)	6 (4)	7 (4)	13 (8)	42 (5)
BRVO	6 (5)	12 (8)	1 (1)	8 (5)	3 (2)	30 (4)
Other	3 (3)	7 (4)	0 (0)	5 (3)	3 (2)	18 (2)
Time since first aflibercept injection						
Less than 1 month	4 (4)	14 (9)	38 (23)	7 (4)	10 (6)	73 (9)
From 1 to 6 months	25 (22)	38 (24)	40 (24)	47 (28)	54 (33)	204 (26)
More than 6 months but less than 1 year	35 (31)	40 (25)	32 (19)	57 (34)	27 (16)	191 (25)
One year or more	49 (43)	65 (41)	58 (35)	58 (34)	72 (44)	302 (39)
No answer	1 (1)	1 (1)	0 (0)	0 (0)	1 (1)	3 (0)
Number of aflibercept injections in the past 12 months						
1–2	12 (11)	24 (15)	73 (43)	54 (32)	30 (18)	193 (25)
3–4	29 (25)	32 (20)	46 (27)	48 (28)	46 (28)	201 (26)
5–6	41 (36)	36 (23)	32 (19)	38 (22)	34 (21)	181 (23)
> 6	32 (28)	66 (42)	17 (10)	29 (17)	54 (33)	198 (26)

BRVO branch retinal vein occlusion, *CRVO* central retinal vein occlusion, *DME* diabetic macular edema, *wAMD* wet age-related macular degeneration

educational materials (Table 5). Most physicians reported receiving the summary of product characteristics (87%), prescriber guide (77%), and patient booklet (54%); 50% reported receiving the intravitreal injection procedure video.

3.2.2 Physician Knowledge

3.2.2.1 Storage and Preparation In general, physician knowledge was high on storage and preparation, ranging

from 74% to 97% on five of six individual items; 42% correctly identified the remaining item "prior to usage, the vial of Eylea may be kept at room temperature for up to 48 hours" as inaccurate (the actual duration is up to 24 hours) [Figs. S-1A and S-1B of the ESM].

3.2.2.2 Dosing and Monitoring For the wAMD, CRVO or BRVO, and DME indications, only physicians who had prescribed and/or administered aflibercept in the previous 6 months for that indication were presented with questions about dosing recommendations (Fig. S-2 of the ESM). The percentage of physicians with correct responses was higher for wAMD (82–94%) and lower for newer or less commonly prescribed indications (CRVO/BRVO: 61–81%; DME: 71–73%). Knowledge of monitoring requirements was more variable, with 28% of physicians correctly indicating that there is no requirement for monitoring between injections for wAMD and 26% correctly indicating this for DME.

Most physicians (73%) correctly responded that 50 µL was the recommended dose for aflibercept. Most physicians (87%) correctly identified the statement "the vial contains more than the recommend dose of Eylea and excess volume should be expelled before injection" as true, and 67% correctly responded that the plunger of the syringe should be depressed until the tip aligns with the 0.05-mL line after removing all of the drug from the aflibercept vial.

3.2.2.3 Safe Use Physicians were asked to tick all statements that apply in response to the question, "what should you do to prepare the patient before the start of treatment with Eylea?" (Fig. 1). Three correct responses were listed among the options and overall, the proportion correct was

Table 5 Physicians' and patients' receipt and review of aflibercept educational materials

Question	Number of participants (%)					
Physicians	France (*N* = 69)	Germany (*N* = 59)	Italy (*N* = 99)	Spain (*N* = 102)	UK (*N* = 99)	Overall (*N* = 428)
Summary of product characteristics						
Received	62 (90)	56 (95)	82 (83)	82 (80)	91 (92)	373 (87)
Reviewed (among those who received it)	50 (81)	49 (88)	77 (94)	71 (87)	84 (92)	331 (89)
Prescriber guide						
Received	57 (83)	56 (95)	71 (72)	65 (64)	81 (82)	330 (77)
Reviewed (among those who received it)	47 (82)	45 (80)	65 (92)	57 (88)	70 (86)	284 (86)
Intravitreal injection procedure video						
Received	39 (57)	33 (56)	50 (51)	37 (36)	53 (54)	212 (50)
Reviewed (among those who received it)	20 (51)	20 (61)	38 (76)	30 (81)	35 (66)	143 (67)
Patient booklet including a patient information audio CD and the patient information leaflet						
Received	43 (62)	38 (64)	45 (45)	31 (30)	73 (74)	230 (54)
Reviewed (among those who received it)	28 (65)	19 (50)	34 (76)	25 (81)	52 (71)	158 (69)
Patients	France (*N* = 114)	Germany (*N* = 158)	Italy (*N* = 168)	Spain (*N* = 169)	UK (*N* = 164)	Overall (*N* = 773)
Patient booklet, "Your Guide to Eylea"						
Received	4 (4)	81 (51)	103 (61)	31 (18)	72 (44)	291 (38)
Reviewed (among those who received it)	4 (100)	65 (80)	98 (95)	18 (58)	64 (89)	249 (86)
Audio CD						
Received	1 (1)	32 (20)	67 (40)	23 (14)	54 (33)	177 (23)
Reviewed (among those who received it)	1 (100)	10 (31)	31 (46)	11 (48)	16 (30)	69 (39)
Patient information leaflet						
Received	30 (26)	37 (23)	113 (67)	21 (12)	68 (41)	269 (35)
Reviewed (among those who received it)	24 (80)	25 (68)	89 (79)	13 (62)	56 (82)	207 (77)

Materials for physicians included the summary of product characteristics, a prescriber guide, an intravitreal injection procedure video, and the patient booklet. Materials for patients included the patient booklet, an audio CD, and an information leaflet

highest for "explain the implications of anti-VEGF treatment" (94%) and "inform the patient to report any signs and symptoms …" (93%); a smaller proportion of the physicians selected "provide the patient booklet …" (63%).

3.2.2.4 Contraindications and Use in Women of Childbearing Potential Overall, knowledge of aflibercept contraindications was high with the proportion of correct responses ranging from 85% for "patients with active severe intraocular inflammation" to 95% for hypersensitivity (Fig. S-3 of the ESM). Physicians were also asked about the recommended use of aflibercept in women of childbearing potential (Fig. S-4 of the ESM). Overall, 48% of physicians correctly responded that "women of childbearing potential must use effective contraception …", and 48% selected the correct time frame for which women of childbearing potential must use effective contraception. While 59% of physicians correctly reported that "Eylea should not be used in pregnancy unless the potential benefit outweighs the potential risk …," 27% of physicians took a more conservative approach and responded that aflibercept should never be used in pregnancy.

3.2.2.5 Injection Procedures Overall, physicians' knowledge of proper injection procedures was high (Fig. S-5 of the ESM). Most physicians (94%) correctly confirmed that topical anesthesia should be used prior to the aflibercept injection. Likewise, 96% of physicians correctly identified the statement "a disinfectant should be applied to the periocular skin, eyelid, and ocular surface" as true. When asked to identify steps that should be taken prior to marking the scleral injection site, a high percentage of the physicians correctly selected "cover the eye with a sterile drape" (86%) and "insert a sterile lid speculum" (88%). Most physicians (83%) correctly responded that the eye should be marked at a distance of 3.5–4.0 mm posterior to the limbus in preparation for the aflibercept injection. Similarly, most physicians (88%) correctly responded that the injection needle should be inserted into the vitreous cavity, avoiding the horizontal meridian and aiming toward the center of the globe.

3.2.2.6 Side Effects When asked how physicians should evaluate a patient's vision immediately after an aflibercept injection, 60% of physicians correctly responded "by hand movements or counting fingers" (Fig. 2). Most physicians (79%) correctly identified the statement "an increase in intraocular pressure has been seen within 60 min after an injection with Eylea" as true.

When asked what they should do in relation to the potential of increased intraocular pressure immediately following an aflibercept injection, 65% of physicians correctly responded "ensure that sterile equipment is available to perform paracentesis, if necessary," and 78% of physicians correctly responded "undertake appropriate monitoring if increased intraocular pressure is suspected (e.g., check for perfusion of the optic nerve head or tonometry)" (Fig. 3).

Physicians were asked to tick all statements that apply in response to the question, "after the Eylea injection, patients

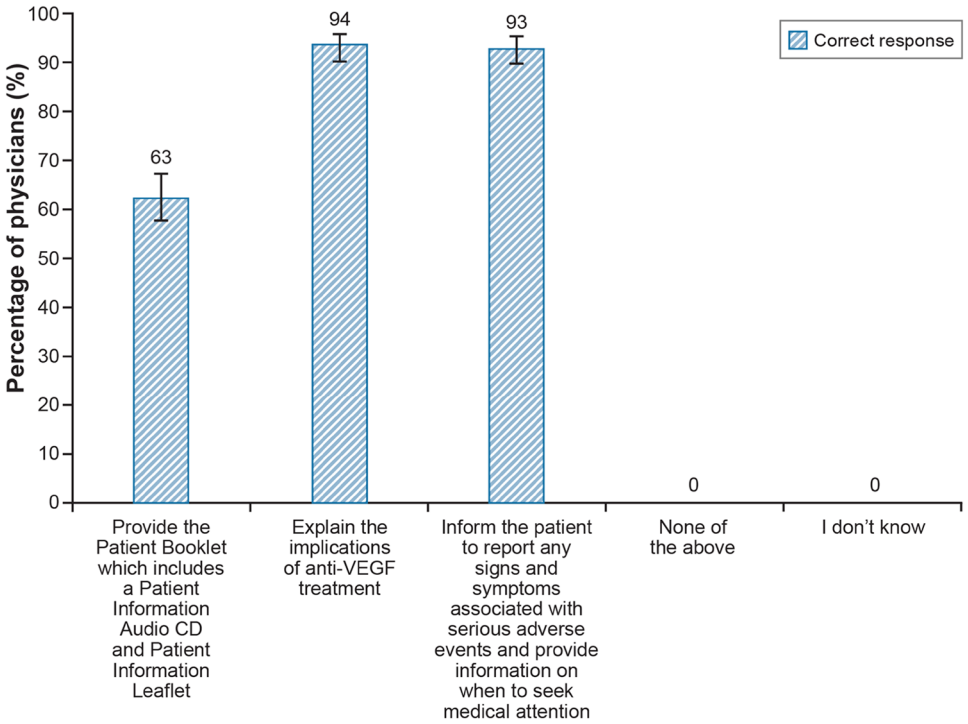

Fig. 1 Physician assessment: What should you do to prepare the patient before the start of treatment with Eylea? Tick all that apply (Question 10) ($N=428$). *VEGF* vascular endothelial growth factor

should be instructed to report any symptoms suggestive of which of the following conditions" (Fig. 4). Overall, a high proportion of physicians correctly selected "intraocular inflammation" (86%) and "endophthalmitis" (94%).

Physicians were given a list of potential signs or symptoms that are known undesirable side effects of aflibercept injection, and each of the potential signs or symptoms was correctly selected by at least 78% of physicians (Fig. 5). Fewer physicians correctly identified that fever (63%) and headache (47%) were not potential related side effects.

3.2.2.7 Differences in Knowledge by Physician Characteristics Given the sex distribution of the sample (73% male), the results were stratified by sex, as well as by age and practice setting; no meaningful differences in knowledge were observed.

3.3 Patient Assessment

3.3.1 Patient Pre-injection Instructions and Receipt and Use of Aflibercept Educational Materials

Most patients (71%) reported that before their first injection of aflibercept, their ophthalmologist (or someone in his or her office) told them what to expect during and after the injection. However, receipt of the educational materials was variable (Table 5).

3.3.2 Patient Knowledge

3.3.2.1 Health Conditions In a series of nine questions, patients were asked whether they should tell their ophthalmologist about certain health conditions before having an aflibercept injection (Figs. 6, 7, 8). Most patients correctly responded to almost all such questions (ranging from 85% to 92% on individual items), with the exception of a question related to pregnancy and breastfeeding, for which correct responses were lower overall (52%). Proportionally more women (67%) than men (33%) answered the question related to pregnancy and breastfeeding correctly (data not shown).

3.3.2.2 Possible Side Effects Patients' knowledge of the possible side effects with aflibercept varied by side effect (Figs. 9, 10, 11). Knowledge was higher for "eye pain" (74% reported correctly), "cloudy or blurred vision" (73%), "red or bloodshot eye" (70%), "sudden appearance or increase in moving spots" (68%), "sensitivity to light" (67%), and "eye infection" (61%). Knowledge was lower for "seeing halos around lights" (57% reported correctly), "sudden flashes

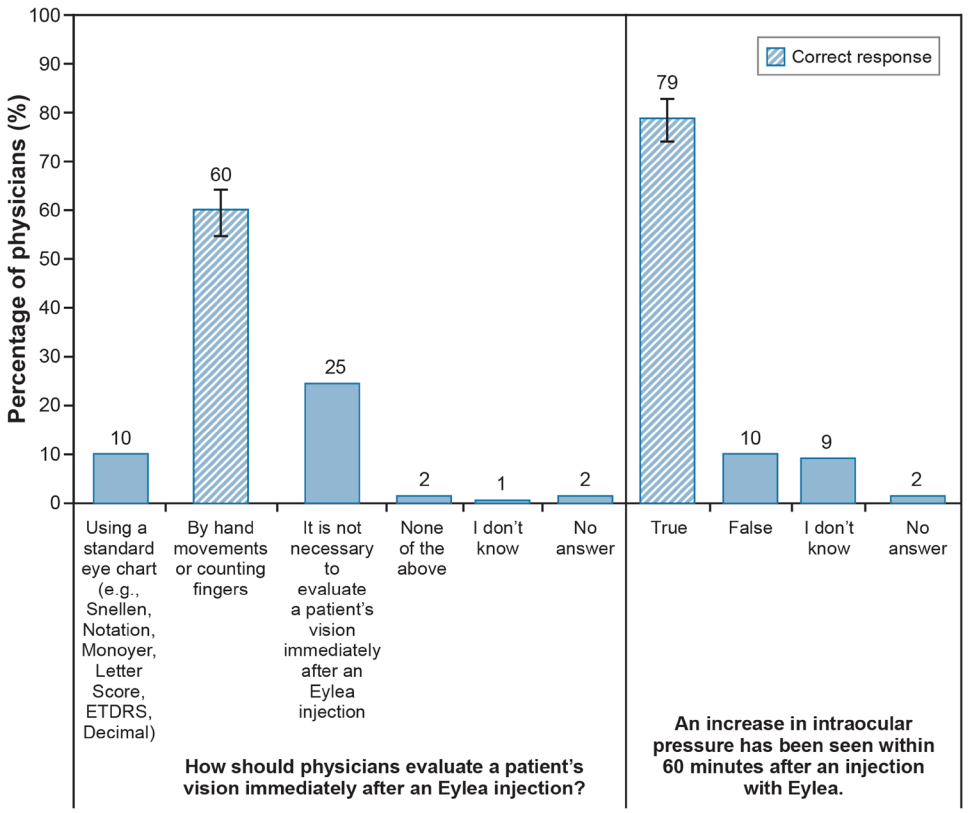

Fig. 2 Physician assessment: How should physicians evaluate a patient's vision immediately after an Eylea injection? (Question 18) and an increase in intraocular pressure has been seen within 60 min after an injection with Eylea. (Question 19) ($N=428$). *ETDRS* Early Treatment Diabetic Retinopathy Study

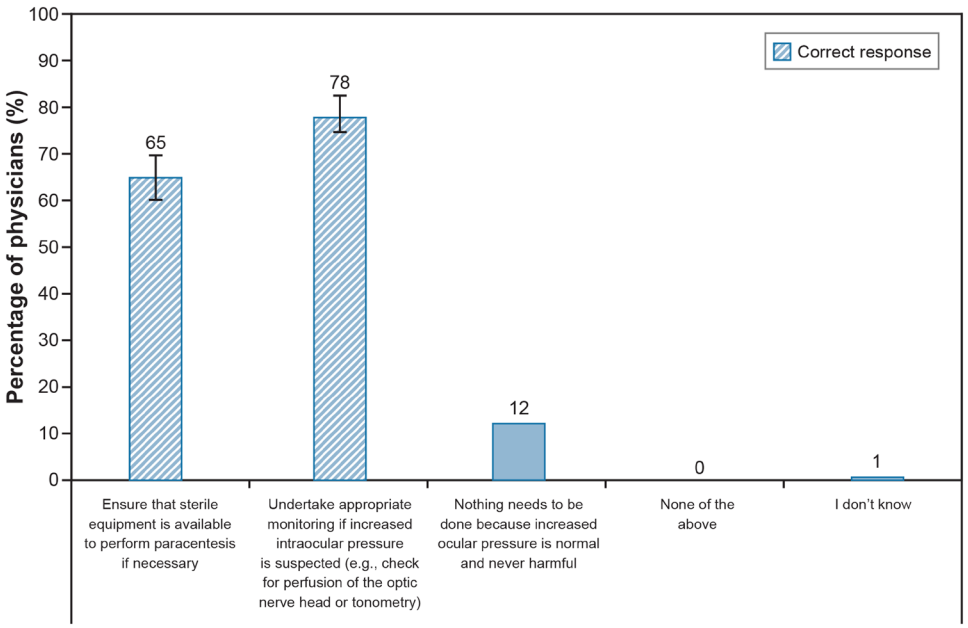

Fig. 3 Physician assessment: What should physicians do in relation to the potential of increased intraocular pressure immediately following an Eylea injection? Tick all that apply. (Question 20) ($N=428$)

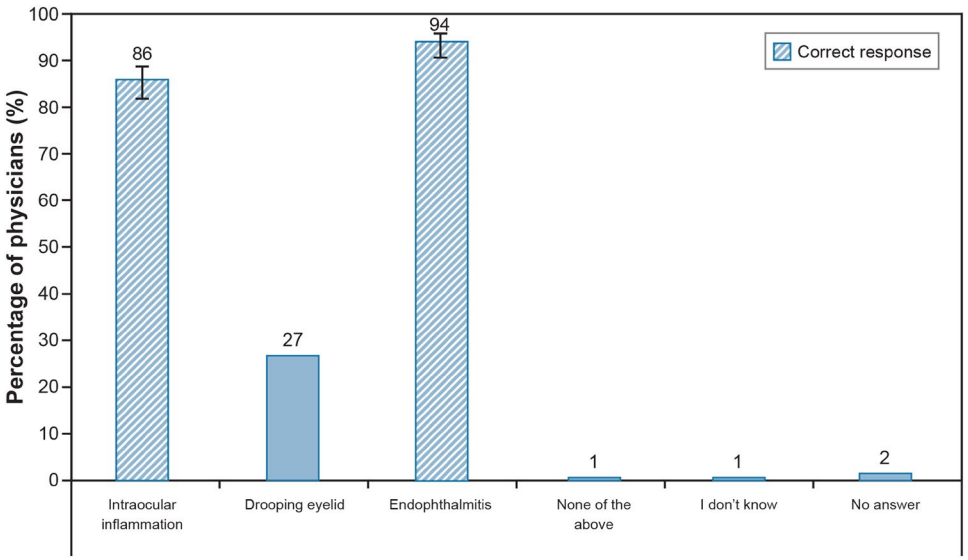

Fig. 4 Physician Assessment: After the aflibercept injection, patients should be instructed to report any symptoms suggestive of which of the following conditions? Tick all that apply. (Question 21) ($N=428$)

of light" (53%), and "detachment of the gel-like substance inside the eye from the retina" (42%). Overall, patients' knowledge of what to do if they think they might be having a side effect from aflibercept was high: 78% of patients correctly indicated that they should speak with their ophthalmologist (Fig. 12).

4 Discussion

Few post-authorization safety studies have described physicians' reported receipt of educational materials in the published literature [9–12]. In only one case was reported receipt as high as 75% [10]. Other studies have reported ranges from 37 to 51% [9, 11, 12]. Moreover, a survey of 800 European physicians found that reported receipt of educational materials ranged from 16% to 69% across participating countries [12]. In our study, most physicians reported receipt of the summary of product characteristics (87%) and prescriber guide (77%). Approximately half reported receipt of the intravitreal injection procedure video (50%) and the patient booklet (54%).

Patient-reported receipt of the educational materials, in contrast, was relatively low (23–38% for individual materials), potentially reflecting poor recall if the materials had indeed been received. Although direct comparison cannot

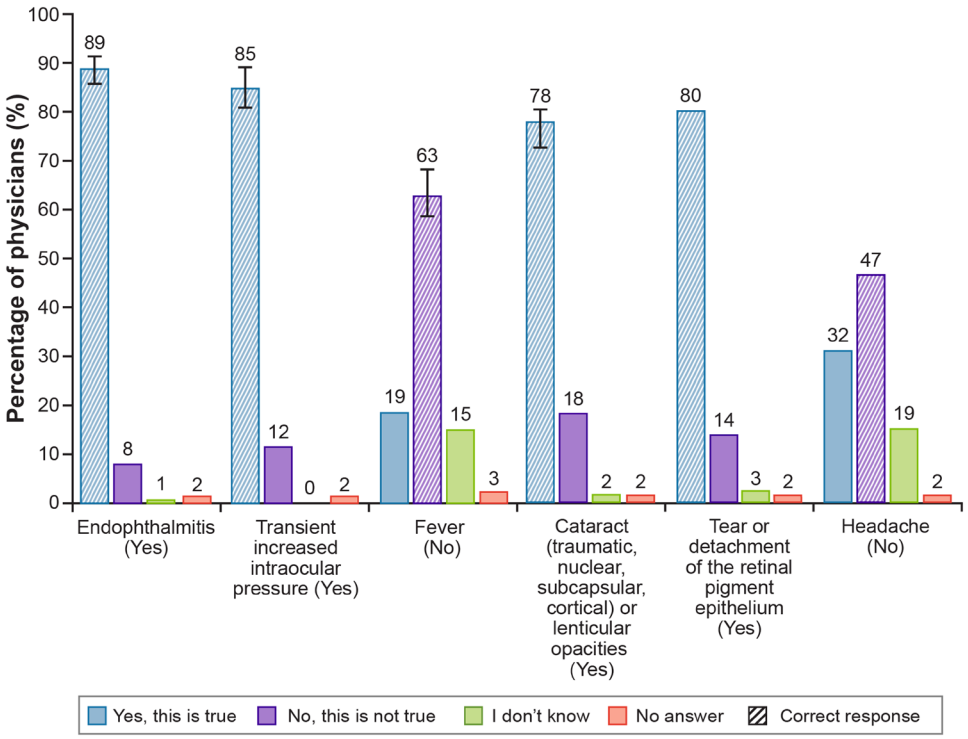

Fig. 5 Physician assessment: Which of the following signs or symptoms are known undesirable side effects of using Eylea? (Question 22) ($N=428$)

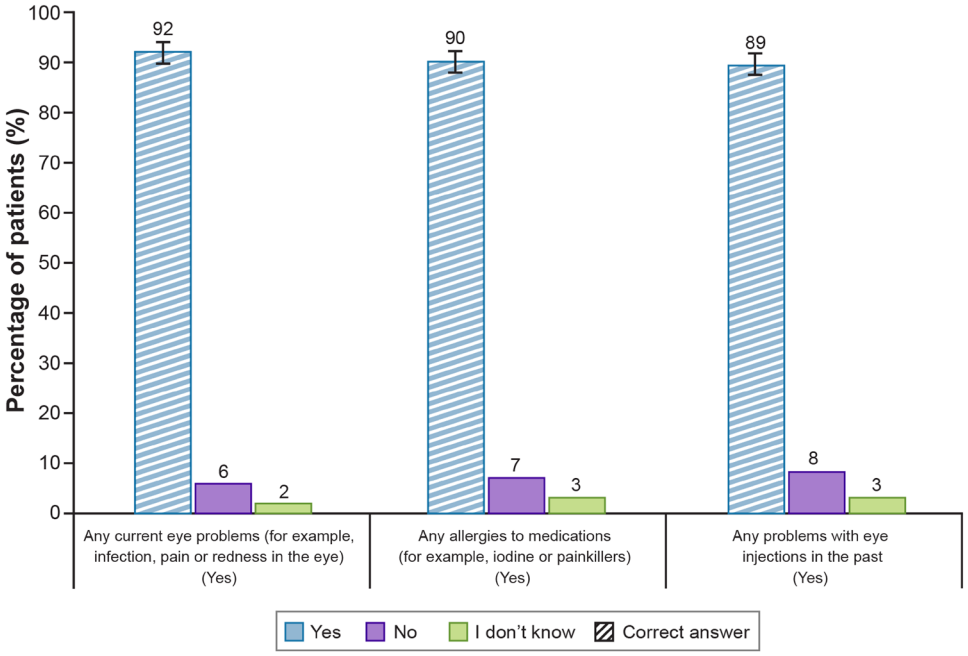

Fig. 6 Patient assessment: Which of the following issues or health conditions should you tell your ophthalmologist about before you have an Eylea injection? (Question 1a, 1b, 1c) ($N=773$)

be made between physician and patient assessments because they involved two independent samples, in general, there was a disconnect between the proportion of physicians reporting receipt of the patient booklet (54%) and the proportion of patients reporting receipt of the patient booklet (38%). A potential driver for this disconnect is that physicians in some countries (e.g., France and Spain) are required to have patients sign an informed consent form with relevant safety information prior to treatment; therefore, it is possible that some physicians could prioritize competing information sources that are legally required over the patient booklet. Despite variability in respondents' receipt of the educational material, it was encouraging that, among physicians

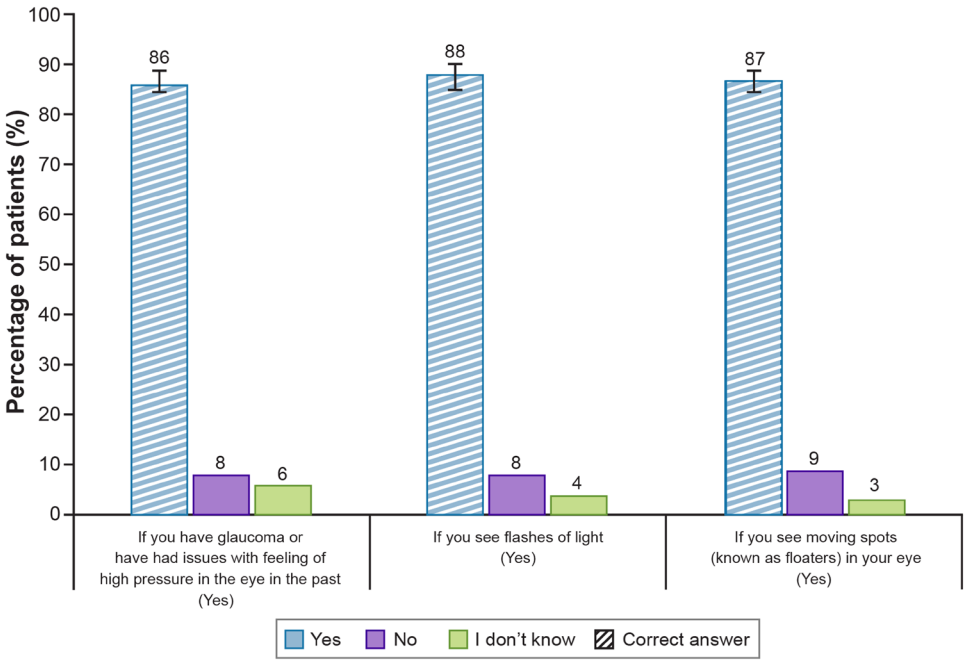

Fig. 7 Patient assessment: Which of the following issues or health conditions should you tell your ophthalmologist about before you have an Eylea injection? (Question 1d, 1e, 1f) ($N = 773$)

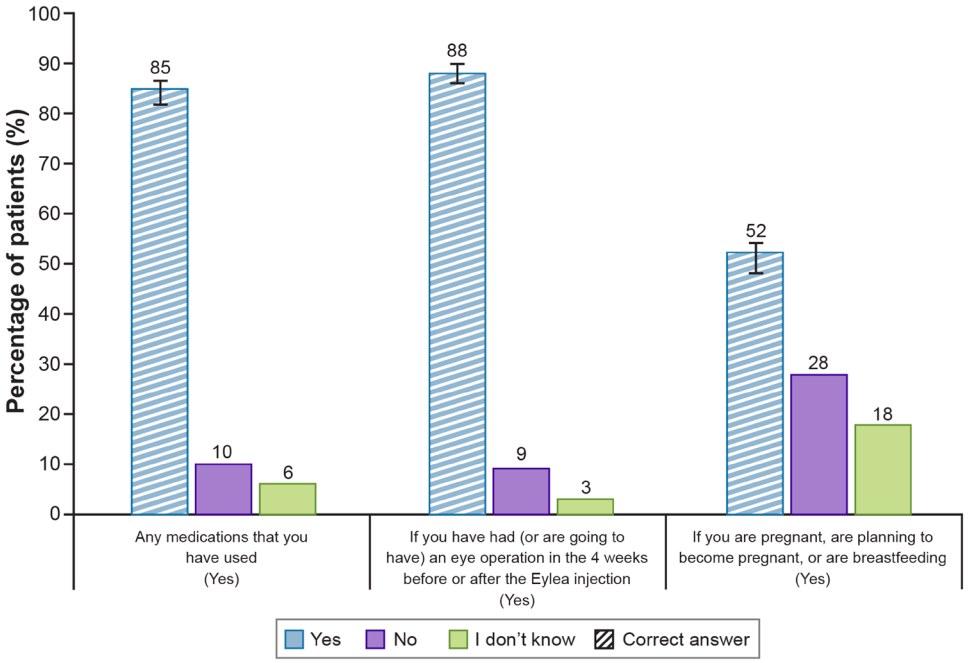

Fig. 8 Patient assessment: Which of the following issues or health conditions should you tell your ophthalmologist about before you have an Eylea injection? (Question 1g, 1h, 1i) ($N = 773$)

and patients who reported having received the material, use was high.

Published information describing acceptable levels of knowledge and behavior related to risk-minimization measures is somewhat limited. Knox and colleagues [13] reported on patient understanding of medication guides from a review of 66 assessment reports submitted to regulatory authorities. Only 30% of studies achieved an 80% knowledge level (% correct) for the most important risk communicated in the medication guide, and the mean knowledge level was 63.8%. A review of risk-minimization studies posted on the European Union electronic Register of Post-Authorisation Studies showed high variability in measures of program success criteria, variability in the nature of reporting, and variability of results, with approximately half of studies reporting having been "successful" but a large percentage in which results were inconclusive (17%) or were not adequately reported to support a conclusion (31%) [14].

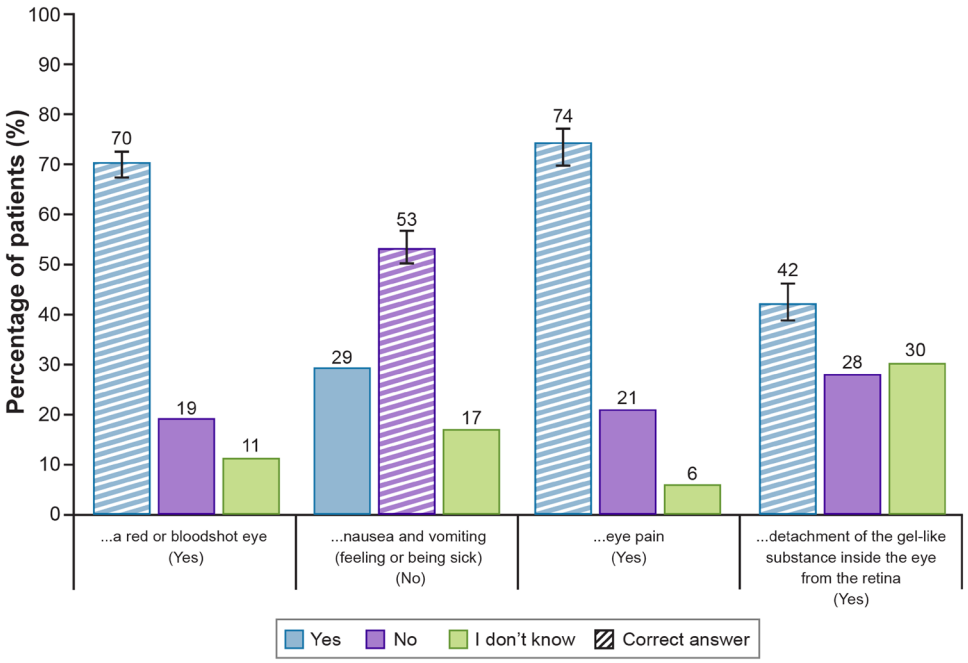

Fig. 9 Patient assessment: We are interested in finding out what you know about possible side effects that a person can have with Eylea. We do NOT want to know about your own personal experiences. Is [… side effect] a possible side effect of Eylea? (Question 2a, 2b, 2c, 2d) ($N=773$)

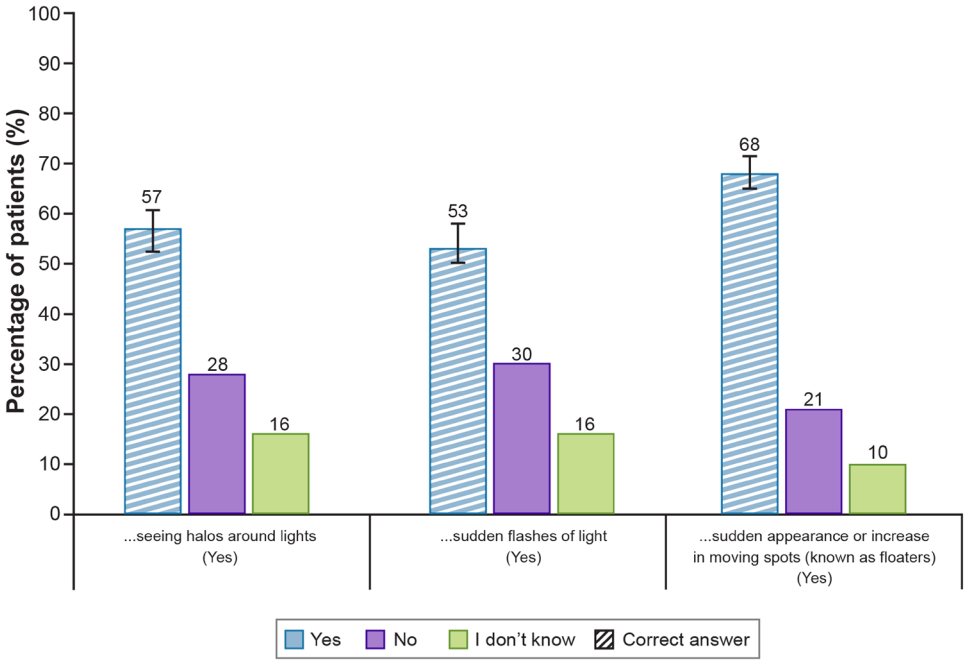

Fig. 10 Patient assessment: We are interested in finding out what you know about possible side effects that a person can have with Eylea. We do NOT want to know about your own personal experiences. Is [… side effect] a possible side effect of Eylea? (Question 2e, 2f, 2g) ($N=773$)

With respect to our study, some of the most important information communicated in the aflibercept educational materials is related to side effects. We found that over 80% of physicians responded correctly to most questions on this topic. Physician knowledge varied across the other information categories. In general, physicians' knowledge of storage and preparation guidelines, safe use, and injection procedures was also high. Knowledge on dosing guidelines (with the exception of monitoring requirements) varied by indication (61–94%), perhaps because some indications were approved recently or are encountered infrequently in clinical practice or because participating physicians prescribed aflibercept for these indications less frequently than for other indications. In general, physicians demonstrated a conservative approach to the monitoring questions, with a minority correctly indicating that there is no requirement for monitoring between injections for wAMD (28%) or DME (26%). Physician knowledge was lower on questions related

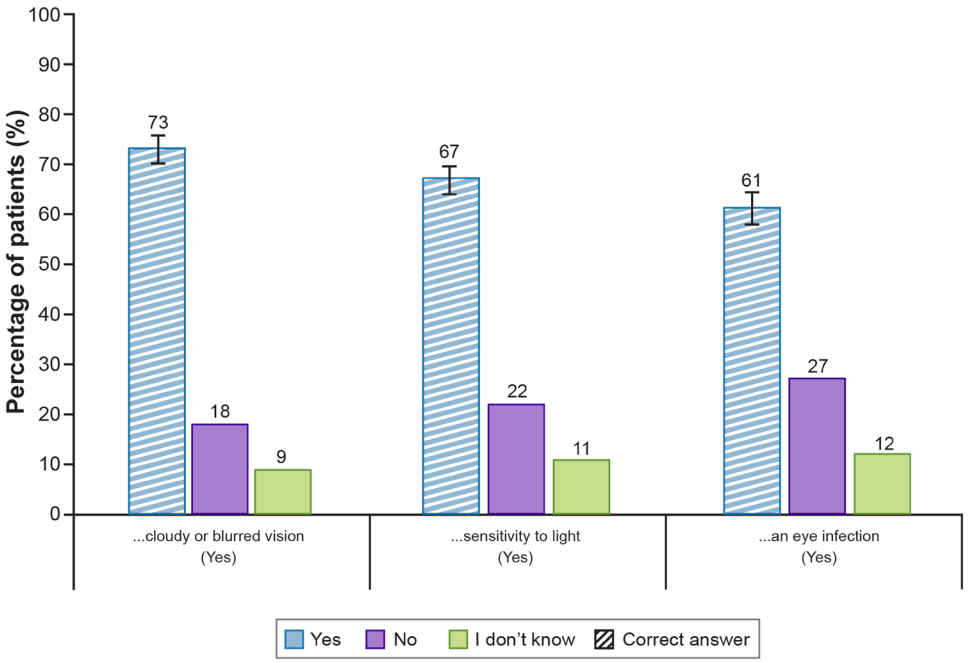

Fig. 11 Patient assessment: We are interested in finding out what you know about possible side effects that a person can have with Eylea. We do NOT want to know about your own personal experiences. Is […side effect] a possible side effect of Eylea? (Question 2h, 2i, 2j) ($N=773$)

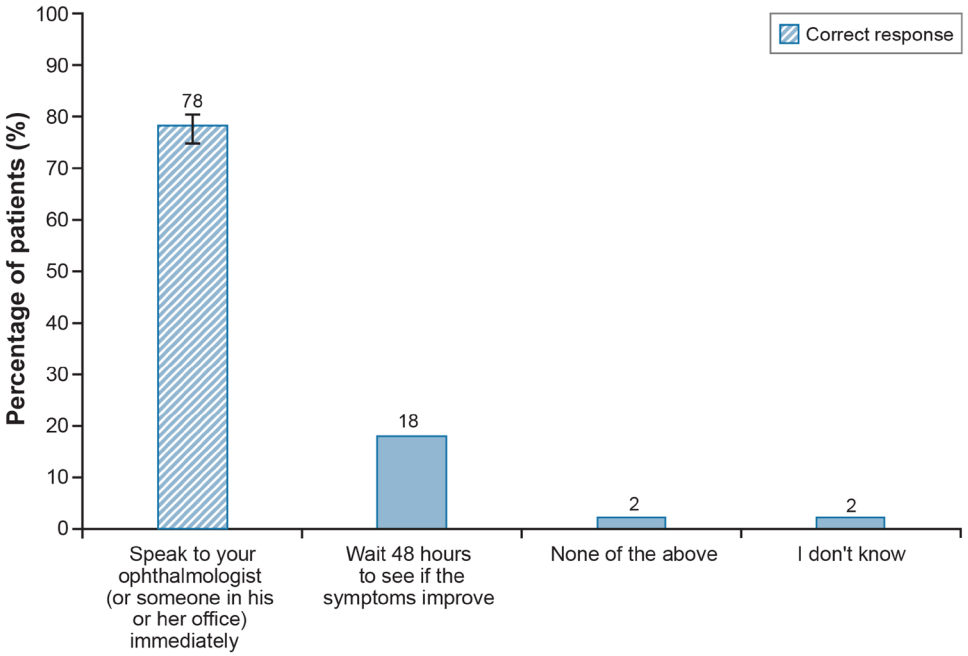

Fig. 12 Patient assessment: What should you do if you think you might be having a side effect from your Eylea injection? (Question 3) ($N=773$)

to aflibercept use in pregnancy (with 48–59% answering these questions correctly); however, in several cases, physicians who answered incorrectly selected another response reflecting a more conservative treatment approach. These findings are largely consistent with those from a study of Canadian physicians' knowledge of safe use for aflibercept, in which 60% of physicians knew that aflibercept should not be used in pregnancy unless clearly indicated by medical need in which benefits outweigh risks and 21% responded more conservatively that aflibercept should never be used in pregnancy [20].

Although patient knowledge was high for health conditions they should tell their ophthalmologist about before having an aflibercept injection (85–92%), approximately half of patients overall, and proportionally more women than men, correctly responded to the question related to pregnancy and breastfeeding. This is likely an effect of the age of the aflibercept patient population; 99% of the patients in the

study were aged 46 years or older. Patient knowledge was high for side effects that are easier to identify but was lower for more complex side effects (e.g., "detachment of the gel-like substance inside the eye from the retina," 42%). Most patients (78%) knew that they should contact their ophthalmologist's clinic immediately if they thought they might be experiencing a side effect.

A key strength of the study is the diversity of physician and patient participants. The targeted numbers of physician and patient respondents were achieved. Physicians were well distributed by their ophthalmology specialty, sex, years treating patients, and aflibercept prescribing practices. The characteristics of patients by demographics and their aflibercept treatment history were also diverse. An additional strength is that the physician assessment was conducted after physicians had received the educational material and had an opportunity to use them in clinical practice, and the patient assessment was conducted after patients had received aflibercept and had the opportunity to receive the educational material. Moreover, the completion rate for the patient assessment was high [773 patients completed the questionnaire among 851 who were invited and eligible (91%)] and exceeded the completion rate among physicians (5.1%). The favorable response rate among patients may have occurred in part because patients were recruited in person by a trusted healthcare professional. Recruitment and participation happened at their doctor's office as part of a regularly scheduled visit; an additional clinic visit was not required. Further, the questionnaire was brief, with 12 questions, and took approximately 10–15 min to complete, thus minimizing the burden on the patient and the site. An additional study strength is that the accuracy of responses among physicians and patients was facilitated by formal cognitive pretesting of the questionnaires.

The results of this study must be considered with several limitations in mind. Although the study was designed to ensure the selection of a diverse and generally representative sample of prescribers and patients, there was no exhaustive list of all aflibercept prescribers and patients from which to draw a random sample. Physician response rates to surveys have been reported to be low in general [15, 16], and particularly low in studies measuring the effectiveness of risk-minimization measures in Europe [9–11]. A low response rate among physicians could result in bias. Impediments to participation, including time, regulatory requirements, and reporting and contract requirements, have been well described by Madison et al. [17]. In addition, the study did not involve any countries in Eastern Europe, potentially limiting its external validity. Disproportionately more patients in our sample did not have a university-level education compared with the general population aged 55–74 years in Europe [18]. In general, study participants may not necessarily represent all relevant prescribers or patients. Moreover, respondents who completed the questionnaire may have differed from non-respondents in characteristics measured in the questionnaire (e.g., knowledge and use of the materials). The direction and magnitude of such potential respondent bias are not known. Another potential limitation of the patient assessment is that the study could influence sites to provide more education to patients than they ordinarily would. Nevertheless, to mitigate potential biases and an "intervention effect," site personnel were trained to provide only limited information about the study before patients' participation and to practice objective interviewing techniques, and patients completed the questionnaire at the site before receiving any additional counseling about treatment. Finally, according to Banerjee and colleagues' hierarchical framework to assess the effectiveness of risk-minimization measures [19], this study does not explore the most valuable endpoints of prescriber behavior and adverse health outcomes, which is an additional limitation, and therefore cannot measure the ultimate success of the risk-minimization measures.

5 Conclusion

Most physicians reported receiving the summary of product characteristics (87%), prescriber guide (77%), and patient booklet (54%); 50% reported receiving the intravitreal injection procedure video. Patient receipt of the educational material was variable (patient booklet: 38%; audio CD: 23%; patient leaflet: 35%). The observed patterns of knowledge among physicians and patients indicated the greatest knowledge of the most important risks emphasized in the educational material and other product information and lower knowledge of more complex aspects of safe use (e.g., concepts related to dosing and monitoring), for which we would assume that physicians would consult the label and/or prescriber guide rather than relying on recall. Likewise, levels of patient knowledge indicated the greatest knowledge of less complex concepts and lower knowledge of more complex concepts and issues less salient to the patient population. Relatively high levels of patient knowledge despite low reported receipt of the educational materials suggests that patients were receiving information from other sources.

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Compliance with Ethical Standards

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Conflict of Interest Elizabeth Andrews, Brian Calingaert, Eric Davenport, Kelly Hollis, Patrick Murphy, Daniel Wolin, and Laurie Zografos are salaried employees of RTI Health Solutions, which received funding from Bayer AG to conduct this study. The contract between RTI Health Solutions and the sponsor includes independent publication rights. RTI International conducts work for government, public, and private organizations, including pharmaceutical companies. Ursula Maria Schmidt-Ott and Zdravko P. Vassilev are salaried employees of Bayer, the study sponsor. Paul Petraro was a salaried employee of Bayer at the time this study was conducted.

Ethics Approval All procedures performed in this study involving human participants were in accordance with the ethical standards of the applicable institutional review board and ethics committees and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

Consent to Participate Informed consent was obtained from all individual participants included in the study.

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