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| APPENDIX A-15: Question |
| **Should one type of hemostatic dressing compared with another type of hemostatic dressing be used for adults and children with severe, life-threatening external bleeding?** |
| **Population:** | Adults and children with severe, life-threatening external bleeding |
| **Intervention:** | Hemostatic dressings (QuikClot Combat Gauze, Neptune- PAD, Chito-Seal) |
| **Comparison:** | Hemostatic dressings (D-Stat Dry, Clo-Sur P.A.D, SyvekPatch) |
| **Main outcomes:** | Death owing to bleeding, cessation of bleeding (restoration of hemostasis), and time to hemostasis, death from any cause, decrease in bleeding, and adverse effects (e.g. wound infection, limb loss, re-bleeding, pain related to an intervention). Where possible, the EtD tables also include information regarding outcomes related to provider ability to use / ease of use / feasibility / satisfaction (for method of bleeding control) and predictors of use/response (for method of bleeding control). |
| **Setting:** | All studies performed in the out-of-hospital setting (direct evidence), as well as studies providing indirect evidence about the effects of interventions collected in combat (military) settings, simulations (i.e. human volunteers, human cadaver or other models excluding animal models), and studies performed in the hospital setting, that clinical content experts judged as performed in sufficiently similar conditions to still be informative.  |
| **Perspective:** | Of the first aid provider and/or patient |
| **Background:** | Traumatic injury is a leading cause of morbidity and mortality and a major cause of death from traumatic injury is uncontrolled bleeding. Tourniquets and hemostatic dressings have the potentially to prevent morbidity and mortality from traumatic bleeding. Therefore, it is easy to see that first aid care is essential to help prevent injury related morbidity and mortality, as injured persons can exsanguinate from severe injuries in only a few minutes.Current first aid recommendations for an individual with severe, life-threatening external bleeding includes applying direct pressure as standard therapy. Tourniquets and hemostatic dressings have been found to control bleeding effectively, therefore may be considered for use when standard measures are unable to control hemorrhage or in the situation where a first aid provider is unable to use standard first aid practices (for tourniquets) or for body areas where a tourniquet cannot be applied or is unable to control bleeding (for hemostatic dressings). There is no or limited data supporting the use of pressure points, elevation, or localized cold therapy.  |
| **Conflict of interests:** | None identified |

# Assessment

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| ProblemIs the problem a priority? |
| Judgement | Research evidence | Additional considerations |
| ○ No○ Probably no○ Probably yes● Yes○ Varies○ Don't know | Traumatic injury is the leading cause of injury related morbidity and mortality throughout the world, resulting in millions of hospitalizations each year. The leading cause of preventable mortality in injured patients is uncontrolled hemorrhage {Jacob 2014 67}. Hemorrhage is cited as the primary cause of death in 35% of traumatic mortalities and often contributes to death ultimately attributed to other causes {Kauvar 2006 S3}. In addition, trauma related deaths disproportionality affects those in low- and middle-income countries where well established pre-hospital trauma systems may not exist {World Health Organization 2018}. | While direct manual pressure is the gold standard for hemorrhage control in life-threatening bleeding, the addition of a hemostatic dressing could enhance the effectiveness of hemorrhage control.  |
| Desirable EffectsHow substantial are the desirable anticipated effects? |
| Judgement | Research evidence | Additional considerations |
| ○ Trivial○ Small● Moderate○ Large○ Varies○ Don't know |

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| **Certainty assessment** | **№ of patients** | **Effect** | **Certainty** | **Importance** |
| **№ of studies** | **Study design** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other considerations** | **one type of hemostatic dressing** | **another type of hemostatic dressing** | **Relative(95% CI)** | **Absolute(95% CI)** |
| Mortality due to bleeding - not reported |
| -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | CRITICAL  |
| Cessation of bleeding - not reported |
| -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | CRITICAL  |
| Time to hemostasis - In-hospital |
| 3  | randomised trials  | not serious  | not serious  | serious | not serious  | none  | Among three RCTs with a total of 750 patients undergoing endovascular procedures, one RCT with 606 patients showed a comparable time to hemostasis with a calcium ion releasing wound dressing pad (Neptune-PAD) and hemostatic thrombin covered bandage (D-Stat Dry), being 11.5 minutes (±8.0) and 12.4 minutes (±6.7) respectively {Schwarz 2009 53}. The second RCT with 90 patients showed a comparable time to hemostasis with a chitosan-based hemostasis pad (Chito-Seal) and a biopolymer-based hemostatic pad (Clo-Sur P.A.D.), being 16.2 minutes (±4.9) and 16.0 minutes (±5.3) respectively {Nguyen 2007 801}.The third RCT with 54 patients showed a comparable time to hemostasis with a poly-N-acetyl glucosamine hemostatic pad (SyvekPatch) and a thrombin covered bandage (D-Stat Dry), being 17.8 minutes (±1.3) and 17.5 minutes (±1.4), respectively {McConnell 2012 e1} | ⨁⨁⨁◯MODERATE  | CRITICAL  |
| Mortality due to all causes - In-hospital |
| 1 | randomised trials  | not serious  | not serious  | serious | very serious | none  | One RCT{Nguyen 2007 801} in the hospital setting with 90 patients undergoing endovascular procedures. This study showed no difference in mortality for chitosan-based hemostasis pad (Chito-Seal ) + manual pressure (ACT ≤ 250 sec) compared with biopolymer-based hemostatic pad (Clo-Sur P.A.D.) + Manual pressure (ACT≤ 250 sec), as no deaths were reported in either of the two study arms (0/47 vs 0/43 [RR=0.92, 95% CI: 0.02-45.22; p=1.0). | ⨁◯◯◯VERY LOW  | IMPORTANT  |

 | Overall, hemostatic dressings demonstrated cessation of bleeding when used and there was minimal difference between the various agents or types. Though the effects may vary based on device, they all show desirable effects in cessation of bleeding. |
| Undesirable EffectsHow substantial are the undesirable anticipated effects? |
| Judgement | Research evidence | Additional considerations |
| ○ Large○ Moderate○ Small○ Trivial● Varies○ Don't know |

| **Certainty assessment** | **№ of patients** | **Effect** | **Certainty** | **Importance** |
| --- | --- | --- | --- | --- |
| **№ of studies** | **Study design** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other considerations** | **one type of hemostatic dressing** | **another type of hemostatic dressing** | **Relative(95% CI)** | **Absolute(95% CI)** |
| Re-bleeding - In-hospital  |
| 2 | randomised trials  | serious | not serious  | serious | serious | none  | Among two RCTs with a total of 696 patients undergoing endovascular procedures, one RCT with 606 patients showed a lower rate of minor bleeding following use of the calcium ion releasing wound dressing Neptune-PAD (20/303 [6.6%]) compared with the hemostatic thrombin covered bandage D-Stat Dry (37/303 [12.2%]) (RR=0.54, 95% CI: 0.32-0.91; p=0.02), no major rebleeding events were observed in either group {Schwarz 2009 53}. The second RCT with 90 patients showed a comparable rate of rebleeding requiring further compression following use of the biopolymer-based hemostatic pad Clo-Sur P.A.D. (10/43 [23.2%]) and the chitosan-based hemostasis pad Chito-Seal (10/47 [21.2%]) (RR=1.09, 95% CI: 0.50-2.37; p=0.82) {Nguyen 2007 801} | ⨁◯◯◯VERY LOW  | IMPORTANT  |

In two case series with a total of 84 patients treated with hemostatic dressing, one study showed a 0/18 (0%) rebleeding rate (Peters 2014), and the other study 2/66 (3%) {te Grotenhuis 2016 1007}.There were five case series with a total of 257 patients receiving hemostatic dressing. Three case series (124 patients) that used chitosan-based dressing {Brown 2009 1, te Grotenhuis 2016 1007, Peters 2014 28} and 1 case series (30 patients) using kaolin-based hemostatic pad (QuikClot Combat Gauze) {Travers 2016 391} reported no adverse effects. However, one series of 10 cases receiving expandable hemostatic mini-sponges reported one case of retained sponges requiring surgical wound extension and retrieval (Warriner 2018 424), and one case series of 83 patients with QuikClot zeolite-based granules reported that 25% of patients experienced mild to severe pain and discomfort associated with the exothermic reaction from QuikClot, with 3 burn cases {Rhee 2008 1093}.There were three case series with a total of 82 patients receiving hemostatic dressing. One case series (64 patients) that used chitosan-based dressing {Wedmore 2006 655} and one case series (14 patients) using kaolin-based hemostatic pad (QuikClot Combat Gauze) {Ran 2010 584} reported no adverse effects. However, one case series that used QuikClot zeolite-based granules reported that 2/4 (50%) patients experienced superﬁcial burns in the soft tissues and at the wound edges as an apparent result of the exothermic reaction {Cox 2009 1537}. | There were no marked adverse effects noted in the above studies, however the actual outcome of adverse effects was not reported specifically. Previously reported undesirable effects of hemostatic agents include: First generation hemostatic dressings with zeolite were associated with exothermic reactions and associated tissue damage. Newer muco-adhesive agents (Chitosan-derived) lack exothermic reaction, are broken down by enzymatic reaction. Because they are shellfish based, there is theoretical risk of allergic reaction although no reports to date. Procoagulant supplement type of hemostatic dressings may not work with hypothermia and potential risk of distal thrombus formation reported.Data from other studies not involving hemostatic dressings compared with each other is also included here for demonstration of possible undesirable effects. |
| Certainty of evidenceWhat is the overall certainty of the evidence of effects? |
| Judgement | Research evidence | Additional considerations |
| ○ Very low● Low○ Moderate○ High○ No included studies |

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| The certainty of the evidence across all outcomes was determined to be very low with a few exceptions. Certainty downgrades were typically due to risk of bias, indirectness and/or imprecision. |

 | Varied outcomes (very low and moderate). For this reason, the certainty has been placed at low. |
| ValuesIs there important uncertainty about or variability in how much people value the main outcomes? |
| Judgement | Research evidence | Additional considerations |
| ○ Important uncertainty or variability○ Possibly important uncertainty or variability● Probably no important uncertainty or variability○ No important uncertainty or variability | No research evidence  | Like other forms of hemostasis for control of severe, life-threatening bleeding, the outcomes of reduced mortality and control of bleeding are valued. The main goal is to have rapid, effective bleeding cessation.There is no specific research evidence regarding the value of hemostatic dressings specifically.  |
| Balance of effectsDoes the balance between desirable and undesirable effects favor the intervention or the comparison? |
| Judgement | Research evidence | Additional considerations |
| ○ Favors the comparison○ Probably favors the comparison● Does not favor either the intervention or the comparison○ Probably favors the intervention○ Favors the intervention○ Varies○ Don't know | Research demonstrates that hemostatic dressings stop hemorrhage and do it more quickly than direct pressure or pressure dressings alone. There was limited difference between the types in the studies.Among three RCTs with a total of 750 patients undergoing endovascular procedures, one RCT with 606 patients showed a comparable time to hemostasis with a calcium ion releasing wound dressing pad (Neptune-PAD) and hemostatic thrombin covered bandage (D-Stat Dry), being 11.5 minutes (±8.0) and 12.4 minutes (±6.7) respectively {Schwarz 2009 53}. The second RCT with 90 patients showed a comparable time to hemostasis with a chitosan-based hemostasis pad (Chito-Seal) and a biopolymer-based hemostatic pad (Clo-Sur P.A.D.), being 16.2 minutes (±4.9) and 16.0 minutes (±5.3) respectively {Nguyen 2007 801}. The third RCT with 54 patients showed a comparable time to hemostasis with a poly-N-acetyl glucosamine hemostatic pad (SyvekPatch) and a thrombin covered bandage (D-Stat Dry), being 17.8 minutes (±1.3) and 17.5 minutes (±1.4), respectively {McConnell 2012 E1}. One RCT in the hospital setting among 90 patients undergoing endovascular procedures. This study showed no difference in mortality for chitosan-based hemostasis pad (Chito-Seal ) + manual pressure (ACT ≤ 250 sec) compared with biopolymer-based hemostatic pad (Clo-Sur P.A.D.) + Manual pressure (ACT≤ 250 sec), as no deaths were reported in either of the two study arms (0/47 vs 0/43 [RR=0.92, 95% CI: 0.02-45.22; p=1.0) {Nguyen 2007 801}Among two RCTs with a total of 696 patients undergoing endovascular procedures, one RCT with 606 patients showed a lower rate of minor bleeding following use of the calcium ion releasing wound dressing Neptune-PAD (20/303 [6.6%]) compared with the hemostatic thrombin covered bandage D-Stat Dry (37/303 [12.2%]) (RR=0.54, 95% CI: 0.32-0.91; p=0.02), no major re-bleeding events were observed in either group {Schwarz 2009 53}. The second RCT with 90 patients showed a comparable rate of re-bleeding requiring further compression following use of the biopolymer-based hemostatic pad Clo-Sur P.A.D. (10/43 [23.2%]) and the chitosan-based hemostasis pad Chito-Seal (10/47 [21.2%]) (RR=1.09, 95% CI: 0.50-2.37; p=0.82) {Nguyen 2007 801}. |  |
| Resources requiredHow large are the resource requirements (costs)? |
| Judgement | Research evidence | Additional considerations |
| ○ Large costs● Moderate costs○ Negligible costs and savings○ Moderate savings○ Large savings○ Varies○ Don't know | No research evidence identified. We were able to review medical supply catalogs and sales websites.  | There would be a cost to purchase and stock devices as well as training to implement them. Training costs would include development of material, training aids, instructor training and first aid provider training.Hemostatic dressings will require initial expense and replacement costs due to use and expiration. Based on review of these sites, in Belgium hemostatic dressings costs: QuickClot: 60€ Selox applicator 40€ or bandage: 60€. In comparison passive dressings (without hemostatic agents): 15€ Simple hemostatic dressings in first aid (used by Belgian Red Cross): +/-1€ New Israeli bandages: 10€.Dressings range in price in different countries, from $10 to $50 USD.There is minimal difference between certain types of hemostatic dressings. |
| Certainty of evidence of required resourcesWhat is the certainty of the evidence of resource requirements (costs)? |
| Judgement | Research evidence | Additional considerations |
| ○ Very low○ Low○ Moderate○ High● No included studies | No research evidence identified.  | Very little data is available to assess the individual and population cost of hemostatic dressing implementation. The cost of these dressings can be found online. |
| Cost effectivenessDoes the cost-effectiveness of the intervention favor the intervention or the comparison? |
| Judgement | Research evidence | Additional considerations |
| ○ Favors the comparison○ Probably favors the comparison○ Does not favor either the intervention or the comparison○ Probably favors the intervention○ Favors the intervention○ Varies● No included studies | No research evidence identified.  | While it is difficult to determine the cost of a single life, the benefit of a life saved outweighs the cost of a single dressing. However, the costs of being prepared for the unlikely event of an uncontrollable junctional bleed likely to be very high from a system point of view. In addition, if widespread use is encouraged in individual lay providers there is a moderately high from an individual point of view. As there is minimal difference between types, providers or those who oversee first aid providers could choose the dressing that is more readily available and cost-effective in their area.As these agents can be used on both junctional and extremity bleeding and can be used as an adjunct to direct manual pressure perhaps these are the most cost-effective intervention.  |
| EquityWhat would be the impact on health equity? |
| Judgement | Research evidence | Additional considerations |
| ○ Reduced● Probably reduced○ Probably no impact○ Probably increased○ Increased○ Varies○ Don't know | No research evidence identified.  | As these agents offer an expense above direct manual pressure alone, this may reduce health equity to rural areas that may be less likely to afford hemostatic dressings but may benefit the most due to prolonged transport times. In addition, on a systems level, some organizations may not be able to purchase these due to the cost.As there is minimal difference between types, providers or those who oversee first aid providers could choose the dressing that is more readily available and cost-effective in their area. |
| AcceptabilityIs the intervention acceptable to key stakeholders? |
| Judgement | Research evidence | Additional considerations |
| ○ No○ Probably no○ Probably yes○ Yes● Varies○ Don't know | * HemCon ChitoGauze – 83% (55/66) providers were "satisfied or very satisfied" with using chitosan-coated gauze dressing {te Grotenhuis 2016 1007}
* HemCon ChitoGauze – Satisfaction rated with a mean of 7.6 (out of 10) {Brown 2009 1}

 | While there are few studies regarding acceptability, these agents are somewhat similar to standard dressings and therefore are likely acceptable to key stakeholders. Studies demonstrate that both military and emergency medical services providers are willing to apply hemostatic dressings. No data is yet available for first aid providers. Some devices have obtained FDA approval, others have not. Many providers have no (or limited) experience with these dressings.As there is minimal difference between types, providers or those who oversee first aid providers could choose the dressing that is more readily available and cost-effective in their area.There is likely regional variability in acceptability. There is a current study underway looking at first aid provider acceptance of hemostatic dressings. This may help determine the level of acceptability.  |
| FeasibilityIs the intervention feasible to implement? |
| Judgement | Research evidence | Additional considerations |
| ○ No○ Probably no● Probably yes○ Yes○ Varies○ Don't know | HemCon ChitoGauze – 83% (55/66) providers were "satisfied or very satisfied" with using chitosan-coated gauze dressing {te Grotenhuis 2016 1007}* HemCon ChitoGauze – Satisfaction rated with a mean of 7.6 (out of 10) {Brown 2009 1}
* Skills testing within 6 months of training and implementation of QuikClot Combat Gauze showed proficiency of 98.5% (326 of 331 providers) {Zietlow 2015 48}.
 | Feasibility data primarily comes from military and emergency medical services implementation.Hemostatic dressings have been used in the military and emergency medical services, however, the data regarding implementation in the lay first aid setting is limited. There are legal and prescribing barriers in some countries as hemostatic dressings are considered medications in countries such as Belgium and Australia. However, there is the consideration that if first aid guidelines recommend either hemostatic dressing or tourniquets this may help overcome those barriers. Training issues must be considered for either agent. In some countries, such as Australia, they are only available through a prescription, making access potentially difficult.As there is minimal difference between types, providers or those who oversee first aid providers could choose the dressing that is more readily available and cost-effective in their area. |

# Summary of judgements

|  | **Judgement** |
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| **Problem** | No | Probably no | Probably yes | **Yes** |  | Varies | Don't know |
| **Desirable Effects** | Trivial | Small | **Moderate** | Large |  | Varies | Don't know |
| **Undesirable Effects** | Large | Moderate | Small | Trivial |  | **Varies** | Don't know |
| **Certainty of evidence** | Very low | **Low** | Moderate | High |  |  | No included studies |
| **Values** | Important uncertainty or variability | Possibly important uncertainty or variability | **Probably no important uncertainty or variability** | No important uncertainty or variability |  |  |  |
| **Balance of effects** | Favors the comparison | Probably favors the comparison | **Does not favor either the intervention or the comparison** | Probably favors the intervention | Favors the intervention | Varies | Don't know |
| **Resources required** | Large costs | **Moderate costs** | Negligible costs and savings | Moderate savings | Large savings | Varies | Don't know |
| **Certainty of evidence of required resources** | Very low | Low | Moderate | High |  |  | **No included studies** |
| **Cost effectiveness** | Favors the comparison | Probably favors the comparison | Does not favor either the intervention or the comparison | Probably favors the intervention | Favors the intervention | Varies | **No included studies** |
| **Equity** | Reduced | **Probably reduced** | Probably no impact | Probably increased | Increased | Varies | Don't know |
| **Acceptability** | No | Probably no | Probably yes | Yes |  | **Varies** | Don't know |
| **Feasibility** | No | Probably no | **Probably yes** | Yes |  | Varies | Don't know |

# Type of recommendation

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| Strong recommendation against the intervention | Conditional recommendation against the intervention | Conditional recommendation for either the intervention or the comparison | Conditional recommendation for the intervention | Strong recommendation for the intervention |
| ○  | ○  | X  | ○  | ○  |

# Conclusions

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| Recommendation |
| Due to limited data there is not strong enough evidence to recommend for or against any one specific hemostatic dressing.  |
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| Justification |
| * The task force recognizes that the use of hemostatic dressings provides an additional material and training expense that may increase healthcare disparity in some cases. In addition, implementation of the use hemostatic dressings in some areas may not be feasible due to restrictions in availability for lay providers. Therefore, we feel that local conditions may dictate the availability and type of hemostatic dressing.
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| Subgroup considerations |
| N/A |

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| Implementation considerations |
| Training materials would need to be developed and be flexible from country to country (or region to region). |

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| Monitoring and evaluation |
| Groups who implement the device should track use and success of use (and adverse events) |

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| Research priorities |
| There is limited research on the use of hemostatic dressings by first aid providers and no clear answer regarding if one type of device or agent is superior to another.**References**Brown MA, Daya MR, Worley JA. Experience with chitosan dressings in a civilian EMS system. J Emerg Med. 2009 Jul;37(1):1–7.McConnell MK, McDilda K, Bridges R, Marsh N, Jenkins G, Dowdy J, et al. Comparison of different methods for achieving hemostasis after arterial sheath removal. J Cardiovasc Nurs. 2012;27(4):E1-5. Nguyen N, Hasan S, Caufield L, Ling FS, Narins CR. Randomized controlled trial of topical hemostasis pad use for achieving vascular hemostasis following percutaneous coronary intervention. Catheter Cardiovasc Interv Off J Soc Card Angiogr Interv. 2007;69(6):801–7.Peters JH. Massive bleeding: the prehospital use of hemostatic bandages. AirRescue Mag. 2014;4(Journal Article):28–31.Ran Y, Hadad E, Daher S, et al. QuikClot Combat Gauze use for hemorrhage control in military trauma: January 2009 Israel Defense Force experience in the Gaza Strip--a preliminary report of 14 cases. Prehosp Disaster Med. 2010 Nov-Dec;25(6):584-8.Rhee P, Brown C, Martin M, Salim A, Plurad D, Green D, et al. QuikClot use in trauma for hemorrhage control: case series of 103 documented uses. J Trauma. 2008;64(4):1093–9. Schwarz T, Rastan A, Pochert V, Sixt S, Schwarzwalder U, Burgelin KH, et al. Mechanical compression versus haemostatic wound dressing after femoral artery sheath removal: a prospective, randomized study. VASAZeitschrift Gefasskrankheiten. 2009;38(1):53–9te Grotenhuis R, van Grunsven PM, Heutz WMJM, Tan ECTH. Prehospital use of hemostatic dressings in emergency medical services in the Netherlands: A prospective study of 66 cases. Injury. 2016;47(5):1007–11. Zietlow JM, Zietlow SP, Morris DS, Berns KS, Jenkins DH. Prehospital Use of Hemostatic Bandages and Tourniquets: Translation From Military Experience to Implementation in Civilian Trauma Care. J Spec Oper Med Peer Rev J SOF Med Prof. 2015;15(2):48–53.  |
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**Other References (not listed in above table)**

Jacobs L and Burns KJ. *The Hartford Consensus to improve survivability in mass casualty events: Process to policy.* Am J Disaster Med. 2014;**9**(1):67-71.

Kauvar DS, Lefering R, and Wade CE. *Impact of hemorrhage on trauma outcome: an overview of epidemiology, clinical presentations, and therapeutic considerations.* J Trauma. 2006;**60**(6 Suppl):S3-11.

World Health Organization. *Injuries*. [cited 2018 21-JUN-2018]; Available from: <http://www.who.int/topics/injuries/en/>.