Short summary of the clinical data of Bactiguard® coated devices

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1 Background on Clinical use of the Bactiguard® coating

Hospital Acquired Infections (HAI) and the development of antibiotic resistant bacteria is an alarming problem worldwide. Sweden is a highly developed country, but despite this, the risk of a patient getting an infection in association within the primary care or hospital care in Sweden is today approximately 9% (1). The situation is similar or worse in other countries. Many of these infections result in serious medical complications and an increased pressure on the hospital care, which already has limited resources. Development of improved and restricted hygiene routines together with new innovative technologies can reduce the number of hospital acquired infections (HAI).

Bacterial adhesion to medical device surfaces is an essential step in the development of device related infections. The Bactiguard® coating is a very thin coating that can be applied to the surface of medical devices, for example catheters, where the risk of infections is high. The Bactiguard® coating consists of noble metals and is only few millionths of a millimetre thin. Bactiguard® coated medical devices have been shown to be effective in reducing device related infections in clinical trials, including approximately 100 000 patients in total. Clinical trials have also shown that the Bactiguard® coating does not generate resistance development in bacteria (2). The Bactiguard® coating has a unique mechanism of action; the coating is permanently attached to the device and the coating prevents bacterial adhesion and without release of toxic amounts of substances. Since the adhesion and colonization of bacteria is prevented, hence, the risk for infections is reduced.

Initially, Bactiguard has focused on a product portfolio preventing device related infections for products for blood, the urinary tract and the respiratory tract. These infections represent 60-70 % of all hospital acquired infections (HAI). The Bactiguard® surface has been tailored for the different therapies; both to prevent infections and at the same time to be tissue friendly (for example blood compatible).

Table 1. Bactiguard coated products

<table>
<thead>
<tr>
<th>Product</th>
<th>Coating</th>
<th>Market approval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bardex I.C</td>
<td>Urinary Foley Catheter, Latex</td>
<td>Bactiguard® coating</td>
</tr>
<tr>
<td>Lubri-Sil I.C</td>
<td>Urinary Foley Catheter, Silicone</td>
<td>Bactiguard® coating</td>
</tr>
<tr>
<td>BIP Foley Catheter</td>
<td>Urinary Foley Catheter, Latex</td>
<td>Bactiguard® coating</td>
</tr>
<tr>
<td>BIP Foley Catheter-Silicone</td>
<td>Urinary Foley Catheter, Silicone</td>
<td>Bactiguard® coating</td>
</tr>
<tr>
<td>Bacti-guard Safe Seldinger</td>
<td>Central venous catheter</td>
<td>Bactiguard® coating</td>
</tr>
<tr>
<td>BIP ETT</td>
<td>Endotracheal tube</td>
<td>Bactiguard® coating</td>
</tr>
<tr>
<td>BIP CVC</td>
<td>Central venous catheter</td>
<td>Bactiguard® coating</td>
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</tbody>
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1.1 Bacterial adhesion

The postulated mechanism of action for preventing bacterial adhesion on Bactiguard® coated medical device surface is a galvanic effect in combination with a fine topography in the sub-micron range which disturbs and prevents microbial surface adhesion and colonization. The effect of microbial colonization reduction has been proven for clinically relevant strains known to cause device related infections of both Gram-positive and Gram-negative bacteria as well as for fungi (3,4). The reduction of microbial colonisation has also been verified...
clinically, Mazzoli et al compared the presence and prevalence of microorganisms of Bactiguard coated Foley catheters compared to an uncoated catheter after 30 days of clinical use\textsuperscript{[5]}. Using a Bactiguard coated Foley catheter in clinic reduced the colonization of bacteria with approximately 60 %.

### 1.2 Clinical use of Bactiguard coated products

Bactiguard\textsuperscript{®} coated medical devices (Foleys and CVC) have been evaluated in clinical investigations, covering over 100 000 patients in total. The clinical studies have been performed in 9 different countries and consist of prospective randomized trials, cohort studies and surveillance studies.

#### 1.2.1 Bactiguard coated Foley Catheters

Up to 40 % of all hospital acquired infections is related to urinary tract infections. These infections can result in serious complications, for example sepsis. Bactiguard developed the Bactiguard coated latex and silicone Foley catheters, Bardex I.C and Lubri-Sil I.C. together with C.R. Bard during the 90’s. The products were CE marked and FDA approved after successful clinical trials. The products are still on the market, and over 130 million catheters have been sold to this date. BIP Foley and BIP Foley Catheter- Silicone are Bactiguards own Foley Catheters, which received market approval 2009 and 2010. Over 100 000 patients has been included in clinical trials evaluating the Bactiguard coated Foleys. The studies have shown that the Bactiguard coated Foley Catheters reduce catheter related urinary tract infections and bacteriuria compared to an uncoated catheter. The major studies are summarized in chapters\textsuperscript{2}

#### 1.2.2 Bactiguard coated CVC’s

Treatment with a Central Venous Catheter (CVC) is necessary for many intensive care patients. Treatment with CVC’s is associated with an increased risk of infection and mortality with up to 35 %\textsuperscript{[6]}. Another challenge with today’s standard catheters is the increased risk of thrombosis. Bactiguard (under the previous company name, Metacot) developed a Bactiguard coated polyurethane Central Venous Catheter together with Fresenius 1995, BactiGuard Safe Seldinger. The product was CE marked 1996 after successful clinical trials of the product. The two publications of the clinical trials show that Bactiguard coated CVCs do not represent
a risk factor for catheter-related thrombosis and are safe to use and that the use of a Bactiguard® coated CVC is effective in reducing catheter-related infections.

Bactiguard has developed a new Bactiguard® coated CVC, BIP CVC, that is designed to have a good blood compatibility and at the same time reduce the risk for catheter-related infections. Tests show that BIP CVC reduces the bacterial adhesion with over 90 % and has a good blood- and tissue friendliness.

1.2.3 Bactiguard coated Endotracheal tubes
Endotracheal tubes (ETTs) are used to provide airway management in patients. Despite the relative short, but necessary life sustaining treatment with an ETT, approximately 15 % of the patients acquire a so called Ventilator Associated Pneumonia (VAP). VAP increases the mortality of the patient with up to 30 %. (7) Patients with VAP requires 6-10 days of additional hospital care, with an increased cost of ten thousands of Euros per infection and patient (8). Bacterial adhesion, colonization and biofilm formation on an ETT contributes to an increased risk of VAP (9,10,11,12). Today, there is one other silver coated ETT on the market (Agento, CR Bard). The Agento ETT has been shown to reduce the bacterial adhesion with over 90 %, using a standardized in vitro test (The Ahearn test) (13). The test has shown to correlate with the reduction of VAP, since clinical trials with the device with over 9000 patients shows that the Agento ETT reduces the risk of infections with 36 % (14).

Bactiguard has developed a Bactiguard® coated ETT, BIP ETT, with excellent tissue friendliness that at the same time reduces the bacterial adhesion of relevant bacteria with over 90 % (The Ahearn test) (15). BIP ETT was approved and CE mark in 2011.

2 Clinical data, Bactiguard coated Foley Catheters
Bactiguard developed the Bactiguard coated latex and silicone Foley catheters, Bardex I.C and Lubri-Sil I.C. together with C.R. Bard in the 90’s. The products were CE marked and FDA approved after successful clinical trials. The products are still on the market, and over 130 million catheters have been sold to this date.

Bactiguard is the manufacturer of BIP Foley Catheter and BIP Foley Catheter-Silicone, Bactiguard coated silicone and latex Catheters. The products have been on the market since 2009/2010.

The aggregated data includes 37 clinical studies covering over 100 000 patients, and were derived from publications, abstracts or posters from conferences, or scientific meetings.

Highlights:
The average reduction of any CAUTI related parameters for Bactiguard coated Foley catheters in comparison to standard uncoated Foley catheters in the entire clinical studies cohort (weighed for each study size) is:

- 36% - for 25 main studies
- 48% - for 12 supportive studies
- 39% - for the entire cohort of 37 main and supportive studies

This entire cohort is presented study by study in the figure below;
The cohort of all studies has been divided to sub-cohorts, based on the type of CAUTI parameter studied as primary end-point, since it is more relevant from clinical and scientific perspective. The results indicate that Bactiguard coating reduces symptomatic CAUTI, asymptomatic Bacteriuria and a mixture of Asymptomatic Bacteremia and symptomatic CAUTI (CDC criteria for CAUTI) by: 42% (bacteriuria), 24% (sCAUTI) and 41% (for CAUTI according to CDC).

- Bactiguard coating reduces CAUTI during short, medium and long term catheterization time.
  - Bacteriuria (and consequently risk for sCAUTI) is reduced up to ~30 catheterization days
  - Reduction of sCAUTI seems to increase with catheterization length (but further data to support this hypothesis is needed)
  - These findings are in agreement with the generally accepted relationship between catheterization time and bacteriuria, and sCAUTI

- Some studies illustrate that the Bactiguard coating is capable of reducing bacterial species which usually cause bacteriuria and sCAUTI in catheterized patients. In long term treatment, the presence of multi-resistant bacterial species seems to be less frequent and potentially disappear.

- The comfort level for patients using Bactiguard coated catheters is reported as similar as or even better than for control catheters. There are no signs of coating metal toxicity to the urethra or patients, and no adverse events related to the coating. Further, no signs of coating resistance have been observed among bacterial strains.

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1 CDC – Center of disease control and prevention, US gov
In summary:
The overall review of the 37 referred studies indicates that BIP Foley Catheter reduces frequency of infection and delays time to infection for both symptomatic Catheter Associated Urinary Tracts Infections and bacteriuria during short, medium and long catheterization time.

The chapters below presents some of the major clinical studies of the Bactiguard coated Foley Catheters in detail and a new study not yet included in the aggregated data above.

2.1 Shumm and Lam, Cochrane review, Types of urethral catheters for management of short-term voiding problems in hospitalised adults (16)

Cochrane is an international non-profit and independent organization, with the aim to make up-to-date, accurate information about effects of health care readily available worldwide. Cochrane produces and disseminates systematic reviews of health care interventions.

The Cochrane report by Shumm and Lam, entitled: “Types of urethral catheters for management of short-term voiding problems in hospitalised adults, 2008” was issued to determine the effect of type of indwelling urethral catheters on the risk of urinary tract infection. All randomized and quasi randomized trials comparing types of indwelling urinary catheters for short-term catheterization in hospitalized adults were evaluated. Short-term catheterization was defined as up to and including fourteen days, or other temporary short-term use as defined by the trialists (for example less than 21 days with data time points at 7 day intervals). The report covered randomized controlled trials and controlled Cohort trials, performed between 1965-2007. Data were extracted by one reviewer and independently verified by a second reviewer and twenty-four randomised trials are covered [16]. Nine of the trials included Bactiguard® coated catheters.

The following types of indwelling catheters were evaluated:

- Antiseptic; silver oxide (Baxter and others) and Bactiguard coated (Bardex I.C.)
- Antibiotic coated
- Standard catheters of different materials

Results

Catheterization less than one week:

- 46% reduction of bacteriuria in favour of Bactiguard coated catheters (RR: 0.54, 95% CI 0.43-0.67)

Catheterization more than one week:

- 36% reduction of bacteriuria in favour of Bactiguard coated catheters (RR 0.64, 95% CI 0.43-0.67)

The authors concluded that the results suggest that the use of silver alloy indwelling catheters (Bactiguard coated urinary catheter) for catheterising hospitalised adults short-term reduces the risk of catheter acquired urinary tract infection. The reviewed investigations show that the clinical use of Bactiguard® coated devices is safe and effective. No adverse effects are reported.
2.2 Karchmer et al, A randomized Crossover Study of Silver-Coated Urinary Catheters in Hospitalized Patients (17)

Karchmer et al performed a 12 month randomized crossover trial comparing rates of nosocomial catheter-associated urinary tract infections (UTIs) in patients with Bactiguard-coated catheter (Bardex IC) and an uncoated catheter. The study included approximately 28,000 patients. The relative risk of infection per 100 Bactiguard coated catheters compared to uncoated catheters was calculated to 0.68 (95% CI 0.54-0.86, P=0.001). The risk of infection declined by 32% among patients that received a Bactiguard coated catheter.

2.3 Rupp et al, Effect of silver-coated urinary catheters, efficacy, cost-effectiveness, and antimicrobial resistance (18)

A 2-year prospective surveillance study in 10 patient care units was conducted to determine the rate of catheter associated UTI, using a Bactiguard coated catheter (Bardex IC). Historic control data was utilized to assess the effect of the coated catheter. Silver susceptibility was determined for microbes responsible for catheter-associated UTI. Data were analyzed using a Poisson regression model. Rates of infection, expressed as UTI/1000 catheter-days and UTI/1000 patient-days, in 2001 and 2002 (when coated urinary catheters were in use), were compared with historical control data for the same units for 1999 and 2000 (when uncoated urinary catheters were employed). The results are presented in the figure below.

![Figure 5. Rate of catheter-associated urinary tract infections (UTI) in the survey patient care units. Silver-alloy/hydrogel coated urinary catheters were introduced in November 2000. Statistically significant decline compared with 1999](image)

The rate of catheter-associated UTI fell from 6.13/1000 catheter days during the period 1999-2000 to 2.62/1000 catheter-days during 2001-2002 (P=0.002). The introduction of a Bactiguard® coated catheter was associated with a significant decline in nosocomial UTI and no silver-resistant urinary pathogens were recovered from patients experiencing catheter-associated UTI during the study period.
2.4 Stenzelius et al, Noble metal alloy-coated latex versus silicone Foley catheter in short term catheterization: A randomized controlled study (2011) (19)

2.4.1 Patients and methods
BIP Foley Catheter has been tested in a randomized clinical trial with the primary endpoint of incidence of catheter related bacteriuria. Consenting consecutive patients were randomized to either a standard silicone Foley catheter (Argyle, All Silicone Foley Catheter; Tyco, Tullamore, Ireland) or the test catheter, a noble metal (silver, gold, palladium) alloy coated-latex catheter (BIP Foley Catheter; Bactiguard, Stockholm, Sweden). For both catheter types the size 12 Ch (Charrière) was used. Included were adult patients undergoing elective orthopaedic surgery in three hospitals in southern Sweden – in Lund, Hässleholm and Trelleborg. Excluded from enrollment were patients with recent (within 3 weeks) use of a urinary catheter or a recent history of UTI, previous radiation therapy over the lower pelvis, latex allergy, cognitive impairment or difficulties in understanding the Swedish language. The primary endpoint was the incidence of bacteriuria, defined as a positive urinary culture with equal to or more than 100 000 cfu/ml. Before removal of the urinary catheter a sample for urinary culture was obtained with the catheter closed for at least 2 h in advance.

2.4.2 Statistics
Differences between the two independent groups were tested for significance with the chi-squared test for nominal data, Mann–Whitney U test for ordinal data and Student’s t test for numerical data.

2.4.3 Results
In total, 625 individuals were assessed for enrollment, of whom 65 were not eligible and 51 were reluctant to participate. The remaining 509 were randomized to the silicone catheter group (n = 255) or the noble metal alloy catheter group (n = 254). Seventy people did not receive any intervention since they did not need a urinary catheter, for various reasons (Figure 1). However, 217 patients in the silicone catheter group received the allocated intervention, compared with 222 patients in the noble metal alloy catheter group. The background data of the participants did not differ significantly between the two groups with regard to age, gender, BMI or smoking habits. The mean age was 67 years (range 20–95, SD 12.5) and 59% were women. There was a similar distribution of background data between the two test groups in the three settings. The use of BIP Foley Catheter resulted in a significant reduction of the incidence of bacteriuria with 73%).

There were no recorded adverse events or discomfort for the patients related to the noble metal coating.

2.4.4 Discussion
It has been estimated that symptomatic UTI occurs in approximately 10–20% of patients with bacteriuria (Garibaldi RA et al, 1982, Hartstein AI et al, 1981, Tambyah PA et al 2000). Furthermore, it has been reported that catheter-associated bacteriuria is a major cause of secondary bloodstream infections (Krieger JN et al, 1983). In a randomized controlled trial of two Foley catheters in almost 28 000 patients, 4.1% of the bacteriuria patients suffered a
secondary bloodstream infection (Karchmer et al, 2000). This risk was 44% lower in patients treated with a silver alloy-coated catheter. It has also been reported that UTIs that result from short-term, indwelling bladder catheterization in acute-care hospitals are associated with a marked increase of dying during the hospitalization (Platt R. 1987). A Cochrane Collaboration review reported that “silver alloy catheters” significantly reduced the incidence of asymptomatic bacteriuria (relative risk 0.54, 95% CI 0.43–0.67) (Schumm K, Lam TB. 2008). The silver alloy catheters in the review were all coated with the same noble metal alloy as the BIP catheters in the current study. Thus, the significant reduction in catheter-associated bacteriuria in this study supports previous results and extends the lowered risk to short-term catheterization.

2.5 Estores et al, Silver hydrogel urinary catheters: evaluation of safety and efficacy in single patient with chronic spinal cord injury (2008) 20

2.5.1 Patients and methods
The patient was a 40-year-old white male who had sixth cervical level American Spinal Injury Association tetraplegia A, had been injured for 23 years, and had been using an indwelling catheter for the same duration. He had been experiencing monthly symptomatic UTIs requiring antibiotic use in the 6 months preceding the study. He had no history of bladder stones, high-dose steroid use, or prostate or bladder surgery. He previously used a latex indwelling catheter that his caregiver changed monthly. We defined symptomatic UTI as the presence of three of the following five conditions: (1) fever (temperature >101 °F), (2) bacteriuria (>100,000 organisms/mL), (3) pyuria (25–50 leukocytes/mm3), (4) self-reported change in color of urine or malodorous urine, and (5) bacteremia or fungemia. After obtaining the patient’s informed consent, we tested his serum silver levels and performed urinalysis and urine cultures. The urinalysis and urine cultures were performed monthly with each catheter change, and the serum silver levels were retested at the end of the 6 months. The patient agreed to be blinded to the type of catheter he was receiving for the 6-month study period.

2.5.2 Results
The patient experienced monthly symptomatic UTIs requiring antibiotic use in the 6 months preceding the study (using an uncoated catheter). During the 6 months, the patient developed no symptomatic UTIs. His serum silver levels before and after the trial remained within normal limits. Although the level of bacteriuria did not change, an interesting observation was that the bacterial flora had changed at the end of the trial. The patient initially had multiple drug-resistant Pseudomonas aeruginosa and enterococcus faecalis at baseline; at the end of study, the isolated organism was Escherichia coli.
2.6 Lederer et al, Multicenter Cohort Study to Assess the Impact of a silver-Alloy and Hydrogel-Coated Urinary Catheter on Symptomatic Catheter-Associated Urinary Tract Infections (2014)²¹

2.6.1 Methods
This before-after cohort study was conducted in seven acute care hospitals (6 community, 1 teaching) ranging in size from 124 to 921 beds. Patients between 18 and 89 years of age, with a significant positive urine culture ≥ 2 calendar days after hospital admission, and who underwent Foley catheterization during their admission were considered to be CAUTI candidates. CAUTI surveillance was conducted at each hospital for ≥ 3 months using a standard, non-silver Foley catheter (STD). An equal number of months of surveillance were performed after the Silver-Hydrogel, SAH (Bactiguard® coated) catheter was introduced. Both the 2009 Centers for Disease Control and Prevention’s (CDC) National Healthcare Safety Network (NHSN) surveillance and a clinical CAUTI definition of infection were used to calculate infection rates.

2.6.2 Results
A total of 64 months of data were collected. Eight-hundred fifty three (853) patients met all inclusion and exclusion criteria (453 STD period; 400 SAH period). A total of 174 CAUTIs occurred in 170 patients in the STD period; 90 CAUTIs occurred in 88 patients in the SAH time period.

A 47% relative reduction in the CAUTI rate was observed with the Bactiguard coated hydrogel catheter compared to the standard catheter when both infection definitions were used (0.945/1000 patient days vs 0.498/1000 patient days). When only NHSN-defined CAUTIs were considered, a 58% relative reduction occurred in the Bactiguard period (0.60/1000 patient days vs 0.25/1000 patient days) (odds ratio = 0.42; P < .0001; 95% CI: 0.34-0.53). In addition, the patient days with antibiotics for CAUTIs decreased from 1165 (standard catheter period) to 406 (Bactiguard period).

The author concluded that the use of the Bactiguard and hydrogel coated urinary catheter reduced symptomatic CAUTI occurrences as defined by both NHSN and clinical criteria.
2.6.3 Conclusions

Use of the Bactiguard and hydrogel coated Foley catheter resulted in a 47% relative reduction in the total (NHSN + clinical definition) CAUTI rate and a 58% reduction in the NHSN-defined CAUTI rate. In addition, the antibiotic days for CAUTI per patient decreased with 60%.

2.7 Summary-Clinical data of Bactiguard coated Foleys

The clinical data on Bactiguard coated Foleys are extensive, covering over 100,000 patients. No adverse event related to the coating has been reported during these clinical trials. The overall review of the 37 referred studies indicates that BIP Foley Catheter reduces frequency of infection and delays time to infection for both symptomatic Catheter Associated Urinary Tracts Infections and bacteriuria during short, medium and long catheterization time. New data also suggests that the antibiotic use can be reduced with 69%.
3 Clinical data- Bactiguard coated Central Venous Catheter (CVC)

There are two publications of a clinical trial of the Bactiguard coated CVC, BactiGuard Safe Seldinger. The two publications present two endpoints; catheter-related infections and thrombosis.

3.1 Goldschmidt et al, Prevention of catheter related Infections by silver coated Central Venous Catheters in Oncological Patients (22)

3.1.1 Patients and methods

The study was performed at the Department of Internal Medicine V, University of Heidelberg. Adult patients with haematological, oncological diseases were admitted to the hospital. The patients required central venous catheter for treatment purposes and were offered the opportunity to participate in the study.

Exclusion criteria:
- Catheterization for less than 48 hours
- Second central venous assess
- Open infection
- Catheter-related infection
- Pregnancy
- Age< 18 years

The study protocol was approved by the Institutional Review Board of the university and informed consent was obtained from the patients. Patients were randomly assigned to receive the coated or uncoated control catheters. When patients required a second (n=29), third (n=9), forth (n=1) or fifth (n=2) catheter, each catheter was recorded as a separate event (total number of catheters n=233). In order to prevent consecutive placement of catheters of the same category, subsequent catheters in the same patient alternated between coated and standard uncoated catheter. Data collected included demographic characteristics, catheter insertion and removal date, diagnosis, chemotherapy, supportive care, prophylactic and therapeutically antibiotic treatment and leukopenia, days of fever, blood pressure and pulse rate two times daily.

3.1.2 Central Venous Catheters

Central venous catheterization was performed with uncoated (standard) and coated 30 cm 5F polyurethane catheters (called Cavatheter/BactiGuard Safe Seldinger, Fresenius AG, Germany). The study catheter carried an external alloy-layer- the Bactiguard® coating (2).

3.1.3 Statistics

For statistical analysis, patients were divided into two groups according to the type of catheter. To exclude differences between both study groups, homogeneity regarding sex distribution, ward, use of antibiotics and diagnosis was tested with X²-tests. Equality of means between both catheter groups was evaluated using Students t-test for age, days of leukopenia.

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2 In the publication, the Bactiguard coating is referred to as "silver-alloy"
< 1,0x10⁹/l and days of insertion. Multivariate analysis of variance was performed to identify the influence of catheter type and diagnosis on the use of antibiotics, microbiological results, days of insertion and days of fever (> 38.5 °C).

3.1.4 Microbiological methods

Blood cultures were obtained from catheters and one peripheral site at the time of catheter removal and in cases of suspected infection. After removal, catheter hub tip segment and intradermal segment were collected into sterile culture tubes using sterile scissors. The segments were cultured semi quantitatively.

3.1.5 Definitions

1. Catheter colonization: Growth of > 15 colony forming units (CFU) in the absence of signs of local or systemic infection.
2. Catheter related bacteraemia: Isolation of the same organism from catheter (> 15 CFU) and blood culture without clinical signs of infection
3. Catheter related septicemia: Isolation of the same organism from catheter (> 15 CFU) and blood culture with clinical signs of infection
4. Local infection: Growth of > 15 CFU of an organism by semi quantitative culture of the intradermal or catheter tip segment and/or local signs of infection. Sterile blood cultures.

Infections with a clinically apparent focus other than exit site or catheter were excluded.

3.1.6 Results

266 patients were enrolled in the study, 153 female and 113 male patients. Distribution of standard vs. silver catheter was homogenous (X² = 0.148, p= 0.93). The care level and the level of training of physicians inserting the catheter were identical in both groups, 132 patients were selected to receive a standard catheter and 134 a coated catheter. 33 inserted catheters were excluded because of catheterization < 48 h (5 patients), failure to notify the study team when the catheter was removed (15 patients) and violations of microbiological test requirements (> 24 h between removal and microbiological examination, 13 patients). The number of excluded catheter was 20 in the standard group and 13 in the silver catheter group.

233 catheters could be evaluated of which 113 were standard catheters and 120 coated catheters. In most cases, catheters were removed at the end of chemotherapy. One catheter was withdrawn due to a malfunction that was unrelated to the silver coating. Differences between standard and coated catheters for females (56.6% vs. 61.7 %) and males were not significant different (X² = 0.610, p = 0.44). The two groups were comparable with respect to patient age and clinical diagnosis. The rates of leukopenia, fever and active infection unrelated to the catheter were not significantly different between the groups. There was no significant difference between the two groups in prophylactic and therapeutically antibiotic treatment. The prevalence of catheter-related infections is presented in the figure below.
Catheter related infection developed in 21.2% of the standard but only in 10.2% of the silver-coated catheters (p = 0.011).

The authors conclude that the coated catheter “is a useful tool for reducing catheter-related infections in high-risk patients”.

3.2 Harter et al, Catheter-related infection and thrombosis of the internal jugular vein in hematologic-oncologic patients undergoing chemotherapy. A prospective comparison of Silver-coated and uncoated catheters (23)

3.2.1 Patients and methods
See chapter above for patients and exclusion criteria. After the removal of the CVC and ultrasound examination of the left and right internal jugular veins was conducted and documented. Criteria considered showing the presence of catheter related thrombosis including visualization of thrombus, absence of spontaneous flow, dilatation of the vein by the Valsalva manuver and compressibility of the jugular vein. For prevention of deep venous thrombosis all inpatients received 10,000 international unit (IE) heparin i.v./die.

3.2.2 Central Venous Catheters
Central venous catheterization was performed with uncoated (standard) and coated 30 cm, 5-F single lumen polyurethane catheters (Cavatheter, Fresenius AG, Germany). The impregnated catheters (BactiGuard, Metacot, Sweden) were coated only externally (not inside distal lumen).

3.2.3 Statistics
Variables between catheter groups were comparable by an uncorrected chi-square test or, when appropriate, Fischer exact test for categoric variables and the Mann-Whitney U test for
continuous variables. Because randomization produced two groups of patients with comparable baseline characteristics, no indication of positive or negative confounding had to be controlled for with multivariable Cox models. Statistical significance was established at an alpha value of 0.05. All P values are two-tailed. Multivariate analysis was performed to identify the influence of catheter-type, age, gender, diagnosis, number of insertions, duration of catheterization, and catheter-associated infection for the development of a catheter-related thrombosis.

### 3.2.4 Results

Catheter-related internal jugular vein thrombosis occurred in 1.5% of all cases. Partial occlusion was found in 0.75% and complete occlusion in 0.75% of the cases. There was no significant difference in the incidence of an internal jugular vein thrombosis between the coated catheter and the uncoated catheter group. There was no difference between the development of catheter-related thrombosis and the underlying disease (two cases of multiple myeloma, one case of breast carcinoma, and one case of non-Hodgkin lymphoma), the number of insertions, or the duration of catheterization (median 10.25 days). Of note, catheter-related thrombosis was not found in 134 instances of first insertion. Simultaneous infection and thrombosis was found in only one patient.

**Table 2. Frequency of catheter-related thrombosis examined by ultrasound (table from publication)**

<table>
<thead>
<tr>
<th>Factor</th>
<th>Standard catheter (n = 113)</th>
<th>Silver coated catheter (n = 120)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visualization of thrombosis</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Absence of spontaneous flow</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Dilatation of the vein by the Valsava maneuver</td>
<td>111</td>
<td>120</td>
</tr>
<tr>
<td>Compressibility of the jugular vein</td>
<td>111</td>
<td>120</td>
</tr>
<tr>
<td>Total no. of catheter-related thromboses</td>
<td>3</td>
<td>1</td>
</tr>
</tbody>
</table>

The authors concluded that the coated CVCs “do not represent a risk factor for a catheter-related thrombosis”.

### 3.3 Summary-Clinical data of Bactiguard coated CVC

The two publications presented above show that Bactiguard coated CVCs do not represent a risk factor for catheter-related thrombosis and are safe to use and that the use of a Bactiguard coated CVC is effective in reducing catheter-related infections.

### 4 Conclusion

Bactiguard coated medical devices has been extensively evaluated in clinical trials from 1995-2013 with more than 100 000 patients. Bactiguard coated medical devices has repeatable been shown to significantly reduce hospital acquired infections both for central venous catheters and urinary catheters. No adverse events related to the Bactiguard coating have been recorded.
5 References

1 Socialstyrelsen, 2014-04-11 (Swedish health authorities)
4 Gabriel M. M et al, Effects of silver on adherence of Bacteria to Urinary Catheters: In vitro studies, Current Microbiology, 1995:30: 17-22
5 Mazzoli S. et al, Bactiguard infection protection by biofilm former bacteria in urological long-term patients. Eurobiofilms 2009. Rom, Sept 02-05
15 Internal data, Bactiguard 2010.