

MEDICAZIONI ANTIMICROBICHE CON CLOREXIDINA: EVIDENZE DI EFFICACIA

*What is new for the prevention of catheter-
related bloodstream infections?*

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RISKS OF DEATH FROM ALL CAUSES, MAJOR CARDIO- VASCULAR EVENTS, AND FATAL INFECTIONS ASSOCIATED WITH DIALYSIS VASCULAR ACCESS TYPES

Reference Annual Event Risk ^a	Vascular Access Comparison	Meta-Analytical RR (95% CI)	Heterogeneity (I ² ; P Value)	Number of Additional Events per 1000 Patients Exposed per Year (95% CI)
All-cause mortality				
0.20 for fistula users	Catheter versus fistula	1.53 (1.40–1.67)	83.9%; <0.01	106 (80–134) excess with catheter
0.24 for graft users	Catheter versus graft	1.38 (1.25–1.52)	86.2%; <0.01	91 (60–125) excess with catheter
0.20 for fistula users	Graft versus fistula	1.18 (1.09–1.27)	82.1%; <0.01	36 (18–54) excess with graft
Major cardiovascular events				
0.10 for fistula users	Catheter versus fistula	1.38 (1.24–1.54)	0%; 0.47	38 (24–54) excess with catheter
0.11 for graft users	Catheter versus graft	1.26 (1.11–1.43)	0%; 0.57	28 (12–46) excess with catheter
0.10 for fistula users	Graft versus fistula	1.07 (0.95–1.21)	0%; 0.52	7 (–5–21) ^b excess with graft
Fatal infections				
0.03 for fistula users	Catheter versus fistula	2.12 (1.79–2.52)	0%; 0.82	28 (20–38) excess with catheter
0.04 for graft users	Catheter versus graft	1.49 (1.15–1.93)	0%; 0.23	17 (5–32) excess with catheter
0.03 for fistula users	Graft versus fistula	1.36 (1.17–1.58)	0%; 0.78	9 (4–15) excess with graft

Pietro Ravani et al. J Am Soc Nephrol 14:465-473, 2013

EPIDEMIOLOGY OF CRBSI

- Incidence of CRBSI reported varies from country to country and even hospital to hospitals.
- A meta-analysis done at the Johns Hopkins University showed that bloodstream infections (BSIs) were the third leading cause of hospital-acquired infections.
- These infections have an attributable mortality rate of 12% to 25%.
- Individuals counteract 250,000 BSIs each year in the U.S., 60% of CRBSIs were caused by micro-organisms from the patient's skin.
- CRBSIs often originate in emergency rooms and intensive-care units, where 5.3 bloodstream infections occur per thousand days of central venous catheter insertion.

Parameswaran R, et al.. Intravascular catheter-related infections in an Indian tertiary care hospital. *J Infect Dev Ctries.* 2011;5:452–8

- CRBSI is one of the most common forms of bacterial infection in patients receiving haemodialysis (HD), with an estimated incidence of 1.2–2.5 per 1000 patient-days

Country	Incidence	Study information
Canada	1.2/1000 Pt-days	N = 527, half of the patients were new HD starts, the other half were continuing HD with access change
USA	2.5/1000 Pt-days	N = 47, inpatients admitted to hospital
USA	0.4/1000 Pt-days	N = 445, outpatients, <i>S. aureus</i> bacteremia only
Spain	1.6/1000 Pt-days	N = 51, outpatients, monitored by surveillance cultures
Canada	1.6/1000 Pt-days	N = 94, outpatients, tunneled cuffed catheters, surveillance cultures

Lata et al. *Canadian Journal of Kidney Health and Disease* (2016) 3:24

- Among outpatient hemodialysis facilities reporting to the NHSN, the pooled mean rate of BSI among patients with permanent CVCs was 4.2 cases per 100 patient-months (roughly 1.4 cases per 1000 catheter-days)₁
- ***Nowadays, the benchmark rate for catheter-related bloodstream infections is about 1 episode per patient for 1000 catheter days*** ₂
- Exit-site care is particularly important for catheter-related infections prevention₃

1. Klevens RM, Edwards JR, Andrus ML, et al. Dialysis surveillance report: National Healthcare Safety Network (NHSN)—data summary for 2006. *Semin Dial* 2008;21:24–28
2. Beathard GA et al. Infection associated with tunnelled hemodialysis catheters. *Semin Dial* 2008; 21: 528-538.
3. Timsit JF et al. A multicentric analysis of catheter-related infection based on a hierarchical model. *Intensive Care Med* 2012, 38:1662-72

PREVENTION OF CATHETER RELATED INFECTIONS (NICE GUIDELINES 7.1-7.4)

- **Guideline 7.1 – Minimise the use of venous catheters**

We recommend that central venous catheters should be employed as a method of **last resort for longer term vascular access** to reduce the overall risk of infectious complications and the burden of central venous stenosis in haemodialysis patients (1B).

- **Guideline 7.2 – Minimising the risk of catheter related infection**

We recommend that aseptic technique should be mandatory at every manipulation of central venous dialysis catheters (2C).

- **Guideline 7.3 – Minimising the risk of catheter related infection**

We recommend that the catheter exit site should be cleaned with Chlorhexidine 2% (1A).

- **Guideline 7.4 – Minimising the risk of catheter related infection**

We suggest that an antimicrobial or antibiotic lock solution be used to reduce catheter related bacteraemia and other infections (1A).

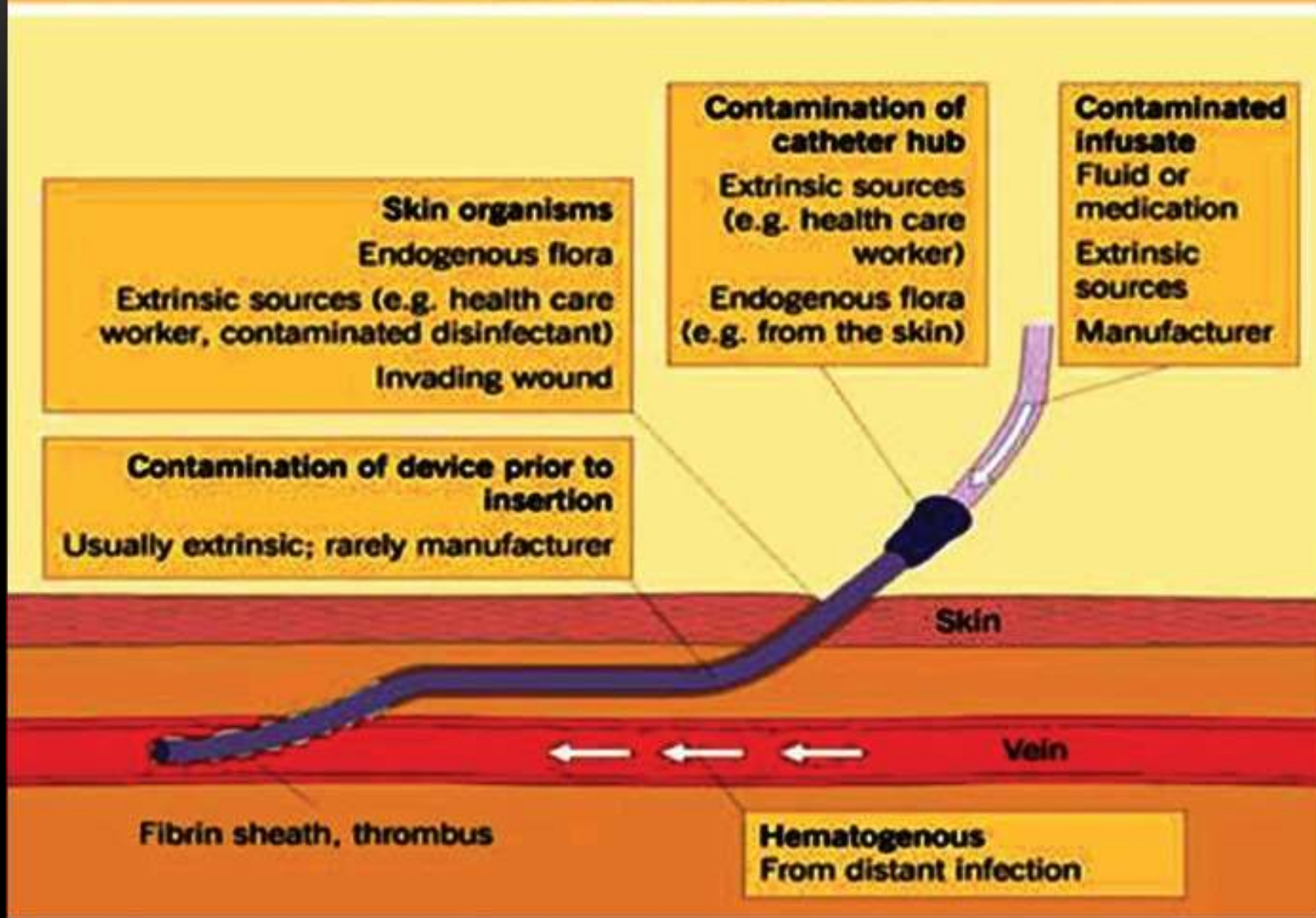
THE EXIT SITE PROBLEM CLINICAL PRACTICE GUIDELINE VASCULAR

ACCESS FOR HAEMODIALYSIS UK RENAL ASSOCIATION 6TH EDITION FINAL VERSION

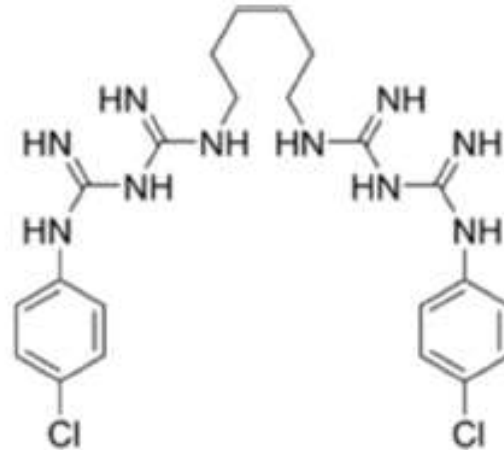
- For venous catheters, the **exit site** remains a potential source of infection.
- The **exit site** should be cleaned with **Chlorhexidine 2%**. This has been shown to be superior to povidine in a number of settings*
- The **exit site** should be covered with a non-occlusive secure dressing to protect the exit site between dialysis
- Patients should be educated on the importance of maintaining the integrity of the dressing and the importance of reporting of problems with the **exit site**.
- At each dialysis the **exit site** should be inspected and evidence of inflammation recorded and appropriate intervention should take place.

*Lancet 2015 Nov 21;386:2069-77 Mimosz O et al. Clean trial investigators

POTENTIAL ROUTES OF INFECTION

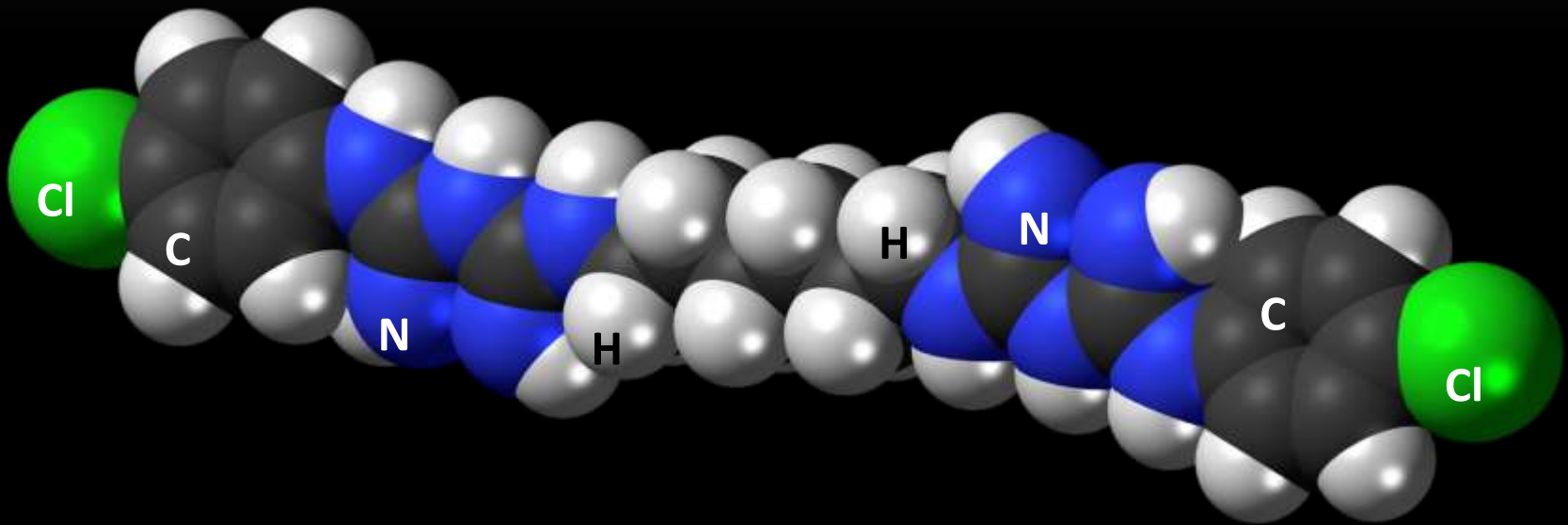
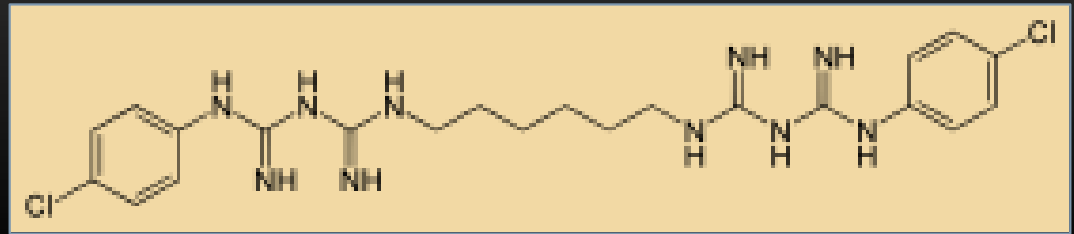


CHLORHEXIDINE CATIONIC POLYBIGUANIDE (BISBIGUANIDE)



- In healthcare, Chlorhexidine Digluconate (CHG) is one of the common forms of Chlorhexidine
 - Soluble in water - - enhances delivery of CHG
 - Commonly used in a solution with alcohol
- Chlorhexidine Diacetate (DHA) has been bonded with polyurethane for use in medical devices

CHLORHEXIDINE



Chlorhexidine is active against Gram-positive and Gram-negative organisms, facultative anaerobes, aerobes, and yeasts

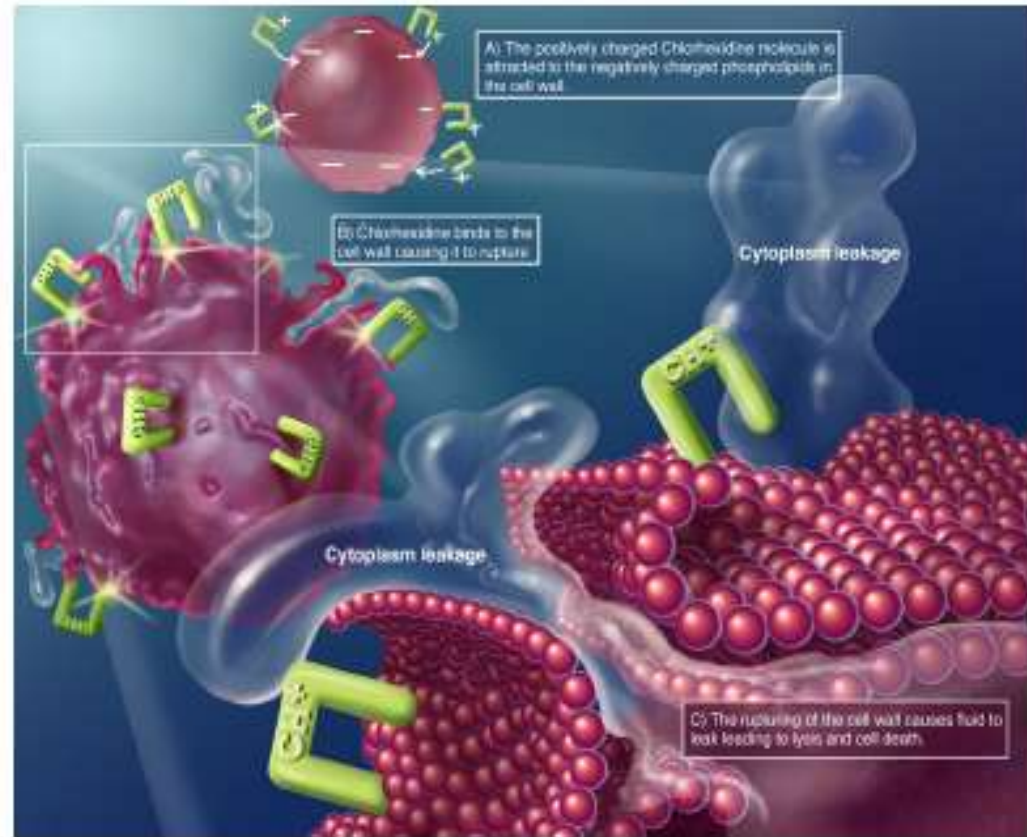
Colour code: Carbon, C: black Hydrogen, H: white Nitrogen, N: blue Chlorine, Cl: green

CHLORHEXIDINE'S MECHANISM OF ACTION

- Broad spectrum (Gram-positive and Gram-negative bacteria, fungi and enveloped viruses)
- Bactericidal and/or bacteristatic depending on concentration
- Works rapidly (can kill 100% of bacteria within 30 seconds)
- Can kill all categories of microbes
 - Little risk for development of resistance

CHLORHEXIDINE'S MECHANISM OF ACTION (2)

- Binds to cell wall –
interferes with osmosis
–Destabilizes, but does not lyse cell
- Then binds to cytoplasmic (inner) membrane – - - - - > leakage of intercellular contents - - - - > cell death
- Some ability to inhibit development of biofilm formation



CHLORHEXIDINE DRESSING & VASCULAR ACCESS

- BioPatch® by Ethicon (Chlorhexidine Sponge)
- Tegaderm CHG® by 3M (Chlorhexidine Gel)
- IV Clear™ by Covalon (Chlorhexidine/Silver Dressing)
- GuardIVa™ by Hemcon (Chlorhexidine/Hemostatic Dressing)



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3M™ and Tegaderm™ are trademarks of 3M.
IV Clear and Covalon are registered trademarks of Covalon Technologies Ltd.
HemoCon and GuardIVa are trademarks or registered trademarks of Hemcon Technologies Incorporated.



I TAMPONI ANTISETTICI A BASE DI CLOREXIDINA PIÙ UTILIZZATI IN COMMERCIO

3M™ Tegaderm™ CHG



Biopatch® johnson johnson

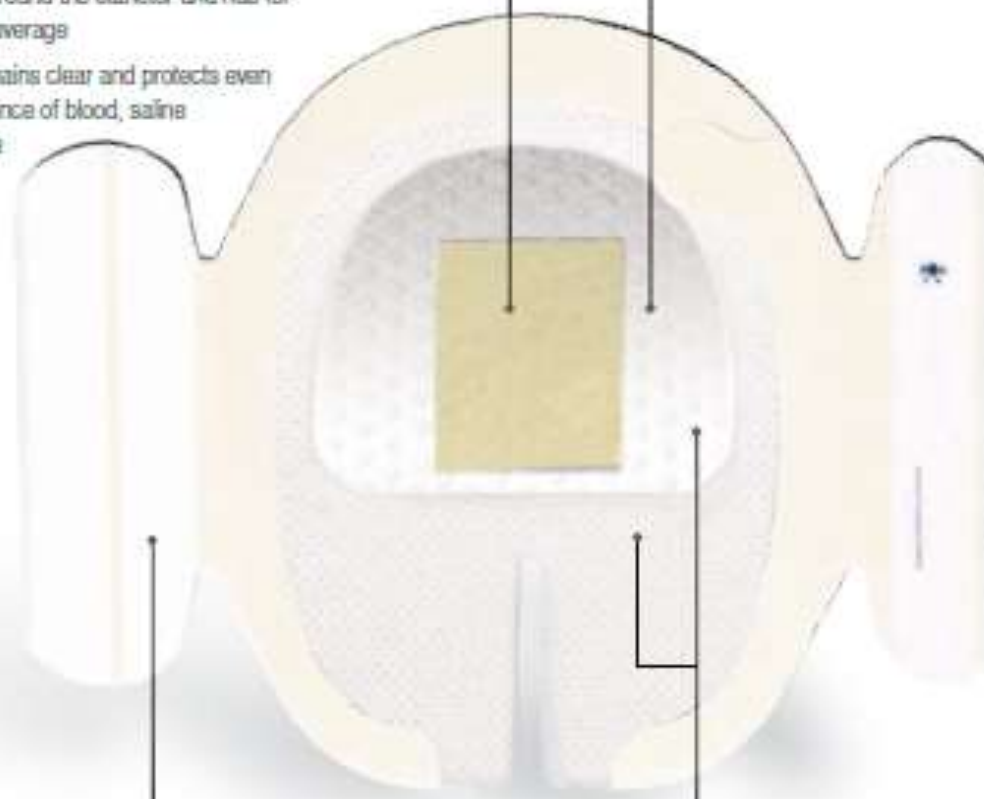


Integrated CHG Gel Pad

- Antimicrobial CHG is integrated into the film, so it can't be dropped, forgotten or applied incorrectly
- Conforms around the catheter and hub for complete coverage
- The gel remains clear and protects even in the presence of blood, saline and exudate

Highly Breathable Transparent Film

- Provides continuous site observation
- Provides a waterproof, sterile barrier to external contaminants including liquids, bacteria and viruses*
- Promotes moisture evaporation and improved securement
- Conforms to body contours, flexes with patient movement



Sterile Tape Strips

- Enhance stabilization**
- Improve protocol compliance
- Are precut for anchoring hubs, lumens and tubing
- Include preprinted labels for documenting dressing changes

Advanced Catheter Securement

- Reinforced stabilization border and notch designed for advanced securement
- Soft cloth border adhesive forms seal around catheter site
- Patterned film adhesive holds strongly, manages moisture and releases gently

THE TECHNOLOGY



- **Description of the technology**

1. The 3M™ Tegaderm™ CHG IV securement dressing (Tegaderm CHG) is a **sterile transparent semipermeable polyurethane adhesive dressing** with an **integrated gel pad containing a 2% concentration by weight of chlorhexidine gluconate (CHG)**.
2. Tegaderm CHG is used to secure percutaneous devices and to cover and protect central venous and arterial catheter insertion sites.
3. It aims to provide an effective barrier against external contamination. The dressing and the integrated gel pad are transparent to allow observation of the catheter insertion site.
4. The integrated gel pad is designed to reduce skin and catheter colonisation in order to reduce CRBSI.

3M™ Tegaderm™ CHG Chlorhexidine Gluconate I.V. Securement Dressings brochure

THE 3M TEGADERM CHG IV SECUREMENT DRESSING FOR CENTRAL VENOUS AND ARTERIAL CATHETER INSERTION SITES

Medical technology guidance Published: 22 July 2015 nice.org.uk/guidance/mtg25

• Recommendations

1. The case for adopting the 3M™ Tegaderm™ CHG IV securement dressing for central venous and arterial catheter insertion sites is supported by the evidence.(1)
2. The 3M™ Tegaderm™ CHG IV securement dressing should be considered for use in critically ill adults who need a central venous or arterial catheter in intensive care or high risk units.
3. The estimated cost saving from using a 3M™ Tegaderm™ CHG IV securement dressing (Tegaderm CHG) instead of a standard transparent semipermeable dressing is £73 per patient

1. Timsit JF et al. Randomised controlled trial of chlorhexidine dressing and highly adhesive dressing for preventing catheter-related infections in critically ill adults *Am J Respir Crit Care med* 2012 Dec 15 ;186: 1272-8

TEGADERM CHG BENEFIT

- **The claimed benefits of 3M™ Tegaderm™ CHG IV presented by the company are¹:**
 1. A 60% reduction in the incidence of CRBSI in adult critical care patients with intravascular catheters.
 2. Reduced risk of mortality due to catheter-related infections.
 3. Reduced incidence of skin and catheter colonisation during treatment with central venous catheters or arterial catheters.
 4. Reduced length of stay in critical care or high dependency units.
 5. Reduced costs for diagnosis of CRBSI.
 6. Reduced material and staff costs for treatment of catheter-related

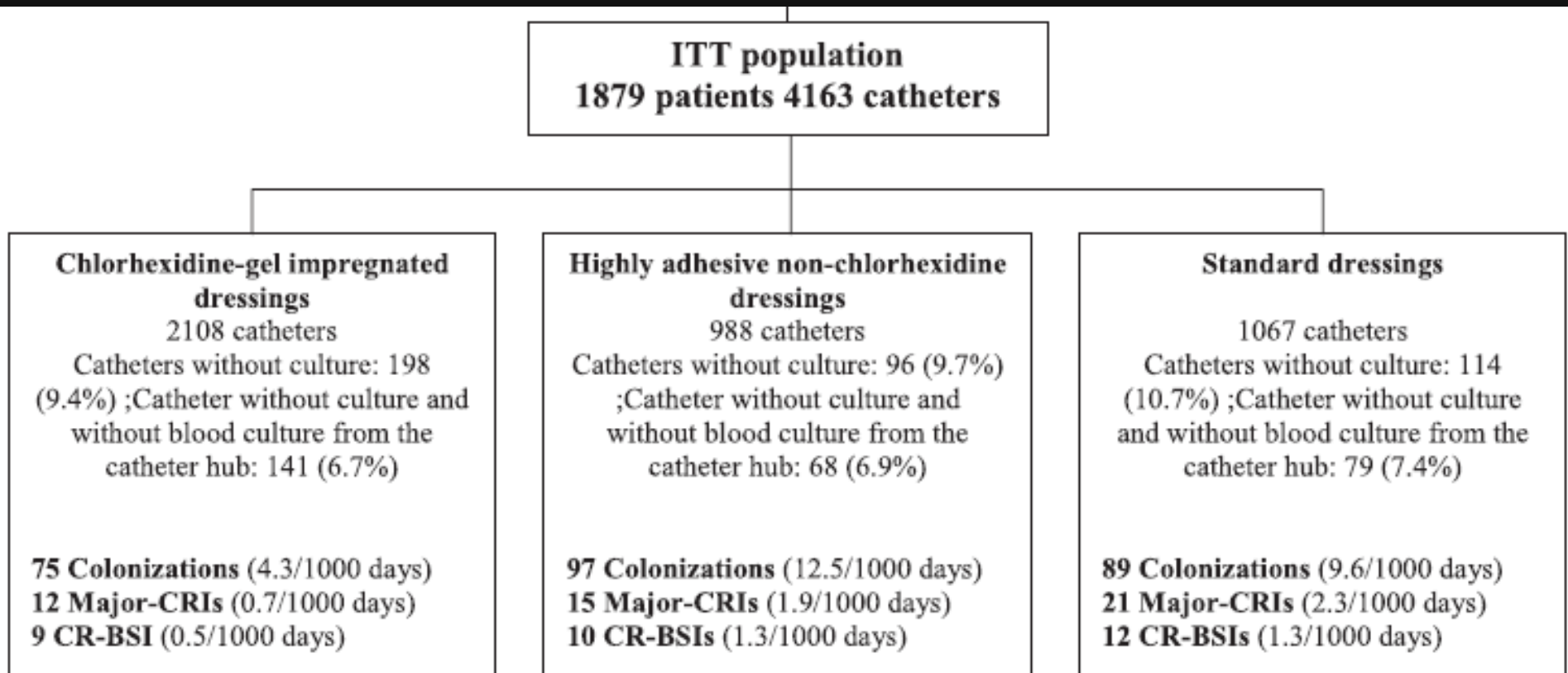
1- Medical technology guidance Published: 22 July 2015 [nice.org.uk/guidance/mtg25](https://www.nice.org.uk/guidance/mtg25)

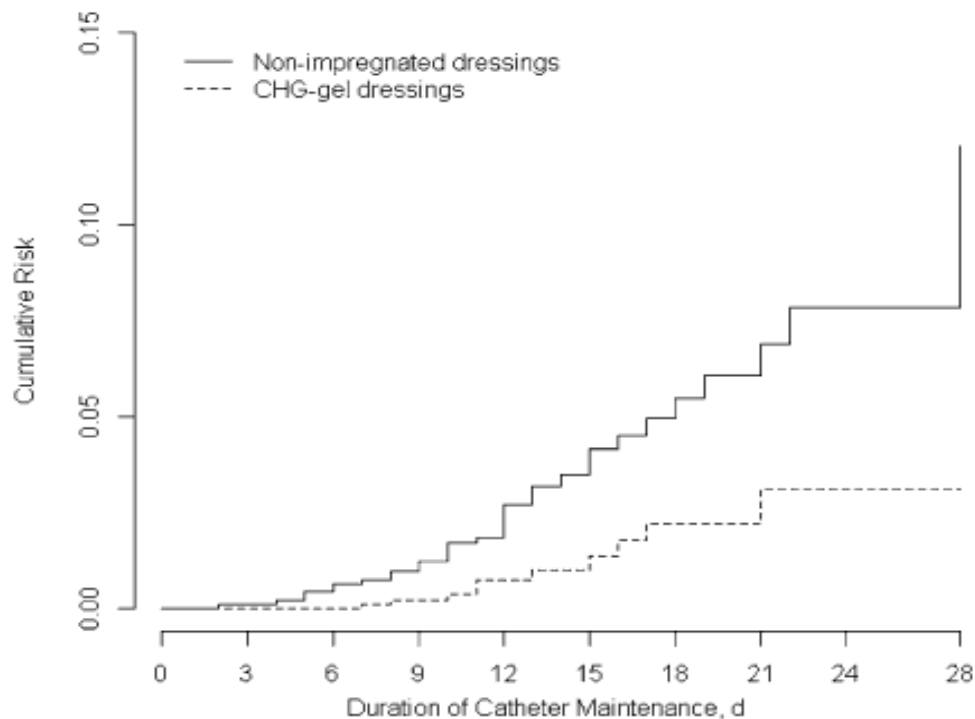
THE EVIDENCE NICE.ORG.UK/GUIDANCE/MTG25

MAIN REFERENCES

- Randomized controlled trial of Chlorhexidine dressing and highly adhesive dressing for preventing catheter-related infections in critically ill adults. *Timsit JF, Mimoz O, Mourvillier B, Souweine B, Garrouste-Orgeas M et al. American Journal of Respiratory and Critical Care Medicine 2012; 186 (12):1272-1278.*
- Growth inhibition of microorganisms involved in catheter related infections by an antimicrobial transparent I.V. dressing containing Chlorhexidine gluconate (CHG). *Hensler JP, Schwab DL, Olson LK, Palka-Santini M. 19th Annual Conference of the European Society of Clinical Microbiology and Infectious Diseases; 2009 May 16-19; Helsinki, Finland*
- Antimicrobial activity of a Chlorhexidine intravascular catheter site gel dressing. (7 days) *Karpanen TJ, Casey AL, Conway BR, Lambert PA, Elliott TSJ Journal of Antimicrobial Chemotherapy 2011; 66: 1777-1784.*
- Chlorhexidine impregnated dressing for prevention of catheter-related bloodstream infection: A meta-analysis. *Nasia Safdar, John C O'Horo, Aiman Ghufuran, Allison Bearden, Maria Eugenia Didier, Dan Chateau, Dennis G. Maki Crit Car Med 2014 Jul;42(7):1703-13*

RANDOMIZED CONTROLLED TRIAL OF CHLORHEXIDINE DRESSING AND HIGHLY ADHESIVE DRESSING FOR PREVENTING CATHETER-RELATED INFECTIONS IN CRITICALLY ILL ADULTS



A

No. of Catheters Maintenance, d

Non-impregnated	2055	1796	1168	731	472	289	181	116	74	44
CHG-gel	2108	1874	1220	746	452	285	162	112	70	45

With chlorhexidine, the major-CRI rate decreased from **2.11 per 1,000** to **0.69 per 1,000 catheter-days** (hazard ratio [HR], **0.328**; 95% confidence interval [CI], 0.174–0.619; $P < 0.0006$)

Chlorhexidine dressings were estimated to prevent one major- CRI for every 71 catheters (95% CI, 57–125 catheters) left for a mean of 10 days

HAZARD RATIOS IN THE INTENTION-TO-TREAT ANALYSIS

Nonchlorhexidine vs. Chlorhexidine Dressings
(941 patients/2,055 catheters vs. 938 patients/2,108 catheters)

Variable	
Catheter colonization	
Incidence (n per 1,000 catheter-days)	10.9 vs. 4.3
Hazard ratio	0.412 (0.306–0.556), $P < 0.0001$
Catheter-related bloodstream infection	
Incidence (n per 1,000 catheter-days)	1.3 vs. 0.5
Hazard ratio	0.402 (0.186–0.868), $P = 0.02$
Major catheter-related infections	
Incidence (n per 1,000 catheter-days)	2.1 vs. 0.7
Hazard ratio	0.328 (0.174–0.619), $P = 0.0006$

TEGADERM™ CHG DRESSING SIGNIFICANTLY IMPROVES CATHETER-RELATED INFECTION RATE IN HEMODIALYSIS PATIENTS.

- A prospective study with a scheme of 2 treatments, std. polyurethane dressing vs. Tegaderm™ CHG dressing, and 2 periods of 6 months.
- 59 patients (39% of center dialysis patients) with a tunneled central venous catheter were randomized for the sequence of treatment.
- Bacterial cultures were performed every month and in occurrence of suspected infection
- At the end of the first 6-months period, every subgroup of patients was switched to the other dressing for other 6-months
- **Catheter-related infections** were chosen as primary outcome variable.
- **Exit-site infections and catheter-related bloodstream infections** were evaluated as secondary outcome variable

Righetti M, et al J Vasc Access. 2016 Sep 21;17(5):417-422

PATIENTS' DATA

Variable	
Sex (female/male)	25/34 (42/58 %)
Age (yrs.)	71.2 ± 1.5 (38-87)
Dialysis vintage (yrs.)	5.1 ± 0.7 (0.2-31.6)
Catheters' duration of use (months)	24.1 ± 1.2 (1.5-73.6)
Charlson comorbidity index (n°)	6.6 ± 0.3 (1.8-14.4)
Diabetes (yes/no)	19/40 (32/68 %)

✓ Data are expressed as means ± m.s.e. (range)

RESULTS

23 of 59 (39%) enrolled patients dropped out of the study:

- ✓ 13 patients (22%) passed away (mean follow-up was 190 days), 7 on standard dressing and 6 on Tegaderm CHG™ dressing;
- ✓ 2 patients (3%) had catheter's removal after native arteriovenous fistula functioning (mean follow-up was 126 days);
- ✓ 8 patients (14%) had Tegaderm CHG™ dressing intolerance due to pruritus and erythema (mean follow-up was 20 days with Tegaderm CHG™ dressing).

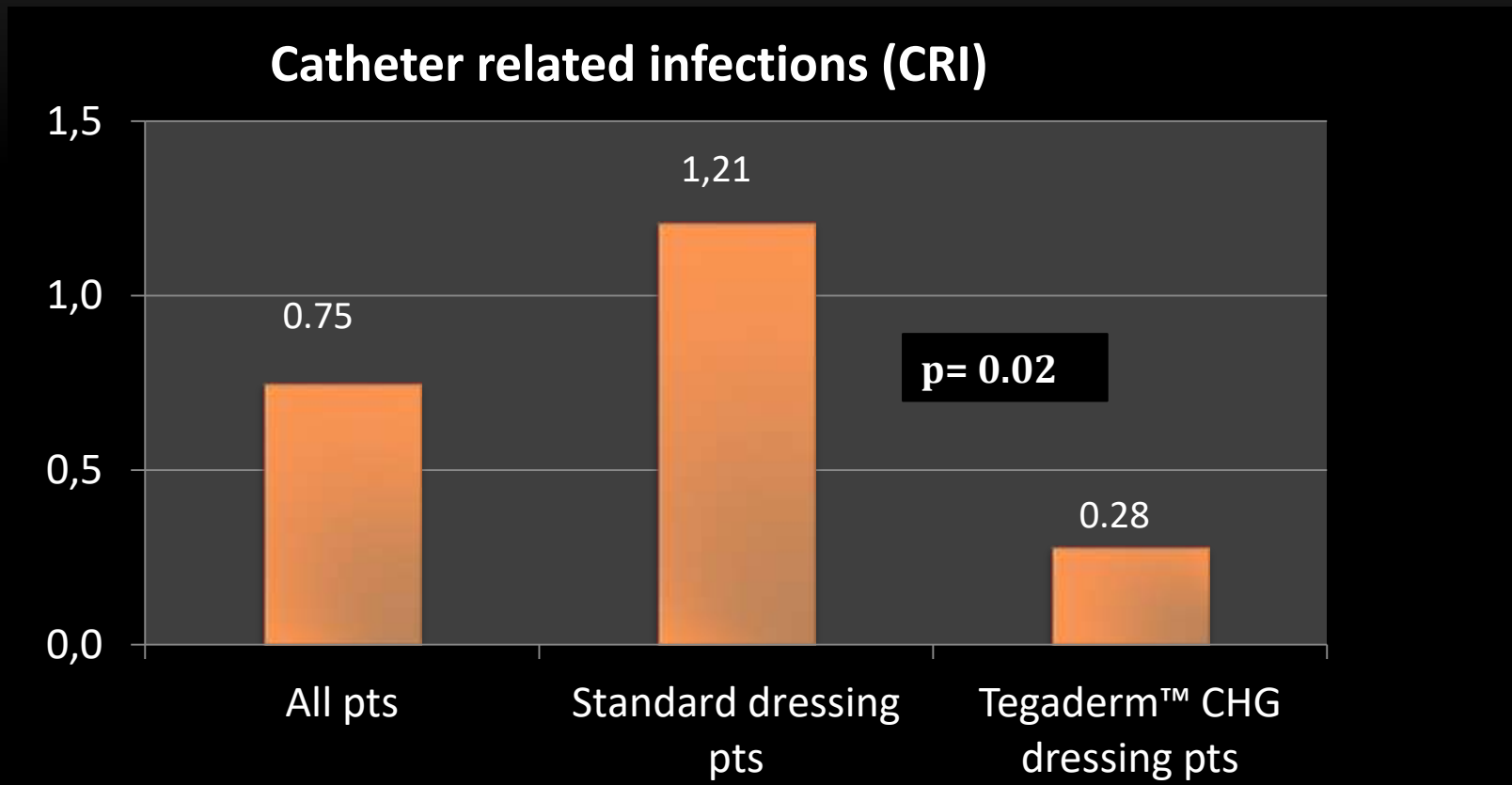
RESULTS

Type of infection	Total	Standard dressing	Tegaderm™ CHG dressing	p
All types (CRI) Cather Related Infections	16	13	3	0.02
Exit-site (ES) Infections	13	11	2	0.02
Bloodstream (CRBSI)	8	7	1	0.05

- ✓ Tegaderm™ CHG dressing significantly lowers catheter-related infections.
- ✓ 5 concurrent ES and CRBSI infections occurred in pts with standard dressing.

Righetti M, et al J Vasc Access. 2016 Sep 21;17(5):417-422

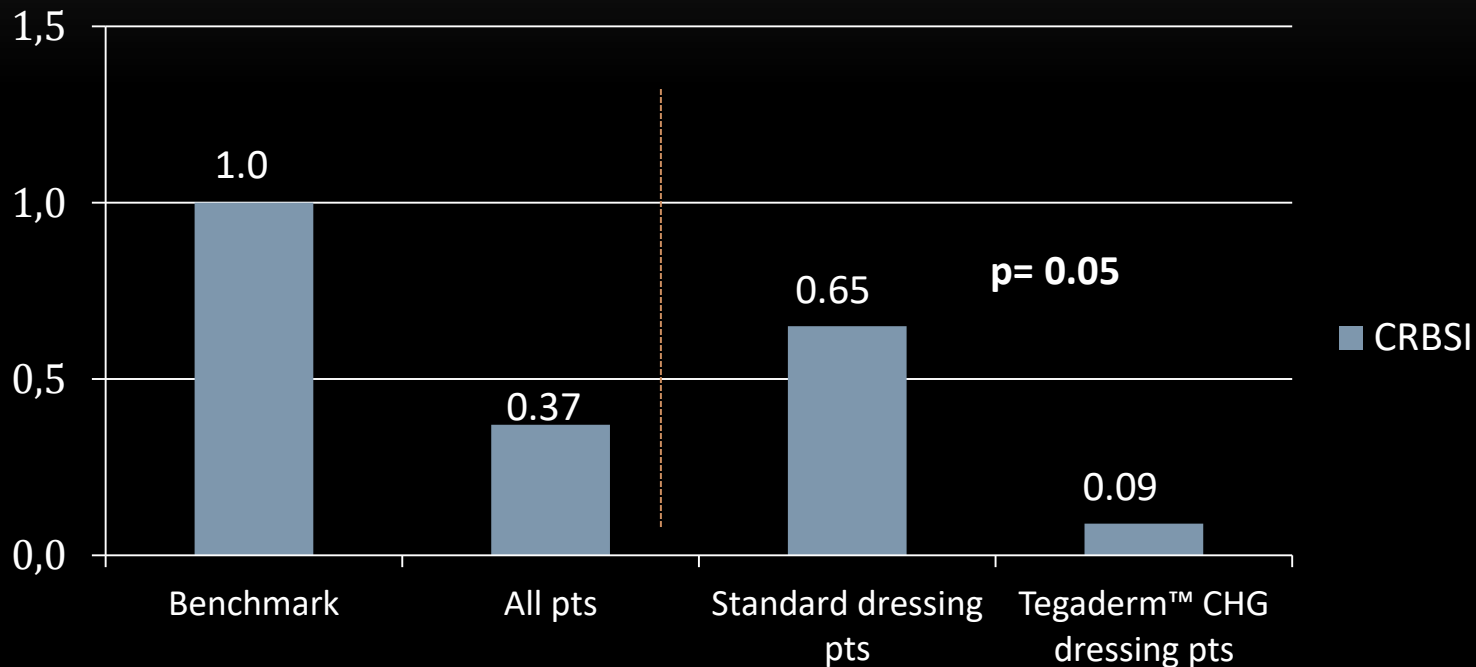
RESULTS (PRIMARY OUTCOME VARIABLE)



- ✓ CRI rate was equal to 0.75 per patient per 1000 cvc days.
- ✓ It was reduced from 1,21 to 0.28 events per patient per 1000 cvc days.
- ✓ It means a 76,9 % reduction.

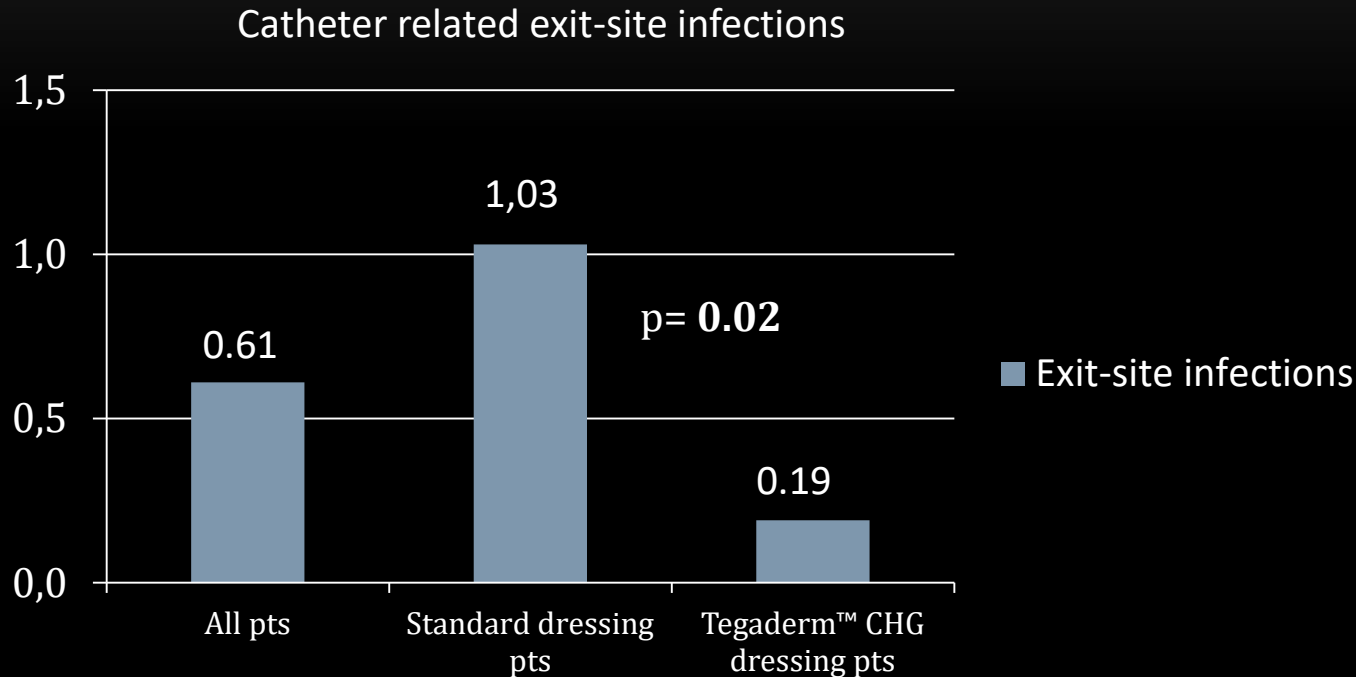
RESULTS (SECONDARY OUTCOME VARIABLE)

Catheter related bloodstream infections (CRBSI)



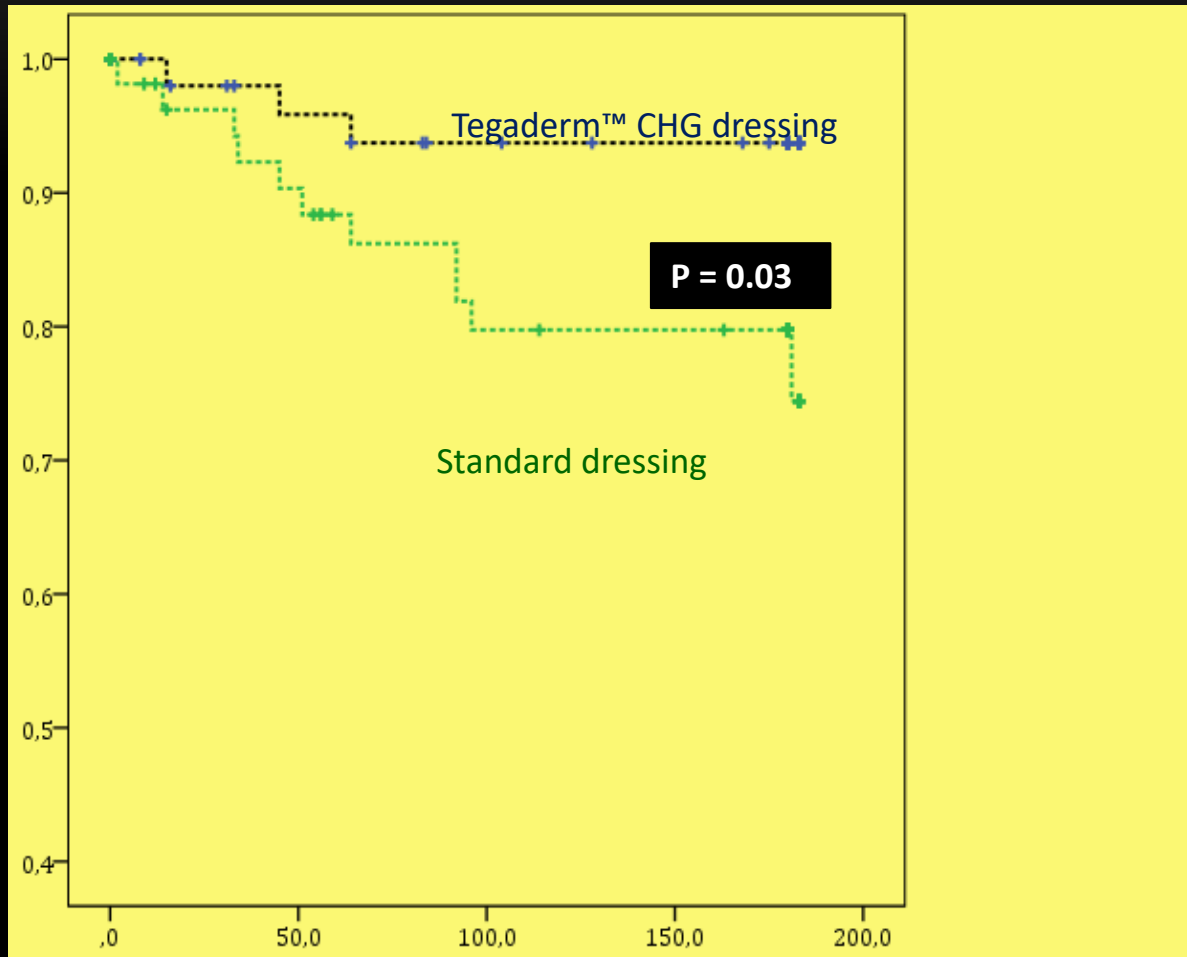
- ✓ CRBSI rate was equal to 0.37 per patient per 1000 cvc days.
- ✓ It was reduced from 0.65 to 0.09 episode per patient per 1000 cvc days
- ✓ It means a 86,1% reduction.

RESULTS (SECONDARY OUTCOME VARIABLE)



- ✓ Exit-site infections rate was equal to 0.61 per patient per 1000 cvc days.
- ✓ It was reduced from 1,03 to 0.19 events per patient per 1000 cvc days.
- ✓ It means a **81,5% reduction**.

RESULTS: KM analysis of CRI for the 2 types of dressings



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RESULTS *(LOGISTIC REGRESSION)*

Variable	B	Wald	Sig	Exp (B)	95% CI (low)	95% CI (high)
Type of dressing	1,45	4,56	0,03	4,28	1.13	16,2

- ✓ Logistic regression analysis shows that the type of dressing (standard vs. Tegaderm™ CHG) is the only variable significantly associated to the binary outcome, catheter-related infection, in our hemodialysis patients ($p = 0,03$)
- ✓ Patients with standard dressing have significantly higher catheter-related infections than patients with Tegaderm CHG™; OR (95% CI) = 4,3 (1,1-16,2)

Variables in the model: sex, age, dialysis vintage, diabetes, CCI, cvc vintage, sequence of treatment

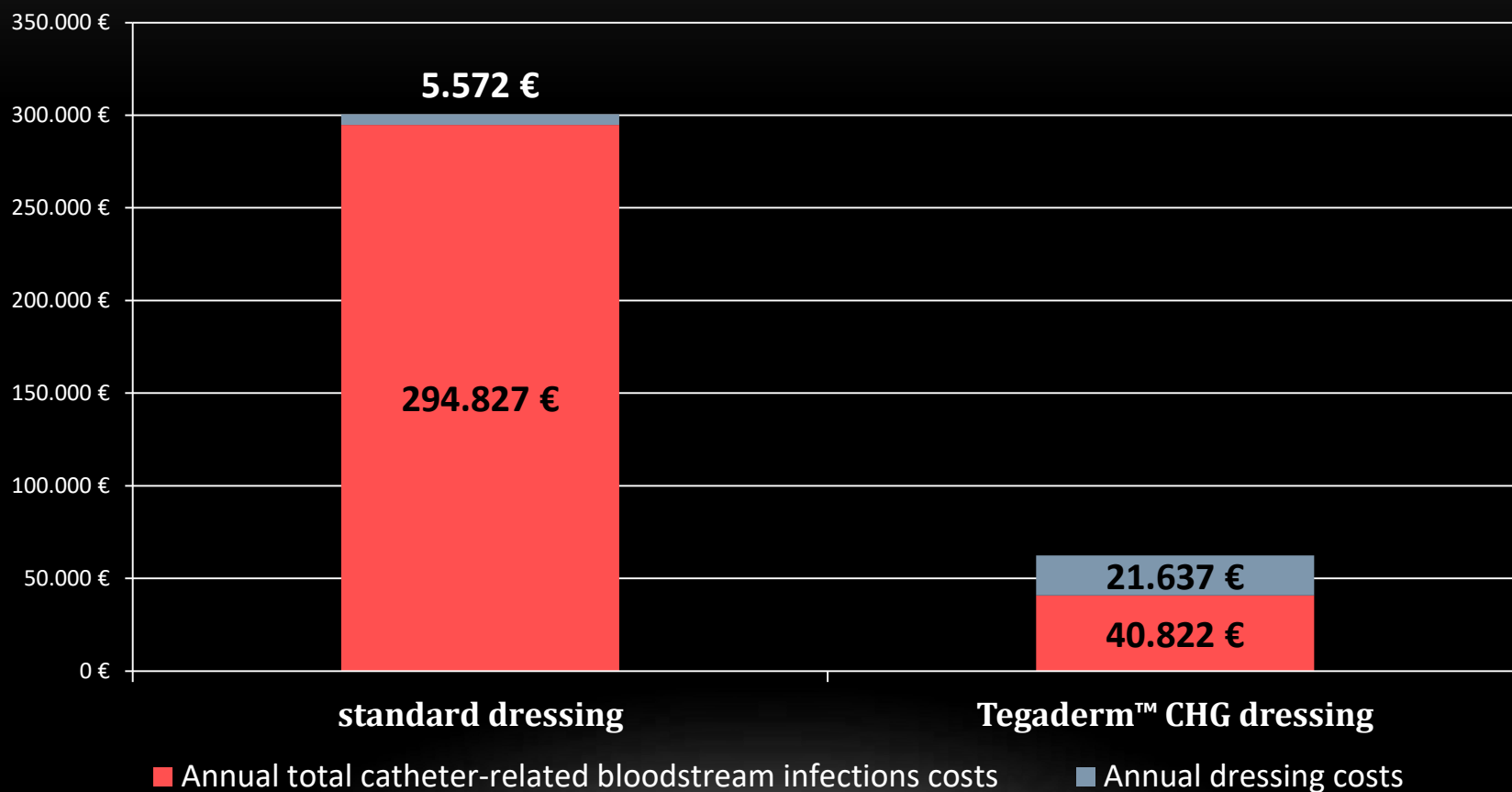
RESULTS (COSTS SAVING RELATED TO THE STUDY'S PATIENTS)

	Standard dressing	Tegaderm™ CHG dressing
Catheters-days per year	21637	21637
N° of dressings per year	9286	3091
CRBSI per year	14,1	1,9
Annual dressing costs	5572 €	21637 €
Annual CRBSI costs	294827 €	40822 €
Annual total costs	300399 €	62459 €

- ✓ Dressing costs (0,6 vs. 7 €, respectively for standard and Tegaderm™ CHG).
- ✓ Total direct and indirect cost for CRBSI equal to \$ 23500 (20963 €).*
- ✓ Estimated annual saving of 237940 € (79%) using Tegaderm™ CHG dressing.

*Kosa SD et al. The economics of hemodialysis catheter-related prophylaxis. Semin. in Dialysis 2013; 26: 482-93.

RESULTS: Annual total healthcare costs for CRBSI



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TAKE HOME MESSAGES

- *Il rischio infettivo nei pazienti in dialisi legato all'accesso vascolare è massimo con l'utilizzo di cvc e minimo con la FAV*
- *La clorexidina gluconato in soluzione alcolica è da considerarsi il miglior antisettico per la gestione dei cvc*
- *La cura dell'exit-site è di fondamentale importanza per la riduzione del rischio infettivo nei pazienti in dialisi*
- *La medicazione dell'exit site con Tegaderm™ CHG si è dimostrata efficace nel ridurre l'incidenza di CRI nei pazienti in trattamento dialitico portatori di cvc a permanenza.*
- *La riduzione del numero di cvc resta comunque il primo obiettivo per un accesso vascolare sicuro nei pazienti in dialisi.*

***Un ringraziamento alle infermiere
del reparto dialisi per la scrupolosa
raccolta dati e la condivisione del
progetto***

Grazie per l'attenzione