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Scientific Update™

Anti-VEGF Therapy: More Than Meets the Eye

Summary of an accredited symposium presented during Vascular 2013

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Intravitreal anti-vascular endothelial growth factor (VEGF)-based therapies have been proven effective in the prevention of vision loss in patients with neovascular ("wet") age-related macular degeneration and diabetic macular edema. However, cardiovascular safety signals related to their potential to suppress systemic VEGF have yet to be recognized by the cardiology community. A collaborative multidisciplinary approach between cardiologists and ophthalmologists is required for the optimal management of patients with a significant risk factor profile for cardiovascular disease (CVD) or established CVD who require intravitreal anti-VEGF injections. At an accredited symposium during the recent Vascular 2013 conference, a renowned expert panel reviewed important information surrounding this emerging issue. This issue of *Cardiology Scientific Update* details the evidence discussed by the panel, key considerations, and recommendations for safe and effective use of these agents in patients with retinal ocular disease.

Age-related macular degeneration (AMD) and diabetic retinopathy and macular edema (DR/DME) are leading causes of visual impairment and blindness worldwide.[1,2] It is estimated that in 2007 there were more than 89 000 Canadians with visual loss caused by AMD and more than 29 000 caused by DR/DME.[3] AMD is broadly classified as either dry (atrophic; nonexudative) or wet (neovascular; exudative). Individuals with dry AMD typically experience a gradual reduction in central vision due to atrophy of the retina. In sharp contrast, those with wet AMD suffer a more precipitous loss of vision secondary to the development of choroidal neovascularization (CNV). Although 90% of those with AMD have dry disease, 80%–90% of all individuals rendered legally blind from AMD have the wet form of the disease.[4] Advanced DR is characterized by the growth of abnormal retinal blood vessels secondary to ischemia. At any time during the progression of DR, patients with diabetes can also develop DME, which involves retinal thickening in the macular area because of leakage from dilated hyperpermeable capillaries and microaneurysms. Vascular endothelial growth factor (VEGF) plays a leading role in the pathogenesis of AMD and DR/DME, and inhibitors of this molecule have been demonstrated to successfully treat these conditions.[5-10] However, one must keep in mind that VEGF has important functions in systemic vascular homeostasis and that the effects of anti-VEGF therapy may compromise patient safety.[11] The main cardiovascular (CV) adverse effects of systemically administered anti-VEGF therapy when used to treat cancer patients include hypertension, thrombosis, and hemorrhage. Although the risks associated with significantly lower doses of intravitreally administered agents are considerably reduced, they should not be overlooked, especially in at-risk patient populations.

This symposium was chaired by Jean C. Grégoire, MD, Assistant Professor of Medicine, Université de Montréal, and Interventional Cardiologist, Montreal Heart Institute. The other panelists were Subodh Verma, MD, PhD, Scientist, Keenan Research Centre, Li Ka Shing Knowledge Institute, Director, Traineeship in Atherosclerosis, Division of Cardiac Surgery, St. Michael's Hospital, and Associate Professor and Canada Research Chair, Atherosclerosis, Department of Surgery, University of Toronto, and Nicholas Giacomantonio, MD, Director of Cardiac Rehabilitation, Primary & Secondary Prevention CDHA, and Cardiologist, QEII Health Sciences Centre, Dalhousie University, Halifax, Nova Scotia.

Common Risk Factors Between CV Disease (CVD) and AMD

Drs. Grégoire and Giacomantonio presented long-term epidemiological studies confirming that CVD and AMD share similar risk factors, including smoking, hypertension, presence of significant carotid plaque, hypercholesterolemia, and elevated body mass index.[12,13] Additionally, similar to CVD, elevated levels of high-sensitivity C-reactive protein is an independent risk factor for AMD and may implicate the role of inflammation in the pathogenesis of AMD.[14] A study by Hogg et al[13] indicated that CVD plays an important role in the development of choroidal neovascularization in older adults, leading to AMD (odds ratio [OR] 7.53;

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95% confidence interval [CI], 2.78–20.41). Furthermore, the Cardiovascular Health Study,[15] a population-based prospective cohort study, suggested that individuals aged ≥69 years with early AMD have a higher risk of coronary heart disease (CHD). Of the 1786 participants who were free of CHD at baseline, 303 developed incident CHD over 7 years. Those with early AMD (n=277) had a higher cumulative incidence of CHD than those without AMD (25.8% versus 18.9%; *P*=0.001). The Atherosclerosis Risk in Communities (ARIC) study[16] further suggested that middle-aged persons with signs of early AMD have a higher risk for stroke, independent of traditional stroke risk factors (4.08% versus 2.14%; relative risk [RR] 1.87; 95% CI, 1.21–2.88 for patients with early AMD versus those without AMD). Similarly, the Blue Mountains Eye Study[17] conducted in Australia showed that, in individuals aged 49–75 years, early AMD predicted a doubling of CV mortality (RR 2.32; 95% CI, 1.03–5.19) over the ensuing 10 years after controlling for traditional CV risk factors (Table 1). In addition, late AMD was associated with a 5-fold higher CV mortality (RR 5.57; 95% CI, 1.35–22.99) and a 10-fold higher stroke mortality (RR 10.21; 95% CI, 2.39–43.60) after adjusting for age and sex. The investigators concluded that these observations might have potential implications for the use of intravitreal anti-VEGF therapies in patients with AMD.

Diabetes confers the largest lifetime risk of any coronary artery disease, Dr. Verma said. Diabetic patients are particularly vulnerable as they have low levels of circulating VEGF. These patients also often require intravitreal anti-VEGF therapies, which further increases their risk of thromboembolic events.

Physiological and Pathological Angiogenesis – A Double-edged Sword

Angiogenesis: definitions, molecular regulation, and biological roles in health and disease

As presented by Dr. Verma, the mechanism of sprouting angiogenesis, the physiological process through which new blood vessels form from pre-existing vessels, is a crucial step in organ growth, development, and repair. It occurs in 4 well-characterized stages.[18] The first step is the stimulation of endothelial cells in pre-existing blood vessels by angiogenic signals. Angiogenesis is typically initiated in hypoxic tissues. Transcription factors known as hypoxia inducible factors (HIFs) are activated by hypoxia; in turn, HIFs directly or indirectly activate several proangiogenic genes, such as basic fibroblast growth factor and VEGF. The activated endothelial cells release extracellular proteinases that degrade the capillary basal lamina, allowing the activated endothelial cells to escape from the original vessel walls and migrate toward the hypoxic gradient. The endothelial cells then proliferate into the surrounding matrix and form solid tubes connecting neighbouring vessels. Finally, these new sprouts form loops and mature to become fully functional vessels. Angiogenesis is a highly dynamic process that involves intense vessel remodeling. Recent evidence has shown that tip cells, which are situated at the extremities of capillary sprouts, control branching of blood vessels.[19,20] Several axon guidance molecules (repulsion and attraction) – such as semaphorins, netrins, ephrins, and slits – have been implicated in vessel proliferation and network formation.[19] Furthermore, alteration of the VEGF gradient leads to modifications in capillary branching and variations in vessel size. Recent data also suggest

Table 1: Longitudinal relationships between age-related macular degeneration (AMD) and cardiovascular-related death[17]

AMD Stage	n (%)	Age group	Relative risk (95% confidence interval)	
			Age- and gender-adjusted	Multivariable-adjusted[a]
Early				
Absent	2723 (6.1)	All ages	1	1
Present	130 (12.3)		0.93 (0.55 to 1.56)	0.95 (0.55 to 1.63)
Absent	2278 (2.9)	<75 years	1	1
Present	69 (10.1)		2.26 (1.02 to 4.98)	2.32 (1.03 to 5.19)
Absent	445 (22.7)	≥75 years	1	1
Present	61 (14.7)		0.61 (0.31 to 1.21)	0.58 (0.28 to 1.20)
Late				
Absent	2802 (6.0)	All ages	1	1
Present	51 (27.4)		1.74 (0.97 to 3.11)	1.56 (0.83 to 2.95)
Absent	2338 (3.0)	<75 years	1	1
Present	9 (22.2)		5.57 (1.35 to 22.99)	—[a]
Absent	464 (21.1)	≥75 years	1	1
Present	42 (28.6)		1.43 (0.76 to 2.67)	1.29 (0.64 to 2.62)

[a] Adjusted for age, gender, hypertension, diabetes, cigarette smoking and body mass index.
[b] There were too few late AMD cases for further multivariable analysis for participants aged <75 years

that angiogenesis is not only controlled by resident endothelial cells within local blood vessels, but that circulating bone marrow-derived endothelial progenitor cells also play a role.[21]

An imbalance in the angiogenic processes described above can lead to numerous malignant, inflammatory, ischemic, infectious, and immune disorders, as noted by Dr. Verma. Uncontrolled angiogenesis in any organ, including the eye, leads to chaotic organization of vasculature with increased permeability and poor perfusion.

VEGF signaling in CV and ocular homeostasis

There are several VEGF ligands, all of which express their angiogenic effects by binding to specific VEGF receptors on the endothelial cell surface.[22-24] VEGF receptor-2 (VEGFR-2), the most important VEGF receptor in angiogenesis, is expressed on almost all organ tissues, where it mediates the majority of VEGF-related angiogenic effects.[22,25,26] Interactions of VEGF with VEGFR-2 on endothelial cells results in increased production of nitric oxide (NO) and prostaglandin I2 (PGI2), and an augmentation in endothelial cell permeability, proliferation, migration, and survival.[27] By maintaining endothelial health, VEGF sustains endothelial cell integrity and vascular tone, promotes homeostasis between endothelial cells and platelets, and protects the glomerular filtration barrier. On the other hand, Dr. Verma warned, blockade of VEGF, particularly systemically, can elicit potential deleterious effects on multiple organ systems, including compromised wound healing, hypertension, arterial thrombosis, cardiac dysfunction, proteinuria, and renal adverse effects. Possible mechanisms behind adverse events related to VEGF inhibition in cancer patients receiving systemic anti-VEGF therapy are listed in Table 2.[27]

The importance of VEGF in CV homeostasis is further validated by experiments in mutant mice.[28] Genetic deletion of VEGF in the endothelial lineage led to progressive endothelial degeneration, microhemorrhages, intestinal perforation, widespread intravascular thrombosis, and sudden death by 25 weeks of age, confirming that systemic effects of anti-VEGF agents can manifest throughout the body. Dr. Verma cited the study by Izumiya et al,[29] which showed that VEGF blockade can have adverse effects outside of the endothelium. In pressure overloaded murine hearts, VEGF blockade promoted rapid progression from compensatory cardiac hypertrophy to failure. Thus, the authors warned that anti-VEGF therapies should be used with caution when treating cancer patients with hypertrophic cardiomyopathy.

Intravitreal Anti-VEGF Therapies: From Bench to Bedside

Molecular structure and pharmacological data

As mentioned, intravitreal anti-VEGF therapies have revolutionized the treatment of many retinal diseases.[5-10] At present, ranibizumab, an antibody fragment developed specifically for intravitreal administration, is the only anti-VEGF therapy approved by Health Canada for the treatment of ocular conditions.[30] However, due to the significant difference in price, many ophthalmologists and retina specialists continue to use bevacizumab, a full-length antibody developed and approved for the intravenous administration and treatment of various cancers, off-label.[31] Although systemic administration of bevacizumab is associated with many serious adverse events (SAEs), Dr. Giacomantonio said that the level of acceptance of the risks of SAEs for a cancer therapy is much higher than for benign conditions. One must also keep in mind that the doses of bevacizumab used to treat malignancies are in the order of

Table 2: Possible mechanism behind adverse effects associated with systemic VEGF suppression in cancer patients[27]

Hypertension
- Decrease in nitroxide and prostaglandin I2 production leading to inhibition of vasodilatation
- Decrease in arteriole and capillary density (rarefaction)

Arterial thrombosis
- Endothelial cell apoptosis
- Disturbance of platelet-endothelial cell homeostasis; platelet aggregation
- Exposure of extracellular matrix to blood cells

Cardiomyopathy
- Increase in peripheral vascular resistance
- Inhibition of VEGF-dependent cardiomyocyte growth in response to ischemia or blood pressure elevation
- Ischemic changes in coronary arterioles

Proteinuria and renal adverse effects
- Disturbance of VEGF-dependent function and interaction between endothelial cells and podocytes in the filtration barrier of glomeruli
- Thrombotic microangiopathy
- Endothelial cell damage

Wound healing issues
- Impaired neovascularization
- Disturbance of platelet-endothelial cell interaction
- Reduction in the VEGF-induced tissue factor on endothelial cell results in compromised coagulation cascade and platelet activation

Bowel perforation
- Ischemic changes in intestinal walls
- Impaired wound healing

400 times higher than those required for the management of AMD and other ocular conditions. Thus, it might be expected that lower doses of the agent used for intravitreal administration and an intact blood-retina barrier would reduce the systemic exposure of the drug; however, both animal and human studies suggest that this may not be the case.[32-36] Radioactivity assays in animals confirmed the presence of radioactive bevacizumab in serum for up to 7 days following an intravitreal injection.[32] This transport from the eye across the blood-retina barrier into the systemic circulation is attributed to the Fc fragment of the molecule and its receptors expressed on multiple ocular tissues.[37,38] It has also been suggested that Fc receptor expression may be upregulated in the eyes with wet AMD.[38]

Dr. Giacomantonio presented the results of 2 recent studies that confirmed that bevacizumab significantly reduces VEGF plasma levels up to 28 days after intravitreal injection in patients with exudative AMD.[33,34] In both studies, intravitreal ranibizumab was not associated with a significant reduction in systemic VEGF levels. Carneiro et al[34] determined that the median VEGF plasma levels were reduced by 42% in bevacizumab-treated patients (from 189.7 pg/mL at baseline to 110.0 pg/mL; *P*=0.0002) 28 days after the third

intravitreal injection compared to 0.7% in ranibizumab-treated patients (from 191.4 pg/mL to 189.97 pg/mL; *P*=0.198). These observations are further confirmed by the IVAN trial that included approximately 600 patients from 23 hospitals and academic institutions in the United Kingdom (UK).[35] After 12 months of treatment, serum VEGF was lower with bevacizumab (geometric mean ratio 0.47; 95% CI, 0.41–0.54; *P*<0.001). Similar to these findings in AMD patients, treatment of individuals suffering from diabetic retinopathy with 1.25 mg intravitreal bevacizumab also resulted in significant decreases from baseline (114.0 pg/mL) in systemic VEGF plasma levels: reductions of 91.5% (9.7 pg/mL) after 1 day and 77.3% (25.9 pg/mL) 1 month after the injection.[36]

As stated by Dr. Giacomantonio, these data provide a biological basis for the systemic and CV differences between ranibizumab and bevacizumab, even when administered via an intravitreal route. Furthermore, the IVAN trial investigators warned that the consequences of differential suppression of circulating VEGF may only become apparent after a longer follow-up.[35]

To what extent do pharmacological data translate into clinical outcomes?

The safety of ranibizumab has been assessed in several large clinical trials that subsequently led to the regulatory approval of the drug. In an analysis of prospective, multicentre ranibizumab studies,[39] the 2 pivotal trials – MARINA[40] and ANCHOR[41] – systemic arterial thrombotic events (ATEs) occurred in 4.6% and 5.0%, of patients treated with 0.5 mg ranibizumab (dose approved in Canada), respectively, compared to 3.8% in the sham arm of the MARINA trial and 4.2% in the photodynamic therapy arm of the ANCHOR trial. This is in line with the rates observed in the general population quoted by Dr. Giacomantonio, where annual age-matched rates of myocardial infarction (MI) and stroke were 2.2% and 4.1%, respectively. He cautioned that physicians must be aware of the significant increase in risk of MI and stroke among AMD patients with a previous history of an ATE; a retrospective analysis including 15 771 new-onset neovascular AMD patients matched with 46 408 controls revealed rates of 7.4% for MI and 35.1% for stroke among the AMD group who had a history of an ATE.[42]

Taking into consideration the Fc fragment and prolonged systemic exposure associated with bevacizumab, Dr. Giacomantonio said that it may be reasonable to question whether intravitreal bevacizumab might pose an even higher risk of ATEs, given the demonstrated cumulative reduction in systemic VEGF associated with its use. As a large trial assessing safety of intravitreal bevacizumab was never conducted, its safety is gauged through various registries and meta-analyses. In a small, population-based study involving 82 patients who were being treated for hypertension, bevacizumab markedly increased BP 3 weeks after intravitreal injection (+11.8/+6.2 mm Hg; *P*<0.001); BP scores remained significantly elevated at 6 weeks' follow-up. BP increases were also seen in patients with normal BP, although to a lesser degree: the increases were significant for both systolic (+5.3 mm Hg; *P*=0.004) and diastolic BP (+4.1 mm Hg; *P*<0.001) at 3 weeks, but not at 6 weeks.[43] Curtis et al[44] conducted a retrospective population-based study of nearly 147 000 Medicare claimants for AMD. Subanalysis of patients who received either first-line bevacizumab (N=21 815) or ranibizumab (N=19 026) identified that ranibizumab was associated with significantly lower risks of incident stroke (adjusted hazard ratio [HR] 0.78; 95% CI, 0.64–0.96), incident MI (adjusted HR 0.83; 95% CI, 0.64–1.08), and all-cause mortality (adjusted HR 0.86; 95% CI, 0.75–0.98) compared with bevacizumab (Figure 1).

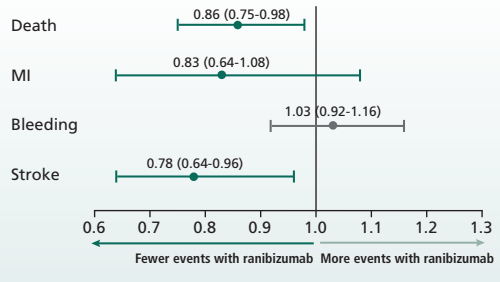
Head-to-head comparison trials

In order to properly assess and compare (power to detect a difference of ~1% with *P*≤0.05 based on the 2-sided Fisher exact test) the safety of bevacizumab with that of ranibizumab, a large clinical trial with almost 7000 patients is required. To date, there are only 3 head-to head comparison trials with over 500 patients each: CATT (United States; N=1200),[45] IVAN (UK; N=600),[35] and GEFAL (France; N=600).[46]

In the CATT trial, treatment with bevacizumab was associated with a significantly higher incidence of systemic SAEs – primarily hospitalization – within 1 year of treatment than ranibizumab (24.1% versus 19.0%; RR 1.29; 95% CI, 1.01–1.66; *P*=0.04). The higher rates of systemic SAEs in bevacizumab-treated patients reported in the first year were also observed during year 2.[47] After adjustment for demographic features and coexisting illnesses at baseline, bevacizumab continued to be associated with a higher proportion of patients having ≥1 systemic SAEs compared to ranibizumab, (39.9% versus 31.7%; *P*=0.009). Due to the observed increase in risk of systemic SAEs with bevacizumab, the IVAN trial Data and Safety Monitoring Committee (DSMC) requested that participating clinicians inform their patients about the safety finding and give them the opportunity to withdraw from the trial.[48] The increased risk of systemic SAEs among bevacizumab-treated patients, according to the IVAN DSMC, is unlikely to be due to chance.

Meta-analysis of 2-year safety outcomes from the IVAN and CATT trials reports significant differences between bevacizumab and ranibizumab in the numbers of systemic SAEs in favour of ranibizumab.[49] A recent meta-analysis of 4 trials (IVAN, CATT, MANTA, and GEFAL),[46] presented at the Association for Research in Vision and Ophthalmology (ARVO) 2013 annual meeting showed an RR of systemic adverse events with

Figure 1: Adjusted hazard ratios of adverse events at 1 year in patients receiving ranibizumab compared with bevacizumab as first-line therapy[44]



Hazard ratios are listed with 95% CI; MI = myocardial infarction
N= 40 841 (21 815 bevacizumab and 19 026 ranibizumab patients)

bevacizumab compared to ranibizumab of approximately 1.3 (Figure 2).

The entrance of additional intravitreal anti-VEGF agents into the market – Health Canada recently approved aflibercept for the treatment of neovascular AMD – will necessitate further comparative studies of their systemic safety.

Canadian contribution to the debate

A recent population-based nested case-control study (N=91 378 older adults with a history of physician-diagnosed retinal disease identified between April 1, 2006, and March 31, 2011) conducted in Ontario revealed that intravitreal injections of bevacizumab and ranibizumab were not associated with significant risks of ischemic stroke, acute MI, venous thromboembolism, or congestive heart failure.[50] In the subgroup of diabetic patients, however, the investigators reported a statistically significant association between bevacizumab use and acute MI versus ranibizumab (adjusted OR 1.76; 95% CI, 1.03–3.00). Dr. Giacomantonio noted the caution of the authors in their discussion about the significance of this finding, due to the particular complexity of their analysis. He also listed several potentially complicating issues with the study methodology, including the lack of a placebo group, numerous assumptions regarding which patients received what therapy, and the absence of data for non-CV SAEs and events not resulting in an emergency room (ER) or hospital admission or resulting in death prior to ER or admission. Thus, it would be unfounded to use the results of this study in order to influence policy makers to list the less expensive drug, bevacizumab, on their formulary.

Lesson Learned

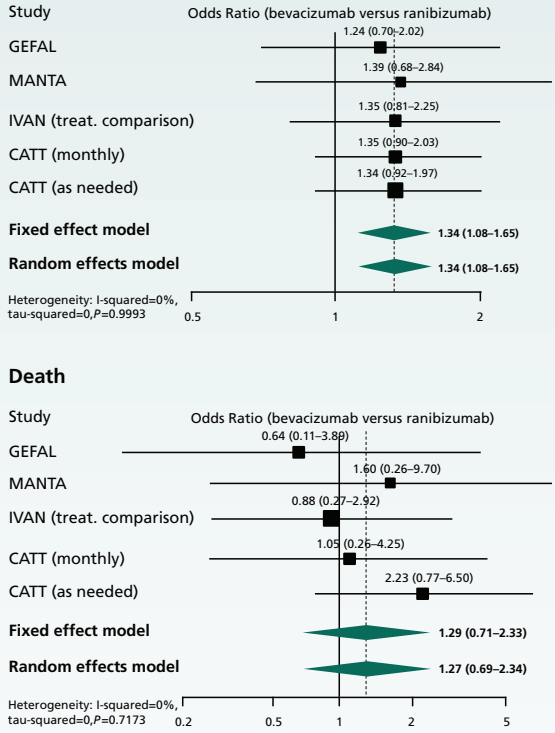
Dr. Giacomantonio cited the recent example of safety signals associated with CV risk in diabetes therapies, rosiglitazone in particular, which have taught the CV community that signals of CV harm cannot be interpreted conclusively from small efficacy-driven trials.[51] Thus, in the absence of large trials, the Food and Drug Administration's guidance document on the CV risk of new antidiabetes therapies[52] recommends careful post marketing surveillance and risk stratification for all drugs with a risk ratio (95% CI) between 1.3–1.8. Taking into consideration that anti-VEGF therapies are now indicated for use in the diabetic population, one could assume that similar requirements should be applied and followed.

Conclusion

Intravitreal anti-VEGF therapy has been proven efficacious in the care of patients with neovascular AMD and DR/DME. However, there are also concerns associated with the underlying risk of adverse outcomes in specific patient subsets. Cardiovascular specialists need to understand safety issues associated with intravitreal anti-VEGF therapies to suggest the right approach for ophthalmologists. At-risk patients must have their risk factors under control prior to initiation of intravitreal anti-VEGF therapy. Lack of a large head-to-head safety trial warrants mandatory post-marketing vigilance registries. Furthermore, in order to allow better clinical application of anti-VEGF therapies and appropriate patient selection, cardiologists and internists should work in collaboration with their ophthalmology colleagues:

- To ensure that patients with hypertension are well controlled
- To assess potential risk in patients with clinically established CVD and coronary artery disease and stratify patients according to their risk factors
- To ensure closer follow-up in patients at highest risk, with a strong emphasis on those with diabetes
- To assist in selecting appropriate therapy for patients with a history of serious gastrointestinal illness, especially bleeding

Figure 2: Safety meta-analysis[46]



Recreated from Kodjikian L, for the GEFAL Study Group. Presented at ARVO 2013. May 7, 2013.

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References:

1. World Health Organization. Causes of blindness and visual impairment. Available at: http://www.who.int/blindness/causes/en. Accessed on October 28, 2013.
2. Foundations for a Canadian Vision Health Strategy: Towards Preventing Avoidable Blindness and Promoting Vision Health. Available at: http://www.vision-health.ca/projects/documents/Foundations-For-A-Canadian-Vision-Health-Strategy.pdf. Accessed on October 28, 2013.
3. Cruess AF, Gordon KD, Bellan L, Mitchell S, Pezzullo L.The cost of vision loss in Canada. 2. Results. *Can J Ophthalmol*. 2011;46(4):315-318.
4. Ferris FL 3rd, Fine SL, Hyman L. Age-related macular degeneration and blindness due to neovascular maculopathy. *Arch Ophthalmol*. 1984;102(11):1640-1642.
5. Wong TY, Liew G, Mitchell P. Clinical update: new treatments for age-related macular degeneration. *Lancet*. 2007;370(9583):204-206.

6. van Wijngaarden P, Qureshi SH. Inhibitors of vascular endothelial growth factor (VEGF) in the management of neovascular age-related macular degeneration: a review of current practice. *Clin Exp Optom.* 2008;91(5):427-437.
7. Nicholson BP, Schachat AP. A review of clinical trials of anti-VEGF agents for diabetic retinopathy. *Graefes Arch Clin Exp Ophthalmol.* 2010;248(7):915-930.
8. Karia N. Retinal vein occlusion: pathophysiology and treatment options. *Clin Ophthalmol.* 2010;4:809-816.
9. Wong TY, Scott IU. Clinical practice: Retinal-vein occlusion. *N Engl J Med.* 2010; 363(22):2135–2144.
10. Mintz-Hittner HA, Kennedy KA, Chuang AZ. Efficacy of intravitreal bevacizumab for stage 3+ retinopathy of prematurity. *N Engl J Med.* 2011;364(7):603-615.
11. Tuñón J, Ruiz-Moreno JM, Martín-Ventura JL, Blanco-Colio LM, Lorenzo O, Egido J. Cardiovascular risk and antiangiogenic therapy for age-related macular degeneration. *Surv Ophthalmol.* 2009;54(3):339-348.
12. Klein R, Peto T, Bird A, Vannewkirk MR. The epidemiology of age-related macular degeneration. *Am J Ophthalmol.* 2004;137(3):486-495.
13. Hogg RE, Woodside JV, Gilchrist SE, et al. Cardiovascular disease and hypertension are strong risk factors for choroidal neovascularization. *Ophthalmology.* 2008;115(6): 1046-1052.
14. Hong T, Tan AG, Mitchell P, Wang JJ. A review and meta-analysis of the association between c-reactive protein and age-related macular degeneration. *Surv Ophthalmol.* 2011;56(3):184-194.
15. Sun C, Klein R, Wong TY. Age-related macular degeneration and risk of coronary heart disease and stroke: the Cardiovascular Health Study. *Ophthalmology.* 2009; 116(10):1913-1919.
16. Wong TY, Klein R, Sun C, et al; Atherosclerosis Risk in Communities (ARIC) Study. Age-related macular degeneration and risk for stroke. *Ann Intern Med.* 2006;145(2):98-106.
17. Tan JS, Wang JJ, Liew G, Rochtchina E, Mitchell P. Age-related macular degeneration and mortality from cardiovascular disease or stroke. *Br J Ophthalmol.* 2008;92(4):509-512.
18. Sturk C, Dumont D. In: Tannock IF, Hill RP, Bristow RG, et al, eds. *Basic Science of Oncology*. 4th ed. New York (NY): McGraw-Hill; 2005:231-248.
19. Eichmann A, Le Noble F, Autiero M, Carmeliet P. Guidance of vascular and neural network formation. *Curr Opin Neurobiol.* 2005;15(1):108-115.
20. Carmeliet P. Angiogenesis in life, disease and medicine. *Nature.* 2005;438(7070):932-936.
21. Szmitko PE, Fedak PW, Weisel RD, Stewart DJ, Kutryk MJ, Verma S. Endothelial progenitor cells: new hope for a broken heart. *Circulation.* 2003;107(24):3093-3100.
22. Ferrara N. Vascular endothelial growth factor: basic science and clinical progress. *Endocr Rev.* 2004;25(4):581-611.
23. Hicklin DJ, Ellis LM. Role of the vascular endothelial growth factor pathway in tumor growth and angiogenesis. *J Clin Oncol.* 2005;23(5):1011-1027.
24. Kawasaki T, Kitsukawa T, Bekku Y, et al. A requirement for neuropilin-1 in embryonic vessel formation. *Development.* 1999;126(21):4895-4902.
25. Ogawa S, Oku A, Sawano A, Yamaguchi S, Yazaki Y, Shibuya M. A novel type of vascular endothelial growth factor, VEGF-E (NZ-7 VEGF), preferentially utilizes KDR/Flk-1 receptor and carries a potent mitotic activity without heparin-binding domain. *J Biol Chem.* 1998;273(47):31273-31282.
26. Hicklin DJ, Ellis LM. Role of the vascular endothelial growth factor pathway in tumor growth and angiogenesis. *J Clin Oncol.* 2005;23(5):1011-1027.
27. Chen HX, Cleck JN. Adverse effects of anticancer agents that target the VEGF pathway. *Nat Rev Clin Oncol.* 2009;6(8):465-477.
28. Lee S, Chen TT, Barber CL, et al. Autocrine VEGF signaling is required for vascular homeostasis. *Cell.* 2007;130(4):691-703.
29. Izumiya Y, Shiojima I, Sato K, Sawyer DB, Colucci WS, Walsh K. Vascular endothelial growth factor blockade promotes the transition from compensatory cardiac hypertrophy to failure in response to pressure overload. *Hypertension.* 2006;47(5): 887-893.
30. Novartis Pharmaceuticals Canada Inc. Lucentis® (ranibizumab injection) Product Monograph. Date of authorization: December 13, 2011.
31. Hoffmann-La Roche Ltd. Avastin® (bevacizumab for injection) Product Monograph. Date of authorization: October 8, 2013.
32. Heiduschka P, Fietz H, Hofmeister S, et al. Penetration of bevacizumab through the retina after intravitreal injection in the monkey. *Invest Ophthalmol Vis Sci.* 2007; 48(6):2814-2823.
33. Barros-Pereira R, Costa R, Falcao M, et al. Plasma levels of vascular endothelial growth factor before and after intravitreal injection of bevacizumab or ranibizumab in the treatment of neovascular age-related macular degeneration. Presented at the Association for Research in Vision and Ophthalmology (ARVO) Annual Meeting. Fort Lauderdale (FL): May 1-5, 2011.
34. Carneiro AM, Costa R, Falcão MS, et al. Vascular endothelial growth factor plasma levels before and after treatment of neovascular age-related macular degeneration with bevacizumab or ranibizumab. *Acta Ophthalmol.* 2012;90(1):e25-30.
35. IVAN Study Investigators, Chakravarthy U, Harding SP, Rogers CA, et al. Ranibizumab versus bevacizumab to treat neovascular age-related macular degeneration: one-year findings from the IVAN randomized trial. *Ophthalmology.* 2012; 119(7):1399-1411.
36. Matsuyama K, Ogata N, Matsuoka M, et al. Plasma levels of vascular endothelial growth factor and pigment epithelium-derived factor before and after intravitreal injection of bevacizumab. *Br J Ophthalmol.* 2010;94(9):1215-1218.
37. Kim H, Fariss RN, Zhang C, Robinson SB, Thill M, Csaky KG. Mapping of the neonatal Fc receptor in the rodent eye. *Invest Ophthalmol Vis Sci.* 2008;49(5):2025-2029.
38. Kim H, Robinson SB, Csaky KG. FcRn receptor-mediated pharmacokinetics of therapeutic IgG in the eye. *Mol Vis.* 2009;15:2803-2812.
39. Mitchell P, Korobelnik JF, Lanzetta P, et al. Ranibizumab (Lucentis) in neovascular age-related macular degeneration: evidence from clinical trials. *Br J Ophthalmol.* 2010; 94(1):2-13.
40. Rosenfeld PJ, Brown DM, Heier JS, et al; MARINA Study Group. Ranibizumab for neovascular age-related macular degeneration. *N Engl J Med.* 2006;355(14):1419-1431.
41. Brown DM, Kaiser PK, Michels M, et al; ANCHOR Study Group. Ranibizumab versus verteporfin for neovascular age-related macular degeneration. *N Engl J Med.* 2006;355(14):1432-1444.
42. Alexander SL, Linde-Zwirble WT, Werther W, et al. Annual rates of arterial thromboembolic events in medicare neovascular age-related macular degeneration patients. *Ophthalmology.* 2007;114(12):2174-2178.
43. Rasier R, Artunay O, Yuzbasioglu E, Sengul A, Bahcecioglu H. The effect of intravitreal bevacizumab (Avastin) administration on systemic hypertension. *Eye (Lond).* 2009;23(8):1714-1718.
44. Curtis LH, Hammill BG, Schulman KA, Cousins SW. Risks of mortality, myocardial infarction, bleeding, and stroke associated with therapies for age-related macular degeneration. *Arch Ophthalmol.* 2010;128(10):1273-1279.
45. CATT Research Group. Ranibizumab and bevacizumab for neovascular age-related macular degeneration. *N Engl J Med.* 2011;364(20):1897-908.
46. Kodjikian L for the GEFAL Study Group. Avastin versus Lucentis for neovascular AMD. Presented at The ARVO annual meeting. Orlando (FL): May 4-8, 2013.
47. Comparison of Age-related Macular Degeneration Treatments Trials (CATT) Research Group,Ranibizumab and bevacizumab for treatment of neovascular age-related macular degeneration: two-year results. *Ophthalmology.* 2012;119(7):1388-1398.
48. Belfast Health and Social Trust. Letter to IVAN PI's Study Team Members and Patient's GPs. Available at: http://cteu.bris.ac.uk/trials/ivan/PIGPSafetyLetter.pdf. Accessed November 3, 2013.
49. Chakravarthy U, Harding SP, Rogers CA, et al. IVAN study investigators. Alternative treatments to inhibit VEGF in age-related choroidal neovascularisation: 2-year findings of the IVAN randomised controlled trial. *Lancet.* 2013;382(9900):1258-67.
50. Campbell RJ, Gill SS, Bronskill SE, Paterson JM, Whitehead M, Bell CM. Adverse events with intravitreal injection of vascular endothelial growth factor inhibitors: nested case-control study. *BMJ.* 2012;345:e4203.
51. Nissen SE, Wolski K. Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes. *N Engl J Med.* 2007;356(24):2457-71.
52. Clinical Perspectives on FDA Guidance for Industry: Diabetes Mellitus – Evaluating CV Risk in New Anti-diabetic Therapies to Treat T2DM. Disponible à : http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071627.pdf. Date de consultation : November 03, 2013

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