Glaucoma and vascular risk factors
What is the evidence?

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On behalf of the Belgian Glaucoma society
Glaucoma or the glaucomas?

- common denominator: optic neuropathy
  - death of retinal ganglion cells
  - loss of axonal nerve fibers

- typical functional and structural defects
  - functional defects = visual field changes
  - structural defects = optic disc damage
The family tree of glaucomatous disease

**Primary glaucomas**
- primary open-angle glaucoma or POAG (IOP elevated or nl)
- primary angle-closure glaucoma (IOP elevated)

**Secondary glaucomas** (IOP elevated)
- 2-ary to other eye diseases (e.g. diabetic retinopathy)
- 2-ary to trauma
- 2-ary to inflammation
- iatrogenic (corticosteroids)

**Congenital glaucoma** (IOP elevated)
Fig. 3-1. Composite drawing of microscopic and gonioscopic anatomy.
The family tree of glaucomatous disease

- **Primary glaucomas**
  - primary open-angle glaucoma or POAG (IOP elevated or nl)
  - primary angle-closure glaucoma (IOP elevated)

- **Secondary glaucomas** (IOP elevated)
  - 2-ary to other eye diseases (e.g. diabetic retinopathy)
  - 2-ary to trauma
  - 2-ary to inflammation
  - iatrogenic (corticosteroids)

- **Congenital glaucoma** (IOP elevated)
Definition of primary open-angle glaucoma (POAG)

- a chronic, progressive optic neuropathy
- characteristic morphological changes at the optic nerve head and retinal nerve fiber layer
- absence of other ocular disease
- absence of congenital anomalies
- open angle
- optic disc changes observed as glaucomatous cupping
- retinal nerve fiber layer changes detected as VF defects
Epidemiology of primary open-angle glaucoma (POAG)

- second leading cause of blindness in Europe and worldwide
- most frequent cause of irreversible blindness
- unusual under age of 50 yrs
- 2% in patients over 60 yrs
- 4% in patients over 80 yrs
- genetic influence (first-degree relative risk X 10)
- racial factors (African > European > Asian people)
Pathogenesis of primary open-angle glaucoma (POAG)

- alterations of the connective tissues at the optic disc are coincident with loss of axons
- axons grouped together at the disc undergo apoptosis together, pointing to the disc as the 1-ary site of injury
- interruption of axonal transport leads to death
- initial ganglion cell death leads to a toxic environment with 2-ary retinal ganglion cell loss
- role of IOP? (pressure theory)
- role of ischaemia? (vascular theory)
Diagnosis of primary open-angle glaucoma (POAG)

- detection of structural and functional defects
  - structural defects:
    - cup/disc ratio (ophthalmoscopy, fundus photography)
    - thinning of nerve fiber layer (OCT)

C/D ratio = 0.3

C/D ratio = 0.9
OCT = optical coherence tomography
Diagnosis of primary open-angle glaucoma (POAG)

- detection of structural and functional defects
- automated perimetry

Figure 4: Visual field test of the left eyes show early (A), moderate (B), and severe (C) stages of functional loss
Treatment for POAG

**Medical treatment**
- Prostaglandins (no systemic side-effects)
- beta-blockers (systemic side-effects)
- alpha-agonists
- topical and systemic carbonic anhydrase inhibitors

**Laser surgery**

**Surgery**
- filtration surgery
- tubes and valves
Risk factors for POAG

- age

- IOP
  - risk of developing glaucoma increases by 10 % for each mm Hg increase in IOP
  - only modifiable risk factor for POAG

- race/ethnicity

- family history of glaucoma
  - first relative  X10
Risk factors for POAG

- myopia
- ocular perfusion pressure
- miscellaneous:
  - diabetes, systemic BP, vascular dysregulation, obstructive sleep apnoe, migraine, Raynaud
POAG normal pressure glaucoma

- IOP within normal range (10 to 21 mm Hg)
- disc damage identical to POAG with high pressure
- VF defects identical to POAG with high pressure
- different disease or part of continuous spectrum?
POAG with normal pressure

1967: MacDougald presents 14 cases (0.7%) of low-tension glaucoma out of 2000 glaucoma patients in the files of the Glaucoma Clinic (Dublin)

“you may feel that this is wasting time on a very low proportion of one’s whole range of patients, but as once we started looking we seem to have suddenly come upon a number of them, I feel that their frequency is probably much higher, and more careful research will yield a considerable increase in the number detected”

Problems of low tension glaucoma, T.J. MacDougald. Transactions of the Ophthalmological Societies of the UK, 1967
## Some hard data…

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Total glaucomas</th>
<th>Total with normal IOP</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Armaly</td>
<td>1966</td>
<td>189</td>
<td>129</td>
<td>68.3</td>
</tr>
<tr>
<td>Bengtsson</td>
<td>1987</td>
<td>33</td>
<td>16</td>
<td>48.5</td>
</tr>
<tr>
<td>Hollows, Graham</td>
<td>1966</td>
<td>20</td>
<td>7</td>
<td>35</td>
</tr>
<tr>
<td>Klein et al</td>
<td>1992</td>
<td>104</td>
<td>33</td>
<td>31.7</td>
</tr>
<tr>
<td>Leibowitz et al</td>
<td>1980</td>
<td>40</td>
<td>21</td>
<td>52.5</td>
</tr>
<tr>
<td>Mason et al</td>
<td>1989</td>
<td>147</td>
<td>53</td>
<td>36.1</td>
</tr>
<tr>
<td>Shiose</td>
<td>1983</td>
<td>151</td>
<td>99</td>
<td>65.6</td>
</tr>
<tr>
<td>Smith</td>
<td>1985</td>
<td>400</td>
<td>120</td>
<td>30</td>
</tr>
<tr>
<td>Sommer et al</td>
<td>1991</td>
<td>194</td>
<td>114</td>
<td>58.8</td>
</tr>
<tr>
<td>Bonomi</td>
<td>2001</td>
<td>60</td>
<td>24</td>
<td>28.5</td>
</tr>
</tbody>
</table>
Effect of IOP lowering on POAG

- Several RCT have shown:
  - IOP lowering reduces rate of progression in patients with POAG.
  - IOP lowering reduces the incidence of POAG in patients with ocular hypertension.
  - IOP lowering also reduces rate of progression in POAG with normal pressure.

- Despite adequate IOP control, a number of patients are relentlessly progressive:
  - E.g. progression still occurred in 12% of patients with 30% IOP reduction in the Collaborative Normal Tension Glaucoma Study.

  ➔ Other factors must be involved!
Some candidates...

- systemic hypertension
- low diastolic ocular perfusion pressure (nocturnal dippers)
- disturbances of the autoregulation of the optic nerve head bloodflow
  - arteriosclerosis
  - vascular dysregulation
blood pressure and IOP

- **meta-analysis of 60 observational studies**
- **Pooled av. Increase in IOP for 5 mm Hg increase in diastolic PP**
  - 0.17 mm HG (95% CI = 0.11-0.23)
- **pooled av. increase in IOP for 10 mm Increase in syst BP**
  - 0.26 mmHg(95% CI = 0.23-0.28)
- **pooled RR for POAG comparing patients with hypertension to those without** :
  - 1.16 (95% CI = 1.05-1.28)

*Zhao et al. The association of blood pressure and POAG: a meta-analysis. AJO, 2014*
Ocular perfusion pressure (OPP) and POAG

- no direct measurements available
- mean OPP = 2/3 mean arterial pressure – IOP (correction for drop in BP between arm and eye in upright position)
- systolic OPP = systemic syst BP – IOP
- diastolic OPP = systemic diastolic BP – IOP
- some studies use posture-correcting formulas, others do not...
- in general BP and IOP measured only once
- some studies adjust for IOP, others do not...
### Table 1. Prevalence, incidence and progression studies investigating Ocular perfusion pressure and glaucoma

<table>
<thead>
<tr>
<th>Reference</th>
<th>Number of patients</th>
<th>Study design and area evaluated</th>
<th>Main outcomes</th>
<th>Adjustment for IOP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prevalence studies</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baltimore eye survey</td>
<td>5308 participants</td>
<td>Population-based prevalence survey (East Baltimore)</td>
<td>DOPP &lt; 30 mmHg had a 6× increased risk of developing POAG compared to individuals with DOPP &gt; 56 mmHg</td>
<td>No</td>
</tr>
<tr>
<td>Tielisch et al. (1995)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Egna-Neumarkt study</td>
<td>4087 participants</td>
<td>Population-based cross sectional study (Bolzano – Italy)</td>
<td>Higher DOPP was associated with decrease prevalence of POAG</td>
<td>No</td>
</tr>
</tbody>
</table>
| (Bonomi et al. 2000b)            |                    |                                                                       | DOPP < 68 mmHg; OR = 1.0  
76 mmHg < DOPP < 68 mmHg; OR = 0.33  
DOPP > 76 mmHg; OR = 0.29                                                                                                                                                                                     |                    |
<p>| Proyecto Ver (Quigley et al. 2001)| 4774 participants  | Population-based survey (Hispanic population from Nogales and Tucson/Arizona) | Lower DOPP was associated with increased prevalence of OAG (OR = 0.96) DOPP &lt; 50 mmHg had a 4× increased risk of developing OAG than DOPP &gt; 80 mmHg                                                                                                                                 | No                 |
| Blue mountains eye study         | 3654 participants  | Population-based survey (Australia)                                   | Higher SOP (for each 10 mmHg) had a 10% increase in OAG prevalence (OR = 1.09; p = 0.05)                                                                                                                                                                           | Yes                |
| (Mitchell et al. 2004)           |                    |                                                                       |                                                                                                                                                                                                             |                    |
| Orzalesi et al. (2007)           | 3972 participants  | Multicentre observational survey (35 academic centres in Italy)      | POAG patients had a significant higher SOP (p = 0.02)                                                                                                                                                                                                                 | No                 |</p>
<table>
<thead>
<tr>
<th>Study</th>
<th>Participants</th>
<th>Study Methodology</th>
<th>Findings</th>
<th>Key Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Omoti et al. (2009)</td>
<td>506 patients</td>
<td>Prospective, cross-sectional, multicentre hospital-based study (Nigeria)</td>
<td>OAG patients had a significant higher SOPP (p = 0.003)</td>
<td>No</td>
</tr>
<tr>
<td>The Beijing eye study (Xu et al. 2009)</td>
<td>3222 participants</td>
<td>Population-based survey (Northern China)</td>
<td>No association between OPP and OAG risk</td>
<td>Yes</td>
</tr>
<tr>
<td>The Singapore Malay eye study (Zheng et al. 2010)</td>
<td>3280 participants</td>
<td>Cross-sectional population-based study (Malay population)</td>
<td>Lower MOPP and DOPP were associated with increased prevalence of POAG</td>
<td>Yes</td>
</tr>
<tr>
<td>Los angeles latino eye study (Memarzadeh et al. 2010)</td>
<td>6130 participants</td>
<td>Cross-sectional population-based study (La Puente/California)</td>
<td>For each ↓ 10 mmHg in MOPP and DOPP – OR = 1.23</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Lower MOPP; DOPP and SOPP and higher SOPP were associated with increased prevalence of OAG</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>SOPP ≤ 80 mmHg-OR = 2.5</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>DOPP ≤ 40 mmHg-OR = 1.9</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>MOPP ≤ 50 mmHg-OR = 3.6</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>SOPP &gt; 150 mmHg-OR = 2.0</td>
<td></td>
</tr>
<tr>
<td>Incidence studies</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Barbados eye study (Leske et al. 2008)</td>
<td>3222 participants</td>
<td>Cohort study (9 years follow-up) of prospective population-based study (Barbados/West Indies)</td>
<td>Lower OPP was associated with increased risk of OAG</td>
<td>Yes</td>
</tr>
<tr>
<td>The Rotterdam study (Hulsman et al. 2007)</td>
<td>5317 participants</td>
<td>Cross-sectional prospective population-based study (Ommoad – the Netherlands)</td>
<td>In subjects taking BP-lowering treatment, DOPP &lt; 50 mmHg – OR = 0.25</td>
<td>No</td>
</tr>
<tr>
<td>The Rotterdam study (Ramdas et al. 2011)</td>
<td>3882 participants</td>
<td>Cross-sectional prospective population-based study (Ommoad – the Netherlands)</td>
<td>No independent significant effect of MOPP on OAG</td>
<td>Yes</td>
</tr>
<tr>
<td>Progression studies</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Early manifest glaucoma trial (Leske et al. 2007)</td>
<td>255 POAG patients</td>
<td>Randomized clinical trial evaluating the efficacy of reducing IOP in patients with early glaucoma</td>
<td>Univariate analysis: SOPP ≤ 125 mmHg HR = 1.39, p = 0.0328</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Multivariate analysis: SOPP ≤ 125 mmHg HR = 1.42, p = 0.0268</td>
<td></td>
</tr>
</tbody>
</table>
OPP and POAG
Results from population based studies

- Low OPP is a risk factor for the prevalence and the progression of glaucoma
- 6 of 14 studies not adjusted for IOP
- Adjustment for IOP means using arterial blood pressure as a proxy measure for OPP
- Most measures carried out once
- All measures carried out a daytime
- Good evidence that BP is lowest at night and IOP highest in the early morning hours (Weinreb et al)
Circadian variation in arterial blood pressure and POAG

- a meta-analysis of 5 studies (n = 286)
- ambulatory BP measurements
- separate data for daytime and nighttime
- definition of nocturnal pressure dip
- assessment of VF over at least 2 years

Bowe et al. Circadian variation in arterial blood pressure and glaucomatous optic neuropathy_A systematic review and meta_analysis. Am J Hypertension, 2015
<table>
<thead>
<tr>
<th>First author/reference citation</th>
<th>Study population</th>
<th>Patients (n)</th>
<th>ABPM method</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kashiwagi et al.(^8)</td>
<td>Patients with NTG</td>
<td>Total: 27</td>
<td>“A&amp;D; Toshimaku, Tokyo” every 30 minutes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Male: 12</td>
<td></td>
</tr>
<tr>
<td>Graham et al.(^{13})</td>
<td>Patients with POAG/NTG</td>
<td>Total: 70</td>
<td>“CH Druck monitor”(^a) every 30 minutes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Male: n.a.</td>
<td></td>
</tr>
<tr>
<td>Collignon et al.(^{12})</td>
<td>Patients with POAG/NTG</td>
<td>Total: 70</td>
<td>“Space Labs Holter” 6-22(^00) every 20 minutes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Male: 35</td>
<td></td>
</tr>
<tr>
<td>Bresson-Dumont et al.(^{19})</td>
<td>Patients with POAG/NTG</td>
<td>Total: 83</td>
<td>“Space Labs Holter” 6-22(^00) every 30 minutes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Male: 35</td>
<td></td>
</tr>
<tr>
<td>Detry et al.(^{25})</td>
<td>Patients with POAG</td>
<td>Total: 36</td>
<td>“Space Labs Holter” 6-22(^00) every 20 minutes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Male: 19</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: ABPM, ambulatory blood pressure measurement; n.a., not available; NTG, normal tension glaucoma; POAG, primary open-angle glaucoma.

\(^a\)Disetronic Medical Systems, Burgdorf, Switzerland.

1078 American Journal of Hypertension 28(9) September 2015
<table>
<thead>
<tr>
<th>Odds Ratio</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.51 [1.22, 10.06]</td>
<td>1999</td>
</tr>
<tr>
<td>2.68 [0.74, 9.73]</td>
<td>1998</td>
</tr>
<tr>
<td>5.62 [1.83, 17.28]</td>
<td>1996</td>
</tr>
<tr>
<td>1.65 [0.41, 6.71]</td>
<td>1996</td>
</tr>
<tr>
<td>3.32 [1.84, 6.00]</td>
<td>systolic nocturnal dip</td>
</tr>
</tbody>
</table>

<table>
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<tr>
<th>Odds Ratio</th>
<th>Year</th>
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<td>1999</td>
</tr>
<tr>
<td>2.68 [0.74, 9.73]</td>
<td>1998</td>
</tr>
<tr>
<td>1.67 [0.31, 9.04]</td>
<td>1996</td>
</tr>
<tr>
<td>1.40 [0.59, 3.31]</td>
<td>1996</td>
</tr>
<tr>
<td>2.09 [1.20, 3.64]</td>
<td>diastolic nocturnal dip</td>
</tr>
</tbody>
</table>
Nocturnal dippers and POAG

- significant association between progression of VF defects in patients with POAG (high pressure and normal pressure glaucoma) and nocturnal blood pressure dips
- OPP fluctuations with ischemic episodes of the optic nerve head
- important to monitor nocturnal BP especially in patients with cardiovascular risk factors or diseases and on antihypertensive or vaso-active medication
- no conclusions about overdipping from the data
- Authors recommend careful adjustment of BP lowering drugs and repeated 24-hor ABPM
POAG and over-dippers

- POAG patients (n = 314)
- mean IOP < 15 mm HG and fluctuations < 5 mmHg
- automated perimetry, 24-hr BP monitoring and diurnal IOP measurements

Distribution of non-dippers, physiological dippers and over-dippers in systemic normotensive and hypertensive patients with POAG
Mean deviation and interquartile ranges in the 3 dipping groups
Median PSD and interquartile ranges

![Graph showing median PSD and interquartile ranges for different groups: Nondipper, Physiological dipper, and Over-dipper. The bars represent PSD in dB, and the ranges are indicated by boxes.

- Nondipper: The PSD for normotensive and hypertensive groups are shown.
- Physiological dipper: The PSD for normotensive and hypertensive groups are shown.
- Over-dipper: The PSD for hypertensive group is shown.

The graph indicates that the PSD is generally worse in the Over-dipper group compared to the other groups.]

worse
Conclusions

- Systemic normotensive patients with nocturnal overdipping had more VF loss than overdippers with systemic hypertension.
- There was no difference between patients with POAG and high IOP and POAG with normal IOP.
- Therefore, ambulatory BP measurements should not be restricted to POAG patients with normal pressure.
POAG and PVD (primary vascular dysregulation)

- disturbance of autoregulation of ocular blood flow
- often patients with low blood pressure, cold extremities, reduced feeling of thirst, low BMI, frequent migraines, altered drug sensitivity
- over-dippers or non-dippers
- unstable oxygen supply
- “a sick eye in a sick body” (J Flammer)

In conclusion...

LETTER TO THE EDITOR

Circadian Arterial Blood Pressure Variation and Glaucoma Progression: More Questions Than Answers?

Hari Jayaram,¹,² Luis Abegão Pinto,³ Verena Prokosch,⁴ Juliane Matlach,¹ Katarzyna Skonieczna,⁵ Karl Mercieca,⁶ Maurizio Digiuni,⁷ Mehmet C. Mocan,⁸ Sergio Mahave,⁹ Sabina Andersson,¹⁰ and David F. Garway-Heath;¹
on behalf of the Writing Committee for the European Glaucoma Panel*⁸

To the Editor: We are delegates of the European Glaucoma Panel comprising young European glaucoma specialists, having recently discussed the article “Circadian Variation in Arterial Blood Pressure and Glaucomatous Optic Neuropathy—A Systematic Review and Meta-Analysis” by Bowe et al.¹

Optic nerve head perfusion is thought to impact all open angle glaucoma phenotypes, but patients with normal tension glaucoma may be more resistant to these changes.
The secret wish of the BGS

- how reliable is a single 24-hrs BP monitoring?
- is this procedure also apt to pick up cardiac rhythm disorders? (S Drance)
- how is autoregulation measured or examined in other vascular beds?
- could we reach a consensus on a standard examination protocol that catches the most important vascular risk factors and use this as a template for the collaboration between ophthalmologist and cardiologist in Belgium?