Review

Implementation of computer simulation to assess flow diversion treatment outcomes: systematic review and meta-analysis

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ABSTRACT

Introduction Despite a decade of research into virtual stent deployment and the post-stenting aneurysmal hemodynamics, the hemodynamic factors which correlate with successful treatment remain inconclusive. We aimed to examine the differences in various post-treatment hemodynamic parameters between successfully and unsuccessfully treated cases, and to quantify the additional flow diversion achievable through stent compaction or insertion of a second stent.

Methods A systematic review and meta-analysis were performed on eligible studies published from 2000 to 2019. We first classified cases according to treatment success (aneurysm occlusion) and then calculated the pooled standardized mean differences (SMD) of each available parameter to examine their association with clinical outcomes. Any additional flow diversion arising from the two common strategies for improving the stent wire density was quantified by pooling the results of such studies.

Results We found that differences in the aneurysmal inflow rate (SMD −6.05, 95% CI −10.87 to −1.23, p=0.01) and energy loss (SMD −5.28, 95% CI −7.09 to −3.46, p<0.001) between the successfully and unsuccessfully treated groups were indicative of statistical significance, in contrast to wall shear stress (p=0.37), intra-aneurysmal average velocity (p=0.09), vortex core-line length (p=0.46), and shear rate (p=0.09). Compacting a single stent could achieve additional flow diversion comparable to that by dual-stent implantation.

Conclusions Inflow rate and energy loss have shown promise as identifiers to discriminate between successful and unsuccessful treatment, pending future research into their diagnostic performance to establish optimal cut-off values.

INTRODUCTION

Computational fluid dynamics has been used for over a decade to assess the hemodynamics of intracranial aneurysms after flow diversion treatment.[1–6] This is because a favorable treatment outcome is largely associated with the efficacy of flow diversion produced by the implanted device; redirecting much of the aneurysmal inflow can 'weaken' the hemodynamic activity inside the sac, thereby promoting thrombosis and accelerating intracranial aneurysm occlusion.[7]

In view of this mechanism, a wide variety of hemodynamic parameters have been proposed to quantify the efficacy of flow-diverting (FD) stents: from those measuring reduction of the aneurysmal inflow strength (eg, aneurysmal inflow rate, intra-aneurysmal average velocity, mean aneurysm flow amplitude)[8–11] to those measuring weakening of the vascular pressure or stress (eg, wall shear stress, pressure drop),[2 12 13] and then to those characterizing changes in flow behavior within the aneurysm sac (eg, relative residence time, vortex core-line length).[8 14 15] Furthermore, many research groups have also attempted to establish hemodynamic identifiers of a successful treatment,[4 9 12 13 16–19] although no consensus has yet been reached.

Owing to the development of virtual stenting techniques,[6 20 21] computational fluid dynamics has also been adopted to investigate the changes in aneurysm hemodynamics following various strategies or maneuvers exercised intra-operatively to enhance the flow diversion, in particular stent compaction and multiple stent deployment. Despite a number of simulation studies having confirmed the effectiveness of these approaches in enhancing the flow diversion,[3 18 19 22] it remains inconclusive as to how much further an additional stent or a stent compaction technique can decrease the aneurysmal inflow.

In the present work we performed a pooled analysis of eligible studies on the aneurysmal hemodynamics after virtual stent treatment, seeking to (1) identify hemodynamic parameters that may be most suggestive of a favorable treatment outcome and (2) quantify the likely additional flow diversion achievable through a stent compaction technique or insertion of an additional stent.

METHODS
Study selection

We conducted the systematic review and meta-analysis in accordance with the PRISMA guidelines. A search for the keyword terms "computational fluid dynamics", "haemodynamics" or "hemodynamics", in combination with "aneurysm(s)", "flow-diverter(s)" or "flow-diverting stent(s)" was performed using PubMed, Medline, and Scopus
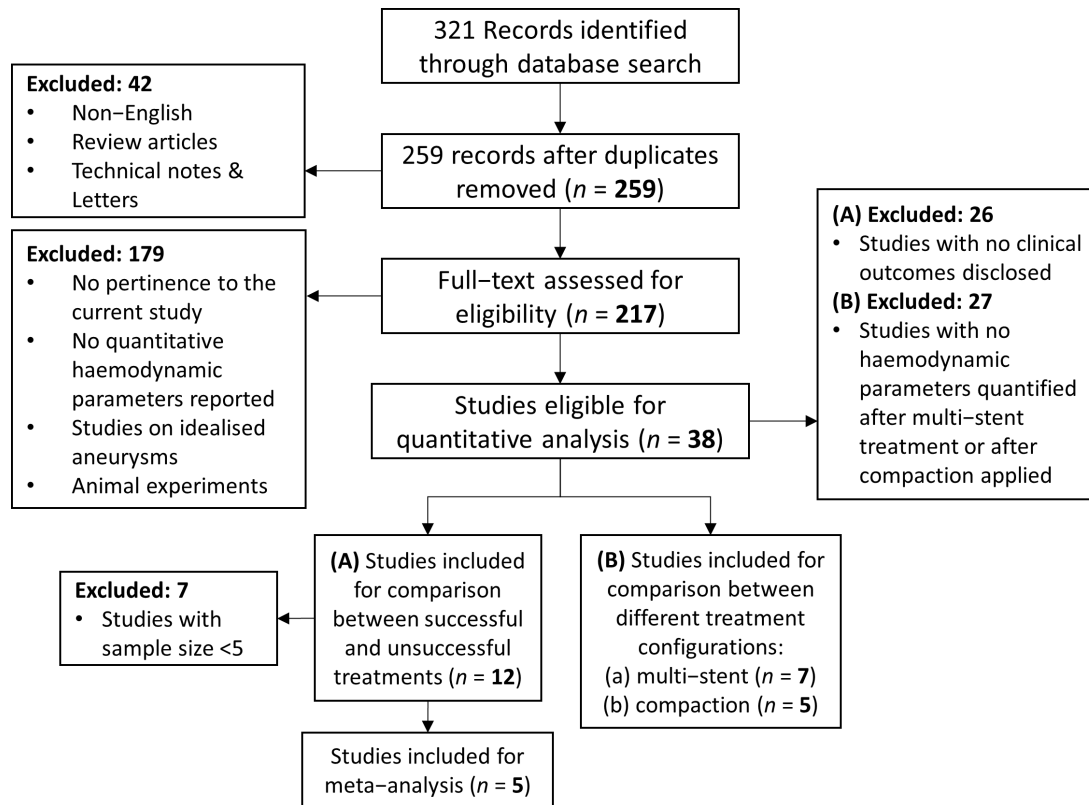
321 Records identified through database search

Excluded: 42
- Non–English
- Review articles
- Technical notes & Letters

259 records after duplicates removed (n = **259**)

Full–text assessed for eligibility (n = **217**)

Excluded: 179
- No pertinence to the current study
- No quantitative haemodynamic parameters reported
- Studies on idealised aneurysms
- Animal experiments

Studies eligible for quantitative analysis (n = **38**)

(A) Excluded: 26
- Studies with no clinical outcomes disclosed

(B) Excluded: 27
- Studies with no haemodynamic parameters quantified after multi–stent treatment or after compaction applied

Excluded: 7
- Studies with sample size <5

(A) Studies included for comparison between successful and unsuccessful treatments (n = **12**)

(B) Studies included for comparison between different treatment configurations:
(a) multi–stent (n = **7**)
(b) compaction (n = **5**)

Studies included for meta–analysis (n = **5**)

Figure 1 Strategy used for literature search and the number of studies included in each analysis.

for articles published in the period from 1 January 2000 to 31 December 2019. From the identified studies, review articles, articles that were written in languages other than English, technical notes, and letters were immediately excluded.

For the remaining articles, three authors (MZ, ST, and MO) independently examined the full text before reaching an agreement on their eligibility to be included in our quantitative analysis according to the following criteria: (1) human aneurysm subjects were included; (2) paired pre- and post-stenting hemodynamic parameters were quantified; and (3) clinical outcomes following a treatment were disclosed (if it was to be analysed for the correlation between hemodynamic changes and clinical outcomes). When serial studies existed describing the results of an overlapping set of subjects, only the most recent one was retained (see figure 1 for the literature search strategy used to screen papers for our quantitative analyses).

Data extraction and normalization

For quantitative analysis we extracted data including (1) name of the first author, (2) year of publication, (3) aim and design of the study, (4) number, type, size, and location of the aneurysms, (5) type of the stents and strategy used for virtual deployments, and (6) all available pre- and post-treatment hemodynamic parameters. These parameters included the aneurysmal inflow rate (IR), intra-aneurysmal average velocity (AAV) and maximal velocity (MAV), average shear strain rate (SR) of blood flow within the aneurysms, energy loss (EL), pressure drop (PD), aneurysmal wall shear stress (WSS) and vortex core-line length (VCL), the relative residence time (RRT) and turnover time (TUT), and transition time (TRT). Two authors (HA and YK) independently performed data extraction, the results of which were consistent.

As the extracted data were reported in various units and formats across different studies, a data normalization procedure

was carried out to ensure validity of between-study comparisons of the hemodynamic outcomes of the treatments. Paired hemodynamic parameters in physical units before (P_{pre}) and after (P_{post}) treatment respectively in the forms of

$$P_{pre} = m_{pre} \pm SD_{pre} \text{ and } P_{post} = m_{post} \pm SD_{post} \qquad (1)$$

were converted into a normalized reduction R (%) in relation to the untreated condition:

$$R\,(\%) = m_r \pm SD_r \qquad (2)$$

where m_r and SD_r denote the mean and SD of the normalized reduction, which were respectively calculated as[23]

$$m_r = \frac{m_{post}}{m_{pre}} \times 100\% , \qquad (3)$$

and

$$SD_r = \frac{\sqrt{m_{pre}^2 \cdot SD_{post}^2 + m_{post}^2 \cdot SD_{pre}^2}}{m_{post}^2} \times 100\% . \qquad (4)$$

Statistical analysis

Statistical analyses were performed using MedCalc version 19.1 (Ostend, Belgium), with GNU Octave 4.4.1 (John W Eaton *et al*, USA) being a supplementary tool. For systematic comparisons between the successfully and unsuccessfully treated groups, we first performed a Shapiro–Wilk test to check for normality of the continuous data, and then an independent Student t-test for normally distributed data or a Mann–Whitney U test for non-normally distributed data. For comparison of hemodynamic changes between various treatment configurations (ie, treatments with single or with dual FD stents, and treatments with or without a stent compaction technique applied), a paired-sample two-sided t-test was used. Throughout the comparisons $p<0.05$ was considered suggestive of statistical significance, while $p<0.005$ was deemed to confirm statistical significance.

A meta-analysis was performed to explore the standardized mean difference (SMD) of six hemodynamic parameters (IR, AAV, EL, VCL, WSS, and SR) between the successfully and unsuccessfully treated groups. Both fixed-effects and random-effects models were used in each analysis, with a Cochran Q test employed to examine the between-study heterogeneity. If a test had suggested significant heterogeneity between studies, results corresponding to a random-effects model were adopted, otherwise results corresponding to a fixed-effects model were adopted. We used funnel plots and Egger's test to examine the publication bias, with $p < 0.05$ being an indication of statistical significance.

RESULTS

Our database search yielded 259 studies after duplicates were removed, of which 38 were deemed eligible for further quantitative analysis.

For systematic analysis of the correlation between hemodynamic and clinical outcomes, 12 studies (involving a total of 153 aneurysms) with clinical outcomes disclosed were included. Of the 12 studies, five with aneurysm sample size greater than five were later included in the meta-analysis (see table 1 for a summary of the studies). We observed no substantial asymmetry in the funnel plots of studies that reported IR or AAV, and Egger's tests did not suggest the existence of publication bias ($p = 0.78$ and $p = 0.89$ for IR and AAV, respectively).

Of the 38 studies, 11 met the inclusion criteria for quantifying the improvements of flow diversion achieved by two respective wire density enhancement techniques—stent compaction (7/11) and dual-stent implantation (5/11) (see online supplemental material 1 for a list of those studies, online supplemental table 1 for a summary, and online supplemental table 2 for details of the normalized hemodynamic parameters extracted from those studies).

Hemodynamic differences between successfully and unsuccessfully treated cases
Quantitative comparison
Our quantitative analyses of 12 studies suggest that the differences in IR ($p = 0.0063$) and EL ($p = 0.0237$) between the successfully and unsuccessfully treated aneurysms were suggestive of statistical significance. However, no statistically significant differences were found for AAV ($p = 0.2881$) or WSS ($p = 0.8280$) (see online supplemental figure 1 for the detailed quantifications and online supplemental material 2 for an additional logistic regression analysis).

Meta-analysis
Consistent with the findings of the quantitative comparison, our meta-analysis of five studies (including a total of 138 aneurysms) shows the differences in normalized IR (SMD −6.05, 95% CI −10.865 to −1.225, $p = 0.01$) and EL (SMD −5.28, 95% CI −7.092 to −3.459, $p < 0.001$) are indicative of statistical significance, in contrast to AAV (SMD −3.22 95% CI −6.985 to 0.537, $p = 0.09$) and WSS (SMD 0.34, 95% CI −0.411 to 1.083, $p = 0.37$) (figure 2 and table 1).

Improvement of flow diversion obtained by increased stent wire density
Table 2 summarizes the improvements in intra-aneurysmal flow reduction obtained by enhancement of the stent wire density across the aneurysm orifice. Our systematic review suggests that overlapping two stents and compacting a single stent can each

markedly improve the flow diversion efficacy, further reducing the IR by $14.4 \pm 5.6\%$ (95% CI 9.3% to 19.6%, $p = 0.0005$) and $16.0 \pm 11.3\%$ (95% CI 6.7% to 25.4%, $p = 0.0051$), respectively, and the AAV by $16.8 \pm 8.7\%$ (95% CI 10.1% to 23.5%, $p = 0.0004$) and $23.3 \pm 14.4\%$ (95% CI 8.3% to 38.4%, $p = 0.0105$) compared with the standard deployment of a single stent. However, the increase of normalized TUT induced by stent compaction was not suggestive of statistical significance ($p = 0.0791$), in contrast to that induced by overlapping stents ($p = 0.0247$) (see online supplemental figures 2 and 3 for statistics on the hemodynamic changes attributable to increasing the stent wire density across the aneurysm orifice).

DISCUSSION
IR and EL reduction might be suggestive of a successful treatment
Our quantitative comparison suggests that only differences in the normalized IR and EL reductions between the successfully and unsuccessfully treated groups were suggestive of statistical significance, and this finding agrees with our meta-analysis.

IR is a so-called 'bulk' hemodynamic parameter measuring the entire quantity of blood flow entering the aneurysm. Strength and angle of the aneurysm inflow have direct impact on the complexity and stability of flow within the aneurysm sac, which are believed to be closely associated with aneurysm occlusion or rupture.[7][13] As a parameter originally proposed to quantify the hemodynamic effects of different anastomosis modes in cardiovascular surgery, EL measures differences in the dynamic pressure and kinetic energy between the aneurysmal inflow and outflow. Being able to immediately quantify the weakening of intra-aneurysmal flow activity, IR and EL have both been proposed as identifiers of a fast aneurysm occlusion; however, differing conclusions were previously reported regarding their association with clinical outcomes.

Paliwal et al[16] reported that, superior to bulk hemodynamic parameters (ie, IR ($p = 0.10$) and AAV ($p = 0.34$)), localised parameters (ie, EL and VCL (both $p < 0.00$)) were more sensitive in capturing the complex intra-aneurysmal flow behaviors, which are likely to manifest greater disruption in successfully treated intracranial aneurysms (table 1). Interestingly, in another study[8] that involved more aneurysm samples (n=84), reductions of the IR, AAV, and SR were all found to be statistically different (all $p < 0.00$), in contrast to TUT ($p = 0.47$), a parameter measuring the average period of time during which fluid particles remain within the aneurysm sac. Chong et al[9] and Mut et al[13] also reported the difference in IR to be statistically significant (both $p < 0.00$), although the former found that the difference in EL between the successful and unsuccessful cases was about three times that of IR.

Animal experiments showed a similar tendency when hemodynamic parameters were used to predict complete aneurysm occlusion. A study of 36 elastase-induced aneurysms in rabbits reported statistically significant differences in IR ($p < 0.03$) and kinetic energy ($p < 0.05$) between fast and slow aneurysm occlusion, in contrast to that of AAV ($p = 0.06$), regardless of aneurysm size.[14] Moreover, their follow-up research into the intra-aneurysmal hemodynamics showed that AAV and SR in the patent regions were about 2.8 times larger than those in the occluded regions ($p < 0.00$),[7] suggesting the usefulness of AAV and SR in predicting localized thrombosis formation.

In accordance with our review of studies on human subjects, together with the findings from animal experiments, IR and EL have shown promise as discriminators between favorable and unfavorable clinical outcomes prior to a real flow diversion

Table 1 Study information and normalized reductions relative to the untreated condition of hemodynamic parameters summarized from studies included in the meta-analysis and systematic review for differences between successfully and unsuccessfully treated cases
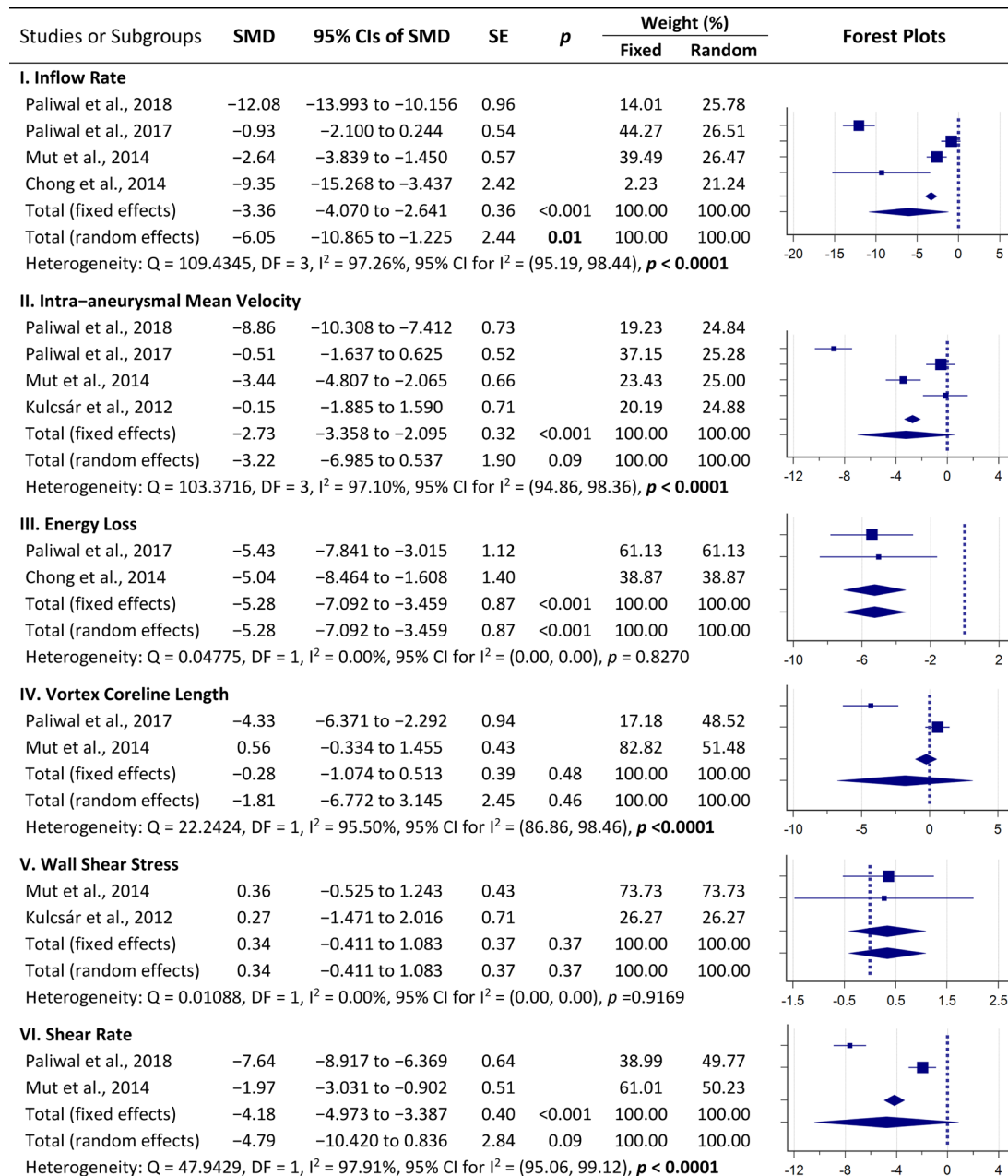
Author, year	No. of IAs	No. of Succ.	IA location	IA type	AR (SD)	Criterion	FD stent model	Virtual stenting technique	IR reduction (SD) S	U	P value	AAV reduction (SD) S	U	P value
Paliwal et al,[8] 2018	84	63	ICA	SW	0.98 (0.17)	CO @6mo	PED	Paliwal et al[33],	0.39 (0.01)	0.59 (0.03)	<0.00*	0.29 (0.01)	0.48 (0.04)	<0.00*
Paliwal et al,[16] 2017	15	10	—	SW	—	CO @12mo	PED	Paliwal et al[33]	0.60 (0.03)	0.66 (0.10)	0.1	0.48 (0.03)	0.51 (0.09)	0.34
Mut et al,[13] 2014	23	15	1 ACOM, 7 ICA (OPH), 10 ICA (CAV), 4 PCOM, ICA (SUP),	SW	10.02 (4.74)	CO @3mo	PED	Mut et al,[34]	0.32 (0.02)	0.72 (0.25)	<0.00*	0.14 (0.02)	0.30 (0.08)	<0.00*
Chong et al,[9] 2014	8	4	5 ICA (SUP); 2 ICA (CAV), 1 Base of skull;	SW	2.39 (0.83)	CO @6mo	Silk	Porous Medium[35]	0.09 (0.02)	0.50 (0.05)	<0.00*	—	—	—
Kulcsár et al,[12] 2012	8	6	ICA	SW	2.08 (1.21)	CO @12mo	Silk	Rhinoceros[12]	—	—	—	0.56 (0.26)	0.60 (0.20)	0.84
Total†	149	99			3.37 (4.96)				0.27 (0.13)	0.35 (0.20)	0.01‡	0.51 (0.15)	0.41 (0.27)	0.29

Author, year	WSS reduction (SD) S	U	P value	SR reduction (SD) S	U	P value	VCL reduction (SD) S	U	P value	TRT increase (SD) S	U	P value	EL Reduction (SD) S	U	P value	TUT increase (SD) S	U	P value
Paliwal et al,[8] 2018	—	—	—	0.29 (0.02)	0.50 (0.04)	<0.00*	—	—	—	—	—	—	—	—	—	2.55 (0.07)	2.56 (0.02)	0.47
Paliwal et al,[16] 2017	—	—	—	—	—	—	0.62 (0.03)	0.90 (0.10)	<0.00*	—	—	—	0.57 (0.03)	0.89 (0.10)	<0.00*	—	—	—
Mut et al,[13] 2014	0.27 (0.33)	0.17 (0.02)	0.38	0.17 (0.06)	0.27 (0.02)	<0.00*	11.29 (10.14)	6.46 (1.21)	0.2	6.00 (1.49)	3.93 (0.93)	0.00*	—	—	—	—	—	—
Chong et al,[9] 2014	—	—	—	—	—	—	—	—	—	—	—	—	0.02 (0.01)	0.43 (0.11)	<0.00*	—	—	—
Kulcsár et al,[12] 2012	0.42 (0.15)	0.36 (0.04)	0.6	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Total†	0.38 (0.20)	0.41 (0.15)	0.83	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—

*Statistical significance confirmed (p<0.005).
†The total counts for number of aneurysms and number of successful cases have included seven additional studies that were not included in the final meta-analysis due to their limited sample size, and the corresponding hemodynamic parameters are averages of those from studies (n=12) included in the systematic review.
‡Suggestive of statistical significance (p<0.05).

AAV, intra-aneurysmal average velocity; ACOM, anterior communicating artery; AR, aspect ratio; CAV, cavernous; CO, complete occlusion; EL, energy loss; IA, intracranial aneurysm; ICA, internal carotid artery; IR, inflow rate; OPH, ophthalmic; PCOM, posterior communicating artery; S, successful; SR, shear rate; Succ, successful cases; SUP, supraclinoid; SW, side-wall; TRT, transition time; TUT, turnover time; U, unsuccessful; VCL, vortex coreline length; WSS, wall shear stress.

Studies or Subgroups	SMD	95% CIs of SMD	SE	p	Weight (%) Fixed	Weight (%) Random	Forest Plots
I. Inflow Rate							
Paliwal et al., 2018	−12.08	−13.993 to −10.156	0.96		14.01	25.78	
Paliwal et al., 2017	−0.93	−2.100 to 0.244	0.54		44.27	26.51	
Mut et al., 2014	−2.64	−3.839 to −1.450	0.57		39.49	26.47	
Chong et al., 2014	−9.35	−15.268 to −3.437	2.42		2.23	21.24	
Total (fixed effects)	−3.36	−4.070 to −2.641	0.36	<0.001	100.00	100.00	
Total (random effects)	−6.05	−10.865 to −1.225	2.44	**0.01**	100.00	100.00	
Heterogeneity: Q = 109.4345, DF = 3, I^2 = 97.26%, 95% CI for I^2 = (95.19, 98.44), ***p* < 0.0001**							
II. Intra–aneurysmal Mean Velocity							
Paliwal et al., 2018	−8.86	−10.308 to −7.412	0.73		19.23	24.84	
Paliwal et al., 2017	−0.51	−1.637 to 0.625	0.52		37.15	25.28	
Mut et al., 2014	−3.44	−4.807 to −2.065	0.66		23.43	25.00	
Kulcsár et al., 2012	−0.15	−1.885 to 1.590	0.71		20.19	24.88	
Total (fixed effects)	−2.73	−3.358 to −2.095	0.32	<0.001	100.00	100.00	
Total (random effects)	−3.22	−6.985 to 0.537	1.90	0.09	100.00	100.00	
Heterogeneity: Q = 103.3716, DF = 3, I^2 = 97.10%, 95% CI for I^2 = (94.86, 98.36), ***p* < 0.0001**							
III. Energy Loss							
Paliwal et al., 2017	−5.43	−7.841 to −3.015	1.12		61.13	61.13	
Chong et al., 2014	−5.04	−8.464 to −1.608	1.40		38.87	38.87	
Total (fixed effects)	−5.28	−7.092 to −3.459	0.87	<0.001	100.00	100.00	
Total (random effects)	−5.28	−7.092 to −3.459	0.87	<0.001	100.00	100.00	
Heterogeneity: Q = 0.04775, DF = 1, I^2 = 0.00%, 95% CI for I^2 = (0.00, 0.00), p = 0.8270							
IV. Vortex Coreline Length							
Paliwal et al., 2017	−4.33	−6.371 to −2.292	0.94		17.18	48.52	
Mut et al., 2014	0.56	−0.334 to 1.455	0.43		82.82	51.48	
Total (fixed effects)	−0.28	−1.074 to 0.513	0.39	0.48	100.00	100.00	
Total (random effects)	−1.81	−6.772 to 3.145	2.45	0.46	100.00	100.00	
Heterogeneity: Q = 22.2424, DF = 1, I^2 = 95.50%, 95% CI for I^2 = (86.86, 98.46), ***p* <0.0001**							
V. Wall Shear Stress							
Mut et al., 2014	0.36	−0.525 to 1.243	0.43		73.73	73.73	
Kulcsár et al., 2012	0.27	−1.471 to 2.016	0.71		26.27	26.27	
Total (fixed effects)	0.34	−0.411 to 1.083	0.37	0.37	100.00	100.00	
Total (random effects)	0.34	−0.411 to 1.083	0.37	0.37	100.00	100.00	
Heterogeneity: Q = 0.01088, DF = 1, I^2 = 0.00%, 95% CI for I^2 = (0.00, 0.00), p =0.9169							
VI. Shear Rate							
Paliwal et al., 2018	−7.64	−8.917 to −6.369	0.64		38.99	49.77	
Mut et al., 2014	−1.97	−3.031 to −0.902	0.51		61.01	50.23	
Total (fixed effects)	−4.18	−4.973 to −3.387	0.40	<0.001	100.00	100.00	
Total (random effects)	−4.79	−10.420 to 0.836	2.84	0.09	100.00	100.00	
Heterogeneity: Q = 47.9429, DF = 1, I^2 = 97.91%, 95% CI for I^2 = (95.06, 99.12), ***p* < 0.0001**							

Figure 2 Meta-analysis of standardized mean differences (SMD) of six different hemodynamic parameters (I–VI) and clinical treatment outcomes using both the fixed-effects and the random-effects models. The forest plots show SMDs of each of these parameters obtained from both the fixed-effects (upper rhombus) and the random-effects (lower rhombus) models.

treatment, pending further investigation into their diagnostic performance to identify the optimal cut-off thresholds.

Additional flow diversion achievable through enhancement of stent wire density

In addition to deployment of an additional stent, a 'push-and-pull' technique to be used during the stent-releasing process has been promoted to enhance the local wire density. Shapiro et al[24] first demonstrated in benchtop experiments that increased wire density can be attained through longitudinal compaction of a single stent. Damiano et al[22] later reported in a hemodynamic study that compacting a single FD stent may outperform deployment of two stents in producing additional reductions of the IR, AAV, and mean WSS.

The results of our systematic review confirmed that stent compaction and dual-stent deployment could both improve the flow diversion efficacy in terms of further reductions of IR (p<0.006) and AAV (p<0.02), which are both indicative of statistical significance. However, stent compaction did not demonstrate statistically significant further improvement of the TUT (p=0.08), in contrast to the deployment of an additional stent (p=0.02). This suggests that bulk hemodynamic parameters may be more prominently affected by a general increase in the stent wire density whereas localized parameters may be more sensitive to how the specific wire configuration was altered across an aneurysm orifice.

Furthermore, compacting a stent may be inappropriate when a patient has a highly curved recipient artery with an aneurysm

Table 2 Change of hemodynamic parameters (relative to the untreated condition) after deployment of an additional stent or when a single stent was deployed with a compaction technique applied compared with standard deployment of a single stent

	Hemodynamic parameters	No of studies	No of IAs	Mean difference	95% CI of difference	SD	P value
Overlapping	IR reduction (%)	4	7	−14.4	−19.6 to −9.3	5.6	0.0005*
	AAV reduction (%)	6	9	−16.8	−23.5 to −10.1	8.7	0.0004*
	WSS reduction (%)	4	6	−27.3	−31.4 to −23.3	3.9	<0.0001*
	TUT change (%)	2	4	47.0	11.3 to 82.7	22.4	0.0247†
Compaction	IR reduction (%)	4	8	−16.0	−25.4 to −6.7	11.3	0.0051†
	AAV reduction (%)	3	6	−23.3	−38.4 to −8.3	14.4	0.0105†
	TUT change (%)	2	4	58.3	−12.5 to 129.0	44.5	0.0791

*Statistical significance confirmed ($p<0.005$).
†Suggestive of statistical significance ($p<0.05$).
AAV, intra-aneurysmal average velocity; IA, intracranial aneurysm; IR, inflow rate; TUT, turnover time; WSS, wall shear stress.

located at the apex of the curvature. Zhang et al[18] pointed out that, in this circumstance, the stent wires might be pushed into the sac of an aneurysm due to the restoring force acting inside the wires, counter-productively resulting in a lower metal coverage ratio across the aneurysm orifice, causing treatment failure.

It should also be noted that enhancement of wire density through implantation of an additional stent may further impair patency of the side-branch arteries jailed by the implanted device.[25] Moreover, stent compaction or dual-stent deployment may increase the occurrence of post-treatment in-stent thrombosis, even when adequate dual antiplatelet therapy is administered.[26] This is still beyond the capability of numerical simulation to accurately predict. Therefore, although flow diversion can be improved through enhancement of stent wire density, whether these techniques can be applied must still take into consideration the patient-specific vascular conditions.

Uncertainties in virtual stent deployment and hemodynamic simulation

The simulation strategies reported in our surveyed studies were based on various combinations of modeling techniques, with few of them being able to be rigorously validated against clinical practice.

The primary factor limiting the fidelity of virtual stent deployment is that the wire configuration of stents deployed in vivo depends substantially on the skill, experience, and predilection of the treating clinicians, especially when a patient exhibits variation or tortuosity in vascular geometry, or for aneurysms with uncommon morphology in difficult-to-approach locations. Even under ideal vascular conditions, the landing position of the stent, the unsheathing process, and the pathway along which a stent is released can be quite different from the scenario modeled by virtual stent deployment.

In addition, only a limited number of studies have evaluated the local microscopic properties (eg, porosity and pore density) of stent wires at the aneurysm orifice. Such data would provide a better understanding of the efficacy of the stent in terms of aneurysmal IR and EL reduction in relation to specific vascular geometries with variations in diameter and curvature of the parent artery.

For analysis of the intra-aneurysmal hemodynamics, the key factors that may be detrimental to simulation accuracy are the adoption of generic vascular boundary conditions (eg, for flow rate and pressure) or the prescription of unphysiological velocity or pressure profiles at vascular openings. In most hemodynamic analyses, generalized inlet flow rates and outlet pressures—rather than patient-specific hemodynamic conditions—were

assumed. This may cause substantial under- or over-estimation of the actual flow diversion produced by a stent, as the aneurysmal inflow was reported to be linearly proportional to the strength of flow in the parent artery.[27 28] A recent study by Najafi et al[29] suggested that adoption of a cycle-average internal carotid artery flow rate derived from patient-specific phase-contrast MRI may help reduce error.

Furthermore, various assumptions were applied in hemodynamic simulation to simplify the description of blood flow (eg, assumption of a Newtonian fluid with constant viscosity and density). Saqr et al[30] recently concluded that the assumption of a Newtonian fluid may be invalid, especially when parameters quantifying the flow close to the vascular wall (eg, WSS) are to be assessed. Other simplifications include assuming the vascular wall to be rigid (ie, the wall would not deform over a cardiac cycle or even after implantation of a FD stent). However, Bouillot et al[31] have recently shown that deformation of the parent artery can be substantial after stent implantation, and Tupin et al[32] reported that the intra-aneurysmal flow pattern may be markedly affected by the compliance of the wall.

All these uncertainties and assumptions may lead to discrepancies between the in vivo aneurysmal hemodynamics and the simulated ones, yet the current imaging techniques lack the capability to capture the subtle in vivo flow patterns within an aneurysm, which could have been used as gold standard to regulate hemodynamic simulation. As a future direction, comprehensive validation and standardization of the protocols for virtual stent deployment and hemodynamic simulation would be useful, after which cogent results of virtual treatment may be used by clinicians in assessing the outcomes prior to real flow diversion treatment.

Limitations

Pursuant to the source studies, the present review has several limitations. The major one is that, although we have surveyed almost all studies ever published that reported post-treatment hemodynamics and aneurysm occlusion status, only five studies met our inclusion criteria for meta-analysis and even then most of the included studies had relatively small sample sizes. The reason is that performing virtual stent deployment and the subsequent hemodynamic analysis demands cutting-edge simulation skills and has a high resource intensity in terms of both manual interaction and computation time. Whether the conclusions drawn from our meta-analysis still hold for a larger group of aneurysm samples deserves further investigation.

The second inherent limitation is that the timepoints at which aneurysm occlusion status was observed varied from 3

to 12 months across the studies we included. Different research groups determined distinct endpoints following their local protocols for postoperative follow-ups. Although the criterion for classifying a treatment as successful was consistently specified as complete occlusion, lack of consistency among the specified observation times may potentially lead to misclassification of some treatment outcomes according to any single standard, thereby clouding exploration of the correlation between the hemodynamic and clinical outcomes.

Another limitation is that we have included two studies from the same group in our meta-analysis, which may potentially lead to duplicates of the included data. However, these two studies reported and focused on different hemodynamic parameters, and had different timepoints at which the status of aneurysm occlusion was assessed. Moreover, we failed to identify any overlapping cases through close examination of the aneurysm geometries.

CONCLUSION

Clinical outcomes following flow diversion treatment were found to be associated with the simulated aneurysm hemodynamics.

Differences in the post-treatment IR reduction (SMD -6.05, 95% CI -10.87 to -1.23, p=0.01) and EL reduction (SMD -5.28, 95% CI -7.09 to -3.46, p<0.001) between successfully and unsuccessfully treated patients were indicative of statistical significance, in contrast to the AAV (p=0.09), mean WSS (p=0.37), SR (p=0.09), and VCL (p=0.46). Deployment of stents with a compaction technique may yield additional enhancement of flow diversion comparable to that achieved through deployment of an additional stent.

Aneurysmal IR and EL have shown promise in discriminating between favorable and unfavorable patient outcomes following flow diversion treatments, pending future large studies into the diagnostic performance to establish the optimal cut-off thresholds.

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