# The Woven EndoBridge (WEB) for Endovascular Therapy of Intracranial Aneurysms: Update of a Systematic Review with Meta-Analysis

Running Title: **WEB Therapy for Intracranial Aneurysms**

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**ABSTRACT**

**Objectives:** Endovascular treatment of wide-neck intracranial aneurysms (IAs) is challenging, especially in bifurcation location. The intra-saccular flow-disruptor Woven EndoBridge (WEB) offers a new concept of endovascular therapy for wide-neck IAs. We performed an update of a systematic review aimed to report the feasibility, effectiveness and safety of WEB device therapy.

**Patients and Methods:** A systematic review was conducted using several electronic databases (including PUBMED and EMBASE), and searching for studies published between October 2015 and December 2017 (those published between January 2010 and September 2015 were searched in our initial systematic review). Outcomes were: success of implantation, peri-procedural and procedure-related complications, mortality, and adequate occlusion (complete occlusion or neck remnant).

**Results:** In total (initial review + update), 12 uncontrolled case-series studies were included, reporting outcomes for 940 patients (68.6% female; mean age, 57 years) harboring 962 IAs. Most IAs were wide-neck bifurcation aneurysms (75%-100%), mainly at middle cerebral artery (37%) and anterior communicating artery (24.6%). Feasibility was 97% (95% confidence interval [CI], 95%-99%), and 9% (95%CI, 5%-14%) of cases required additional treatment. There were 14% (95%CI, 9%-19%) of peri-procedural complications. After a median clinical follow-up of 7 months, mortality was 5% (95CI%, 1%-10%) and was higher in series with larger proportions of ruptured IAs. At last angiographic follow-up (median, 7 months; range, 3-27.9 months), adequate occlusion rate was 81% (95%CI, 73%-88%).

**Conclusion:** Although WEB showed high rates of adequate aneurysm occlusion at mid-term, procedure-related complications and mortality rates were not negligible. Future studies should compare the WEB device with other treatment options.

## 1. INTRODUCTION

While endovascular therapy has become the first-line approach for intracranial aneurysms (IAs) over surgical clipping, management of wide-neck IAs, especially in bifurcating locations remains challenging using regular coiling [1, 2]. Other endovascular methods, such as complex stenting, double balloon-assisted coiling or flow diverters have been tested and were shown to improve treatment feasibility. However, these approaches are technically complicated and hampered by non-negligible morbidity and mortality [3-5]. The Woven EndoBridge device (WEB; Sequent Medical, Aliso Viejo, California, USA) is thought to overcome these limitations and improve the safety of complex endovascular techniques. Initial studies showed favorable safety and effectiveness profiles; however, most of these were retrospective, single center studies [6, 7].

We have previously published the first systematic review on the WEB, accounting for existing data up to September 2015 [8]. To include newly published studies, we present an update of our systematic review and meta-analysis aimed to assess the feasibility, safety and effectiveness of the WEB device for endovascular therapy of IAs.

## 2. PATIENTS AND METHODS

This review was reported according to the "Preferred Reporting Items for Systematic Reviews and Meta-analyses" (PRISMA) guidelines [9].

### 2.1 Eligibility Criteria

We included any study design, without restriction of language, except commentaries, letters, technical notes, case reports and case series with fewer than 10 patients. The population of interest was patients with bifurcation aneurysms, either ruptured or unruptured, with any aneurysm anatomic characteristics. The intervention was endovascular treatment with any of the WEB devices (WEB-DL, WEB-SL, or WEB-SLS). Any potential comparators were considered.

We were interested in the following outcomes: (1) Technical success and implantation failure rates, as evaluated and published in each study according to authors' definition of a successful or failed implantation, including additional treatments required to achieve adequate occlusion; (2) Adequacy of angiographic aneurysm occlusion, defined according to the scale chosen by study

authors. As to-date there is no standard scale to measure the occlusion adequacy in WEB treated aneurysms, we defined "adequate occlusion" as either complete occlusion or neck remnant (a definition applied by most authors); (3) Safety outcomes which included mortality and complications as defined by each study authors, assessed at last clinical follow-up. Complications were divided into peri-procedural complications and non-procedural related complications, as defined by the authors.

### 2.2 Search Strategy

Studies were searched in several electronic databases (EMBASE, PUBMED, ClinicalTrials.gov, Database of Abstracts of Reviews of Effectiveness and Health Technology Assessment databases). In our first systematic review, we searched for studies published between January 2010 and September 2015 [8]. Here, our updated search period was October 2015 to December 2017. A combination of free-text and thesaurus terms relevant to 'WEB device' and 'Intracranial Aneurysms' were used to identify literature. Our search equations are available upon request. Reference lists of relevant studies were scanned to identify additional citations. One author (X.A.) performed the literature search.

### 2.3 Study Selection

Two reviewers (N.T. & U.S.G.) independently screened all titles/abstracts and full-text of potentially relevant citations was assessed. Disagreements were discussed and resolved through consensus or recourse to a third reviewer (B.G.).

During the process, two reviewers (N.T. & X.A.) screened studies with potential overlap in patient populations, on the basis of: author names, participating centers and study time frame. When an overlapping cohort was identified, only the most comprehensive and latest report was included in the final analysis. If the reviewers were unable to verify the uniqueness of participating patients, the paper was excluded from final analysis.

Study selection flow and exclusion reasons are documented in the PRISMA flow-chart (**Figure 1**).

### 2.4 Data extraction and Quality Assessment

Two reviewers (N.T. & U.S.G.) independently extracted relevant data using an *a priori* defined pre-piloted extraction sheet. Data extracted included study author or study name, originating country, sample size, patient characteristics, IA characteristics, feasibility, effectiveness, and safety outcomes of interest. The data extracted were cross-checked and any disagreements were resolved by discussion or recourse to another reviewer (B.G. or X.A).

Two reviewers (N.T. & U.S.G.) independently assessed the quality of included studies. Since all included studies were uncontrolled case series, these were assessed using the "Quality Assessment Tool for Case Series Studies" published by the National Institutes of Health [10]. Studies were rated as poor, fair, or good. Final quality rating for each study was reached by consensus between the two reviewers.

### 2.5 Data synthesis and analysis

Study and population characteristics were summarised in tables and text.

We built 95% confidence intervals (CIs) of the estimates using the Wilson method and calculated a pooled estimate for proportions with a random-effect model to account for the heterogeneity across studies using the *metaprop* command on STATA14 (Statacorp LP, College Station TX, USA) [11]. In all analyses, we assessed heterogeneity of findings using the Cochran's *Q* test (P value threshold of 0.05) and calculating the $I^2$ statistic. For clinical and angiographic outcomes, we attempted to detect bias using funnel plot and undertook the Egger's test [12].

We considered exploratory analyses stratifying the outcomes according to study quality rating, presence of an adjudication committee, presence of an independent core laboratory, type of WEB device used. We also considered undertaking exploratory random-effect meta-regressions to evaluate the impact of the proportion of ruptured intracranial aneurysms on complications and mortality or to evaluate the impact of the aneurysm location on complications.

## 3. RESULTS

Of the 247 records identified from our updated search and screened at title/abstract level, 55 were examined for full-text, of which eight articles [13-20] corresponding to nine primary studies were included (**Figure 1**). One of these [20] included a pooled data analysis of three primary studies (WEBCAST and the French observatory, which were included in our initial review [21, 22]; and WEBCAST 2 [17]).

In addition, three studies were kept from our initial review [23-25], while one by Behme et al. [26] was eventually excluded because we concluded that some of the patients from the latter study were likely to be reported in other case series included in our update. Last, we identified an assessment report from the French Health Technology Assessment body on the WEB device, which did not contain further primary research data [27].

In total, accounting for our initial review and our update, we selected a total of 12 primary studies with a total of 940 patients (68.6% female; mean age, 57 years) harboring 962 IAs. Included studies did not provide individual patient data, and therefore no individual patient-data meta-analysis could be undertaken.

### 3.1 Characteristics of included studies

All studies were uncontrolled case-series. Seven were prospective [13, 14, 17, 18, 21, 22, 24], four were retrospective [15, 19, 23, 25] and one combined retrospective and prospective data [16]. Eleven studies were conducted in Europe, and one study included US patients [14]. Three studies were single-center while nine were multicenter (2 to 27 centers).

Baseline characteristics are summarized in **Supplemental Table 1**. The range of sample sizes was 22 to 150 patients. The most common aneurysm location was the middle cerebral artery bifurcation (356/962; 37%), followed by anterior communicating artery (237/962; 24.6%), basilar artery (214/962; 22.2%), and internal carotid artery (76/962; 7.9%). The aneurysmal neck was ≥4 mm in 75% to 100% of cases, and aneurysms had a size of <10 mm in long axis diameter in 35% to 96% of cases. Two studies exclusively included patients with ruptured aneurysms, while in other studies, the proportion of patients with ruptured aneurysms was less than 50%.

### 3.2 Feasibility of WEB Placement

The WEB device was successfully placed in 97% (95%CI 95%-99%) of cases (**Figure 2**). We could not compare placement feasibility, or any other outcome with the generation of WEB device used, as most studies did not report WEB generation-specific results. The proportion of patients requiring the use of additional devices in the initial procedure was 10% (95%CI 5%-15%) and highly heterogeneous across studies ($I^2$=76.38%). These treatments included additional coiling or stenting when required (large aneurysm, WEB protrusion, etc.).

### 3.3 Safety Outcomes

The median clinical follow-up was 7 months (range, 1-13.8 months). The proportion of peri-procedural complications was 14% (95%CI, 9%-19%) with high heterogeneity ($I^2$=76.87%) across studies (**Figure 2**). The majority of peri-procedural complications (91/130; 70%) were thrombo-embolic, and 14/130 (10.8%) were reported as procedure-related hemorrhage. Other complications (IA rupture, brain edema etc.) were less common.

Of overall complications, procedure-related and non-procedure related complication rates were 14% (95%CI, 9%-19%) and 0% (95%CI, 0%-1%), respectively. We found no correlation between the proportion of ruptured IAs within case-series and peri-procedural or procedure-related complications. Similarly, meta-regressions did not show correlation between aneurysmal location and the rate of complications (both procedure-related and over peri-procedural).

For mortality at last follow-up in the WEBCAST, WEBCAST 2 and French observatory studies, we used data from the pooled analysis [20] and not those reported in each individual study, as the pooled analysis paper reported a longer patient follow-up compared to each individual study.

At last clinical follow-up, mortality was 5% (95%CI, 1%-10%) (**Figure 2**) and was increased in studies with higher proportions of patients harboring ruptured IAs.

### 3.4 Effectiveness Outcomes

Angiographic evaluation was performed at a median of 7 months (range, 3-27.9 months). Outcomes for the WEBCAST, WEBCAST 2 and French observatory studies were also extracted from the pooled analysis [20]. The proportion of adequate occlusion was 81% (95%CI 73%-88%), with no significant differences according to the duration of follow-up (**Figure 2**).

### 3.5 Study Quality Assessment

Overall, quality assessment was performed for 12 studies. All studies were uncontrolled case-series. The quality rating for five studies was considered "good", one study was rated as "poor" while the other six where considered "adequate". Owing to the small number of articles, we found irrelevant to undertake exploratory sub-group analyses according to study ratings.

The main study quality limitations were the lack of clear description of the intervention method, no proper statistical analysis and no clear definition on the patient selection criteria. Most studies also did not include an adequate follow-up period. This resulted in large variability in data reporting, leading to a significant risk of bias in most studies. There was also a large heterogeneity in terms of methods for the assessment of outcomes in all studies. Nine of the studies had a central core laboratory or independent reader for angiographic analysis, and only five studies were conducted with an adjudication committee for adverse events, using various grading scores for anatomic evaluation and occlusion adequacy. We found funnel plot asymmetry for both peri-procedural and procedure-related complications which is likely to be related to the reported heterogeneity of these outcomes, rather than a risk of publication bias (**Supplemental Figure 1**).

## 4. DISCUSSION

Based on a total of 940 patients harboring 962 IAs, our update of a systematic review with meta-analysis provides a comprehensive view of the effectiveness and safety of WEB therapy. Compared to our previous work [8], we found nine newly published studies on WEB, which confirms the relevance of this update.

We found high rates of successful WEB implantation, with little heterogeneity across studies. Adequate occlusion was achieved in 81% of cases, despite unfavorable anatomical IAs presentation in most case-series. However, the definition of "adequate occlusion" varied between studies, limiting the ability to directly compare this outcome across studies. Longer follow-up is required to better assess the natural history of such neck remnants, especially with the risk of WEB compression over time [28]. Moreover, aneurysm occlusion success was categorized according to different scales in each study, with unknown reproducibility. These results, however, are limited by lack of a consensus in assessment and follow-up of WEB occluded aneurysms. Therefore, it is clear that a more accurate scoring system is required in order to improve reporting quality in future studies.

We found an overall complication rate of 14%, with large heterogeneity across studies. This may be partially explained by the large inconsistency in the definition of such "complications" by each author, which limits the ability to directly compare the rates of complications across studies. Another explanation could be the absence of an adjudication committee to analyze complications in most studies. Despite substantial rates of complication after WEB treatment, mortality was relatively low (5%; 95%CI 1%-10%), and closely related to the rate of ruptured aneurysms in each study. Although this rate may be favorable compared to some of the other endovascular techniques, other techniques have better safety profiles than the WEB. For example, complex stenting is associated with 10% of procedure-related morbidity and 1% mortality [29].

When taking into account safety outcomes reported with other treatment techniques such as coiling or stenting of IAs, it becomes even more evident that using WEB is not yet the optimal treatment. Further studies with appropriate design on the WEB device are warranted to identify the specific indications in which it will carry the highest clinical benefit.

### 4.1 Overall Perspective

The previously discussed methodological limitations in the included studies are widespread in the field of interventional neuroradiology, and specifically in clinical studies on novel devices such as the WEB. There is no uniform scoring system to assess adequacy of aneurysm occlusion, and long-term studies have not yet been published addressing the evolution of WEB treated patient with a neck remnant. Some authors have recently reported the risk of WEB compression across time. These initial results show that long-term follow up data on patients treated with the WEB device is clearly required to better evaluate its long-term efficacy and safety.

Further limitations were the heterogeneity in patient selection criteria and peri-procedural/late complication definitions. All the aforementioned inconsistencies result in large heterogeneity between studies, which in turn restricts the ability of a clinician to compare published data when deciding on the use a specific device. The lack of direct comparative data, along with indirect comparisons showing that WEB has similar success and complication rates to other devices, limits the availably of the WEB device. In this context, in March 2016 the French Health Technology Assessment body rejected the reimbursement of WEB devices due to insufficient comparative data [27].

As a first step to gain more evidence regarding the WEB device, we suggest the implementation of an international registry by the WEB manufacturer. The registry would include all the newly treated patients with WEB devices worldwide, and would prospectively collect feasibility, effectiveness and safety outcomes. This registry could be made publicly available and enable a better informed clinical decision-making.

### 4.2 Where do we go from here?

To date, several devices are available for endovascular treatment of wide-neck IAs (**Supplemental Table 2**). Based on the existing gap in evidence, a head-to-head comparison of WEB with existing treatment methods (endovascular or surgical) should be encouraged using an appropriate study design, ideally a randomized controlled trial (RCT). We recommend performing a future RCT to evaluate all various devices, and in turn compare those with detachable coils, which are the current standard treatment method. Furthermore, it may be prudent in the future to implement uniform study protocols as widely as possible, to analyze the performance of any new device entering the field. This should include all the relevant parameters requiring evaluation (i.e. patient selection, grading scales, complications definitions, follow up period, anti-platelet therapy etc.), similar to standards implemented in other medical fields. Such protocols would enable the data acquired from each procedure to contribute more effectively and accurately to the scientific evaluation of the device, and eventually contribute to a better clinical decision-making.
Before more evidence becomes available, our results can be seen as an updated summary of the benefits / risks balance for the WEB.

### 4.3 Limitations

This study has some limitations. The vast majority of included studies were retrospective case-series, without independent core laboratory for angiographic images analysis. Even the largest multicenter trials, such as WEBCAST, WEBCAST 2, the French observatory and WEB-IT, were uncontrolled prospective studies, and therefore did not employ proper patient randomization or comparison to other devices. In order to ensure a relevant study selection and avoid inclusion of studies with overlap in the treated population, we have employed a rigorous screening process which was absent in other recent published reviews. In our review, we have included only studies reporting unique patients' results, while omitting any study with potentially

duplicate cohorts. This exclusion method resulted in resulted in removal of studies originating from centers reporting WEB experience in multiple studies, without specifically addressing the question whether their cohorts were indeed unique.

## 5. CONCLUSION

Our data show that the use of the WEB for endovascular therapy of wide-neck bifurcation IAs is technically successful in most cases, and results in ~80% adequate occlusion at median follow-up of 7 months. The safety of the WEB device will need to be confirmed by further studies, ideally with direct comparison to other devices, especially given the non-negligible rates of peri-procedural complications and mortality.

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**Figure Legends**

**Fig 1** PRISMA flow chart

**Fig 2 top left** Additional treatment requirement

**Fig 2 top right** Peri-procedural complications, sorted by rate of ruptured IA

**Fig 2 bottom left** Mortality at last clinical follow-up, sorted by rate of ruptured IA

**Fig 2 bottom right** Adequate occlusion at last angiographic follow-up, divided by central corelab evaluation

**Supplemental Fig 1** Funnel plots for publication bias analysis

**Top left –** Funnel plot asymmetry for peri-procedural complications

**Top right –** Funnel plot asymmetry for procedural related complications