Comparative analysis of antiglaucoma generic and original eye drugs in Split-Dalmatia County

Mastnak, Viktor Marin

Master's thesis / Diplomski rad

2017

Degree Grantor / Ustanova koja je dodijelila akademski / stručni stupanj: **University of Split, School of Medicine / Sveučilište u Splitu, Medicinski fakultet**

Permanent link / Trajna poveznica: https://urn.nsk.hr/urn:nbn:hr:171:138683

Rights / Prava: In copyright / Zaštićeno autorskim pravom.

Download date / Datum preuzimanja: **2024-03-28**

SVEUČILIŠTE U SPLITU
MEDICINSKI FAKULTET
UNIVERSITAS STUDIORUM SPALATENSIS
FACULTAS MEDICA

Repository / Repozitorij:

MEFST Repository

zir.nsk.hr

UNIVERSITY OF SPLIT

dabar
DIGITALNI AKADEMSKI ARHIVI I REPOZITORIJI

UNIVERSITY OF SPLIT
SCHOOL OF MEDICINE

Viktor Mastnak

COMPARATIVE ANALYSIS OF ANTIGLAUCOMA GENERIC AND ORIGINAL EYE DRUGS IN SPLIT- DALMATIA COUNTY

Diploma Thesis

Academic year:

2016/2017

Mentor:

Assist. Prof. Veljko Rogošić, MD, PhD.

Split, September 2017.

UNIVERSITY OF SPLIT
SCHOOL OF MEDICINE

Viktor Mastnak

COMPARATIVE ANALYSIS OF ANTIGLAUCOMA GENERIC AND ORIGINAL EYE DRUGS IN SPLIT- DALMATIA COUNTY

Diploma Thesis

Academic year:

2016/2017

Mentor:

Assist. Prof. Veljko Rogošić, MD, PhD.

Split, September 2017.

CONTENT

1. INTRODUCTION 1

1.1 Glaucoma 2

1.2 Classification of different types of Glaucoma 3

1.2.1 Congenital Glaucoma 3

1.2.2 Primary open-angle glaucoma (POAG) 3

1.2.3 Primary closed angle glaucoma (PCAG) 5

1.2.4 Secondary Open Angle Glaucoma (SOAG) 6

1.2.5 Secondary closed-angle glaucoma (SCAG) 8

1.3 Risk factors for development of glaucoma 8

1.4 Diagnosis of glaucoma 9

1.4.1 Routine eye examination 9

1.4.2 Measuring the intraocular pressure 9

1.4.3 Examining the anterior chamber angle (gonioscopy) 10

1.4.4 Evaluating the optic disc (ONH) 10

1.4.5 Slit lamp exam 10

1.4.6 Measuring central corneal thickness (CCT/ pahimetry) 10

1.4.7 Testing the Visual Field (vF) 11

1.4.8 Optic coherence tomography (OCT) 11

1.5 Therapy of glaucoma 11

1.5.1 Original antiglaucoma drugs 12

1.5.2 Generic antiglaucoma medication 15

1.5.3 Laser treatment of glaucoma 18

1.5.4 Surgical therapy of glaucoma 18

1.5.5 Combined therapy 18

1.6 Treatment Guidelines from the European Glaucoma Society 19

1.6.1 Recommendations for Anti-Glaucoma Drug (AGD) prescriptions 19

1.6.2 EGS on Prostaglandin Analogues 19
1.6.3 EGS on Generic Medications 20
2. OBJECTIVES 21
3. PATIENTS AND METHODS 23
3.1 Methods and gathering of data 24
3.2 Statistical analysis 24
4. RESULTS 25
5. DISCUSSION 35
6. CONCLUSIONS 38
7. LITERATURE 40
8. SUMMARY 45
9. SAŽETAK 47
10. CURRICULUM VITAE 49

Acknowledgements

I want to thank my parents Koraljka and Boris for their patience, love and support through the years, my brother Bastian for being a true brother and my grandparents Radovan, Stefanie, Grgo and Vedrana for their unconditional "grandparent" love. Much love goes out to my friends and colleagues particularly my mechanic, the piano man, the captain, the master of toasts, fortune and my sparring partner.

I also want to express special thanks to my mentor Veljko Rogošić, MD, PhD. for offering his kindness and expertise at any time and my co-mentor Lucija Vanjaka Rogošić, MD, PhD. for her courtesy in offering help for statistical and analytical processing of data.

1. **INTRODUCTION**

1.1 **Glaucoma**

The term „glaucoma“ originates from the ancient Greek word glaukos, meaning “bright, glowing, shiny” specifically for the sea: grey-bluish and comes from the blue-grey discoloration of the iris after chronic inflammation (1).

In the routine practice of ophthalmology, the term glaucoma is applied to all patients having an increased intraocular pressure (IOP) with or without glaucomatous damage, as well as to patients suffering from glaucomatous damage (with or without high IOP).

An elevated intraocular pressure is an important risk factor for glaucoma. Many people have an average IOP of 10-21 mmHg with a mean value of 15 mmHg. The most common cause for an increase in IOP is a decreased outflow of aqueous humour through the iridocorneal angle and high resistance in the trabecular meshwork. Nevertheless almost 40% of glaucoma patients have normal intraocular pressure (Normal tension glaucoma), but are very sensitive to blood pressure fluctuations (2,3).

In glaucoma, retinal nerve cells and retinal nerve fibres progressively die, leading to cupping or excavation of the nerve head. Consequentially, the connection between the eye and brain, which is crucial for vision, is gradually destroyed. Light can be seen but transmission of visual information to the brain is interrupted. As a result, defects in the visual field develop which, in the beginning, go unnoticed by the patient. Early detection of glaucoma is crucial (3).

The International Glaucoma Association (IGA) estimates that about 2% of people in the UK over the age of 40 are affected by Glaucoma (4). The global prevalence of glaucoma for population aged 40–80 years is 3.54%. Especially Africa and Asia show higher numbers in incidence of Glaucoma. In 2013, the number of people (aged 40–80 years) with glaucoma worldwide was estimated to be 64.3 million, increasing to 76.0 million in 2020 and 111.8 million in 2040 (5).

In the Croatian town Split, the regional capital of the Split-Dalmatian County, the mean incidence of acute closed angle glaucoma in the years between 1985 -1999 was 4.1 on 100.000 inhabitants in the whole population (6).

1.2 Classification of different types of Glaucoma

1.2.1 Congenital Glaucoma

Primary congenital glaucoma is rare but has an important impact on child's development and quality of life. Early detection and appropriate therapy make a major difference in the visual outcome and can prevent lifelong disability. Surgical treatment is unavoidable. According to the age of appearance it is divided into (13,14):

I. Primary congenital glaucoma (PCG): from birth to >2 years of life

II. Late-onset childhood open angle glaucoma or Infantile glaucoma: onset >2 to puberty

III. Juvenile glaucoma: from puberty to 35 years

In secondary congenital glaucoma many pathogenic mechanisms are possible. Medical treatment usually is non-effective nor is it doable in long term. Medications which include oral Carbonic Anhydrase Inhibitors (CAIs) can be used in the time while decision is made about the surgical approach and in case of failed surgery while awaiting for further options (15).

The treatment of primary congenital glaucoma cases is particularly challenging because of the nature of the disease and the difficulties in operating them and examining patients in this age group. Treatment has to be adapted to the leading anomaly and the mechanism of IOP elevation. If possible concerned patients should be referred to tertiary care centres (15).

1.2.2 Primary open-angle glaucoma (POAG)

Open-angle glaucomas are chronic progressive optic neuropathies (ON) that are defined by characteristic morphological changes at the optic nerve head (ONH) and retinal nerve fibre (RNFL) without other ocular disease or congenital anomalies. Progressive retinal ganglion cells (RGC) death and visual field loss (VFL) are associated with these changes. Glaucoma is the second leading cause of blindness both in Europe and worldwide. It is the most frequent cause of irreversible blindness. POAG is treated by reducing intraocular pressure using medication, laser, surgery or sometimes in combination (16).

Consideration of risk factors helps to identify patients for early detection and to guide management decisions about the initiation and increase of treatment in established glaucoma patients.

Risk factors are: Age, intraocular pressure (IOP), race, family history, pseudoexfoliation (PEX), central corneal thickness (CCT), myopia, ocular perfusion pressure, diabetes m., systemic blood pressure (BP), migraine, Raynaud Syndrome and obstructive sleep apnoea.

Factors that are linked with the advance of established POAG have been identified by large RCT. The factors are: Age, IOP, pseudoexfoliation, CCT, disc haemorrhages (15).

POAGs divide into several types:

I. High pressure glaucoma (POAG/HPG)

The risk for POAG advances continuously with the level of IOP without evidence of a threshold IOP for the onset of the condition. The aetiology is not known. It can start in early adulthood. Typical Symptoms of HPG are that the condition is asymptomatic until field loss advances, elevated IOP without treatment, characteristic glaucomatous damage at the optic nerve head and detectable glaucomatous defects in the visual field and in optical coherence tomography (OCT) in correspondence to the optic disc damage. Treatment forms are: drugs including monotherapy or combination therapy in selected patients, different types of filtration surgery like penetrating and non-penetrating procedures or laser trabeculoplasty (ALT or SLT) with adjunctive medical therapy when needed (15).

II. Normal pressure glaucoma (POAG/NPG)

Aetiology is not known. It can occur from the age 35 onwards. It stays asymptomatic until field loss advances. Symptoms are optic nerve head damage typical of glaucoma and disc haemorrhages. Treatment options are medical therapy: any effective and tolerated drug alone or in combination whose IOP lowering effect is efficient to reach or maintain the target IOP. Vasoconstrictive drugs or medications with systemic hypertensive effects should not be used. Laser trabeculoplasty is also a treatment option (15).

III. Infantile forms of glaucoma

It can occur beyond infancy, usually after puberty or early adulthood and can be hereditary. There is no enlargement of the globe and it is asymptomatic until field loss is advanced. IOP is elevated without treatment. There is diffuse optical nerve head damage with glaucomatous defects which are present in visual field. No congenital or developmental anomalies are present. Therapy is any effective and well tolerated topical regimen. Laser trabeculoplasty is not recommended due to poor and short lived IOP lowering effect (15).

IV. Ocular hypertension (OH)

The aetiology is unknown. Signs and Symptoms include IOP above 21 mmHg without treatment. The visual field is normal. Optic disc and retinal nerve fibre layer are normal. No history or signs of other eye disease or steroid use should be present. Other risk factors are not known. A modest increase in IOP is not a sufficient reason for treatment but should be considered in patients with repeated IOP in the high 20s. If left untreated up to 9.5% develop glaucoma over a 5 year follow up. Each patient should be assessed individually (15).

1.2.3 Primary closed angle glaucoma (PCAG)

Angle closure is defined by presence of irido-trabecular contact (ITC). This can be either appositional or synechial. Gonioscopy is the standard technique for diagnosing ITC. Primary Angle closure result from crowding of the anterior segment and usually occurs in eyes with smaller than average anterior segment dimensions. PAC damages ocular tissue in many ways. High IOP values cause the iris to suffer ischemic damage. Angle closure leads to 50% of all glaucoma blindness in the world and also the most visually destructive form of glaucoma. PAC is more common among Asian people than those from Europe as population surveys shown (43). Primary glaucoma cases have to be examined and an open anterior chamber angle should be shown on gonioscopy before PACG is excluded (17).

Provocative tests for angle-closure are of little use since even when they are negative, a potential for angle-closure persists. In addition those tests can be dangerous by leading to an acute angle-closure attack even while the patient is monitored.

The mechanisms responsible for angle closure are described in terms of anatomical location of obstruction to aqueous flow: at the pupil, the iris, the ciliary body, the lens and behind the lens.

1. Acute angle closure (AAC) with pupillary block mechanism

It is defined by circumferential iris apposition to the trabecular meshwork with fast and excessive rise in IOP that does not resolve spontaneously. Symptoms are: IOP > 21 mmHg often 50-80 mmHg, decreased visual acuity, corneal edema, blurred vision with pain and "halos". Iridectomy or Iridotomy together with medical treatment is performed (15).

2. Acute Angle-Closure (AAC) with plateau iris configuration

In plateau iris configuration the iris plane is flat and narrowing the anterior chamber angle due to insertion of the iris anteriorly on the ciliary body. This alters the position of the peripheral iris in relation to trabecular meshwork (18).

3. Intermittent Angle-Closure (IAC)

Here signs may vary according to the amount of iridotrabecular contact of chamber angle and mimic acute angle-closure in mild form.

4. Chronic angle closure glaucoma (CACG)

CACG is defined by permanent synechial closure of any extent of the chamber angle as confirmed by gonioscopy. Signs include peripheral anterior synechiae of any degree at gonioscopy. The IOP is above 21 mmHg. There is usually no pain, visual disturbances occur according to functional states (15).

1.2.4 Secondary Open Angle Glaucoma (SOAG)

Secondary glaucomas are a heterogeneous group of conditions in which elevated IOP is the leading pathological factor causing glaucomatous optic neuropathy. SOAG can be caused by ocular disease or iatrogenic: (15)

I. Secondary Open-Angle glaucoma caused by ocular disease
    a. Exfoliative (pseudoexfoliative) glaucoma
        i. XFG is the most common type o secondary open-angle glaucomas. It usually occurs in persons older than 60 years. It is asymptomatic until visual field loss is advanced. One or both eyes are affected usually asymmetrical. IOP is above 21 mmHg, frequently higher than in average POAG cases (19).

b. Pigmentary Glaucoma (PG)
    i. Melanin granules cause an increase of trabecular meshwork outflow resistance and lead to an elevation of IOP. It represents 1-1.5% of all glaucoma cases. Patients may experience transient visual blurring or halos during episodes of IOP rise. It can be either unilateral or bilateral (20).
c. Lens induced open-angle Glaucoma
    i. The trabecular meshwork outflow pathways are obstructed by lens particles and/or inflammatory cells. Patients usually suffer from unilateral pain with redness and inflammation. Vision is reduced and IOP is elevated (21).
d. Glaucoma associated with intraocular haemorrhage
    i. Either acute bleeding in the anterior chamber or long standing blood in the vitreous of any source can cause IOP elevation. Symptoms are pain and eye irritation. Elevated IOP is more often due to recurrent haemorrhage or re-bleeding (15).
e. Glaucoma due to intraocular tumour
    i. It represents with reduced aqueous humor outflow due to primary or secondary intraocular tumours mainly of the anterior segment. Symptoms and signs are elevated IOP. A highly variable clinical picture, combining evidence of both tumour and glaucoma (22).
f. Open angle glaucoma due to ocular trauma
    i. This condition can be caused by blunt non-penetrating or penetrating trauma to the eye. Trauma can lead to reduced trabecular outflow due to traumatic changes to the trabecular meshwork. Penetrating injury may damage one or more intraocular structures leading to elevated IOP (15).

II. Iatrogenic secondary open-angle glaucomas
a. Glaucoma due to corticosteroid treatment

Topical, intravitreal as well as high dose and long term systemic corticosteroid therapy may induce acute or chronic IOP elevation. Corticosteroids lead to changes in the trabecular extracellular matrix which can cause decreased outflow (23, 24).

b. Secondary open-angle glaucoma due to ocular surgery and laser therapy
    i. Ocular surgery can cause secondary open-angle glaucoma by intraocular haemorrhage, inflammatory reaction, lens material, pigmentay loss from uveal tissue, or trauma (25).

1.2.5 Secondary closed-angle glaucoma (SCAG)

There are many different causes of secondary closed-angle glaucoma and the clinical signs vary according to the underlying condition

I. Secondary closed-angle glaucoma with pupillary block

Pupillary block pushes the iris forward to occlude the angle. It can be caused by enlarged swollen lenses, anterior lens dislocation (Trauma, zonular lexity, Marfan Syndrome, etc.)

II. Secondary closed-angle glaucoma without pupillary block

The trabecular meshwork is obstructed by iris tissue or a membrane. The iris and/or a membrane are progressively pulled forward to occlude the angle. IOP is >21mmHg (15).

1.3 Risk factors for development of glaucoma

1. Age

   The prevalence of glaucoma increases dramatically with age. Two studies reported a 6% and 4% increased risk per year of age as baseline of developing glaucoma (15).
2. Intraocular pressure

   Higher IOP has been consistently associated with the prevalence and incidence of glaucoma. The risk of developing glaucoma increases by 11-12% in Caucasians, 10% in people of African origin and 18% in Latinos for each 1 mmHg in IOP (26-27).
3. Race/Ethnicity

   The prevalence of glaucoma is several times higher in African Americans and Afro Caribbeans than in Caucasians (28-29).
4. Positive Family History of Glaucoma

   Studies have shown that the risk factor of having glaucoma 4-9 times higher for individuals having first degree relative with glaucoma compared to those who do not have glaucoma (30-31).

5. Pseudoexfoliation (PEX)

   Population based studies reported that pseudoexfoliation is associated with 11 fold increased risk of development of glaucoma (26).
6. Central corneal Thickness (CCT)
7. Myopia

   A Dutch study showed that subjects with high myopia (>4D) had a 2.3-fold increased risk for developing glaucoma (27).
8. Ocular perfusion pressure

   Population based studies have shown that low ocular perfusion pressure is associated with increased glaucoma prevalence (28,32).
9. Other factors

   Systemic and/or systemic vascular risk factors like Diabetes mellitus, systemic blood pressure, ocular perfusion pressure, migraine, Raynaud syndrome and obstructive sleep apnoea (15).

1.4 Diagnosis of glaucoma

Early diagnosis of glaucoma is of great importance because treatment is likelier to succeed when begun early than when damage to the nerve has already progressed to an advanced stage. Detecting glaucoma is only possible if the patient visits the ophthalmologist and early state changes of glaucomatous damage are sometimes hardly differentiated from variations that are harmless. There is often a period of uncertainty as to whether or not the patient will develop glaucomatous damage (3).

1.4.1 Routine eye examination

The ophthalmologist will first check visual acuity (VA), a measure of the optical resolution or the eyes discernment, i.e. how well one can read and recognize things, people, traffic signs, etc. from a distance and up-close. If the visual acuity is identical to the general healthy population, it is 1.0, 100%, or 20/20. A patient with visual acuity of 0.5 (50%) or 20/40 needs the chart letters 20 to size of someone having 20/20 vision. In glaucoma, visual acuity stays normal for quite some time. However many glaucoma patients suffer form a reduced visual acuity because they also have other eye diseases, such as cataract (3).

1.4.2 Measuring the intraocular pressure

Tonometry is another term for measuring the IOP. The international standard in ophthalmology is The Goldmann applanation tonometer (GAT). Applanation tonometry

measures the force that is necessary to flatten (i.e. to applanate) a defined part of the cornea. The instruments are calibrated so that the IOP can be read from a graduated dial.

Non-contact devices flatten the cornea using a jet of air. An optic receiver detects when and how fast the cornea has been flattened to a predetermined degree. This method's advantage lies in the face that local anaesthetic is not required and potential contamination from a tonometry cylinder is prevented. However, the measurement is not as accurate as Goldmann's tonometry, particularly with high IOP levels (3).

1.4.3 Examining the anterior chamber angle (gonioscopy)

The examination of the chamber angle is called gonioscopy. The method is used when investigating the cause for an IOP increase or when there is some indication that the angle could close, thereby triggering an acute glaucoma attack. The physician uses a special contact glass, a gonio lens, to perform gonioscopy. After applying a local anaesthetic, the gonio lens is placed upon the eye. Using this technique, the angle can be checked for material that should not be there. (blood, cell-debris or signs of inflammation) (3)

1.4.4 Evaluating the optic disc (ONH)

Evaluating the optic disc is the most important step in diagnosing glaucoma. The size of the optic nerve head (ONH) is assessed first as well as the cup-disc ratio (CDR). Atrophy around the papilla can indicate glaucomatous damage, but it can also occur in other diseases and even in healthy eyes. However a small haemorrhage at the rim of the optic disc is almost always sign of glaucoma, especially when other eye diseases have been ruled out. Disc haemorrhages are markers of progressing glaucomatous damage. Local vasoconstriction of retinal vessels is a local sign of glaucoma (3).

1.4.5 Slit lamp exam

The slit lamp is a special ophthalmological microscope that swivels so that the eye and its interior parts can be viewed from various angles. It is equipped with a light source that is also moveable. The light beam usually takes the form of a slit, thereby enabling the eye to be examined in different layers, i.e. "optical sections" (3).

1.4.6 Measuring central corneal thickness (CCT/ pahimetry)

Corneal thickness can be measured with optical devices, nowadays with ultrasound and laser pahimeters. At the given real IOP, the thicker the cornea, the higher are the measured IOP values, and vice versa. The IOP Diagnosis can be overestimated or

underestimated (ocular hypertensives, persons with thin corneas). It must be noted that an IOP at which glaucomatous damage occurs or progresses is always too high. It is to date not clear whether thin cornea is a risk factor for glaucomatous damage independent of IOP level but we know it is associated with myopia (3).

1.4.7 Testing the Visual Field (vF)

Evaluation of the visual field is called perimetry. It plays a critical role in diagnosing glaucoma and in monitoring the diseases progression. Only perimetry can provide conclusion about patient's visual function and is of primary importance in analysing the progression of changes in visual field. In glaucoma, typical visual field defects appear. Characteristic nerve fibre bundle defects are caused by the demise of one or several adjusting nerve fibre bundles. There are a lot of other non specific defects in glaucoma that generally make it difficult to assess whether a visual field defect is due to glaucoma or to some other disease. In glaucoma, the type of the defect is less important than the total amount of tissue and functional loss.

1.4.8 Optic coherence tomography (OCT)

The loss of nerve fibers that lead from the retinal surface to the optic disc is one component of glaucomatous atrophy. OCT is a diagnostic instrument for measuring the nerve fiber layer thickness. It employs the basic imaging principle similar to the ultrasound B-scan. (3).

1.5 Therapy of glaucoma

The goal of glaucoma treatment is to maintain the patient's visual function and related quality of life (QoL), at sustainable costs. The cost of treatment in terms of inconvenience and side effects as well as financial implications for the individual and society requires careful evaluation. Quality of life is closely linked with visual function and, overall, patients with early to moderate glaucoma damage have good visual function and modest reduction in quality of life (QoL), while quality of life is considerably reduced if both eyes have advanced visual function loss. Individualized glaucoma treatment aims at providing glaucoma management tailored to the individual needs of the patient (3). Patients with severe functional loss or younger patients with manifest disease should have more aggressive treatment and closure follow up than patients with little or no risk, e.g., patients with ocular hypertension or elderly patients with mild field loss and low IOP levels. Intraocular pressure can be reduced by: different medications, laser treatments or Surgery (3).

1.5.1 Original antiglaucoma drugs

1.5.1.1 Parasympatomimtic agents/ cholinergic agents

The neurotransmitter released by the nerve cell endings is called acetylcholine. Drugs that mimic the effect of acetycholine are called cholinergic agents or parasympatomimetics.

Pilocarpine:

Pilocarpine is the most important drug from among the cholinergic agents. It is a so called alkaloid that is a basic component produced by plants. It is available as eye drops and ointment, administered in concentration ranging from 0.5% to 3%, and easily penetrates into the eye. About half an hour after application the IOP starts to drop, and the lowering effect lasts between 4-8 hours. It must be administered at least 3-4 times a day (3,37).

1.5.1.2 Sympathomimetic Agents (Alpha-2 selective agonist)

Substances that mimic or enhance the effects of the sympathetic nervous system are called sympathomimetic agents. Alpha 1 receptors are located post-synaptically and have a sympathomimetic effect while alpha 2 receptors are located pre- and post-synaptically ultimately exhibiting an sympatholytic effect. In glaucoma therapy, alpha-2 selective medications are generally used, including drugs such as clonidine, apraclonidine and brimonidine (3).

I. Brimonidine (Alphagan, Allergan Pharmaceuticals Ireland, Westport, Ireland)

Alphagan is available in form of eye drops, 2 mg/ml. The drug is administered in concentration of 0,2%. The mechanism of action is diminished production of aqueous humor and eases uveoscleral flow (3,37).

1.5.1.3 Sympatholytic Agents (β-Blockers)

Sympatholytic Agents inhibit the sympathic part of the nervous system. Beta receptors in the ciliary body are responsible for the production of aqueous humour and their blockage leads to decreased production of aqueous humour and lowering of eye pressure. They provoke following side-effects: allergies, dry eyes, worsening of accommodation, reactivation of lung disease such as asthma, AV block, hypotension, weakness and depression (3).

I. Timolol: (Timalen, Jadran Galenski laboratorij d.d., Rijeka, Croatia)

Timalen is a non-selective beta-blocker. It is available as eye drops, 2mg/ml and 5mg/ml. The medication is applied two times daily in a concentration of 0.25% to 0.5%. Blocking beta receptors leads to decreased production of aqueous humor and lowering of IOP. It has the most significant effect in lowering IOP amongst all beta blockers. Its main side effect is bronchospasm in prone patients (3,37).

II. Betaxolol: (Betoptic, Alcon Cusi S.A., EI Masnou, Barcelona, Spain; Alcon Couvreur N.V., Puurs, Belgium)

Betoptic is a selective beta-blocker available as eye drops, 5 mg/ml. It is applied two times daily in a concentration of 0.5%. Betoptic has better effect compared to Timalen. It predominantly blocks beta-1 receptors and causes less problems with asthmatic patients than Timalen. It can speed up microcirculation and is neuroprotective (3,37).

III. Levobunolol: (Vistagan, Allergan Pharmaceuticals Ireland Ltd., Westport, Ireland)

Vistagan is available as eye drops, 5 mg/ml. The drug is applied two times in a concentration of 0.5%. By blocking beta receptors which are responsible for the production of aqueous humour in the ciliary body it leads to reduction of production of aqueous humour and a reduction of IOP (3,37).

1.5.1.4 Carbonic Anhydrase Inhibitors (CAI)

Carbonic Anhydrase is an enzyme that catalyzes the transformation of carbon dioxide and water into bicarbonate and vice versa. The enzymes activity can be blocked by carbonic anhydrase inhibitors (CAI). CAI lead to vasodilation in ocular as well as cerebelar blood vessels. This vasodilatative effect may be quite advantagous in the treatment of glaucoma (3).

I. Dorzolamid: (Trusopt, Merck Sharp & Dohme – Chibret, Clermont – Ferrand, France)

Trusopt is available as eyedrops, 20 mg/ml. The drug exerts its effect in inhibiting carbonic anhydrase, which results in lowered lower production of aqueous humour. It is applied 2-3 x per day (3,37).

II. Brinzolamid (Azopt, S.A. Alcon Couvreur N.V., Puurs, Belgium)

Azopt is available as eyedrops, 10mg/ml. The drug is applied two times daily in 1% local concentration. The drug inhibits carbonic anhydrase what results in lowered production of aqueous humour. Azopt has the same effect in lowering IOP like Oftidor and Trusopt but is available as suspension and not solution (3,37).

1.5.1.5 Analogues of prostaglandines and prostamides

Analogues of prostaglandin were only recently introduced into ophthalmology as opposed to inhibiting drugs that are being used since a long time in modern ophthalmology. The mechanism of these drugs works by increasing uveoscleral outflow of aqueous humour. It is the first line of antiglaucomatous treatment (AGT) (3).

I. Latanoprost: (Xalatan, Pfizer Manufacturing Belgium NV, Puurs, Belgium)

Xalatan is available in form of eye drops in 50mg/ml. The medication reduces IOP by accelerating outflow of aqueous humour and is the only anti-glaucoma medication that has an influence on the uveoscleral angle. It increases the uveoscleral angle for a prolonged period and needs application only once daily. The most important side effect of Xalatan is conjuctival hyperemia, so called „red eye“ leading to itching and a feeling of foreign body in the eye. It also can lead to irreversible pigmentation of the iris, prolongation of eyelashes and macular edema (3,37).

II. Bimatropost, prostamid (Lumigan, Allergan Pharmaceuticals Ireland, Ireland)

Lumigan is available in form of eye drops, 0.1 mg/ml, 0.3 mg/ml. The drug i applied once daily in the evening. Lumigan increases the flow of aqueous humour via the trabecular meshwork and uveoscleral angle. Side effect are moderate conjuctival hyperaemia (3,37)

III. Travoprost: (Travatan, S.A. Alcon Couvreur N.V., Puurs, Belgium)

Travatan is available as eye drops in 40 mg/ml. The medication is applied once daily in 0.004% concentration. The mechanism of action is the increase in uveoscleral outflow. Its side effects are similar to Xalatan (3,37).

IV. Tafluprost: (Saflutan, Merck Sharp & Dohme B.V., Haarlem, Netherlands; Laboratoire Unither, Coutances, France)

Saflutan is available as eye drops in 15 mg/ml. Its mechanism of action is in the increase of uveoscleral outflow of aqueous humour (3,37).

1.5.1.6 Fixed-dose combination drugs (FDC)

Most therapies of glaucoma are limited to the use of mono-component drugs. A second drug from a different group is given if reduction of IOP with mono-component drugs is insufficient. Most commonly in use are combinations of two or three drugs from different groups with the maximum number of drops. Today pharmaceutical companies are preparing combinations in fixed form with two antiglaucoma drugs in one bottle (3). These are:

I. **Analogues of prostaglandin/prostamid + β-Blockers**
   - Latanoprost + Timolol (Xalacom, Pfizer Manufacturing Belgium NV, Puurs, Belgium)
   - Travoprost + Timolol (Duotrav, S.A. Alcon Couvreur N.V., Puurs, Belgium)
   - Bimatropost + Timolol (Ganfort, Allergan Pharmaceuticals Ireland, Westport, Ireland)

II. **CAIs + β-Blockers**
   - Dorzolamid + Timolol (Cosopt, Merck Sharp & Dohme B.V., Haarlem, Netherlands; Laboratories Merck Sharp & Dohme – Chibret, Clermont – Ferrand, France)
   - Brinzolamid + Timolol (Azarga, S.A. Alcon Couvreur N.V., Puurs, Belgium)

III. **A-2 Agonists + β-Blockers**

Brimonidin + Timolol (Combigan, Allergan Pharmaceuticals Ireland, Westport) (3)

Lately all Antiglaucoma Drugs are used without preservatives due to the susceptibility of the anterior eye segment to their toxic effects. Benzalkonium chloride (BAK) and Polyquad are the main conservans that are excluded because of their tendancy to cause ocular surface disease (OSD).

1.5.2 Generic antiglaucoma medication

A generic drug is supposed to be identical or bioequivalent to a brand name drug in dosage form, safety, strength, route of administration, quality, performance characteristics and

intended use. Despite their chemical identity to their branded counterparts, they are typically sold for lower price compared to the price of the original drug (7).

As global spending on medicinal products continues to rise, the availability of lower-cost generic substitutes is increasingly driving health care decision-making. Generic compounds may differ from innovator agents with regards to performance under environmental stress, relative acidity and bottle size/rigidity. Matching ingredient profiles may therefore not result in consistently comparable drug compositions and clinical effects (8).

Ophthalmic generic compounds, however, must be identical in strength, dosage form, route of administration, have the same indications/contraindications, and abide by the same Good Manufacturing Practices standards as innovator agents (9).

1.5.2.1 Sympathomimetic agents (Alpha-2 selective agonist)

I. Brimonidine: (Luxfen, Pharma Stulln GmbH, Stulln, Germany; Sanitas AB, Kaunas, Lithuania)

Luxfen is available in form of eye drops in 2mg/ml. The mechanism of action is diminished production of aqueous humor and eases uveoscleral flow. It provokes reversible local side effects after 6 months of treatment, moderate decrease of blood pressure,tiredness and dry mouth. It can be combined with Timolol.

II. Brimonidine: (Bimanox, Jadran Galenski laboratorij d.d., Rijeka, Croatia)

Bimanox is available in form of eye drops in 2mg/ml. The drug decreses aqueous humor production and facilitates uveoscleral outflow. Side effects are similar to Luxfen.

1.5.2.2 Sympatholytic agents (β-Blockers)

I. Timolol: (Timlatan, S.C. Rompharm Company S.R.L., Otopeni, Romania)

1.5.2.3 Carbonic anhydrase inhibitors

I. Dorzolamid: (Oftidor, S.C. Rompharm Company S.R.L., Otopeni, Romania).

Oftidor is available as eyedrops, 20 mg/ml. It is administered twice daily in a 2% solution. It leads to moderate IOP reduction. There are indications that dorzolamide exerts positive influence on ocular perfusion and is therefore of special benefit for patients who suffer from a disturbed bloodflow. Side effects may be slight burning sensation in the eye, bitter taste in the mouth and allergic reactions (3,37).

I. Dorzolamid: (Dorzol, Jadran Galenski laboratorij d.d., Rijeka, Croatia)

Dorzol is available as eyedrops, 20 mg/ml. The drug exerts its effect in inhibiting carbonic anhydrase, which results in lowered lower production of aqueous humor.

I. Dorzolamid (Ulom, Pliva Hrvatska d.o.o., Zagreb, Croatia)

Ulom is available as eyedrops, 20 mg/ml. The drug exerts its effect in inhibiting carbonic anhydrase, which results in lowered production of aqueous humor (3,37).

1.5.2.4 Analogues of prostaglandines and prostamid

I. Latanoprost (Latanox, Jadran Galenski laboratoriji d.d., Rijeka, Croatia)

Latanox is available as eye drops in 50 mg/ml. The mechanism of action of this drug is in the increase of uveoscleral outflow of aqueous humor. It has similar side effects to Xalatan.

II. Latanoprost (Latapres, S.C. Rompharm Company S.R.L., Otopeni, Romania)

Latapres is available as eye drops in 50 mg/ml. Its mechanisms and side effects are similar to Latanox (3,37).

1.5.2.5 Fixed-dose combination drugs (FDC)

Carbonic anhydrase inhibitors + β-Blockers

- Dorzolamid + Timolol (Oftidorix, Famar S.A., Athens, Greece)
- Dorzolamid + Timolol (Glaumax, Jadran Galenski laboratorij d.d., Rijeka, Croatia)
- Dorzolamid + Timolol (Ulom plus, Pliva Hrvatska d.o.o., Zagreb, Croatia) (3,37)

1.5.2.6 Systemic Antiglaucoma Drugs

Hyperosmotic agents such as oral glycerine and intravenous mannitol can rapidly lower IOP by decreasing vitreous volume. They do not cross the blood-ocular barrier and therefore exert oncotic pressure that dehydrates the vitreous. Side effects associated with the hyperosmotic agents can be severe and include headache, back pain, diuresis, circulatory overload with angina, pulmonary edema and heart failure, and central nervous system effects such as obtundation, seizure, and cerebral hemorrhage. Because of these potentially serious side effects, they are not used as long-term agents. They are typically used in acute situations to temporarily reduce high IOP until more definitive treatments can be rendered (3).

1.5.3 Laser treatment of glaucoma

Indications for Laser treatment of glaucoma is failure and contraindication of medication therapy, meaning a failure of lowering IOP or continuous deterioration of the visual field. There are several laser procedures (3):

I. **Laser iridotomy**

Laser iridotomy is performed with a YAG laser cutting a small hole in the iris without surgical incision on the surface of the eye. The treatment is short and painless. Side effects are reversible loss of visual acuity. Anti-inflammatory eye drops are used several days after surgery (3).

II. **Laser trabeculoplasty (ALT/SLT)**

To avoid surgery, argon laser tabeculoplasty or selective argon trabeculoplasty (SLT) is used. It is used for primary open-angle glaucoma. Only 60% of patients are responsive to the therapy while the effects of the surgery last 3 years. SLT can be repeated (3).

1.5.4 Surgical therapy of glaucoma

The aim of surgical therapy is the decrease and stabilization IOP to maintain the existing visual acuity and visual field. Indications for surgery are high IOP despite medical or laser therapy or when the damage progresses despite conservative therapy. Methods of operative treatment are: trabeculotomy, deep sclerotomy and viscocanalostomy. The aim is to increase the outflow of aqueous humor (3).

1.5.5 Combined therapy

Nowadays there is a possibility of combined laser and medical treatment. A high number of patients require ongoing medical therapy after glaucoma surgery (3).

1.6 Treatment Guidelines from the European Glaucoma Society

The aim of glaucoma therapy is to maintain the patient's visual and quality of life, at sustainable costs. Careful evaluation hast to be applied to the cost of treatment in terms of inconvenience and side effects as well as social and individual financial implications. Quality of life is linked with visual function. Patients with early to moderate glaucomatous damage have good visual function and therefore only small reduction in quality of life. Quality of life is considerably reduced if both eyes are affected by visual function loss (15).

For this reason it is important to have individualized treatment of glaucoma that aims at providing glaucoma management tailored to the individual needs of the patient. Severe functional loss or young patients with manifested disease have to be exposed to more aggressive treatment and close follow-up than little or no risk patients (15).

1.6.1 Recommendations for Anti-Glaucoma Drug (AGD) prescriptions

The European Glaucoma Society (EGS) recommends initiating treatment with monotherapy. A meta analysis of randomized controlled trials has shown that the highest reduction of IOP is obtained with prostaglandins followed by non-selective beta blockers, alpha adrenergic agonists, selective b-blockers and finally topical carbonic anhydrase inhibitors (38).

If initial therapy is unsuccessful with no reach in target pressure or intolerance for the drug, another monotherapy should be tried before adding a second drug. This rule applies also to prostaglandin analogues (PGA) used as first choice. As there are non-responders to certain PGAs it is advised to switch to another PGA or another class of monotherapy. Laser therapy may also be therapeutical (15).

If first choice monotherapy is tolerated but fails to provide a lowering of pressure to the target IOP addition of a second drug should be considered. The recommendation by the EGS is to combine agents with different modes of action, one affecting production of aqueous humour and another influencing outflow for example. Because polydrug regiments for treatment of glaucoma may lead to bad adherence to the drugs, reduced efficacy through wash-out medications and increased exposure to preservatives (39) fixed-dose combination therapy, when available, is advised (15).

1.6.2 EGS on Prostaglandin Analogues

Since PGAs have been developed in the 1990s, they have progressively replaced beta-blockers as first-choice/first-line treatment. The reason for that is that they are simply the most effective IOP-lowering agents, lacking relevant systemic side effects and requiring just

once-daily administration (40). The primary mechanism of action of prostaglandins is to maximize uveoscleral outflow which reduces IOP by 25%-35%. The reduction of IOP starts 2-4 h after the initial administration with its highest effect within 8-12 h (15). Also patients that are treated with PGAs have reduced short term IOP variability compared to patients treated with other classes of drugs (41). When combined with most other drug classes, PGAs exhibit additional IOP lowering. There are fewer than 10% non-responders to prostaglandin therapy (e.g. eyes with fewer reduction of IOP 10% or 15% from baseline) (42). Mild conjunctival hyperaemia is a common finding but usually decreases over time.

1.6.3 EGS on Generic Medications

By definition generic drugs are indistinguishable to brand name drugs in dosage, route of administration, strength, intended use and performance characteristics. For ophthalmological purposes this concept of "essential similarity" is problematic as it is hard to prove through clinical studies. With systemic drugs, bioequivalence studies from blood samples can be performed. Here, plasma concentrations within certain borders that equal the original drug can be determined. Such studies are impossible for topical eyedrops. There are no requires for clinical studies for generic approval in ophthalmology and 10% difference in concentration of the active principle between generic drugs and originals is considered acceptable. Whereas the active principle is assumed equal, there can be variations in adjuvants. The problem lies in the different adjuvants that may lead to alterations in viscosity, osmolarity and pH of the eye drops and therefore lead to tolerability and corneal penetration issues. Nevertheless there is a huge demand for generic glaucoma drugs as many of them are becoming of patent. For Latanoprost the generic share is 65% in Europe. The advice of the European Glaucoma Society is to monitor the patients' IOP closely when switching from branded to generic drugs (15).

2. **OBJECTIVES**

The primary aim of this research is to find out the total number of anti-glaucoma drugs in Split-Dalmatia county from 2012-2016, especially with regards to consumption of original anti-glaucoma drugs against their generic counterparts and comparison between fixed (combined) and mono therapy. Also we want to show if the prescription of prostaglandin analogues has risen through the years.

In addition, we want to prove that the guidelines of the European Glaucoma Society (EGS) are respected by showing that in Split-Dalmatia County the number of original anti-glaucoma therapy, fixed-dose combinations and prostaglandin analogues are trending compared to other groups of medications.

3. PATIENTS AND METHODS

3.1 Methods and gathering of data

For the completion of the study it was necessary to collect data about the number of consumed anti-glaucoma drugs (AGD) in the Split-Dalmatian County from 2012-2016 from glaucoma patients. The data about AGD was collected in pharmacies of the Split-Dalmatia County. The data is gathered from 36 pharmacies in the Split-Dalmatia County.

The data gave following insight:

1. The total number of anti-glaucoma drugs (AGD) in Split-Dalmatia County

2. The number of sold AGD divided in groups in Split-Dalmatia County

3.2 Statistical analysis

The gathered data was inserted into Microsoft Office Excel for Windows. For statistical analysis the software Statistic 8.0 was used. In the processing of the data we used the Pearson correlation coefficient. The results were interpreted at a significance level of $p<0.05$.

4. **RESULTS**

The table beneath shows the total amount of original glaucoma drugs divided in their specific subgroups. The consumed amount of each drug group is shown through the years 2012-2016 as well as the percentage to the total amount of original drugs (Tabel 1).

Table 1. Presentation of total amount of original anti-glaucoma drugs consumed in Split-Dalmatia County from the years 2012-2016

	YEAR						
ORIGINAL ANTIGLAUCOMA DRUGS	2012	2013	2014	2015	2016	TOTAL	% of consumed drugs from 2012-2016 yr.
MONOCOMPONENT ALPHA 2 AGONISTS							
ALPHAGAN	9631	10437	10885	10943	12229	54125	7.2
BETA BLOCKERS							
TIMALEN 0.25 %	1324	1311	1392	1271	1156	6454	0.85
TIMALEN 0.5 %	39202	36047	34196	33253	32347	175045	23.2
BETOPTIC 0.5 %	7575	7187	7331	7582	8338	38013	5.0
VISTAGAN 0.5 %	5174	5195	4586	3821	346	19122	2.5
LOCAL CAI							
AZOPT	19196	18560	18466	16127	15900	88249	11.7
TRUSOPT	4061	3977	4434	4852	5517	22841	3.0
PROSTAGLANDINS AND PROSTAMIDE							
XALATAN	18897	18499	19986	21258	21583	100223	13.3
LUMIGAN 0.01 %	0	0	30	478	1712	2220	0.29
LUMIGAN 0.03 %	3612	4202	3933	3385	2072	17204	2.3
TRAVATAN	6510	5947	5048	4358	3941	25804	3.4
SAFLUTAN	0	181	1316	1492	2241	5230	0.69
SUM OF MONOCOMPONENT DRUGS	**115182**	**111543**	**111603**	**108820**	**107382**	**554530**	
FIXED DOSE COMBINATIONS PROSTANGLANDINS AND PROSTAMIDE AND BETA BLOCKERS							
XALACOM	3377	3940	4686	5606	6477	24086	3.2
DUOTRAV	867	916	909	971	858	4521	0.6
GANFORT	1755	2087	2231	2119	2072	10264	1.36
LOCAL CAI AND BETA BLOCKERS							
AZARGA	2019	2560	3343	3802	4033	15757	2.1
COSOPT	23047	26519	28211	29872	33018	140667	18.6
ALPHA 2 AGONISTS AND BETA BLOCKERS							
COMBIGAN	284	893	1404	1607	1322	5510	0.73
SUM OF FDC DRUGS	**31349**	**36915**	**40784**	**43977**	**47780**	**200805**	
TOTAL SUM	**146531**	**148458**	**152387**	**152797**	**155162**	**755335**	100

The second table shows the total amount of generic glaucoma drugs also divided into their specific subgroups. The consumed amount of each drug group is shown through the years 2012-2016 as well as the percentage to the total amount of generic drugs (Tabel 2).

Table 2. Presentation of total amount of generic anti-glaucoma drugs consumed in Split-Dalmatia County from the years 2012-2016.

	YEAR						
GENERIC ANTIGLAUCOMA DRUGS	2012	2013	2014	2015	2016	TOTAL	% of consumed drugs from 2012-2016 yr.
MONOCOMPONENT ALPHA 2 AGONISTS							
LUXFEN	0	0	181	316	408	905	3,1
BIMANOX	0	0	34	227	80	341	1,2
BETA BLOCKERS							
TIMLATAN	0	0	59	342	431	832	2,9
LOCALCAI							
DORSOL	0	91	361	649	115	1216	4,2
OFTIDOR	0	0	38	112	249	399	1,4
ULOM	0	0	2	3	21	26	0,1
PROSTAGLANDINS AND PROSTAMID							
LATANOX	3311	4051	3908	4263	4768	20301	70,5
LATAPRES	0	0	107	358	405	870	3,0
SUM OF MONOCOMPONENT DRUGS	**3311**	**4142**	**4690**	**6270**	**6477**	**24890**	86,5
FIXED DOSE COMBINATIONS LOCAL CAI AND BETA BLOCKERS							
GLAUMAX	0	149	681	932	769	2531	8,8
OFTIDORIX	0	0	361	536	437	1334	4,6
ULOM PLUS	0	9	19	5	0	33	0,1
SUM OF FDC DRUGS	**0**	**158**	**1061**	**1473**	**1206**	**3898**	13,5
TOTAL SUM	**3311**	**4300**	**5751**	**7743**	**7683**	**28788**	100

Figure 1 shows the total amount of consumed drugs in Split-Dalmatia County divided into original and generic monocomponent vs. fixed-dose combinations. Due to the European Glaucoma Society guidelines original mono and fixed combinations take by far the biggest percentage.

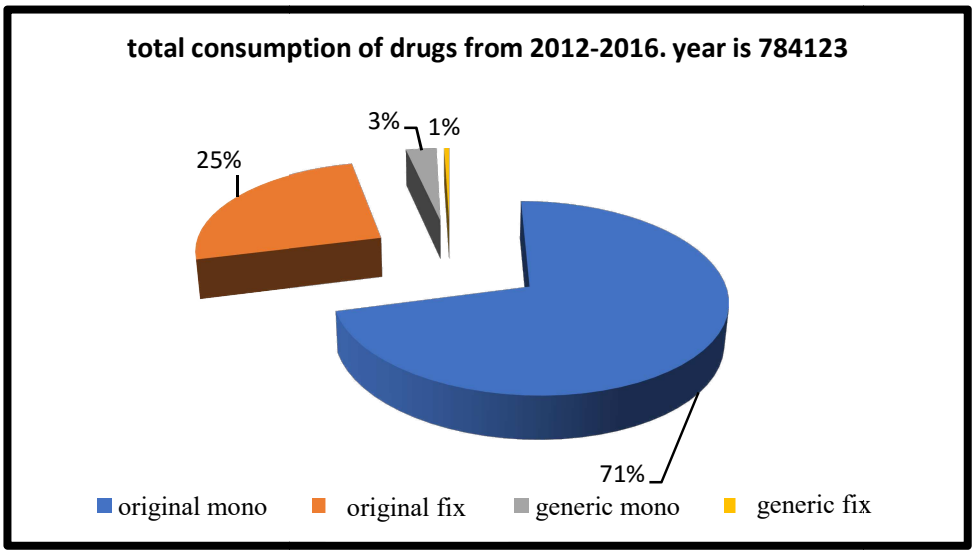


Figure1. Presentation of the consumed share of individual groups of anti-glaucoma drugs compared to the total amount of consumed drugs in Split-Dalmatia County from the years 2012-2016.

Of the total amount of consumed anti-glaucoma drugs (n=784123), the highest amount takes consumption of original mono-component drugs (n=554530 or 71%) which makes it 2,8 times more than consumption of original fixed dose combination drugs, 23,7 times more than generic monocomponent drugs and 71 times more than generic fixed dose combination drugs.

The amount of original drugs spent (n= 755335) in Split- Dalmatia county is 26 times higher compared to generic drugs (n=28788). Among original drugs, 73% are monocomponent drugs while 14% are fixed dose combination drugs (Table 1. and 2.)

Figure 2 shows the total amount of consumed anti-glaucoma medications through the years of 2012-2016. We can see a rise of 13003 drugs in 5 years which can mean a rising awareness for glaucoma detection a treatment initiation.

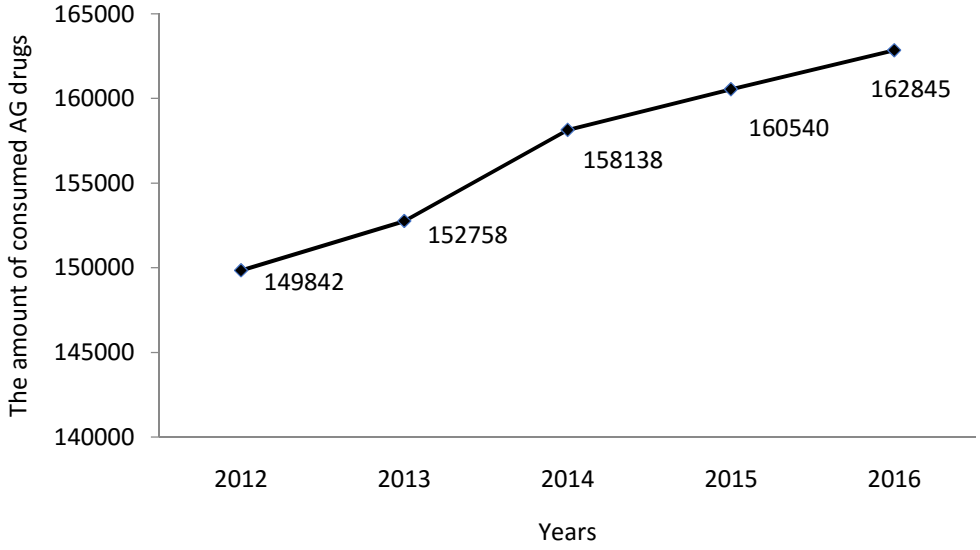


Figure 2. Presentation of the amount of consumed anti-glaucoma drugs in Split- Dalmatia County from 2012- 2016. The amount of drugs consumed is rising through years (r=0.987; p=0.002)

Figure 3 shows the consumption share of the individual drug groups through the year from 2012-2016. We can see respect to the Guidelines of the European Glaucoma Society by increasing share of original fixed combinations.

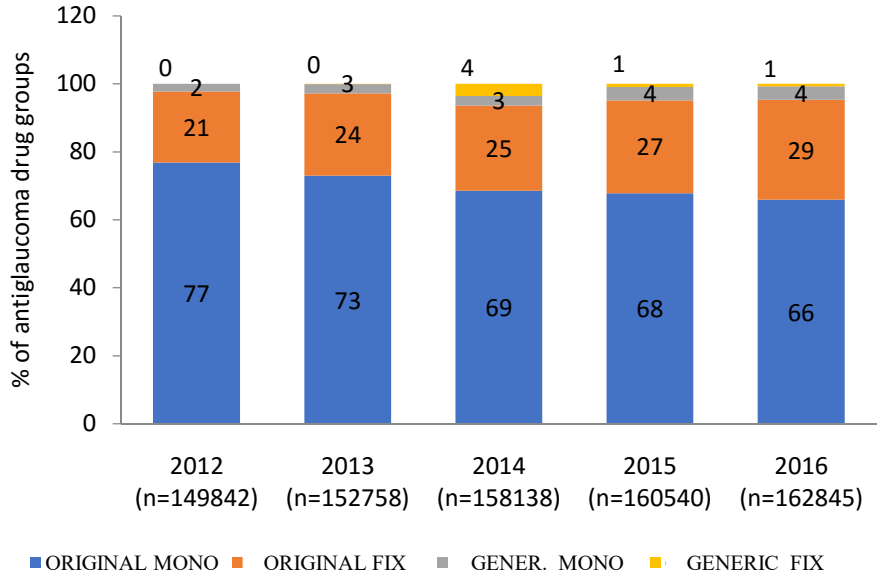


Figure 3. Presentation of consumption share (%) of individual anti-glaucoma drug groups from 2012-2016.

Consumption share of the original mono-component drugs shows a decreasing trend from 2012- 2016. (r=0,9313; p=0,021). Consumption share of these drugs in total consumption for the year 2012 is 77%, while consumption share of original mono-component drugs in the year 2016 is 66%. The decrease in consumption share through 4 years is 11%.

Consumption share of the original fixed dose combination drugs shows an increasing trend from 2012- 2016. (r=0,965; p=0,008). Consumption share of these drugs in total consumption for 2012 is 21%, while consumption share of original fixed-dose combination drugs in the year 2016 is 29%. The increase in consumption share through 4 years is 8%.

Consumption share of the generic mono-component drugs shows an increasing trend from 2012- 2016. (r=0,945; p=0,015). Consumption share of these drugs in total consumption for the year 2012 is 2%, while consumption share of generic monocomponent drugs in the year 2016 is 4%. The increase in consumption share through 4 years is 2%.

Consumption share of generic fixed-dose combination shows an increasing trend from 2012-2016. (r=0894; P=0,040).

Figure 4 shows the consumption share in percent of the individual groups of original drugs from the total amount of original drugs from 2012-2016.

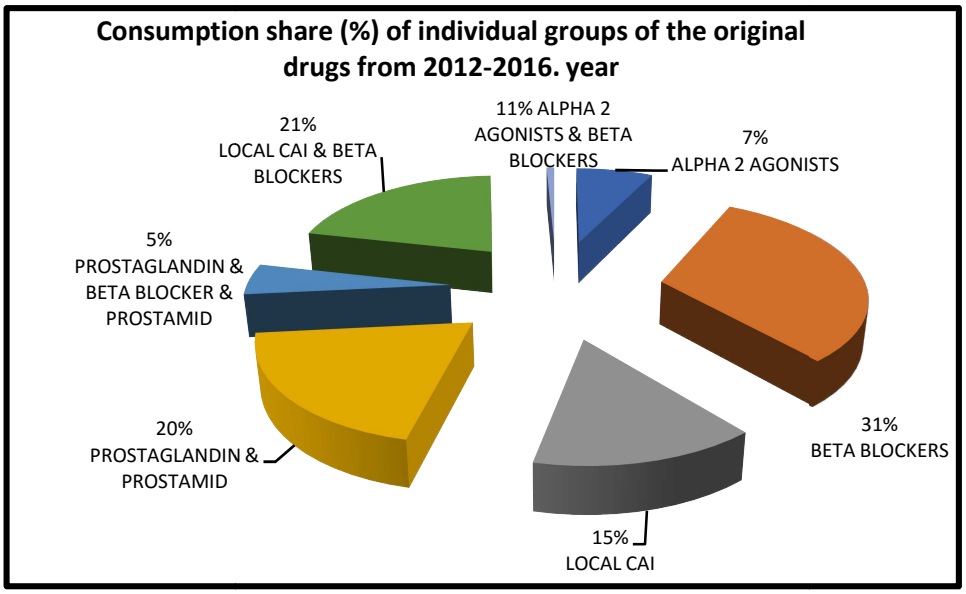


Figure 4. Consumption share (%) of individual groups of the original anti-glaucoma drugs in Split- Dalmatia county from 2012- 2016. compared to the total amount of consumed anti-glaucoma drugs(n= 755335)

From this figure we can see that the high number in prostaglandin/ prostamide analogues and fixed-combination drugs prove the validity of the European Glaucoma Society guidelines.

The highest consumption rate of beta-blockers shows their superiority in first-line treatment of increased ocular pressure.

Figure 5 shows the consumption share in percent of the individual groups of generic drugs from the total amount of generic drugs from 2012-2016.

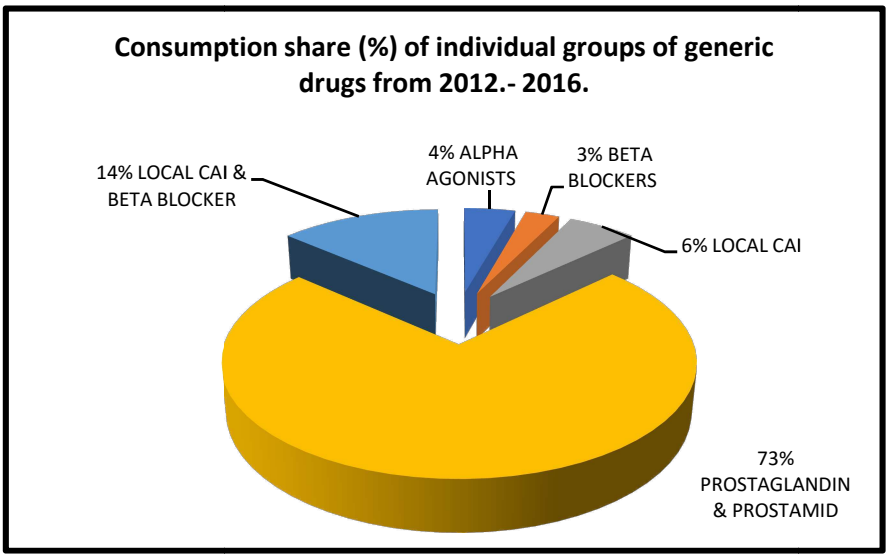


Figure 5. Consumption share (%) of individual groups of the original anti-glaucoma drugs in Split- Dalmatia county from 2012- 2016 compared to the total amount of consumed anti-glaucoma drugs (n= 755335)

Figure 4 shows that the biggest consumption rate among generic drugs are prostaglandin/ prostamide analogues (73%), followed by local CAI and beta-blockers (14%) and local CAIs (6%) which fits the guidelines of the EGS.

Figure 6 shows the rise of consumption of prostaglandin/ prostamide analogues through the years 2012-2016. The blue curve shows the original prostaglandins and the orange curve their generic counterparts.

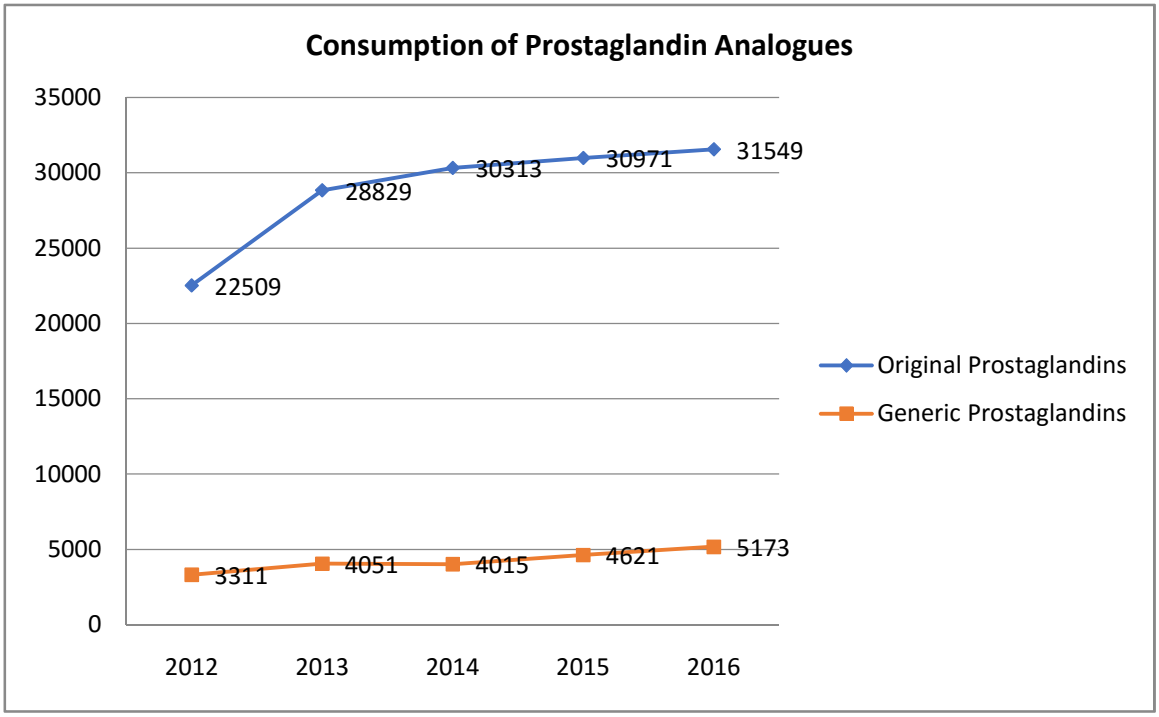


Figure 6. Presentation of the amount of consumption of original and generic prostaglandin/ prostamide analogue drugs in Split- Dalmatia county from 2012- 2016.

The amount of consumed original prostaglandin analogues has an increasing trend from 2012-2016. (r=0.8692; P=0,007).

The amount of consumed generic prostaglandin analogues has an increasing trend from 2012-2016. (r=0.9384; P=0,002)

5. **DISCUSSION**

Right now, the World Health Organization (WHO) regards glaucoma as the third most common cause for blindness worldwide. It is responsible for 15% of all registered cases with an incidence of 2.4 million people per year. In people over the age of 50 glaucoma is the second most common cause of blindness (33). Estimates say that about 70 million people worldwide are affected by glaucomatous damage with only half of them being aware of the diagnosis. Even less percent of the affected receive adequate treatment. Minimum seven million people with glaucoma are blind in both eyes with the numbers increasing (3).

The treatment of glaucoma is often complicated by individually differing responses and adherence rates to identical therapies, leading to variable outcomes (11). To make matters more elaborate, standard measurements of therapeutic response, such as IOP-lowering, are subject to relative imprecision and poor visit-to-visit repeatability (12).

Lowering of the increased ocular pressure (IOP) is essential because IOP is the only factor that can be influenced (3). The initial therapy of glaucoma is medical therapy in form of drugs. Topical or local use in form of eye drops is the most common application form. The cost of IOP lowering medications can be a significant monthly strain on the budgets of patients and although patients may report that they are using daily medical therapy, data reveals just under 50% of persistence in annual use of therapy (34). Introducing generic glaucoma eye drops into the market has lowered costs for patients and lead to more adherence in some patient groups, albeit raising concerns for equivalence in efficacy and possible side effects (35).

The ophthalmological community struggles with the concept of “essential similarity” of generic medications as it is hard to prove through clinical studies. The bioequivalence of systemic drugs can be studied from blood samples. Here plasma concentrations within certain borders that equal the original drug can be determined. Such studies are impossible for topical eyedrops. There are no requires for clinical studies for generic approval in ophthalmology and 10% difference in concentration of the active principle between generic drugs and originals is considered acceptable. Whereas the active principle is assumed equal, there can be variations in adjuvants. The problem lies therein that different adjuvants may lead to alterations in viscosity, osmolarity and pH of the eye drops and therefore lead to tolerability and corneal penetration issues. Nevertheless there is a huge demand for generic glaucoma drugs as many of them are becoming off patent. For Latanoprost the generic share is 65% in Europe. In the year 2007 a study from the Indian Journal of Ophtalmology published that Xalatan (original

Latanoprost) reduced IOP by 37% on average while generic Latanoprost reduced IOP by only 25% (36).

The advice of the European Glaucoma Society is to monitor the patients' IOP closely when switching from branded to generic drugs (15).

The following results will show the numbers of prescriptions of anti-glaucoma medication in the Split-Dalmatia County. From the results we will be able to see if there is a general trend in the counties medical community prescribing original drugs over their generic counterparts, if there are more prescriptions of fixed-dose combinations and also if the number of prescribed prostaglandin analogues has risen.

In our study we showed that of the total amount of consumed anti-glaucoma drugs (n=784123), the highest amount takes consumption of original mono-component drugs (n=554530 or 71%) which makes it 2.8 times more than consumption of original fixed dose combination drugs, 23,7 times more than generic mono-component drugs and 71 times more than generic fixed dose combination drugs. The amount of original drugs spent (n=755335) in Split- Dalmatia County is 26 times higher compared to generic drugs (n=28788). Among original drugs, 73% are monocomponent drugs while 14% are fixed dose combination drugs.

Consumption share of the original mono-component drugs shows a decreasing trend from 2012-2016 while consumption share of the original fixed dose combination drugs shows an increasing trend from 2012- 2016. Furthermore, consumption share of the generic mono-component drugs shows an increasing trend from 2012.- 2016 and also consumption share of generic fixed dose combination drugs shows an increasing trend from 2012-2016. (r=0,253; p=0,681).

Also we can see that the amount of consumed original prostaglandin analogues has an increasing trend from 2012-2016 (r=0.8692; P=0,007) and the amount of consumed generic prostaglandin analogues also has an increasing trend from 2012-2016 (r=0.9384; P=0,002).

Conclusively we can say that the increasing trend in prescribing prostaglandin analogues, the increasing trend in prescribing fixed-dose combinations and generally much higher sales numbers in original anti-glaucoma medications show the tendency in the Split-Dalmatia counties' ophthalmological community to follow the recommendations of the European Glaucoma Society(EGS).

6. **CONCLUSIONS**

1. There is a greater number of original anti-glaucoma medication prescriptions than generic ones.
2. We can see an increasing number of fixed-dose combination therapy in Split-Dalmatia County from 2012-2016.
3. The prescription of generic and original prostaglandin analogues in the Split-Dalmatia County is increasing constantly from 2012-2016.
4. The rising trend of fixed-dose combinations, the high numbers of original brand drugs over generic ones and the increase of prostaglandin analogue sales show a tendency to follow guidelines by the Split-Dalmatia County with respect to the European Glaucoma Society (EGS).
5. Recent development has shown that original anti-glaucoma Drugs are made without preservatives due to the susceptibility of the anterior eye segment to their toxic effects. Benzalkonium chloride (BAK) and Polyquad are the main conservans that are excluded because of their tendency to cause ocular surface disease (OSD).

7. **LITERATURE**

1. Gemoll W. Griechisch-deutsches Schul- und Handwörterbuch: Durchgesehen und erweitert von Karl Vretska. 9. Edition. München: Freytag; 1965.

2. Ronald D. Glaukom- Eine vaskuläre Neuropathie. Deutsches Ärzteblatt.2008;Vol.11:562-4.

3. Flammer J, Gugleta K, Hauenstein-Stümpfig D, Mozaffarieh M, Schneider P. Glaucoma. 3. Edition. Seattle etc: Hogrefe & Huber Publishers; 2006

4. Garway-Heath DF. Glaucoma A Guide. International Glaucoma Association. [Internet].2012 [Quoted 2017 September 16]Available from: www.glaucoma-association.com

5. Tham YC, Li X, Wong TY, Harry A. Quigley. Aung T, Cheng CY. Global Prevalence of Glaucoma and Projections of Glaucoma Burden through 2040. Ophtalmology. 2014:121(11): 2081-90.

6. Ivanišević M, Erceg M, Smoljanović A, Trošić T. The incidence and seasonal variations of acute primary angle-closure glaucoma. Coll Antropol. 2002;26(1):41-5.

7. FDA. What are generic drugs?[Internet]. 2017[Quoted 2017 September 16] Avilable from: https://www.fda.gov/Drugs/ResourcesForYou/Consumers/BuyingUsingMedicineSafely/UnderstandingGenericDrugs/default.htm

8. Aref AA. Generic drugs for the treatment of ocular conditions: changing the treatment landscape. Expert Review of Clinical Pharmacology. 2014;Vol.7,No5:551-3.

9. Novack GD. Quality of generic drugs. Ocul Surf 2013; Vol.11,No1:54-6.

10. Kahook MY, Fechtner RD, Katz LJ, et al. A comparison of active ingredients and preservatives between brand name and generic topical glaucoma medications using liquid chromatography-tandem mass spectrometry. Curr Eye Res 2012; Vol.37,No. 2:101-8.

11. Susanna RJr. Unpredictability of glaucoma progression. Curr Med Res Opin 2009; Vol. 25, No.9:2167-77.

12. Rotchford AP, King AJ. Repeatability of measurements of effectiveness of glaucoma medication. 2012;Vol.96,No.12:1494-7.

13. Papadopulos M, Khaw PT. Advances in the management of pardiatric glaucoma. Eye (Lond) 2007;21(10):1319-25.

14. Weinreb RN, Papadopulos S, M. Consensus on Childhood glaucoma. Amsterdam: Kugel publications, 2013.

15. Augusto AB, Bagnasco L, Barton ABK, Baudouin C, Bengtsson B, Alain Bron. Terminology and Guidelines for Glaucoma. 4th Edition. PubliComm. Savona. 2014.

16. Tielsch JM, Katz J, Singh K, et al. Secondary glaucoma after paediatric cataract surgery. Br J Ophtalmol 2007;91(12):1627-30.

17. Ritch R, Shields MB, Krupin T. The glaucomas. 2nd Edition. USA: Mosby SL. 1996

18. Ritch R, Chang B, Liebmann J. Angle Closure in Younger Patients. Ophthalmology. 2003; 110(10):1880-9.

19. Hollo G, Konstas. Exfoliation syndrome and exfoliative glaucoma, 2nd Edition. Savona: Publicomm S.r.l., 2012.

20. Gottanka J, Johnson P, Grehn H, Lutjen-Drecoll F. Histologic findings in pigment dispersion syndrome and pigmentary glaucoma. J Glaucoma 2006;15(2):142-51.

21. Papaconstantinou D, Georgalas K, Kourtis S. Lens induced glaucoma in the elderly. Clin Interv Aging. 2009:4:331-6.

22. Radcliff N, Finger M. Eye cancer related glaucoma: current concepts. Surv Ophtalmol 2009;54(1):47-73.

23. Detry-Moel M, Escarmelle A, Hermans I. Refractory ocular hypertension secondary to intravitreal injection of triamcincolone acetonide. Bull soc Belge Ophtalmol 2004(292):45-51

24. Jones R, Rhee DJ. Corticosteroid-induces ocular hypertension and glaucoma:a brief review and update of the literature. Curr Opin Ophtalmol 2006;17(2):163-7.

25. Mangouritsas G, Mourtzoukos S, Portaliou DM, et al. Glaucoma associated with the management of rhefmatogenous retinal detachment. Clin Ophtalmol 2013;7:727-34.

26. Le A, Mukesh BN, McCarty CA, Taylor HR. Risk factors associated with the incidence of open-angle glaucoma: the visual impairment project. Invest Ophthalmol Vis Sci. 2003 Sep;44(9):3783-9.

27. Czudowska MA, Ramdas WD, Wolfs RC, Hofman A, De Jong PT, Vingerling JR, Jansonius NM. Incidence of glaucomatous visual field loss: a ten-year follow-up from the Rotterdam Study. Ophthalmology. 2010 Sep;117(9):1705-12.

28. Leske MC, Connell AM, Schachat AP, Hyman L. The Barbados Eye Study. Prevalence of open angle glaucoma. Arch Ophthalmol. 1994 Jun;112(6):821-9.

29. Tielsch JM, Sommer A, Katz J, Royall RM, Quigley HA, Javitt J. Racial variations in the prevalence of primary open-angle glaucoma. The Baltimore Eye Survey. JAMA. 1991 Jul 17;266(3):369-74.

30. Wolfs RC, Klaver CC, Ramrattan RS, van Duijn CM, Hofman A, de Jong PT. Genetic risk of primary open-angle glaucoma. Population-based familial aggregation study. Arch Ophthalmol. 1998 Dec;116(12):1640-5.

31. Leske MC, Nemesure B, He Q, Wu SY, Fielding Hejtmancik J, Hennis A. Patterns of open-angle glaucoma in the Barbados Family Study.Ophthalmology.2001Jun;108(6):1015-22.

32. Quigley HA, West SK, Rodriguez J, Munoz B, Klein R, Snyder R. The prevalence of glaucoma in a population-based study of Hispanic subjects: Proyecto VER. Arch Ophthalmol. 2001 Dec;119(12):1819-26.

33. Flanagan JG. Glaucoma update: Epidemiology and new approaches to medical management. Ophtalmic Physiol Opt. 1998; 18:126-32.

34. Schwartz GF, Quigley HA. Adherence and persistence with glaucoma therapy. Surv Ophthalmol. 2008; 53:557-68.

35. Stein JD, Shekhawat N, Talwar N, Balkrishnan R. Impact of the introduction of generic latanoprost on glaucoma medication adherence. Ophthalmology. 2015;122(4):738-47.

36. Narayanaswamy A, Neog A, Baskaran M, et al. A randomized, crossover, open label pilot study to evaluate the efficacy and safety of Xalatan in comparison with generic latanoprost (Latoprost) in subjects with primary open angle glaucoma or ocular hypertension. Indian J Ophthalmol. 2007;55:127-31.

37. Popović S, Suic S. Glaukom. U: Šikić J, Cerovski B, Čurković T, Dorn V, Katušić D, Kordić R et al. Oftalmologija. Zagreb: Narodne Novine. 2003;(10):111-20.

38.Van der Valk R, Webers CA, Schouten JS, et al. Intraocular pressure-lowering effects of all commonly used glaucoma drugs: a meta-analysis of randomized clinical trials. Ophtalmology 2005;112(7):1177-85.

39. Olthoff CM, Schouten JS, van de Borne BW, Webers CA. Noncompliance with ocular hypotensive treatment in patients with glaucoma or ocular hypertension an evidence-based review. Ophthalmology 2005;112(6):953-61.

40. Boland MV, Ervin AM, Friedmann DS, et al. Comparative effectiveness of treatments for open-angle glaucoma: a systematic review for the U.S. Preventive Services Task Force. Ann Intern Med 2013;158(4):271-9.

41. Stewart WC, Konstas AG, Kruft B, et al. Comaparison of 24-hour intraocular pressure fluctuation studies and the efficacy of glaucoma medicines. J Ocul Pharmacol Ther 2010;26(2):175-80.

42. Aptel F, Cucherat M, Denis P. Efficacy and tolerability of prostaglandin analogs: a meta-analysis of randomized controlled trials. J Glaucoma 2008;17(8):667-73.

43. Foster PJ, Johnson GJ. Glaucoma in China: how big is the problem? Br J Ophtalmol 2001;85(11):1277-82.

8. **SUMMARY**

Aim of the thesis: The primary aim of this research in medical anti-glaucoma therapy is to find out the total number of anti-glaucoma drugs in Split-Dalmatia county in the last 5 years, especially with regards to consumption of original anti-glaucoma drugs against their generic counterparts and comparison between fixed (combined) and mono therapy. Also we want to show if the prescription of prostaglandin analogues has risen through the years.

Patients and methods: In this research we used data of the number of anti-glaucoma drugs used in Split- Dalmatia County between the years of 2012 and 2016 from glaucoma patients. The data is collected in pharmacies of the county. In this research the data gathered from the pharmacies have been retrospectively statistically and analytically analysed. The data was processed in Microsoft Excel and Microsoft Word programs.

In the processing of the data we used the Pearson correlation coefficient. The results were interpreted at a significance level of $p<0.05$. The data was processed and shown with the help of Microsoft Excel and Microsoft Word programs.

Results: In our study we showed that of the total amount of consumed anti-glaucoma drugs (n=784123), the highest amount takes consumption of original mono-component drugs (n=554530 or 71%) which makes it 23.7 times more than generic mono-component drugs. The amount of original drugs spent (n= 755335) in Split- Dalmatia county is 26 times higher compared to generic drugs (n=28788). Among original drugs, 73% are monocomponent drugs while 14% are fixed dose combination drugs. Consumption share of the original mono-component drugs shows a decreasing trend from 2012- 2016 while consumption share of the original fixed dose combination drugs shows an increasing trend from 2012- 2016. Also we can see that the amount of consumed original prostaglandin analogues has an increasing trend from 2012-2016 (r=0.8692; P=0.007) and the amount of consumed generic prostaglandin analogues also has an increasing trend from 2012-2016 (r=0.9384; P=0.002).

Conclusion: Conclusively we can say that the increasing trend in prescribing prostaglandin analogues, an increasing trend in prescribing fixed-dose combinations and generally much higher sales numbers in original anti-glaucoma medications show the tendency in the Split-Dalmatian counties' ophthalmological community to follow the guidelines of the European Glaucoma Society.

9. **SAŽETAK**

Naslov: Usporedba generičkih i originalnih antiglukomskih ljekova u Splitsko-dalmatinskoj županiji

Cilj istraživanja: Primarni cilj ovog istraživanja je istražiti ukupan broj antiglaukomskih lijekova (AGL) u Splitsko-dalmatinskoj županiji u zadnjih 5 godina(2012-2016), pogotovo usporedba konzumiranih originalnih antiglaukomskih lijekova sa genericima, zatim usporedbu između fiksne antiglaukomske terapije i monoterapije, te dali je porastao broj prodanih analoga prostaglandina/prostamida kroz 2012.-2016. god.

Materials and methods: Za izradu ovog istraživanja bilo je nužno prikupiti podatke o broju potrošnji antiglaukomskih lijekova od 2012. do 2016. godine na području Splitsko-dalmatinske županije.

U obradi podataka smo koristili Pearson koeficijenta korelacije. Podaci su interpretirani na razini značajnosti $p<0,05$. Podatke, dobivene od ljekarna, smo obradili retrospektivno statistički i analitički. Rezultate smo prikazali tabelarno i grafički uz pomoč Microsoft Excel-a i Word-a.

Results: U našem istraživanjem smo pokazali da od 2012.do 2016. god. Ukupan broj potrošenih ljekova je 784123, sa največim brojem potrošnje originalnih monokomponentnih lijekova (n=554530 ili 71%). Ima ih 23,7 puta više od generičkih monokomponentnih lijekova. Ukupan broj originalnih lijekova (n=755335) u Splitsko-dalmatinskoj županiji je 26 puta veči uspoređdeno sa generičkim lijekovima (n=28788). U skupini originalnih lijekova 73% su monokomponentni lijekovi i 14% su fiksne kombinacije lijekova. Udio potrošnje originalnih monokomponentnih lijekova pokazuje padajuču tendeciju od 2012. do 2016. god. dok udio potrošnje originalnih fiksnih kombinacija pokazuje povečavanje od 2012. do 2016. god. Osim toga smo pokazali da je broj potrošenih originalnih analoga prostaglandina pokazuje povečavanje od 2012-2016 ($r=0,8692;P=0,007$) i broj potrošenih generičkih analoga prostaglandina pokazuje rast od 2012. do 2016. god. ($r=0,9384;P=0,002$).

Zaključak: Na kraju možemo zaključiti da je veči broj potrošenih analoga prostaglandina, kombinirane fiksne terapije i generalno puno veči broj potrošenih originalnih antiglaukomskih lijekova pokazuje tendeciju Splitsko-dalmatinske oftalmološke zajednice sljediti preporuke i smijernice Europskog glaukomskog društva (EGS).

10. **CURRICULUM VITAE**

Personal Information

Name/ Surname: Viktor Mastnak

Adress: Am Burgstalltobel 8, 87527 Sonthofen, Germany

Telephone: ++385/(0)99-2012-151

E-mail: viktor.mastnak@gmail.com

Nationality: German

Date and place of birth: 27.05.1993, Bad Kreuznach, Germany

EDUCATION

-2003-2011 Gymnasium Sonthofen

-2011-2017 University of Split School of Medicine

NATIVE LANGUAGE

German

OTHER LANGUAGES

Croatian

English