### A SYSTEMATIC REVIEW AND META-ANALYSIS OF THE EFFECTIVENESS OF SURGICAL DECOMPRESSION IN TREATING PATIENTS WITH MALIGNANT MIDDLE CEREBRAL ARTERY INFARCTION

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### Abbreviations

ABI	Acute Brain Injury
BMT	Best Medical Therapy
CI	Confidence Interval
CSF	Cerebrospinal fluid
DC	Decompressive craniectomy
GCS	Glasgow Coma Scale
GOS	Glasgow Outcome Scale
GOS-E	Extended Glasgow Outcome Scale
ICHn	Intracranial hypertension
ICP	Intracranial pressure
IV	Inverse variance
MCI	Malignant middle-cerebral-artery infarction
mRS	Modified Rankin Scale
NOS	Newcastle- Ottawa Scale
NRT	Non-randomised trials
OR	Odds ratio
РІСО	population, intervention, control, and outcomes
QoL	Quality of Life
RCT	Randomised controlled trials
RoB	Risk of bias

#### ABSTRACT

**Background** Malignant infarction of the middle-cerebral-artery (MCI) is life threatening. It is associated with a mortality as high as 80% and survival often at the expense of serious disability. Limited success of medical therapies has resulted in decompressive craniectomy (DC) being increasingly used as a treatment for MCI, though evidence of its efficacy is inconclusive. In this study, the efficacy of DC in improving survival, or survival free of severe disability, was assessed.

**Methods** A meta-analysis was performed to approximate the efficacy of DC for treating MCI, considering age and time-to-surgery. A systematic literature review was conducted on Medline, Embase and Cochrane library databases to 01 August 2018. Death and severe disability at 3, 6, 12 and 36 months follow-up were assessed, comparing best medical therapy with DC.

**Results** 18 studies were eligible for inclusion and represented 987 individuals who received DC. Nine of these were RCTs (n=374 DC). Early DC (<48h from onset of stroke) reduced mortality (OR=0.18, 95%CI=0.11, 0.29; P<0.00001) but not unfavourable outcome (modified Rankin Scale (mRS)>4) (OR=1.38, 95%CI=0.47, 4.11; P=0.56) at 12 months follow-up. This survival benefit was maintained regardless of age.

**Conclusion** Early DC reduces mortality but does not appear to improve favourable outcomes in patients aged younger or older than 60 years following MCI. RCTs incorporating quality of life assessments are warranted for MCI patients, in addition to defining the optimal timing and benefits of DC in older patients.

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#### **INTRODUCTION**

Acute brain injury (ABI), defined as injury to the brain that occurs after birth, is one of the leading causes of death and disability in adults worldwide. <sup>1,2</sup> Malignant stroke is a common cause of ABI. In a subgroup of patients with supra-tentorial stroke (approximately 1-10%), malignant middle cerebral artery infarctions (MCI) can occur. <sup>3</sup> These patients develop space-occupying brain oedema resulting in raised intracranial pressure (ICP), with subsequent ischaemic cell death and brain herniation. The prognosis is poor, with mortality as high as 70-80% and majority of survivors left with severe disabilities. <sup>4,5</sup>

The poor outcome is, at least in part, attributed to intracranial hypertension (ICHn), defined as ICP greater than 15-20mmHg. <sup>6</sup> Conventional treatment worldwide is aimed at reducing ICP using head elevation, osmotic agents, controlled hyperventilation, hypothermia and sedatives.<sup>7</sup> Once brain swelling is sufficient to produce clinical and radiological signs, however, case-fatality is higher, despite optimal medical treatment. <sup>8,9</sup> Decompressive craniectomy (DC), with removal of cranium and subsequent durotomy/duroplasty, is an aggressive approach shown to reduce ICP and improve blood flow to ischaemic tissue in patients with refractory ICHn. <sup>10,11</sup>

Although DC is effective in reducing ICP it is accompanied by a myriad of non-trivial complications. <sup>12</sup> More importantly, there is a concern that survivors suffer permanent severe disability. A pooled analysis of randomised controlled trials (RCTs) showed that DC significantly reduced mortality and improved favourable outcome defined as modified Rankin scale (mRS)  $\leq$  3 in patients with MCI. <sup>13</sup> However, the inclusion of HAMLET trial showed a non-significant benefit associated with DC (mRS  $\leq$  4). <sup>14</sup> Moreover, important questions regarding the effect of patient age, timing of surgery and the issue of defining a

'favourable' outcome remain unclear.

The present systematic review and meta-analysis of all available studies aimed to establish the effectiveness of DC on mortality and associated long-term outcomes in patients following MCI, with special consideration of patient age and optimum timing for surgery.

#### METHODS

A systematic literature review was conducted on MEDLINE, EMBASE, Cochrane library database and Controlled Trials metaRegister to define the role of DC in patients with MCI. Details of the search strategies that incorporated search criteria used by a previous Cochrane review <sup>14</sup> are given in Supplementary File 1. The last search update was 1<sup>st</sup> of August 2018. The titles, abstracts and keywords of relevant articles were examined to assess for eligibility, followed by screening of reference lists from retrieved articles to identify additional studies. The study selection process was performed according to the guidelines of PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) and documented using a PRISMA flow diagram (Figure 1). <sup>15</sup>

#### **Study Eligibility**

All clinical trials were eligible for inclusion, with no restriction on language or time of publication. The inclusion criteria were: 1) studies including adult patients over 18 years of age with MCI. MCI was defined as patients with acute ischaemic infarction with space-occupying cerebral oedema, as evident on radiology; 2) studies comparing DC to medical treatment alone as control. Medical treatment or best medical therapy (BMT) was defined as non-surgical therapies to control ICP such as hyperosmolar solutions, sedation and paralysis, hyperventilation, barbiturates, and moderate hypothermia. Cerebrospinal fluid (CSF) drainage in patients with ICP monitoring was also regarded as a medical therapy <sup>6</sup>; 3)

primary outcomes assessed were death and disability defined by mRS or Glasgow outcome scale (GOS)/ extended-GOS (GOS-E) (if mRS score was unavailable), or a description of level of independence, at 3, 6, 12 or 36 months follow-up.

Exclusion criteria were: 1) no comparison with medical treatment group; 2) unavailability of outcome data in an extractable format such as odds ratios (OR), relative risks, or results from which these could be calculated, at 3, 6, 12, or 36 months follow-up; and 3) reviews, meta-analysis, guidelines, case reports, letters to editor, comments, duplicate studies.

#### **Data Extraction**

The following data were extracted and tabulated from MCI studies into standardised data extraction forms by two authors independently: study design, sample size, patient eligibility criteria, patient demographics such as age and gender, surgical procedure, National Institute of Health Stroke Scale (NIHSS) score, vascular territories and site of infarction, presence of preoperative clinical signs of herniation, time to surgical decompression, neurological outcomes as measured by mRS or GOS, mortality rates and duration of follow-up. Discrepancies were resolved by discussion between all authors.

#### Quality assessment

Each study underwent a quality assessment by two authors independently. For the RCTs the Cochrane Collaboration's risk of bias (RoB) tool <sup>16</sup> was used to assess selection bias, attrition bias, performance bias, detection bias, and reporting bias. The limitation of NRTs falling short of full randomisation when allocating individuals to treatment group is recognised, and a careful assessment of RoB in NRT methodology was conducted. In particular, assessment

of selection bias, bias due to confounding, and bias in measurement of interventions, was made using a modified version of Newcastle-Ottawa scale (NOS).<sup>17</sup>

#### Outcome

The primary outcome measures evaluated in this meta-analysis were: 1) death at 3 months, 6 months, 12 months and 36 months for MCI patients undergoing DC or BMT, and 2) unfavourable outcome defined as mRS score of >4. <sup>18</sup>. Conventionally, an mRS score of 4 is included in the unfavourable outcome category and defines moderately severe disability where patients require assistance with walking and attending own bodily needs. An mRS of 5 indicates severe disability; bedridden, incontinent, requiring nursing care and attention. Given that survival following MCI with no or slight disability is rare, investigators of recent RCTs include an mRS of 4 in the favourable outcome category. <sup>19</sup> Thus, data processed in the present study reflects this change for purposes of standardisation.

#### Statistical analysis

A summary of dichotomous outcome data in the form of odds ratios (ORs) and their corresponding 95% confidence intervals (CIs) were calculated. These were combined by a random effects meta-analysis model using the inverse variance (IV) method for pooled OR, followed by the Z-test to evaluate statistical significance (a p-value of less than 0.05 was considered statistically significant). The heterogeneity between studies was assessed using Chi-squared statistical test and I<sup>2</sup> statistic, where a p<0.10 was considered to be statistically significant. I<sup>2</sup> values up to 60% referred to moderate heterogeneity. <sup>20</sup> Sensitivity analyses were performed to investigate heterogeneity for all statistically significant findings. Assessment of publication bias was conducted by qualitative evaluation of funnel plots for asymmetry. All statistical analyses were performed using Review Manager 5.3 (RevMan) (Nordic Cochrane Centre) and reviewed by an information data analyst (HW).

#### RESULTS

Figure 1 presents the process from study identification (24,950 records) to selection. Of the 24,950 records identified initially, the majority were excluded because they were reviews, case reports, duplicates, comments or irrelevant patient meet our population, intervention, control, and outcomes (PICO) criteria. Further, full texts were analysed and 18 studies comprising of nine RCTs and nine NRTs satisfied our inclusion criteria. These included 497 patients in the surgery group and 486 patients in the conservative group. Of these nine were RCTs (379 patients) and nine were NRTs with (613 patients). The main study characteristics are summarised in Table 1.

Assessments for RoB in nine RCTs and nine NRTs are summarised in Supplementary Table S1 and S2. Briefly, randomisation methods were adequately described in eight studies and allocation concealment in two studies. The main issues with RCTs were in reference to lack of allocation concealment, blinding of outcome assessment, and early termination of trials due to observation of large effects early. <sup>12,13,19,21</sup> Only 12 patients in the MCI studies <sup>19,22,23</sup> were lost to follow up. Therefore, no attrition adjustments were required. The assessment of RoB in NRTs showed minimal risk of bias in all studies (>6/9 points on the Newcastle-Ottawa Scale).

#### **Decompressive Craniectomy in Malignant Cerebral Infarction.**

#### Primary outcome: death at the end of follow-up

Figure 2a presents a forest plot showing the pooled results of 18 studies for risk of death associated with DC versus BMT in patients with MCI. The pooled results of five studies at 3

months (OR 0.17 95%CI 0.07-0.44; p=0.0002;  $I^2$ =40%), 11 studies at 6 months (OR 0.25 95%CI 0.14-0.43; p<0.00001;  $I^2$ =54%), eight studies at 12 months (OR 0.18 95%CI 0.11-0.29; p<0.00001;  $I^2$ = 0%), and one study at 36 months (OR 0.21 95%CI 0.07-0.61); p = 0.004) suggest a statistically significant association between DC and reduced risk of death.

#### Primary outcome measure: unfavourable outcome

A forest plot showing the pooled results for risk of unfavourable outcome (defined as mRS =5) associated with DC versus BMT in patients with MCI is shown in Figure 2b. The pooled results of three studies at 3 months (OR 0.53 95%CI 0.19-1.46; p = 0.22;  $I^2 = 0$ ; p = 0.22), eight studies at 6 months (OR 1.03 95%CI 0.43-2.47; p = 0.94;  $I^2 = 58\%$ ), and seven studies at 12 months (OR 1.38 95%CI 0.47-4.11; p = 0.56;  $I^2 = 39\%$ ) suggested there was no significant difference between DC and BMT in terms of proportion of survivors with an unfavourable outcome. One study at 3 years also reflected this trend.

#### Subgroup analysis of outcomes at 6 months: age <60 versus age >60 years

Figure 3 presents the subgroup analysis, stratified by age. DC significantly reduced mortality in younger patients (OR 0.28 95% CI 0.15, 0.54; p=0.0001;  $I^2=12\%$ ) and older patients OR 0.14 95%CI 0.07, 0.28; p<0.00001; I2 10%) at 6 months follow-up. No significant difference in unfavourable outcome was found in younger (OR 0.99 95%CI 0.18,5.53; p=0.99;  $I^2=$ 61%) or older patients (OR 0.66 95%CI 0.24, 1.85; p=0.43;  $I^2=0\%$ ).

# Subgroup analysis of outcomes associated with early (<48hours) versus late DC (>48 hours)

Table 2 presents the subgroup analysis, stratified by timing of DC. Early DC (<48 hours) significantly reduced mortality at 3 months follow up (OR 0.10, 95%CI 0.04, 0.23,

p<0.00001), 6 months follow up (OR 0.22 95%CI 0.13, 0.39, p<0.00001), 12 months followup (OR 0.15, 95%CI 0.09, 0.26, p<0.00001), and 3 years follow-up (OR 0.09 95%CI 0.02, 0.40, p=0.002). However, early DC did not demonstrate a significant decrease in proportion of patients with an unfavourable outcome at any of the follow up periods. DC performed after 48 hours following MCI was not associated with improved outcomes at any of the follow up periods.

# Heterogeneity and sensitivity analyses for mortality and unfavourable outcome in MCI patients

A sensitivity analysis of the MCI studies was performed to investigate the heterogeneous results at 6 months for mortality ( $I^2 = 54\%$ ) and unfavourable outcome ( $I^2 = 58\%$ ) (Table 3). Exclusion of NRTs resulted in reduction of heterogeneity of pooled results for both mortality ( $I^2 = 18\%$ ) and unfavourable outcome ( $I^2 = 0\%$ ) to acceptable levels.

#### Assessment of publication bias

Assessment of publication bias was carried out using funnel plots. The OR were plotted on a logarithmic scale to ensure that the results of same magnitude but opposite directions were spaced equidistant from 1.0. The funnel plots did not demonstrate any obvious asymmetry (Figure 4).

#### DISCUSSION

Evidence from eight studies in our pooled analysis demonstrates a significant survival advantage associated with DC in patients of all ages, when performed within 48 hours of onset of stroke. However, early DC may not reduce poor functional outcome in survivors, and DC performed after this time may not reduce mortality or unfavourable functional outcome.

This present analysis included a larger number of RCTs than previous meta-analyses that showed DC improved survival and functional outcome (mRS  $\leq$  3) in patients with MCI but had a non-significant increase in proportion survivors with a favourable outcome defined as mRS  $\leq$  4. <sup>13,24</sup> Moreover, the definition of unfavourable outcome in this study (mRS > 4) was consistent with recent trials. <sup>13,16,25</sup> Although an mRS of 4 is usually identified as an unfavourable outcome, it is argued that considering the severity of a condition like MCI, recovery back to an mRS score of 1 or 2 is highly unlikely. Thus, we included an mRS of 4 in the favourable outcome category, with results showing that early DC significantly reduced mortality but not unfavourable outcome at the end of follow-up.

Importantly, outcome definition by researchers based on scales with a strong emphasis on motor functions may not reflect what is acceptable to the patient. <sup>27</sup> Thus, a more appropriate approach may involve conducting QoL assessments. A recent systematic review of QoL of patients following DC reported that most disabled patients (mRS >3) and carers were satisfied with their life and would opt to have the procedure again. <sup>28,29</sup> In addition, an analysis of quality-adjusted life-years (QALYS) in patients with MCI, reported more QALYs achieved with DC compared to BMT. <sup>30</sup> QoL assessments were lacking and of poor quality in the included studies. In addition, the QoL assessments in included RCTs were limited to patients that did not suffer from significant aphasia and neurological deficits. <sup>13,19,21,21</sup> Future studies that consider QoL and psychological states of patients are therefore warranted.

The subgroup analysis stratified by age demonstrated a survival advantage in all age groups

but did not find a significant association between DC and poor functional outcome. Previous meta-analyses have suggested age to be a strong predictor of poor functional outcome (mRS $\geq$  4) after DC in older patients. <sup>31,32</sup> The contrasting result could be due to the small number of studies in the present analysis that included older patients and the corresponding definition of 'older'. For example, some studies defined older patients as >60 years, whilst others as >70 years, resulting in exclusion of patients between 60 and 70 years of age. <sup>33</sup> The DESTINY II trial provides the strongest evidence so far for DC in older patients. Although case fatality was comparable with younger patients, functional outcome was worse in the older patients compared to the younger group in previous trials (19% versus 4%). <sup>24</sup> Together, these results suggest that higher age may be an important predictor of poor outcome, though further studies are warranted to determine an age threshold, if one exists, for MCI patients.

The timing of surgery is another important factor determining outcomes after MCI. Our analysis suggests that late DC (>48 hours) may not improve outcomes in MCI patients. This may be due to cerebral oedema increasing over time, reaching its peak and typically leading to death within 72-96 hours <sup>34</sup> thus, rendering later decompressive surgery ineffective. Notably, the HAMLET and HeADDFIRST trials allowed patients to receive DC up to 96 hours. In these patients, no significant benefits were associated with later DC. Interestingly, in the HAMLET trial the mortality rate in the control group was significantly lower than the early DC group suggesting an underlying bias in assigning patients to the later DC group. Often patients undergoing surgery early do so because of rapid clinical deterioration. As such, pre-treatment prognostic factors may be accountable for the apparent lack of effectiveness of delayed DC. In addition, the lack of time subgroup analysis in HeADDFIRST trial makes the efficacy of delayed DC uncertain. <sup>35</sup> Accordingly, further randomised comparative studies are required to establish the effectiveness of delayed DC. Yet, since the effectiveness of early DC has been established, there is currently no reason to

employ a watchful waiting approach (waiting for patient to deteriorate clinically) following a diagnosis of MCI.

Some limitations of this study should be considered. First, the outcomes were based on mRS and GOS scales which neglected psychosocial functions and QoL. Second, the outcome assessment was not fully blinded in any study, which may have resulted in a degree of observer bias (though some trials did use partial blinding and combining the results of these trials argues against any major bias). Third, due to the small number of patients included in each individual trial, the conclusions derived from subgroup analyses on expected prognostic factors, such as age and timing to intervention, are not sufficiently powered to show quantitative differences between treatment effects. Fourth, although the technique of DC was standardised in most studies, the medical treatment was not consistent, and often left to the discretion of the attending physician. In the HAMLET trial for example, more patients in the control arm received osmotherapy than in the DC arm. Similarly, more DC patients were cared for in an NCC unit than control group. However, if osmotherapy was significantly effective, the outcomes differences between groups would have been smaller and insignificant.

#### CONCLUSIONS

Despite these limitations, this meta-analysis demonstrated a survival benefit associated with hemicraniectomy in patients with MCI both under and over the age of 60 years. Yet, there was no significant difference favouring DC over BMT in terms of unfavourable outcome. As such, whether DC should be performed in patients over the age of 60 years remains controversial. Nonetheless, the likelihood of patients undergoing surgery is expected to increase. This comes with expected rise in morbidity and associated care burden. For clinicians, although challenging, it is imperative to communicate the potential range of outcomes and the expected QoL. Large, multicentre RCTs are required to determine efficacy of DC in older patients. These should incorporate long-term QoL assessment in addition to mortality and disability.

Importantly, much can be learned about DC from MCI trials for other causes of ABI, as it is the only ABI condition with numerous RCTs and reviews. Despite this, the issue of benefit of DC has remained a contentious topic and perhaps RCTs may not be the optimal research methodology to address these questions. Continued prospective data collection for assessment of type and timing of DC in patients with different causes of ABI are recommended. Individual units across the UK could all collect such data on a nationally agreed/ approved database.

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#### **Declaration of interests**

We declare no competing interests.

#### Contributions

WG and JS designed and oversaw the study. WG conducted the meta-analyses and in conjunction with JS did the primary validation and interpretation of data. WG wrote the

paper, with HF contributing to substantial edits. WG participated in the statistical analyses whilst HW supervised the process. All authors contributed and critically reviewed the final version of the manuscript.

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#### **FIGURE LEGENDS**

**Figure 1: PRISMA flow diagram for MCI studies.** Adapted from Moher, et al., (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA statement.

Figure 2a: Forest plot with OR estimating with 95% CI for the mortality outcome (defined as mRS=6) associated with DC versus BMT for studies grouped into RCTs and NRTs, and their pooled results at 3 months, 6 months, 12 months and 3 years follow-up. CI, confidence interval; DC: Decompressive craniectomy; BMT: best medical therapy; OR, odds ratio; mRS: modified Rankin Scale; IV: inverse variance; RCT: randomised controlled trials; NRTs: non-randomised trials.

Figure 2b: Forest plot with OR estimating with 95% CI for unfavourable outcome (defined as mRS=5) associated with DC versus BMT for studies grouped into RCTs and NRTs, and their pooled results at 3 months, 6 months, 12 months and 3 years follow-up. CI, confidence interval; DC: decompressive craniectomy; BMT: best medical therapy; OR, odds ratio; mRS: modified Rankin scale; IV: inverse variance; RCT: randomised controlled trials; NRTs: non-randomised trials.

Figure 3: Forest plot with OR estimating with 95%CI for (A) mortality outcome and (B) unfavourable outcome (defined as mRS=5) associated with DC versus BMT for individual studies and subgroup population stratified by age at 6 months follow-up. CI, confidence interval; DC: decompressive craniectomy; BMT: best medical therapy; OR, odds ratio; mRS: modified Rankin scale; IV: inverse variance.

**Figure 4: Funnel plot for assessment of publication bias**. No obvious asymmetry was detected. OR: odds ratios, SE: standard error, logOR: Natural logarithm of the OR.

#### APPENDIX

#### MCI Search Strategy

#### **CENTRAL/ MEDLINE Searched August 2018**

- 1. stroke\$ or cerebral vascular or cerebrovasc\$ or cva
- 2. cerebrovascular disorders/ or cerebrovascular disease/ or brain ischemia/ or hypoxiaischemia, brain/ or carotid artery diseases/ or carotid artery, internal, dissection/ or intracranial arterial diseases/ or cerebral arterial diseases/ or "intracranial embolism and thrombosis"/ or intracranial embolism/ or intracranial thrombosis/ or stroke/
- 3. exp brain infarction/
- 4. (brain or cerebral or intracranial) near3 (oedema or edema or swell\*)
- 5. MeSH descriptor Decompression, Surgical explode all trees

#### **EMBASE: searched August 2018**

- cerebrovascular disorders/ or cerebrovascular disease/ or brain ischemia/ or hypoxiaischemia, brain/ or carotid artery diseases/ or carotid artery, internal, dissection/ or intracranial arterial diseases/ or cerebral arterial diseases/ or intracranial embolism/ or intracranial thrombosis/ or intracranial embolism/ or stroke/
- 2. stroke\$ or cerebral vascular or cerebrovasc\$ or cva

decompress\$ or craniectom\$ or craniotom\$ or hemi?craniect\$ or trepa\$ or treph

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Table 1 Summary of	study character	istics							
Name, Study ID (First author, publication date)	Study design, Country	No. of patients DC/C	Mean age DC ±SD	Mean age C ±SD	% male DC	% male C	Time to surgery (hours)	Outcome assessed u	Follow 1p period (months)
HeADDFIRST Frank, 2014 <sup>35</sup>	Pilot RCT, USA	N=24 DC=14 C=10	52.3±6.8	57.9±12.4	64.0	60.0	Within 96h (4 PR)	Mortality mRS	3,6
HAMLET Hofmeijer, 2009 <sup>13</sup>	RCT, Netherlands	N=64 DC=32 C=32	50±8.3	47.4±9.8	63.0	56.0	Within 96h (3 PR)	Mortality mRS	12
HAMLET (at 3 years) Guerts, 2013 <sup>36</sup>	RCT, Netherlands	N=64 DC=32 C=32	50±8.3	47.4±9.8	63.00	56.0	Within 96h 3 PR	Mortality mRS	36
Slezins, 2012 <sup>22</sup>	RCT, Latvia	N=28 DC=11 C=13	57.2± 8.2	65±16	75.0	75.0	21	Mortality mRS	12
Zhao, 2012 <sup>37</sup>	RCT, China	N= 47 DC=24 C=23	63.5.0	64.0	75.0	9.69	<48	Mortality mRS	6, 12
Chua, 2015 <sup>23</sup>	RCT, Philippines	N=29 DC= 16 C= 13	50.3±9.5	50.1±7.0	85.0	82.0	NA	Mortality mRS	9
DESTINY Juttler, 2007 <sup>21</sup>	RCT, Germany	N=32 DC=17 C=15	43.2±9.7	46.2±4	47.0	47.0	24.4±6. 9	Mortality mRS	6, 12
DESTINY II Juttler, 2014 <sup>26</sup>	RCT, Germany	N=112 DC= 49 C=63	70.0	70.0	51.0	31.0	28	Mortality mRS	6,12
DECIMAL Vahedi, 2007 <sup>25</sup>	RCT, France	N=38 DC=20 C=18	43.5±9.7	43.3±7.1	45.0	50.0	20.5±8. 3	Mortality mRS	6,12
Raffiq, 2013 <sup>38</sup>	R Malaysia	N=125 DC= 90 C= 35	53.8 ±7.17	53.8±7.17	NA	NA	26.8	Mortality mRS	9
Sengeze, 2016 <sup>39</sup>	R, Turkey	N= 42 DC=20 C= 22	65.5±10.9	73±10.5	NA	NA	54±20.9	Mortality	12
Akins, 2016 <sup>40</sup>	R,	N= 30 DC=12 C= 18	43.0	48.0	39.0	39.0	NA	Mortality	3

	USA							mRS	
Tsai, 2012 (18)	R,	N=79 DC=37 C=42	65.5±15.8	75.9±13.8	48.6	52.4	48	Mortality	6
х г	China							mRS	
Rai, 2014 (19)	P,	N=60 DC=36 C=24	<b>44.63</b> ±12.2	57.12±19.2	75.00	99	56	Mortality	3,6,12
	India		n	8				mRS	
Yu, 2012 (20)	R,	N=131 DC= 58 C= 73	62.1±12.36	72.64±9.35	60.3	49.3	48	Mortality	9
	Korea							mRS	
Yang, 2005 (21)	R,	N=24 DC=10 C= 14	58.7	65.9	50.00	71.4	62.1±37	Mortality	e
, ,	China							mRS	
Wang, 2006 (22)	R,	N=62 DC= 21 C= 41	62±13.58	66.73±13.1	57	65.9	48	Mortality	9
	Taiwan			6				mRS	
Rahmanian, 2014	P,	N=60 DC=30 C=30	59±13.5	32.1±11	36.70	53.3	24-48	Mortality	Э
(23)	Iran							mRS	
DC: Decompressive c	raniectomy, RCT	: randomised controlled tria	ds, R: retrospe	ctive, P: prost	ective, (	C: contr	ol group, S	D: standard d	eviation,

Ĥ NA: not available in the study, PR: post randomisation, BMT: best medical treatment, mRS: modified Rankin Scale

outcome	e in early a	nd late DC	-	-	·	
Туре	Follow-	Outcome	No. of	No. of	OR (95% CI)	P value
of DC	up		studies	participant		
				S		
	3	mortality	2	120	0.10 [0.04, 0.23]*	<0.00001
	months	mRS=5	2	84	0.51 [0.14, 1.86]	0.31
Early	6	mortality	9	686	0.22 [0.13, 0.39]*	<0.00001
<48h	months	mRS=5	6	416	0.89 [0.31, 2.56]	0.83
	12	mortality	6	310	0.15 [0.09, 0.26]*	<0.00001
	months	mRS=5	2	106	0.36 [0.08, 1.57]	0.82
	3 years	mortality	1	39	0.09 [0.02, 0.40]*	0.002
		mRS=5	1	39	2.71 [0.10, 70.65]	0.55
	3	mortality	2	48	0.26 [0.02, 3.28]	0.30
	months	mRS=5	1	24	0.56 [0.11, 2.90]	0.49
Late	6	mortality	1	24	0.83 [0.16, 4.44]	0.83
DC	months	mRS=5	1	24	1.30 [0.23, 7.38]	0.77
>48h	12	mortality	2	106	0.36 [0.08, 1.57]	0.17
	months	mRS=5	1	64	15.94 [0.86,	0.06
					296.1]	
	3 years	mortality	1	24	0.57 [0.10, 3.18]	0.52
		mRS=5	1	24	Not estimable	

 Table 2: OR estimates with corresponding 95% CI for mortality and unfavourable outcome in early and late DC

DC: Decompressive craniectomy, mRS= modified Rankin Scale, OR: odds ratio, CI: confidence interval. Bold font = statistical significance

## Table(s) Click here to download Table(s): WNS Table 3 .docx

Table 3 Suroutcome.	nmary of	results and	l sensitivity analyses	s for mortality and	d unfavour	able
Study subgroup	No. of studies	No. of patients	Statistical method	Effect estimate (95% Cl)	P value	I <sup>2</sup>
Summary:	mortality					
3 months	4	138	OR (IV, Random, 95% CI)	0.23 (0.07, 0.71)*	0.01	38%
6 months	11	734	OR (IV, Random, 95% CI)	0.25 (0.15, 0.43)*	<0.00001	54%
12 months	8	416	OR (IV, Random, 95% CI)	0.18 (0.11, 0.29)*	<0.00001	0
3 years	1	63	OR (IV, Random, 95% CI)	0.21 (0.07, 0.61)*	0.004	NA
Summarv:	unfavoura	able outcon	ne			
3 months	3	108	OR (IV, Random, 95% CI)	0.53 (0.19, 1.46)	0.22	0
6 months	8	464	OR (IV, Random, 95% CI)	1.03 (0.43, 2.47)	0.94	58%
12 months	7	374	OR (IV, Random, 95% CI)	1.38 (0.47, 4.11)	0.56	39%
3 years	1	63	OR (IV, Random, 95% CI)	3.20 (0.13, 81.50)	0.48	NA
Sensitivity :	analyses fo	or the mort	tality outcome exclu	iding NRTs		
3 months RCTs	1	24	OR (IV, Random, 95% CI)	0.83 [0.16, 4.44]	0.83	NA
6 months RCTs	6	277	OR (IV, Random, 95% CI)	0.22 [0.12, 0.40]*	<0.00001	18%
12 months RCTs	6	314	OR (IV, Random, 95% CI)	0.17 [0.10, 0.28]*	<0.00001	0%
Sensitivity :	analyses fo	or the unfa	vourable outcome e	excluding NRTs		
3 months RCTs	1	24	OR (IV, Random, 95% CI)	0.56 [0.11, 2.90]	0.49	NA
6 months RCTs	6	277	OR (IV, Random, 95% CI)	1.79 [0.92, 3.48]	0.08	0
12 months RCTs	6	314	OR (IV, Random, 95% CI)	1.50 [0.36, 6.22]	0.58	52%

OR= Odds ratio; IV= inverse variance; CI= confidence interval; NA= heterogeneity not applicable as only one study has been pooled; I<sup>2</sup>= heterogeneity \*= statistical significance



**PRISMA 2009 Flow Diagram** 

#### Figure(s) Click here to download high resolution image

	Study or Subgroup	Events T	otal	Events	Total	Weight	IV, Random, 95% CI		IV, Rando	m, 95% CI	
	Frank 2014 Subtotal (95% C0	5	14		10 10	19.8% 19.8%	0.83 (0.16, 4.44) 0.83 (0.16, 4.44)		-		
	Total events Heterogeneity: Not a Test for overall effect	splicable	- 0	4							
	3.1.2 NRTs										
	Akins 2016	1	12	1	18	12.0%	0.45 [0.04, 4.98]		-		
	Rai 2014		10 16	19	24	28.8%	0.08 (0.02, 0.27)	-			
	Yang 2005 Subsetal (ISSN CD	1	10	9	14	12.4%	0.05 (0.01, 0.64)	·	-		
	Total events Heterogeneity: Tau <sup>2</sup>	16 0.00, Chi*	- 1.5	51 8. df = 3	(Ø - 1	0.540; t <sup>2</sup> =	ox ox		-		
	Total (95% CI)		102		96	100.0N	0.17 [0.07, 0.44]		٠		
	Heterogeneity: Tau <sup>4</sup> Test for overall effect	0.45; CHI	- 6.6	65. df = 4 .00025	0-10	0.360; t <sup>4</sup> =	40%	0.01	0.1 Favours (DC)	10 Favours (BMT)	10
		Treatme	nt	Centr	ol	- 0.045,1	Odds Ratio		Odds	Ratio	
months follow up	Study or Subgroup 1.2.1 RCTs	Events 7	otal	Events	Total	Weight	IV, Random, 95% Cl		IV, Rando	m, 95% CI	
months follow up	Chus 2015	5	13	6	13	6.4N	0.52 (0.10, 2.66)			-	
	Frank 2014 Juttler 2007	5	17	1	10	6.2%	0.83 (0.16, 4.44)	11			
	Juttler 2014	36	49	- 44	63	12.6%	0.21 [0.09, 0.47]				
	Vahedi 2007 Zhao 2012	5	20	14	23	7.1%	0.10 10.02, 0.43	=	141.122		
	Subtotal (95% CI) Total events	37	137	90	140	46.2%	0.22 (0.12, 0.40)		+		
	Heterogeneity: Tau <sup>4</sup> Test for overall effect	= 0.11; Chi <sup>4</sup> t Z = 4.93 (	- 6. P < 0	10, <i>df</i> = 000001)	5 (P =	0.30); i <sup>2</sup> -	185				
	3.2.2 NRTs										
	Ral 2014	12	36	20	24	8.6%	0.10 (0.03, 0.36)				
	Tsai 2012	7	37	10	42	10.2%	0.09 (0.03, 0.27)	1			
	Wang 2006 Yu 2012	28	58	52	- 73	3.18	0.38 [0.18, 0.78]			1 C C C C C C C C C C C C C C C C C C C	
	Subtotal (95N CI) Total events Heterogeneity: Tau <sup>4</sup>	80 - 0.64; Chi <sup>4</sup>	- 14	130 .52, df -	40.	51.8%	0.29 (0.13, 0.66) * = 72%		•		
	Test for overall effect Total (95% CI)	t: Z = 2.93 (	379		355	100.0%	0.25 (0.15, 0.43)				
	Total events	- 0.38; Chi <sup>4</sup>	- 23	220 1.69, df -	100	- 0.02%	* - 54N	0.01	0.1	1 10	10
	Test for overall effect	E 2 = 5,210	10	A	= 1 (P	- 0.581.1	- 0%		Nevoara (pc.)	Levence (BMI)	
	Test for overall effec Test for subgroup d	t 2 = 5.21 ( flerences: C		0.30, 81		2010 W	- 19 E.				
	Test for overall effer Test for subgroup d Study or Subgroup	t Z = 5.21 ( flerences: C) Treatmen Events To	ri otal	Contro Events	ii Total	Weight 1	Odds Ratio IV, Random, 95% CI		Odds IV, Rando	Ratio m, 95% CI	
alas mente falless	Test for overall effec Test for subgroup d Study or Subgroup 3.3.1 RCTs Holmelier 2009	1: 2 = 5.21 ( flerences: C Treatmen Events: To 7	ni otal 32	Contro Events	ii Total 32	Weight 17.3%	Odds Ratio IV, Random, 95% CI 0.19 (0.06, 0.57)		Odda IV, Rando	Ratio m, 95% CI	
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relve months follow	Test for overall effect Test for overall effect Test for subgroup d 3.1.1 &CTs Holmeijer 2009 juttler 2004 Steps 2012 Valued 2007 Zhao 2012 Subteal (95% CI) Total events Heterogeneity: Tau <sup>2</sup> + Test for overall effect 3.3.2 NRTs Rai 2016 Subteal (95% CI) Total events Heterogeneity: Tau <sup>2</sup> + Test for overall effect Subteal (95% CI) Total events Heterogeneity: Tau <sup>2</sup> + Test for overall effect Subteal (95% CI) Total events Heterogeneity: Tau <sup>2</sup> + Test for overall effect Total events Heterogeneity: Tau <sup>2</sup> + Test for overall effect Test for	2 = 5.21 ( flerences: C Treatimer Events To 5 4 20 5 4 21 20 5 4 21 20 5 4 21 20 5 4 21 21 21 21 21 21 21 21 21 21	11 004al 32 17 17 47 13 20 24 15 1 20 20 20 20 20 20 20 20 20 20	Contro Dvents 19 8 47 12 14 16 11 16 11 16 11 16 12 17 19 39 19 39 19 39 19 39 19 39 19 39 19 39 19 39 19 39 19 39 19 39 39 55 19 55 19 53 7 47 12 14 16 16 19 50 19 19 50 19 19 50 19 19 20 19 20 20 20 20 20	1 Total 32 15 52 13 18 23 163 18 23 163 18 23 163 19 -1 24 45 19 -1 269 10 -1 10 -1 -1 -2 -2 -2 -2 -2 -2 -2 -2 -2 -2	Weight 1 17.3% 8.1% 11.0% 9.2% 10.7% 80.0% 1.80% 7.0% 20.0% 1.00.0% 1.00.0% 1.00.0% 1.00.0%	Odds Ratio N, Random, 955 C) 0.19 [0.04, 0.94] 0.24 [0.10, 0.54] 0.24 [0.10, 0.54] 0.24 [0.10, 0.54] 0.10 [0.02, 0.35] 0.17 [0.10, 0.28] 0.17 [0.10, 0.28] 0.13 [0.04, 0.45] 0.39 [0.16, 5.04] 0.31 [0.05, 2.06] 699 0.18 [0.11, 0.29] 0N = 0% Odds Ratio N, Random, 95% CJ 0.21 [0.07, 0.61] 0.21 [0.07, 0.61]		Odds IV, Rando	Ratio n, 95N CI 10 Favours (BMT) Ratin m, 95N CI	300

#### Figure(s) Click here to download high resolution image

	Study or Subgroup	Treatmen Events Tr	nt Iotal	Contro Events	k Total	Weight	Odds Ratio IV, Random, 95% Cl		Odds Ratio IV, Random, 95% CI	
hree months follow up	3.4.1 RCTs		1.58	- 2020		1.000				
	Frank 2014 Subsetal (95% CD)	5	14	5	10	38.0%	0.56 (0.11, 2.90)			
	Total events	5		5		-	Also farest and the			
	Heterogeneity: Not a	oplicable								
	Test for overall effect	c Z = 0.70 (P	P = 0.	.45)						
	3.4.2 NRTs									
	Rahmanian 2014	3	30	\$	30	44.3N	0.56 (0.12, 2.57)			
	Yang 2005	1	10	3	14	17.6%	0.41 (0.04, 4.62)	13		
	Subtotal (95% CI)	170	40	i . Nati	44	62.0%	0.51 [0.14, 1.86]		-	
	Total events	4					2225			
	Test for overall effect	t Z = 1.02 (7	F = 0.	.31)	· · ·	0.836.4	- 036			
	Total (95% CI)		54		54	100.0%	0.53 (0.19, 1.46)		-	
	Total events	9	12	13		and the	Real Marca	12	10 mm	
	Heterogeneity: Tau"	+ 0.00; Chr	= 0.0	15, df = 2	(Ø = 1	0.97); 1" •	- 0%	0.01	0.1 10	100
	Test for overall effect Test for subgroup di	CZ = 1.24 0	1 = 0.	22) 0.05. df -	-10	- 0.931, 1	- M		Favours (DC) Favours (BMT)	8357
	160 tot task of a	Jereinen w.	No.	NOR W	1.4.9	a destroy of			COOPERATIVE GOLDEN A	
	Study or Subgroup	Treatment Events Tr	n otal (	Contro Events	l Fotal	Weight	Odds Ratio IV, Random, 95% CI		Odds Ratio IV, Random, 95% Cl	
x months follow up	1.5.1 RCTs					in the second				_
	Chue 2015	2	13	0	11	5.9K	5.00 [0.22, 116.03]			-
	Frank 2014 Netfler 2007	3	14	2	10	8.18	1.30 (0.23, 7.36)			
	Juttler 2014	14	49		63	18.7%	2.75 [1.05, 7.23]			- 3
	Vahedi 2007	2	20	0	18	6.0%	5.00 (0.22, 111.43)			-
	Zhao 2012 Subtotal (95% CI)	5 7	24	3	23	15.0N	0.95 (0.23, 3.83)		-	
	Total events	29		18			Box is factored and the			
	Heterogeneity: Tau <sup>2</sup> - Test for overall effect	0.00; Chi <sup>4</sup>	- 3.8	16, cf = 5	(P = 0	.57k i <sup>4</sup> -	0%			
	152 NRTs	1001 1000	1.00							
	Raffig 2013		90		35	16.28	0.13 (0.04, 0.47)	- 94		
	Wang 2006	12	21	22	41	17.98	1.15 (0.40, 3.32)			
	Subtotal (95% Lu		in		70	34.00	0.40 (0.03, 3.34)			
	Total constants	16		11						
	Total events Heterogeneity: Tau <sup>8</sup> -	16 1.96; Chi <sup>4</sup>	- 6.5	31 6, df = 1	(P = 0	.01); I <sup>#</sup> -	85N			
	Total events Heterogeneity: Tau <sup>4</sup> - Test for overall effect	16 1.96; Chi <sup>4</sup> 2 = 0.84 (P	- 6.5	31 6, df = 1 40)	(P = {	0.01); I <sup>4</sup> -	85N			
	Total events Heterogeneity: Tau <sup>4</sup> - Test for overall effect Total (95N CI) Total events	16 • 1.96; Chi* - Z = 0.84 (P 2 45	- 6.5 ! - 0	31 6, df = 1 40) 49	(P = { 236	100.0%	85X 1.03 (0.43, 2.47)		+	
	Total events Heterogeneity: Tau <sup>4</sup> - Test for overall effect Total (95N CI) Total events Heterogeneity: Tau <sup>4</sup> -	16 1.96; Chi <sup>4</sup> 2 = 0.84 (P 2 45 0.82; Chi <sup>4</sup>	- 6.5 ' - 0 248 - 16:	31 6, df = 1 40) 49 67, df =	0° = ( 216 7 0° =	1.01); 1 <sup>4</sup> - 100.0% 0.02); 1 <sup>4</sup>	- 85N 1.03 (0.43, 2.47) - 58N	201		100
	Total events Hebrogeneity: Tau <sup>4</sup> - Test for overall effect Total (95% CI) Total events Hebrogeneity: Tau <sup>4</sup> - Test for overall effect Test for subgroup diff	16 1.96; Ch <sup>2</sup> 2 = 0.84 (7 45 0.82; Ch <sup>2</sup> 2 = 0.07 (7 between cests; Ch	= 6.5 = 0.7 748 = 16: = 0.1 = 0.1 = 1	31 6, df = 1 40) 43 67, df = 94) 1.75, df =	0 = 1 216 70 =	100.03); 1 <sup>4</sup> - 100.0% 0.92); 1 <sup>4</sup> - 0.19), 1	- 85N 1.03 (0.43, 2.47) - 58N - 42.8N	0.01	0,1 10 Favours (DC) Favours (BMT)	100
	Total events Hebrogeneity: Tau <sup>8</sup> - Test for overall effect Total (95% C) Total events Hebbrogeneity: Tau <sup>8</sup> - Test for overall effect Test for subgroup diff	16 1.96; Chi <sup>4</sup> 2 = 0.84 (P 45 0.82; Chi <sup>2</sup> 2 = 0.07 (P lerences; Chi	= 6.5 = 0. 248 = 16. = 0. = 1 = 1	31 6, df = 1 40 43 67, df = 94) 1.75, df =	0 = ( 216 70 =	100.03); 1 <sup>4</sup> - 100.0% 0.92); 1 <sup>4</sup> - 0.19), 1	- 85N 1.03 (0.43, 2.47) - 58N - 42.8N	6.01	0,1 10 Favours (DC) Favours (BMT)	100
	Total events Hebrogeneity: Tau <sup>4</sup> - Test for overall effect Total (95% CI) Total events Hebrogeneity: Tau <sup>4</sup> - Test for overall effect Test for subgroup diff	16 1.96; Chi <sup>4</sup> , 2 = 0.84 (P 45 0.82; Chi <sup>4</sup> , 2 = 0.07 (P lerences; Chi Treatman Events; To	= 6.5 = 0.7 248 = 16.7 = 0.7 = 1 = 1 = 1 = 1 = 1	31 6, df = 1 40) 43 67, df = 94) L75, df = Contro Events 1	07 = 1 216 7 (7 = 1 (7 -	1.01); 1 <sup>4</sup> - 100.0N 0.02); 1 <sup>4</sup> - 0.19), 7 Weight	- 85% 1.03 (0.43, 2.47) = 58% <sup>1</sup> = 42.8% Odds Ratio IV, Randon, 95% CL	6.01	0,1 10 Favours (DC) Favours (BMT) Oddis Ratio IV, Random, 95% C)	100
	Total events Networgeneity: Tau <sup>4</sup> - Test for overall effect Total (95% CI) Total events Networgeneity: Tau <sup>4</sup> - Test for sverall effect Test for subgroup diff Study or Subgroup 3.6.1 BCTs Notmeliet 2009	16 1.96; Chi <sup>4</sup> , 2 = 0.84 (P 45 0.82; Chi <sup>4</sup> , 2 = 0.07 (P leteroces; Chi Treatman Events; To 6	- 6.5 - 0. 248 - 16. - 0.1 r - 1 r - 1 otal	31 6, cf = 1 40) 67, df = 94) L75, df = Contro <u>Events 1</u> 0	0 = 1 216 7 (P = 1 (P - 4 <u>Total</u> 12	1.03); 1° - 100.0% 0.02); 1° - 0.19), 1 Weight 11.0%	- 85% 1.03 (0.43, 2.47) = 58% - 42.8% Odds Ratio IV, Random, 95% Cl 15.54 (0.86, 296.15)	0.01	0,1 Favours (DC) Favours (BMT) Odds Ratio IV, Random, 95% CI	100
velve months follow	Total events Netwogeneity: Tau <sup>4</sup> - Test for overall effect Total (95% CI) Total events Networsgeneity: Tau <sup>4</sup> - Test for swall effect Test for subgroup diff Study or Subgroup 3.6.1 RCTs Nofmeijer 2009 Juttler 2007	16 1.96; Chi <sup>4</sup> , 2 = 0.84 (7 45 0.82; Chi <sup>4</sup> , 7 2 = 0.07 (7 letences; Chi Treatman Events; To 6 1	= 6.5 = 0.7 248 = 16.7 F = 1 rt otal 32 17	31 6, cf = 1 40) 67, df = 94) L75, df = <u>Events</u> 0 2	0° = 1 216 7 (P = 1 (P - 1 (P	1.03); 1° - 100.0% 0.02); 1° - 0.19); 7 weight 11.0% 13.9%	- 85% 1.03 (0.43, 2.47) = 58% '= 42.8% Odds Ratio IV, Random, 95% CI 15.94 (0.86, 296.15) 0.41 (0.03, 5.00)	\$.01 -	0,1 10 Favours (DC) Favours (BMT) Odds Ratio IV, Random, 95% CI	10
velve months follow	Total events Netwogeneity: Tau <sup>8</sup> - Test for overall effect Total (95% CI) Total events Networks Tau <sup>8</sup> - Test for overall effect Test for subgroup dif Study or Subgroup dif Study or Subgroup 3.6.1 &CTs Nofmeijer 2009 Juttler 2014	16 1.96; Chi <sup>4</sup> , 2 = 0.84 (7 45 0.82; Chi <sup>4</sup> , 2 = 0.07 (7 lerences; Chi Treatman Events; To 6 1 9	= 6.5 = 0.7 248 = 16.7 1 <sup>2</sup> = 1 nt otal 32 17 47	31 6, cf = 1 40) 67, df = 94) L75, df = <u>Events</u> 0 2 5 0	0 = 1 216 7 0 = 1 0 1 1 1 5 52 52	100.01); 1 <sup>o</sup> - 100.0% 0.02); 1 <sup>o</sup> - 0.190, 7 weight 11.0% 13.9% 32.0%	- 85% 1.03 (0.43, 2.47) = 58% '= 42.8% Odds Ratio IV, Random, 95% CI 15.94 (0.86, 296.15) 0.41 (0.03, 5.00) 2.70 (0.84, 868)	0.01	0,1 10 Favours (DC) Favours (BMT) Odds Ratio IV, Random, 95% CI	10
velve months follow	Total events Netwogeneity: Tau <sup>2</sup> - Test for overall effect Total (95% CI) Total events Networks Tau <sup>2</sup> - Test for overall effect Test for subgroup dif <u>Study or Subgroup</u> 3.6.1 RCTs Nofmeijer 2009 Juttler 2007 Juttler 2014 Siezins 2012 Volsed 2007	16 1.96; Chi <sup>4</sup> , 2 = 0.84 (7 45 0.82; Chi <sup>4</sup> , 2 = 0.07 (7 ferences: Chi Treatman Events To 6 1 9 0 0	= 6.5 = 0, 248 = 16, '= 0, if = 1 nt otal 32 17 47 11 20	31 6, df = 1 40) 67, df = 94) 1.75, df = Contro Events 1 0 2 5 0 0 0 0	0° = 1 216 7 0° = 1 0° 4 10 13 62 13 14	100,0% 100,0% 0.02): ( <sup>2</sup> - 0.19), ( <sup>2</sup> - 0.	- 85% 1.03 (0.43, 2.47) = 58% '= 42.8% Odds Ratio IV, Random, 95% Cl 15.94 (0.86, 296.15) 0.41 (0.03, 5.00) 2.70 (0.84, 8.68) Not estimable Not estimable	<b>0.01</b>	0,1 10 Favours (DC) Favours (BMT) Odds Ratio IV, Random, 95% CI	10
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velve months follow	Total events Netwogeneity: Tau <sup>2</sup> - Test for overall effect Total (95% CI) Total events Networks Tau <sup>2</sup> - Test for overall effect Test for subgroup dif <u>Study or Subgroup</u> 3.6.1 &CTs Nofmeijer 2009 Juttler 2007 Juttler 2012 Sizeins 2012 Valued 2007 Zhao 2012 Subtotal (95% CI)	16 - 1.96; Chi <sup>*</sup> , 2 = 0.84 (7 45 - 0.82; Chi <sup>*</sup> , 2 = 0.07 (7 ferences: Chi Treatman Events To 6 1 9 0 0 2 1 1	= 6.5 = 0. = 16. = 0.1 = 11 otal 32 17 47 11 20 24 151	31 40 49 67, df = 1 47 67, df = 9 49 1,75, df = Contro Events 1 0 2 5 0 4 1 2 5 0 4 1 2 5 0 4 1 2 5 0 4 1 2 5 0 1 2 1 2 1 2 1 2 1 2 1 2 1 2 1 2 1 2 2 1 2 2 1 2 2 1 2 2 2 2 2 2 2 2 2 2 2 2 2	0 = 1 216 70 = 10 4 fotal 13 15 62 13 18 23 163	100.03; 1° - 100.05 0.02); 1° - 0.19), 7 Weight 11.05 13.95 32.95 21.65 79.35	- 85% 1.03 (0.43, 2.47) = 58% '= 42.8% Odds Ratio IV, Randow, 95% Cl 15.94 (0.86, 296.15) 0.41 (0.03, 5.00) 2.70 (0.84, 8.68) Not estimable 0.43 (0.07, 2.63) 1.50 (0.36, 6.22)	b.o1	0(1 10 Favours (DC) Favours (BMT) Oddis Ratio PV, Random, 95% CI	10
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welve months follow	Total events Meterogeneity: Tau <sup>2</sup> - Test for overall effect Total (95N CI) Total events Meterogeneity: Tau <sup>2</sup> - Test for overall effect Test for overall effect Test for subgroup diff Study or Subgroup 3.6.1 RCTs Mofmeijet 2009 Juttier 2007 Juttier 2007 Juttier 2007 Juttier 2007 Juttier 2014 Siezins 2012 Vabed 2007 Zhao 2012 Subtotal (95N CI) Total events Meterogeneity: Tau <sup>2</sup> - Test for overall effect 3.6.2 NRTs	16 1.96; Chi <sup>4</sup> , 2 = 0.84 (7 45 0.82; Ch <sup>2</sup> , 2 = 0.07 (7 ferences: Ch Treatmer Events: Ti 6 1 9 0 0 2 18 = 1.07; Ch <sup>2</sup> : Z = 0.56 (7)	= 6.5 = 0.7 248 = 16.7 = 0.1 f <sup>2</sup> = 1 17 17 11 20 24 151 = 6.3 1-0.1 17 11 20 24 151 = 0.4 151 151 151 151 151 151 151 15	31 (6, df = 1 40) 43 67, df = 94) L75, df = Contro Events 1 0 2 5 0 0 4 11 12, df = 3 58)	0°=1 216 70°= 10° 10° 15 62 15 62 13 18 18 18 18 0°=0	100.0% 0.02); f <sup>2</sup> 0.02); f <sup>2</sup> 0.190, f 0.190, f 11.0% 13.9% 32.0% 21.6% 7%3%	<ul> <li>85%</li> <li>1.03 (0.43, 2.47)</li> <li>58%</li> <li>42.8%</li> <li>Odds Ratio IV, Randon, 95% Ci</li> <li>15.94 (0.36, 296, 15) 0.41 (0.03, 5.00) 2.70 (0.86, 296, 15) 0.41 (0.03, 5.00) 2.70 (0.86, 6.22)</li> <li>1.50 (0.36, 6.22)</li> <li>52%</li> </ul>	b.01 -	0.1 10 Favours (DC) Favours (BMT) Oddis Ratio IV, Random, 95% (D	10
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velve months follow	Total events Meterogeneity: Tau <sup>2</sup> - Test for overall effect Total (95N CI) Total events Meterogeneity: Tau <sup>2</sup> - Test for overall effect Test for overall effect Test for subgroup dif Study or Subgroup 3.6.1 RCTs Motmejet 2009 Juttler 2007 Juttler 2007 Juttler 2007 Juttler 2007 Juttler 2007 Juttler 2007 Juttler 2007 Juttler 2014 Slezins 2012 Vabedi 2007 Zhao 2012 Subtotal (95N CI) Total events Neterospeneity: Tau <sup>2</sup> - Test for overall effect 3.6.2 NRTs Raj 2014 Subtotal (95N CI) Total events	16 - 1.96; Chi <sup>4</sup> , 2 = 0.84 (7 45 - 0.82; Ch <sup>2</sup> , 2 = 0.07 (7 ferences: Ch Treatmer Events: Ti 6 1 9 0 0 2 18 = 1.07; Ch <sup>2</sup> 1 3	= 6.5 = 0. = 16. = 0.1 = 1 = 1 = 1 = 1 = 1 = 1 = 1 =	31 (6, cf = 1 40) 43 67, df = 94) L75, df = 2 5 0 0 4 11 12, df = 3 54) 2 2 2 2	$0^{p} = 1$ 216 7 $0^{p} = 1$ 10 <sup>p</sup> 4 Total 32 15 62 15 62 13 13 14 163 0^{p} = 0 24 24	100.0% 0.02); f <sup>2</sup> 0.02); f <sup>2</sup> 0.190, f 0.190, f 11.0% 13.9% 32.0% 21.6% 7%3%	<ul> <li>35%</li> <li>1.03 (0.43, 2.47)</li> <li>58%</li> <li>42.8%</li> <li>Odds Ratio IV, Randon, 95% Ci</li> <li>5.94 (0.36, 296, 15) 0.41 (0.03, 5.00) 2.70 (0.54, 8.64) Not estimable 0.43 (0.07, 2.63) 1.50 (0.36, 6.22)</li> <li>52%</li> <li>1.00 (0.15, 6.48)</li> </ul>	b.01 -	0.1 10 Favours (DC) Favours (BMT) Oddis Ratio IV, Random, 95% D	100
velve months follow	Total events Hebrogeneity: Tau <sup>2</sup> - Test for overall effect Total (95N CI) Total events Hebrogeneity: Tau <sup>2</sup> - Test for overall effect Test for overall effect Test for overall effect Study or Subgroup dif Study or Subgroup Juttler 2000 Juttler 2007 Juttler 2014 Slezins 2012 Vabed 2007 Zhao 2012 Subtotal (95N CI) Total events Hebrogeneity: Tau <sup>2</sup> - Test for overall effect 3.6.2 NRTs Baj 2014 Subtotal (95N CI) Total events Hobrogeneity: Not as Test for overall effect	16 1.96; Chi <sup>4</sup> , 2 = 0.84 (7 45 0.82; Chi <sup>2</sup> , 2 = 0.07 (7 ferences: Chi Treatmer Events: Ti 6 1 9 0 0 2 18 = 1.07; Chi <sup>4</sup> : Z = 0.36 (7 3 splicable - 2, 20, 00 (7 - 2, 20, 00) (7 - 2, 20,	= 6.5 = 0. 248 = 16: - 0. - 1 - 1 - 0. - 1 - 0. - 1 - 0. -	31 40 40 40 57, df = 1 40 57, df = 9 94) L75, df = Contro Events 1 0 2 5 0 0 4 11 12, df = 3 5-40 2 2 2 2 200	$\varphi = 1$ 216 7 $\varphi = -1 \varphi$ , 1 $\varphi$ ,	100.0% 0.02); f <sup>2</sup> 0.02); f <sup>2</sup> 0.190, f 0.190, f 11.0% 13.9% 32.9% 21.6% 79.3% 21.6% 79.3%	- 85N 1.03 (0.43, 2.47) - 58N - 42.8N Odds Ratio IV, Randon, 95X CI 15.94 (0.84, 296.15) 0.41 (0.03, 5.00) 2.70 (0.84, 8.68) Not estimable Not estimable Not estimable 0.43 (0.72.653) 1.50 (0.16, 6.22) 52N 1.00 (0.15, 6.48)	0.01	0,1 10 Favours (DC) Favours (BMT) Oddis Ratio IV, Random, 95% C)	10
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velve months follow	Total events Hebrogeneity: Tau <sup>2</sup> - Test for overall effect Total (95N CI) Total events Hebroggeneity: Tau <sup>2</sup> - Test for overall effect Test for overall effect Test for overall effect 3.6.1 RCTs Hofmeijer 2009 Juttier 2007 Juttier 2014 Siezins 2012 Vahed 2007 Zhao 2012 Subtotal (95N CI) Total events Hebrogeneity: Tau <sup>2</sup> - Test for overall effect 3.6.2 NRTs Rai 2014 Subtotal (95N CI) Total events Hebrogeneity: Not ad Test for overall effect	16 1.96; Chi <sup>4</sup> , 2 = 0.84 (7 45 0.82; Chi <sup>2</sup> , 2 = 0.07 (7 ferences: Chi Treatmer Events Ti 6 1 9 0 0 2 18 = 1.07; Chi <sup>2</sup> 12 = 0.56 (7 3 splitable 1.2 = 0.00 (7 21 = 0.58; Chi <sup>2</sup>	= 6.5 = 0. 248 = 16: - 0. - 0. - 16: - 0. - 0. - 17: - 0. - 0	31 40 49 67, df = 1 40 40 40 5 0 0 11 12, df = 3 5 0 0 4 11 12, df = 3 5 13 14, df = 4	$\varphi = 1$ 216 7 $\varphi = -1$ 4 Total 13 15 52 15 163 $\varphi = 0$ 24 24 147 $\varphi = -1$	100.0% 100.0% 0.02); f <sup>2</sup> 0.19), f 11.0% 13.9% 32.9% 21.6% 79.3% 1.10% f <sup>2</sup> 20.7% 100.0% 110% f <sup>2</sup>	<ul> <li>35%</li> <li>1.03 (0.43, 2.47)</li> <li>58%</li> <li>42.28</li> <li>Odds Ratio IV, Randon, 95% CI</li> <li>15.94 (0.86, 296.15)</li> <li>0.41 (0.03, 5.00)</li> <li>2.70 (0.84, 8.68)</li> <li>Not estimable Not estimable Not estimable</li> <li>1.00 (0.15, 6.48)</li> <li>1.00 (0.15, 6.48)</li> <li>1.38 (0.47, 4.11)</li> <li>39%</li> </ul>	0.01	0,1 10 Favours (DC) Favours (BMT) Odds Ratio IV, Random, 95% D	10
welve months follow	Total events Hebrogeneity: Tau <sup>2</sup> - Test for overall effect Total (95N CI) Total events Hebroggeneity: Tau <sup>2</sup> - Test for overall effect Test for overall effect Test for subgroup dif <u>Study or Subgroup</u> 3.6.1 RCTs Hofmeijer 2009 Juffer 2007 Juffer 2007 Juffer 2007 Zhao 2012 Subtotal (95N CI) Total events Hebrogeneity: Tau <sup>2</sup> - Test for overall effect 3.6.2 NRTs Rai 2014 Subtotal (95N CI) Total events Hebrogeneity: Tau <sup>2</sup> - Test for overall effect	16 1.96; Chi <sup>4</sup> , 2 = 0.84 (7 45 0.82; Chi <sup>2</sup> , 2 = 0.07 (7 ferences: Chi Treatmer Events Ti 6 1 9 0 0 2 18 = 1.07; Chi <sup>2</sup> 18 = 1.07; Chi <sup>2</sup> 12 = 0.56 (7 3 pplicable 1 Z = 0.56 (7) 21 = 0.58; Chi <sup>2</sup>	= 6.5 = 0. 248 = 16: = 0. i <sup>2</sup> = 1 i <sup>2</sup> = 1 17 17 11 24 151 = 6.3 1= 1. 36 1= 1. 36 1= 1. 36 1= 1. 36 1= 1. 36 1= 1. 37 1= 1. 36 1= 1. 37 1= 1. 36 1= 1. 36 1= 1. 37 1= 1. 36 1= 1. 36 1= 1. 36 1= 1. 36 1= 1. 36 1= 1. 36 1= 1. 36 1= 1. 36 1= 1. 37 1= 1. 36 1= 1. 36 1= 1. 37 1= 1. 36 1= 1. 36 1= 1. 36 1= 1. 36 1= 1. 37 1= 1. 36 1= 1. 36 1= 1. 36 1= 1. 36 1= 1. 36 1= 1. 37 1= 1. 37	31 6, cf = 1 40) 43 67, df = 94) 1,75, df = Contro Events 1 0 2 5 0 0 4 11 12, df = 3 5-80 2 2 2 00) 13 14, df = 4 5-60 13 14, df = 4 5-60 13 14, df = 4 5-60 13 14, df = 4 5-60 13 14, df = 4 5-60 15 15 15 15 15 15 15 15 15 15	$\varphi = 1$ 216 7 $\varphi = -1$ 4 Fotal 13 15 52 15 52 15 163 $\varphi = 0$ 24 24 24 24 24 24 24 24 24 24	100.0% 0.02); f <sup>2</sup> 0.02); f <sup>2</sup> 0.02); f <sup>2</sup> 0.02); f <sup>2</sup> 0.02); f <sup>2</sup> 0.02); f <sup>2</sup> 11.0% 13.9% 13.9% 13.9% 21.6% 7%.3% 21.6% 7%.3% 20.7% 20.7% 100.0% 100.0%	<ul> <li>35N</li> <li>1.03 (0.43, 2.47)</li> <li>58N</li> <li>42.8N</li> <li>Odds Ratio IV, Randon, 95N CI</li> <li>95.94 (0.86, 296.15) 0.41 (0.03, 5.00) 2.70 (0.86, 296.15) Not estimable Not estimable 0.43 (0.07, 2.63) 1.50 (0.36, 6.22)</li> <li>52N</li> <li>1.00 (0.15, 6.48)</li> <li>1.08 (0.47, 4.11)</li> <li>39%</li> </ul>	0.01	0,1 10 Favours (DC) Favours (BMT) Odds Ratio IV, Random, 95% D	10
welve months follow	Total events Hebrogeneity: Tau <sup>2</sup> - Test for overall effect Total (95N CI) Total events Hebroggeneity: Tau <sup>2</sup> - Test for overall effect Test for overall effect Test for subgroup dif Study or Subgroup 3.6.1 RCTs Hofmeijer 2009 Juttier 2007 Juttier 2007 Juttier 2007 Juttier 2007 Juttier 2007 Zhao 2012 Subtotal (95N CI) Total events Hebrogeneity: Tau <sup>2</sup> - Test for overall effect 3.6.2 NRTs Rai 2014 Subtotal (95N CI) Total events Hebrogeneity: Tau <sup>2</sup> - Test for overall effect Total events Hebrogeneity: Tau <sup>2</sup> - Test for overall effect Total events Hebrogeneity: Tau <sup>2</sup> - Test for overall effect	16 1.96; Chi <sup>4</sup> , 2 = 0.84 (7 45 0.82; Ch <sup>2</sup> , 2 = 0.07 (7 ferences: Ch Treatmer Events Tr 6 1 9 0 0 2 18 = 1.07; Chi <sup>2</sup> ; Z = 0.56 (7 3 pplicable ; Z = 0.59 (7 2 - 0.55; Chi <sup>2</sup>	= 6.5 = 0. 248 = 16: = 0. # = 1 32 17 47 11 24 151 = 6.3 36 P = 1. 36 P = 1. 36 P = 1. 36 P = 0. 17 18 19 10 10 10 10 10 10 10 10 10 10	31 6, cf = 1 40) 43 67, df = 94) L75, df = Centro Events 1 0 2 5 0 0 4 11 12, df = 3 5 8 2 2 2 00) 13 14, df = 4 561, cf = 1 6 7 8 9 12 13 14, df = 4 13 14, df = 4 5 15 15 15 16 16 17 16 17 17 17 16 17 17 17 17 17 17 17 17 17 17	P = 1 216 7 $P = 1$ 1 $P = 1$ 32 15 13 15 21 15 23 15 23 16 3 P = 1 24 24 24 187 P = 1 19 15 15 21 21 15 21 21 21 21 21 21 21 21 21 21	100.0% 0.02); f <sup>2</sup> 0.02); f <sup>2</sup> 0.190, f 11.0% 13.9% 32.9% 21.6% 20.7% 20.7% 20.7% 100.0%	<ul> <li>35%</li> <li>1.03 (0.43, 2.47)</li> <li>58%</li> <li>42.8%</li> <li>Odds Ratio IV, Random, 95% CI</li> <li>0.41 (0.03, 5.00)</li> <li>2.70 (0.84, 296.15)</li> <li>0.43 (0.07, 2.43)</li> <li>1.50 (0.15, 6.48)</li> <li>1.00 (0.15, 6.48)</li> <li>1.38 (0.47, 4.11)</li> <li>39%</li> <li>405</li> </ul>	0.01	0,1 10 Favours (DC) Favours (BMT) Odds Ratio PV, Random, 95% C)	100
welve months follow	Total events Hebrogeneity: Tau <sup>2</sup> - Test for overall effect Total (95N CI) Total events Hebroggeneity: Tau <sup>2</sup> - Test for overall effect Test for overall effect Test for overall effect 3.6.1 RCTs Hofmeijer 2009 Juttier 2007 Juttier 2007 Juttier 2007 Juttier 2007 Juttier 2007 Zhao 2012 Subtotal (95N CI) Total events Hebrogeneity: Tau <sup>2</sup> - Test for overall effect 3.6.2 NRTs Rai 2014 Subtotal (95N CI) Total events Heberogeneity: Tau <sup>2</sup> - Test for overall effect Total events Heberogeneity: Tau <sup>2</sup> - Test for overall effect Total events Heberogeneity: Tau <sup>2</sup> - Test for overall effect Test for overall effect Test for overall effect Test for overall effect Test for subgroup diffect Test for subgroup diffect	16 1.96; Chi <sup>4</sup> , 2 = 0.84 (7 45 0.82; Ch <sup>2</sup> , 2 = 0.07 (7 ferences: Ch Treatmer Events T 6 1 9 0 0 2 18 = 1.07; Chi <sup>2</sup> ; Z = 0.56 (7 3 pplicable ; Z = 0.50 (7 Yereatmer ; Z = 0.50 (7 Ferences: Ch 1 3 pplicable ; Z = 0.50 (7 Ferences: Ch Treatmer Events T	= 6.5 = 0. 248 = 16: = 0. 1 <sup>2</sup> = 1 32 17 47 11 24 151 = 0.3 17 = 0. 1 <sup>2</sup> = 1 32 = 0. 1 <sup>2</sup> = 1 32 = 0. 1 <sup>2</sup> = 1 1 <sup>2</sup>	31 6, cf = 1 40) 43 67, df = 94) L75, df = Contro Events 1 0 2 5 0 0 4 11 12, df = 3 5 2 2 2 00) 13 14, df = 4 56) 2 2 2 00) 13 14, df = 4 56) 2 2 2 00) 13 14, df = 4 56) 2 2 2 00) 13 14, df = 4 56) 2 2 2 00) 13 14, df = 4 56) 2 2 2 0 0 15, df = 1 16 17 17 18 19 19 19 19 19 19 19 19 19 19	(P = 1 216 7 (P = 1 (P - 1 (P - 1 (P - 1 (P - 2 (P - 2 (P - 2 (P - 2 (P - 2 (P - 1 (P - 1 (P - 1 (P - 1 (P - 1 (P - 2 (P - 1 (P - 1 (P - 2 (P	100.0% 0.02); P 0.02); P 0.190, f 11.0% 13.9% 32.9% 21.6% 20.7% 20.7% 20.7% 100.0% 116; P - 0.740, P	<ul> <li>35%</li> <li>1.03 (0.43, 2.47)</li> <li>58%</li> <li>42.8%</li> <li>Odds Ratio IV, Random, 95% CI</li> <li>5.94 (0.86, 296.15) 0.41 (0.03, 5.00) 2.70 (0.86, 296.15) Not estimable Not estimable 0.43 (0.07, 2.63) 1.50 (0.36, 6.22)</li> <li>52%</li> <li>1.00 (0.15, 6.48) 1.00 (0.15, 6.48)</li> <li>1.38 (0.47, 4.11)</li> <li>39%</li> <li>05</li> <li>Odds Ratio IV, Random, 95% CI</li> </ul>	0.01	0,1 10 Favours (DC) Favours (BMT) Odds Ratio PV, Random, 95% CI	100
welve months follow 'hree years follow up	Total events Meterogeneity: Tau <sup>2</sup> - Test for overall effect Total (95N CI) Total events Meterogeneity: Tau <sup>2</sup> - Test for overall effect Test for overall effect Test for overall effect Study or Subgroup dif Study or Subgroup Juttler 2009 Juttler 2009 Juttler 2007 Juttler 2007 Juttler 2007 Juttler 2007 Juttler 2014 Slezins 2012 Vabedi 2007 Zhao 2012 Subtotal (95N CI) Total events Meterogeneity: Tau <sup>2</sup> - Test for overall effect 3.6.2 NRTs Raj 2014 Subtotal (95N CI) Total events Meterogeneity: Not at Test for overall effect Total (95N CI) Total events Meterogeneity: Tau <sup>4</sup> - Test for overall effect Total (95N CI) Total events Meterogeneity: Tau <sup>4</sup> - Test for overall effect Test for subgroup diff Study or Subgroup Guerts 2013	16 1.96; Chi <sup>4</sup> , 2 = 0.84 (7 45 0.82; Ch <sup>2</sup> , 2 = 0.07 (7 ferences: Ch Treatmer Events T 6 1 9 0 0 2 18 = 1.07; Chi <sup>2</sup> : Z = 0.56 (7 3 pplicable : Z = 0.59 (7 Ference: Ch 3 pplicable : Z = 0.59 (7) Treatmer Events T 3 pplicable : Z = 0.59 (7) Treatmer Events T 1 1 1 1 1 1 1 1 1 1 1 1 1	= 6.5 = 0. 248 = 16. = 0.1 1 <sup>2</sup> = 1 17 = 1. 32 17 11 20 24 151 = 6.3 16 = 1. 36 7 = 0. 151 = 0. 17 = 1 17 = 0. 17 = 1 17 = 1 17 = 0. 17 = 1 17 = 0. 17 = 0. 18 = 0. 19 = 0. 10 = 0. 10	31 (6, cf = 1 40) 43 57 57 57 57 67 67 67 67 67 67 67 67 67 6	P = 1 216 7 $P = 1$ 1 $P = 1$ 1 $P = 1$ 1 $P = 1$ 24 24 24 187 P = 1 24 187 24 187 24 187 24 24 187 24 24	100.0% 0.02); f <sup>2</sup> 0.02); f <sup>2</sup> 0.190, f 11.0% 13.9% 32.0% 21.6% 7%3% 20.7% 20.7% 20.7% 100.0%	<ul> <li>35%</li> <li>1.03 (0.43, 2.47)</li> <li>58%</li> <li>42.8%</li> <li>Odds Ratio IV, Randon, 95% CI</li> <li>5.94 (0.86, 296, 15) 0.41 (0.03, 5.00) 2.70 (0.86, 296, 15) 0.41 (0.03, 6.02)</li> <li>15.94 (0.86, 296, 15) 0.41 (0.03, 6, 296, 15) 0.43 (0.07, 2.63)</li> <li>1.50 (0.36, 6.22)</li> <li>52%</li> <li>1.00 (0.15, 6.48)</li> <li>1.38 (0.47, 4.11)</li> <li>39%</li> <li>- 0%</li> <li>Odds Ratio IV, Random, 95% CI</li> <li>3.20 (0.13, 81, 50)</li> </ul>	0.01	0,1 10 Favours (DC) Favours (BMT) Odds Ratio PV, Random, 95% CI	100
welve months follow hree years follow up	Total events Neterogeneity: Tau <sup>2</sup> - Test for overall effect Total (95N CI) Total events Neterogeneity: Tau <sup>2</sup> - Test for overall effect Test for overall effect Test for overall effect Study or Subgroup dif Study or Subgroup Juttler 2009 Juttler 2009 Juttler 2007 Juttler 2007 Juttler 2014 Slezins 2012 Vabedi 2007 Zhao 2012 Subtotal (95N CI) Total events Neterogeneity: Tau <sup>2</sup> - Test for overall effect 3.6.2 NRTs Rai 2014 Subtotal (95N CI) Total events Neterogeneity: Not a Test for overall effect Total (95N CI) Total events Neterogeneity: Tau <sup>4</sup> - Test for overall effect Total (95N CI) Total events Neterogeneity: Tau <sup>4</sup> - Test for overall effect Total (95N CI) Total events Neterogeneity: Tau <sup>4</sup> - Test for overall effect Test for overall effect Test for overall effect Test for overall effect Test for subgroup dif Study or Subgroup Guerts 2013 Total (95N CI)	16 1.96; Chi <sup>4</sup> , 2 = 0.84 (7 45 0.82; Ch <sup>4</sup> , 2 = 0.07 (7 ferences: Ch Treatmer Events T 6 1 9 0 0 2 18 = 1.07; Chi <sup>2</sup> : Z = 0.56 (7 3 pplicable : Z = 0.59 (7 Ferences: Ch 7 21 = 0.58; Ch <sup>4</sup> : Z = 0.59 (7 Ferences: Ch 1 3 pplicable : Z = 0.59 (7 Treatmer Events T 3 pplicable : Z = 0.59 (7 Treatmer Events T 3 1 1 1 1 1 1 1 1 1 1 1 1 1	= 6.5 = 0. 248 = 16: = 0: 1 <sup>2</sup> = 1 17 = 1 32 17 11 20 24 151 = 0.3 35 1 <sup>2</sup> = 0. 36 1 <sup>2</sup> = 0. 1 <sup>3</sup> 1 <sup></sup>	31 6, cf = 1 40) 43 57, df = 594) L75, df = Contro Events 1 0 2 5 0 0 4 11 12, df = 3 5 0 0 4 11 12, df = 3 5 0 0 13 14, df = 4 56) 2 2 2 00) 13 14, df = 4 56) 0 0 0 4 11 12, df = 3 5 0 0 0 0 4 11 12, df = 3 5 0 0 0 0 11 12, df = 3 5 0 0 0 0 13 14, df = 4 5 0 0 0 0 13 14, df = 4 5 0 0 0 0 0 13 14, df = 4 5 0 0 0 0 0 13 14, df = 4 5 0 0 0 0 13 14, df = 4 5 0 0 0 0 0 13 14, df = 4 5 0 0 0 0 0 0 0 0 0 0 0 0 0	P = 1 216 7 $P = 1$ 1 $P = 1$ 1 $P = 1$ 1 $P = 1$ 2 $1$ 2 $1$ 1 $1$ 1 $1$ 2 $1$ 1 $1$ 2 $1$ 1 $1$ 2 $1$ 1 $1$ 2 $1$	100.0% 0.02): 1° 0.02): 1° 0.02): 1° 0.02): 1° 0.02): 1° 100.0% 11.0% 12.0% 21.6% 7%.3% 21.6% 7%.3% 20.7% 20.7% 20.7% 100.0% 100.0% 100.0%	<ul> <li>35%</li> <li>1.03 (0.43, 2.47)</li> <li>58%</li> <li>42.8%</li> <li>Odds Ratio IV, Randon, 95% CI</li> <li>0.41 (0.03, 5.00)</li> <li>0.41 (0.03, 5.00)</li> <li>0.41 (0.03, 6.296, 15)</li> <li>0.41 (0.03, 6.48)</li> <li>Not estimable Not estimable 0.43 (0.07, 2.63)</li> <li>1.50 (0.36, 6.22)</li> <li>52%</li> <li>1.00 (0.15, 6.48)</li> <li>1.38 (0.47, 4.11)</li> <li>39%</li> <li>0%</li> <li>Odds Ratio IV, Random, 95% CI</li> <li>3.20 (0.13, 81.50)</li> <li>3.20 (0.13, 81.50)</li> <li>3.20 (0.13, 81.50)</li> </ul>	0.01	0,1 10 Favours (DC) Favours (BMT) Odds Ratio PV, Random, 95% CI	100
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welve months follow hree years follow up	Total events Neterogeneity: Tau <sup>2</sup> - Test for overall effect Total (95N CI) Total events Neterogeneity: Tau <sup>2</sup> - Test for overall effect Test for overall effect Test for overall effect Study or Subgroup dif Study or Subgroup Juttier 2007 Juttier 2007 Juttier 2007 Juttier 2007 Juttier 2007 Juttier 2007 Juttier 2007 Juttier 2007 Juttier 2007 Juttier 2014 Siezins 2012 Vabedi 2007 Zhao 2012 Subtotal (95N CI) Total events Neterogeneity: Tau <sup>2</sup> - Test for overall effect 3.6.2 NRTs Rai 2014 Subtotal (95N CI) Total events Neterogeneity: Not al Test for overall effect Total (95N CI) Total events Neterogeneity: Tau <sup>2</sup> - Test for subgroup dif Study or Su	16 1.96; Chi <sup>4</sup> , 2 = 0.84 (7 45 0.82; Ch <sup>2</sup> , 2 = 0.07 (P ferences: Ch Treatmer Events T 6 1 9 0 0 2 18 = 1.07; Chi <sup>2</sup> 2 = 0.56 (7 3 pplicable t Z = 0.59 (7 Treatmer Events T 1 uplicable 1 1 uplicable 1 1 0 1 0 0 0 0 0 0 0 0 0 0 0 0 0	= 6.5 = 0. 248 = 16: = 0.1 1 <sup>2</sup> = 1 17 11 20 24 151 = 0.3 35 P = 1. 36 P = 1. 36 P = 1. 37 187 = 0.3 31 31 31 31 31 31 31 31 31 3	31 6, cf = 1 40) 43 57, df = 94) L75, df = Contro Events 0 0 4 11 12, df = 3 56) 2 2 2 00) 13 14, df = 4 56) 2 2 2 00) 13 14, df = 4 56) 0 0 0 0 0 0 0 0 0 0 0 0 0	P = 1 216 7 $P = -1$ 1P1 1P1 1S - 2S -	100.0% 0.02): 1° 0.02): 1° 0.02): 1° 0.02): 1° 0.02): 1° 100.0% 11.0% 120.7% 20.7% 20.7% 100.0% 100.0% 100.0%	<ul> <li>35%</li> <li>1.03 (0.43, 2.47)</li> <li>58%</li> <li>42.8%</li> <li>Odds Ratio IV, Randon, 95% CI</li> <li>15.94 (0.36, 296, 15) 0.41 (0.03, 5.00) 2.70 (0.84, 8.68) Not estimable 0.43 (0.07, 2.63) 1.50 (0.36, 6.22)</li> <li>52%</li> <li>1.00 (0.15, 6.48)</li> <li>1.38 (0.47, 4.11)</li> <li>39%</li> <li>0%</li> <li>Odds Ratio IV, Random, 95% CI</li> <li>3.20 (0.13, 81.50)</li> <li>3.20 (0.13, 81.50)</li> </ul>	0.01	0,1 10 Favours (DC) Favours (BMT) Odds Ratio PV, Random, 95% CI	10

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Study or Subgroup 4.1.1 age <60 Chua 2015 Juttler 2007 Raffig 2013 Tsal 2012	Events 5 3	Total	Events	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
4.1.1 age <60 Chua 2015 Juttler 2007 Raffig 2013 Teal 2012	5 3	13	2				
Chua 2015 Juttler 2007 Raffig 2013	5 3	13				1	
Juttler 2007 Raffiq 2013 Test 2012	3		5	11	8.4%	0.52 [0.10, 2.66]	
Raffiq 2013		17	8	15	8.6%	0.19 [0.04, 0.94]	
Teal 2012	27	90	19	35	22.6%	0.36 [0.16, 0.81]	
12412012	10	18	2	4	5.1%	1.25 [0.14, 10.94]	
Vahedi 2007	5	20	14	18	9.6%	0.10 [0.02, 0.43]	
Zhao 2012	1	8	6	10	4.1%	0.10 [0.01, 1.10]	• • • • • •
Subtotal (95% CI)		166		93	58.5%	0.28 [0.15, 0.54]	-
Total events	51		55				
Test for overall effect: 7	Z = 3.86	(P = 0.0	0001)	316-05			
buttler 2014	16	40	44	63	22.6%	0 21 10 09 0 471	
Tsai 2012	4	24	28	38	12.1%	0.07 10.02 0.261	
7han 2012	2	16		13	6.8%	0.09 10.01 0 571	
Subtotal (95% CI)		89		114	41.5%	0.14 [0.07, 0.28]	•
Total events	22		80				
Heterogeneity: Tau <sup>2</sup> = (	0.04; Chi	2 = 2.2	2, df = 2	(P = 0.	33); I <sup>2</sup> =	10%	
Test for overall effect: 2	Z = 5.51	(P < 0.)	00001)	(1943) FT 533	19190		
Total (95% CI)		255		207	100.0%	0.21 [0.12, 0.35]	•
Total events	73		135				
Heterogeneity: Tau <sup>2</sup> = /	0.14; Chi	2 = 10.	49, df =	8 (P = 1	0.23); 12 .	24%	ton of the local statement of the statem
Test for overall effect: 2	Z = 5.95	(P < 0.0	00001)	100 C 100 C 100			0.01 0.1 1

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	Experim	ental	Cont	rol		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
4.2.1 age <60	- 000	1			1997	a successive and the second	
Chua 2015	2	13	0	11	8.0%	5.00 (0.22, 116.03)	
Juttler 2007	1	17	2	15	11.1%	0.41 [0.03, 5.00]	
Raffig 2013	4	90	9	35	22.7%	0.13 [0.04, 0.47]	
Vahedi 2007	2	18	0	18	8.1%	5.61 (0.25, 125.45)	
Zhao 2012 Subtotal (95% CI)	2	8 146	1	10 89	10.5% 60.3%	3.00 [0.22, 40.93] 0.99 [0.18, 5.53]	-
Total events	11		12				
Heterogeneity: Tau <sup>2</sup> = Test for overall effect	2.26; Ch Z = 0.01	$i^2 = 10.$ (P = 0.)	37, df = 99)	4 (P =	0.03); I <sup>z</sup> -	- 61%	
4.2.2 age >60							
Juttler 2014	3	16	4	13	17.3%	0.52 [0.09, 2.90]	· · · · · · · · · · · · · · · · · · ·
Zhao 2012 Subtotal (95% CI)	4	35	8	55 68	22.3%	0.76 [0.21, 2.73] 0.66 [0.24, 1.85]	-
Total events	7		12		2 7007103-		
Heterogeneity: Tau <sup>2</sup> = Test for overall effect	0.00; Ch Z = 0.79	$i^2 = 0.1$ (P = 0.1)	2, df = 1 43)	(P = 0	.73); l <sup>2</sup> =	0%	
Total (95% CI)		197		157	100.0%	0.71 [0.26, 1.94]	-
Total events	18		24				
Heterogeneity: Tau <sup>2</sup> = Test for overall effect	0.76; Ch Z = 0.67	$P^2 = 10.$ (P = 0.	78, df = 50)	6 (P =	0.10); 12	- 44%	0.01 0.1 1 10 100 Favours (DC) Favours (BMT)



Supplementary Material (Video/Media Files) Click here to download Supplementary Material (Video/Media Files): Supplementary Tables.docx