

**Supplementary Table 1.** Effects of Timolol, Dorzolamide and DTFC on intraocular pressure and ocular and systemic vascular parameters.

<b>DRUG</b>	<b>AUTHORS</b>	<b>STUDY TYPE</b>	<b>IOP</b>	<b>OCULAR AND SYSTEMIC VASCULAR PARAMETERS</b>	<b>INSTRUMENT and MEASURES</b>
Dorzolamide	Harris et al. 1996 (18)	double-masked, counterbalanced fashion study 11 healthy eyes	15.7 +/- 0.7 to 13.7 +/- 0.7 mmHg (p < 0.05)	unaltered blood velocity or resistance index in any retrobulbar vessel. accelerated capillary dye transit in the macula and optic nerve head	CDI SLO
Dorzolamide	Pillunat et al. 1999 (19)	double-masked, randomized clinical trial, 15 healthy subjects Dorzolamide TTD for 3 days	12.5 mmHg to 11.0/10.5 mmHg	NS in dorzolamide-treated volunteers temporal 310/329/315 AU, nasal 387/402/399 AU (HRF) NS temporal 12.98/12.6/11.7 AU, nasal 16.6/16.9/15.7 AU (LDF) BP and HR unchanged	HRF Laser Doppler Flowmetry (Oculix 4000)
Dorzolamide	Martinez et al. 1999 (20)	clinical trial 26 POAG initial and advanced 13 controls	significant in POAG eyes initial and advanced	PSV, EDV, CRV minimal velocity significantly higher after dorzolamide. RI significantly lower in OA and CRA in all groups after dorzolamide.	CDI
Timolol Timolol-Dorzolamide	Schmidt et al. 1999 (21)	clinical trial 14 POAG patients 4 weeks only Timolol 4 weeks Timolol-Dorzolamide	highly significantly reduced after timolol. The effect was additively enhanced by dorzolamide	dorzolamide significantly increased OPA Systemic perfusion parameters unchanged.	OPA
DTFC vs Timolol	Brogliatti et al. 2000 (22)	Clinical trial 20 POAG patients	- 5,40 mm hg (p<0.05)	Volume, Flow, Velocity from +10.62% to +16.01% NS	HRF
Timolol	Lubeck et al 2001 (23)	prospective open-label study, 12 POAG patients	significant reduction after 2 hours after 3 weeks	no changes in HR, BP after 3 weeks no changes in HRF parameters	HRF
Timolol, Dorzolamide Latano-prost	Arend et al. 2003 (24)	prospective, randomized, crossover study 14 POAG	significant reduction after all the treatment	only dorzolamide significantly shortened AVP times, HR, SBP, DBP and OPP not significantly altered	fluorescein angiography SLO HR, SBP, DBP, OPP
Dorzolamide Timolol	Fuchsjager-Mayrl et al. 2005 (25)	RCT crossover 140 pt POAG/OH 70 Timolol 70 Dorzolamide	similar reduction	Timolol: ocular hemodynamic parameters unchanged Dorzolamide increases hemodynamic parameters independently of IOP decrease (NS)	HRF OPP:2/3 MAP-IOP

Latanoprost/Timolol Dorzolamide/Timolol	Martinez and Sanchez 2007 (26)	RCT 32 newly diagnosed POAG	LTFC $p < 0.0001$ , from 26.5 (3.4) (95% CI 25.7-27.4) to 19.3 (1.9) (95% CI 18.6-20.0) DTFC to 19.3 (1.6) (95% CI 18.7-19.9) after treatment with DTFC	DTFC significantly increased EDV OA from 7.55 (1.16) to 9.32 (1.22), $p < 0.0001$ , and in PCA from 4.41 (0.70) to 5.36 (0.60), $p < 0.0001$ , and significantly decreased RI OA from 0.775 (0.036) to 0.725 (0.032), $p < 0.0001$ , and in PCA from 0.694 (0.045) to 0.634 (0.034)	CDI
DTFC and Latanoprost	Quaranta et al. 2008 (27)	RCT 27 POAG patients DTFC + Lat or viceversa	DTFC lowers 24-hour pressure (mean +/- SD: 15.4 +/- 1.9 vs. 16.7 +/- 1.7 mm Hg; $P = 0.004$ )	both therapies significantly increased ODPP vs baseline	SBP, DBP, ODPP
Dorzolamide Timolol  DTFC	Rolle et al. 2008 (28)	clinical trial crossover study 28 POAG patients early to moderate	Dorzolamide -12.03%; $P < 0.001$ ; Timolol -13.70%; $P < 0.001$ . Dorzolamide-21.40%; $P < 0.001$ ; Timolol-21.25%; $P < 0.001$ ; DTFC in group I (-10.60%; $P < 0.001$ ) and in group II -8.80%; $P < 0.001$	after dorzolamide increased (+11.89% at rim level; NS). between T1 and T3 at rim level in group I (+30.03%; $P > 0.05$ ) and when all patients were considered globally (+20.81%; $P < 0.05$ ) ODPP after dorzolamide (+ 7.24%; $P < 0.01$ ), Timolol (+ 6.08%; $P < 0.05$ ), globally (+ 6.71%; $P < 0.001$ ); after DTFC between T2 -T3(+2.60%; $P < 0.01$ ).	HRF AFFPIA  ODPP
Bimatoprost, Travoprost, Timolol, Latanoprost, Dorzolamide, DTFC, LTF	Stewart et al. 2008 (29)	meta-analysis IOP reduction 11 studies 383 POAG/OH patients	Dorzolamide - 19% 24-hour pressure reduction  DTFC 26% after the evening dose		
LTFC vs DTFC	Januleviciene et al. 2009 (30)	prospectiverandomized double masked parallel study-1 year therapy 30 POAG patients	DTFC -5.0 mm Hg LTFC -5.44 mmHg	DTFC OP +10.46%, ODPP +10.67% LTFC OP 7.47%, ODPP +5.61% only DTFC reduction of RI VF stable with both treatments	CDI  ODPP  VF
Dorzolamide vs Timolol	Fuchsjager-Mayrl et al. 2010 (31)	RCT 140 OH/POAG patients autoregulation	Timolol POAG $-21.5\% \pm 12.3\%$ OHT $-23.5\% \pm 12.8\%$ Dorzolamide POAG $-18.7\% \pm 12.3\%$ OHT $(-20.8\% \pm 12.6\%$	significant association between all ocular hemodynamic parameters and SBP ( $r = 0.23-0.42$ ). The association between HRF parameters and BP was higher than the association between FPA and BP	HRF, Fundus Pulsation Amplitude

DTFC vs LTFC	Januleviciene et al. 2011 (32)	RCT 18 months follow-up 30 POAG	similar IOP lowering effect over 18 months of observation (P = .653)	DTFC showed statistically significantly higher OPP, SPP, and DPP at 1, 6, and 18 months visit	BP, OPP, ODPP, CDI, POBF, scanning laser polarimetry, VF
DTFC	Eliacik et al. 2015 (33)	observational study 22 newly diagnosed patients with PXG	22.3 ± 2.1 mmHg at baseline and reduced to 17.4 ± 2.3 mmHg at the 3(rd) month (p < 0.05)	Reduced: PSV (p = 0.044) RI- 0.04 unit (p < 0.001) in the temporal short PCA	CDI
DTFC	Lee et al. 2016 (34)	RCT 44 newly diagnosed NTG	after 4 weeks mean IOP values 12.9 ± 2.8 (8 am), 12.9 ± 2.7 (10 am), 12.7 ± 2.7 (12 pm), 13.4 ± 2.5 (4 pm) and 13.4 ± 2.3 mmHg (8 pm). Mean IOP reduction -14.4 %.	After DTFC mean OPP 46.7 ± 6.3 mmHg and mean DOPP 61.1 ± 8.1 mmHg. OPP and ODPP showed no statistically significant interaction effects	BP, OPP, ODPP
DTFC vs LT	Lee et al. 2016 (35)	RCT crossover 44 newly diagnosed NTG	diurnal IOP no difference between the groups: average IOP reduction of 13.1% with latanoprost and 12.3% with DTFC. ΔIOP between the treatments -0.19 ± 0.18 mmHg	mean OPP 46.68 ± 6.15 mmHg in DTFC group, 47.39 ± 6.61 mmHg in latanoprost group. NS (p = 0.248). Mean ODPP 61.05 ± 7.78 mmHg in DTFC group and 61.91 ± 9.19 mmHg in latanoprost group. NS p = 0.290	BP, OPP, ODPP
Carteolol Brimonidine Dorzolamide	Lin et al. 2021 (36)	retrospective, nonrandomized, comparative study: 131 NTG patients: 80 carteolol-treated eyes, 27 brimonidine-treated eyes and 24 dorzolamide-treated	decreased significantly in the carteolol-treated, brimonidine-treated, and dorzolamide-treated eyes.	post treatment MOPP values in all 3 groups NS from baseline data. Only Dorzolamide increases in the peripapillary superficial retinal VD + 4.3 %, especially in the superior-nasal area (VD: +11.1 %) significant	OCT-A MOPP
Timolol Latanoprost	Kolli et al. 2021(37)	RCT 121 healthy volunteers evaluated at baseline, after 1 week of timolol 0.5% bid and after 1 week of latanoprost 0.005% dosed nightly	significant reduction	ODPP significantly increased with both Timolol +1.3 mmHg and Latanoprost +3.1 mmHg. OSPP increased with Latanoprost +2.8 mmHg but decreased with Timolol -1.3 mmHg OPP values calculated with MAP were not significantly different (P = 0.068)	ODPP, OSPP

DTFC	Pakravan et al.2021 (38)	prospective, interventional case series 33 newly POAG patients treated with Cosopt (BID) for one month and then switched to three times a day (TDS) for an additional month.	Cosopt BID -8.9 mmHg -28% Cosopt TDS further reduction -2.7 mmHg -12%	DTFC BID significantly reduced the mean 24-h systolic BP; mean 24 h OPP at baseline, month 1, and month 2 was 48.12±11, 51.71±10.1, and 53.1±9.6 mmHg (ps = .04 and .03, respectively) mean 24-h HR from baseline (p< 0001), mean 24-h systolic BP and HR remained unchanged with Cosopt TDS compared to BID (p = .62).	BP, OPP, SBP, HR
PF-Tafluprost, PF-DTFC P-Latanoprost	Park et al. 2022 (39)	multicenter, prospective, interventional, non-randomized 107 patients	IOP changes were comparable among all three treatment groups.	PF-Tafluprost and PF-Dorzolamide/Timolol showed statistically and clinically significant reductions in OSDI	
Timolol	Tuleski et al.2022 (40)	41 healthy cats, after one drop of timolol 0,5% ophthalmic solution		Timolol reduced HR (19%), and fractional shortening from LV (20.3%) and LA (16.6%). Septal S' decreased by 51% (from 7.7 to 5.2 cm/s) and lateral S' dropped by 43.1% (7.3 to 5.1 cm/s). It did not separate the mitral diastolic waves	TDI

Abbreviations: CDI: Color Doppler Imaging; SLO: Scanning Laser Ophthalmoscope; HRF: Heidelberg Retina Flowmeter; OPA: Ocular Pulse Amplitude; OPP: ocular perfusion Pressure; HR: Heart Rate; SBP: Systemic Blood Pressure; DBP: Diastolic Blood Pressure; ODPP: Ocular Diastolic Perfusion Pressure; AFFPIA: Automatic Full Field Perfusion Image Analyzer software; POBF: Pulsatile Ocular Blood Flow; VF: Visual Field; OCT-A: Optical Coherence Tomography Angiography; MOPP: Mean Ocular Perfusion Pressure; OSPP: Ocular Systolic Perfusion Pressure; TDI: Tissue Doppler Imaging