A SYSTEMATIC LITERATURE REVIEW OF THE EFFICACY AND SAFETY OF MICROINCISION VITRECTOMY SURGERY TOOLS IN VITREORETINAL DISEASES

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INTRODUCTION AND AIMS

Approximately 34 million individuals are affected by retinal diseases in Europe alone.[1] Pars plana vitrectomy (PPV) is a surgical treatment for retinal disease, involving the removal of the eye's vitreous gel, and subsequent retinal repair. Vitrectomy is used to treat various conditions including diabetic retinopathy, retinal detachment, or retinal tears. The advent of small-gauge microincision vitrectomy surgery (MIVS) has greatly improved vitrectomy procedures, reduced complications and increased their application in a range of vitreoretinal conditions.

The primary objective of this SLR was to synthesize the clinical and real-world evidence on the efficacy and safety of Alcon's suite of retinal surgery vitrectomy tools:

- **CONSTELLATION®** Vision System
- **MIVS®** Platform of Micro-incisional Tools
- **ULTRAVIT®** High Speed Vitrectomy Probes
- **EDGEPLUS®** Valved Trocar Cannula System
- Integrated **PUREPOINT®** laser

METHODS

- The SLR study questions and study selection criteria were specified using the PICOS framework (Table 1)
  - Two main research questions were developed to address the objective of the SLR:
    1. What is the **clinical efficacy and safety** of Alcon's retinal surgery portfolio?
    2. What is the effectiveness and safety of Alcon's retinal surgery portfolio **in the real-world setting?**
- Electronic database searches were conducted in EMBASE, MEDLINE and the Cochrane Library
- Search was supplemented with hand searches of grey literature, including health technology assessment (HTA) databases
- Titles and abstracts of studies were reviewed according to the pre-specified inclusion/exclusion criteria
- Articles included during the first phase of the screening were then reviewed in full according to the pre-specified criteria

Table 1. PICOS framework for the Systematic Literature Review

Component	Selection Criteria
Population	• Patients of any age requiring retinal surgery/vitrectomy
Intervention	• Alcon's Surgical Portfolio • **CONSTELLATION®** Vision System, **ULTRAVIT®** Probes, **EDGEPLUS®** Cannula System, **PUREPOINT®** Laser, and MIVS Tools
Comparators	• No restrictions
Outcomes	• Best Corrected Visual Acuity (BCVA) • Anatomical outcomes and intra-ocular pressure (IOP) • Operation times/length • Surgical success and complications • Vision-Related Quality of Life
Study Type	• Clinical trials of any design • Observational studies • Restricted to English language

RESULTS

Summary of Included Publications

- The PRISMA diagram in Figure 1 shows the number of identified records, included studies and reasons for exclusion
- In total, 70 publications met the inclusion criteria for the SLR
- 20 publications were comparative, and were included for further analysis:
  - 14 studies were observational studies, of which 12 were retrospective
  - 6 studies were randomised controlled trials
  - 10 studies compared different gauge sizes; 6 studies compared the CONSTELLATION® and ACCURUS® vision systems, and 2 studies compared each valved and non-valved cannulas, and angled incision technique, respectively
  - 10 studies were conducted in Asia, and 5 in the United States

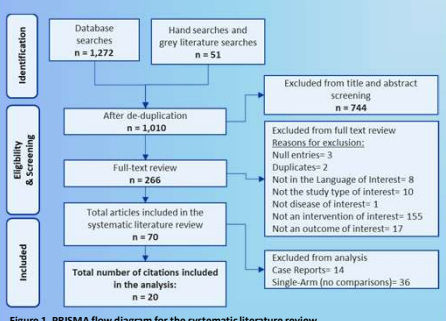


Figure 1. PRISMA flow diagram for the systematic literature review

Baseline Characteristics

- The 20 included publications[2-21] investigated 3,163 patients , and a total of 3,547 eyes

Gender (%); n=16 publications

32 – 78% 22 – 68%

Mean Age (Years); n=19 publications

40 – 78

Mean Pre-Operative BCVA (logMAR); n=14 publications

0.08 – 2.06

Mean Pre-Operative IOP (mmHg); n=12 publications

9.8 – 16.2

1. Best Corrected Visual Acuity (BCVA)

- No significant differences in the magnitude of BCVA improvement from baseline were observed when comparing **CONSTELLATION®** and **ACCURUS®** (Table 2)

Table 2. Change from baseline in BCVA when using ACCURUS® and CONSTELLATION®

Author (Year)	Interventions	Time of Assessment (Final)	Subgroup	N of Patients	Baseline Mean LogMAR	Change from Baseline	P-Value
Mao (2017)[2]	CONSTELLATION® vs. ACCURUS®	11 months	20G ACCURUS®	20	1.1	-0.88	NR
			25G CONSTELLATION®	20	1.05	-0.79	
Sano (2016)[3]		7-14 months	25G ACCURUS®	143	1.51	-0.95	NR
			25G CONSTELLATION®	183	1.53	-1.13	
Mitsui (2016)[4]		6 months	27G ACCURUS®	32	0.13	-0.14	NR
			25G CONSTELLATION®	36	0.27	-0.16	

*NR : Not Reported

- When using CONSTELLATION® vision system, gauge size has **no significant effect** on change from baseline in logMAR BCVA (Table 3)

Table 3. Change from baseline in BCVA using different CONSTELLATION® gauges

Author (Year)	Gauge(s)	Time of Final Assessment	Subgroup	N of patients	Baseline Mean LogMAR	Change from Baseline	p-value
Dell'Omo (2013)[5]	20 vs. 25	20 - 25 months	20G	44	0.47	-0.26	NR
			25G	41	0.69	-0.36	
Kim (2015)[6]	23 vs. 25	1 week	23G	159	0.22	0.07	<0.001
			25G	80	0.21	-0.1	
Kumar (2014)[7]		1 year	23G	25	1.28	-0.29	NR
			25G	25	1.29	-0.38	
Li (2018)[8]	25 vs. 27	6 months	25G	34	1.9	-0.9	NR
			27G	58	1.7	-0.6	
Romano (2016)[9]		6 months	25G	15	1.5	-1.16	NR
			27G	15	1.5	-1.19	
Rizzo (2017)[10]		6 months	25G	20	1.31	-1.15	< 0.001
			27G	20	1.65	-1.56	
Mori (2018)[11]		6 months	25G	100	62.5*	45.1	N.S.
			27G	100	64.1*	46.5	

*Measured using ETDRS

- Two studies reported that the magnitude of BCVA improvement tended to be greater when using valved cannulas with the CONSTELLATION® vision system[17,18]

2. Intraocular Pressure (IOP)

- IOP changes are **reduced** when using the CONSTELLATION® vision system compared with ACCURUS® (Table 4)

Table 4. Change from baseline in IOP (mmHg) when using ACCURUS® and CONSTELLATION®

Author (Year)	Interventions	Time of Assessment (Final)	Subgroup	N of Patients	Mean IOP at Baseline (mmHg)	Mean Change in IOP	p-value
Yang (2017)[12]	CONSTELLATION® vs. ACCURUS®	Intra-op	25G ACCURUS®	32	16.2	-8.6	0.043
			25G CONSTELLATION®	29	15.9	-0.8	
Mao (2017)[2]		1 day	20G ACCURUS®	20	14.9	5.1	<0.001
			25G CONSTELLATION®	20	15	-1.5	
Mitsui (2016)[4]		6 months	27G ACCURUS®	32	12.7	-0.7	NR
			25G CONSTELLATION®	36	12.2	-0.2	

- When using CONSTELLATION®, different gauges do not show significantly different changes in IOP (Table 5)

Table 5. Change from baseline in IOP using different CONSTELLATION® gauges

Author (Year)	Intervention	Time of Assessment (Final)	Subgroup	N of Patients	Mean IOP at Baseline (mmHg)	Mean Change In IOP	p-value
Kim (2015)[6]	23G vs. 25G	1 week	23 G	159	13.7	-0.8	N.S
			25 G	80	13.2	0.3	
Kumar (2014)[7]		6 months	23 G	25	13.8	-0.24	N.S
			25 G	25	12.6	0.04	
Mori (2018)[11]	25G vs. 27G	1 week	25 G	100	14.6	0.7	N.S
			27 G	100	14.5	0.8	
Naruse (2017)[13]			25 G	100	14.5	1	N.S
			27 G	100	14.5	0.5	
Takashina (2017)[14]		1 month	25 G	15	13.2	1.9	N.S
			27 G	12	12.2	2.1	
Romano (2016)[9]		6 months*	25 G	15	15.2	0.9	N.S
			27 G	15	14.7	-0.1	
Li (2018)[8]			25 G	58	9.8	4.5	<0.05†
			27 G	34	11.6	3	<0.05†

† versus baseline
*Final time of assessment for the study Li (2018) was approximately 6 months.

- The use of valved cannulas does not appear to impact post-operative IOP

3. Operation Times and Success

- Surgeries conducted with valved cannulas show **greater** success rates than non-valved cannulas when using the CONSTELLATION® vision system (n=1 publication)
- CONSTELLATION® vision system shows significant reduction in surgical time when compared to ACCURUS® (Table 6)
- Surgical time is reduced when using smaller gauge tools with CONSTELLATION® vision system (Table 7)

Table 6. Surgical time using different gauges, comparing CONSTELLATION® vs ACCURUS®

Author (Year)	Vision System	Gauge	Surgical Time (minutes)	P-value
Mitsui (2016)[4]	CONSTELLATION®	25G	6.2	<0.0001
	ACCURUS®	27G	9.9	
Mao (2017)[2]	CONSTELLATION®	25G	13.5	<0.001
	ACCURUS®	20G	42	
Murray (2013)[15]	CONSTELLATION®	NR	31	<0.004
	ACCURUS®	NR	35	
	CONSTELLATION®	NR	37*	<0.001
	ACCURUS®	NR	43*	
Rizzo (2011)[16]	CONSTELLATION®	25G	18	NR
	ACCURUS®	25G	26	

*Murray (2013) reports surgical time for both vitrectomy alone, and combined with phacovitrectomy, respectively

Table 7. Surgical time using different gauges of CONSTELLATION®

Author (Year)	Vision System	Gauge	Surgical Time (minutes)	p-value
Kumar (2014)[7]	CONSTELLATION®	23G	44.7	<0.001
		25G	49.3	
Mori (2018)[11]	CONSTELLATION®	25G	39.2	0.0015
		27G	44.7	
Naruse (2017)[13]	CONSTELLATION®	25G	32.7	0.0323
		27G	36.7	
Romano (2016)[9]	CONSTELLATION®	25G	35.4	0.52
		27G	36.1	
Li (2018)[8]	CONSTELLATION®	25G	56.7	0.894
		27G	55.7	
Rizzo (2017)[10]	CONSTELLATION®	25G	19.6	NR
		27G	23.2	
Takashina (2017)[14]	CONSTELLATION®	25G	29.7	NR
		27G	30.8	
	CONSTELLATION®	25G PV	38	
		27G PV	37	

- CONSTELLATION® vision system shows **higher** surgical success rates compared to ACCURUS® (Figure 2)[2,3,5]
- No differences in surgical success rate were observed between 25G and 27G vitrectomy using CONSETLLATION® (Figure 3)[8,9]

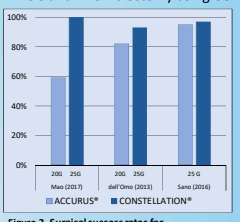


Figure 2. Surgical success rates for CONSTELLATION® and ACCURUS®

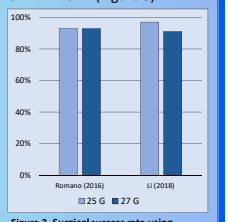


Figure 3. Surgical success rate using different gauges with CONSTELLATION®

4. Safety

- The most frequently reported adverse events/complications across all publications include:
  - Hypotony (n=11 publications; Range: 0 – 20% of patients)[5,6,8,9,11,13,17-21]
  - Ocular Hypertension (n=9 publications; Range: 0 – 25% of patients)[5,8-11,13,17-19]
  - Retinal detachment (n=9 publications; Range: 0 – 18% of patients)[2,3,5,8,11,13,16,19,20]
  - Intraocular bleeding or vitreous hemorrhage (n=9 publications; Range: 0-24% of patients)[2,3,5,7,9,11,13,14,19]
- CONSTELLATION® shows a trend towards reducing the risk of retinal breaks compared to ACCURUS®
- Higher gauge/small instruments appear to have a superior safety profile; 25G vitrectomy appeared to have a superior safety profile over 20G and 23G vitrectomy
- Surgical technique (incision angle or cannula type) does not appear to have any effect on the safety profile of vitrectomy (n=4 publications)[17,18,20,21]

5. Vision Related Quality of Life

- No publications identified in this review reported on vision-related quality of life

DISCUSSION AND CONCLUSION

Overall, MIVS is a safe and efficacious procedure, leading to improvements in visual acuity regardless of which system or tool gauge is used

CONSTELLATION® vs. ACCURUS®

- CONSTELLATION and ACCURUS® show similar improvements from baseline in BCVA
- CONSTELLATION® compared to ACCURUS® demonstrates:
  - Superior surgical success rates, particularly when compared to 20G ACCURUS®
  - Shorter operative times
  - Lower rates of post-operative hypotony
  - Trend towards lower rates of retinal breaks

Gauge Size

- Gauge size does not significantly impact BCVA outcomes
- Smaller gauges may reduce:
  - Surgical times
  - The need for wound suturing

Effect of Tool Features

- Valved cannulas may have higher rates of anatomical success in repairing retinal detachment

Limitations and remaining questions

- This SLR uncovered a high degree of heterogeneity in study design, populations and their vitreoretinal pathology, time of assessment, and surgical tools across studies
  - These differences result in difficulties in comparing outcomes across trials
  - Consistency in measuring and reporting of outcomes is required to reliably make comparisons across studies
- Further research and comparative trials are necessary to fully elucidate the effects of cannula valve status

Disclosures

Amaris is an independent consulting firm. Leighton Morris is an employee of Alcon Laboratories. This study was funded by Alcon Laboratories Inc., Fort Worth, TX, USA

Abbreviations

BCVA: Best Corrective Visual Acuity; G: Gauge; IOP: Intraocular Pressure; LogMAR: Logarithm of the Minimum Angle of Resolution; MIVS: Microincisional Vitrectomy Surgery; NR: Not Reported; NS: Not Significant; PPV: Pars Plana Vitrectomy; PV; Phacovitrectomy; SLR: Systematic Literature Review.

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For additional questions please contact Leighton Morris at [redacted] or Graham Gauthier at [redacted]

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