Title

Dressings and securements for the prevention of peripheral intravenous catheter failure (SAVE Trial) in adults: a pragmatic, randomised, controlled, superiority trial.

ABSTRACT (300 words)

Background: Two billion peripheral intravenous catheters (PIVCs) are used globally each year, but optimal dressing and securement methods are not well established. We compared the effectiveness and costs of three alternative approaches to standard non-bordered polyurethane dressings.

Methods: Pragmatic, open, parallel, superiority, randomised controlled trial in two hospitals. Adults (≥18 years) with PIVCs of expected use >24 hours were randomly assigned (1:1:1:1) to (i) Tissue Adhesive with Polyurethane dressing, (ii) Bordered Polyurethane dressing, (iii) Securement Device with Polyurethane dressing, or (iv) Polyurethane dressing (controls). Randomisation was centralised, computer-generated, stratified, with concealed allocation. The primary outcome was PIVC failure (composite of dislodgement, occlusion, phlebitis, primary bloodstream, local infection). Participants and clinicians were not masked but infections were blind-adjudicated. Analysis was intention to treat. Trial registration: ACTRN12611000769987.

Findings: Of 1807 randomised patients, 1697 (94%) had the primary endpoint available. PIVC failure was: 163/427 (38%) Tissue Adhesive with Polyurethane (absolute risk difference [ARD] -4·5%, 95% CI -11·1–2·1%, p=0·19); 169/423 (40%) Bordered Polyurethane (ARD -2·7%, 95% CI -9·3%–3·9%, p=0·44); 176/425 (41%) Securement Device with Polyurethane (ARD -1·2%, 95% CI -7·9%–5·4%, p=0·73); and 180/422 (43%) Polyurethane controls. Between-group secondary outcomes were not significantly different for PIVC dwell, product durability, skin/PIVC colonisation, or PIVC failure type, except occlusion was less frequent for Tissue Adhesive with Polyurethane, than Polyurethane alone (16% vs 22%, Hazard Ratio

[HR] 0·89, 95% CI 0·80–0·99, p=0·027). There were three primary bloodstream infections (0.18%), of which one was PIVC-related, and 2% of participants had adverse skin reactions. Total costs were not significantly different between groups, but excluding infection costs, non-bordered Polyurethane was least costly. Overall, 66% PIVCs required dressing reinforcement. **Interpretation:** Current dressing and securement methods are commonly associated with PIVC failure, adverse events, and poor durability. Cost is currently the major factor to consider in choice of products.

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Keywords (MeSH): Vascular Access Devices; Occlusive Dressings; Catheterisation, Peripheral; Catheter-Related Infections; Infection Control; Randomised Controlled Trial

Panel: Research in context (515 words)

Evidence before this study

We searched Medline, CINAHL, Cochrane Collaboration databases, and clinical trials registries for randomised controlled trials (RCTs) comparing any methods of dressing and securement method for peripheral intravenous catheters (PIVCs). Our search terms were "peripheral", "intravenous", "catheter/device/cannula", "dressing", "securement", "polyurethane/transparent/occlusive", "gauze", "tape", "failure", "phlebitis", "infection", "occlusion", "dislodgement/accidental removal/migration", "infiltration", "premature removal" and "complications". There was no language or date restriction. We also searched reference lists of articles identified. We published a systematic review in 2015 (last search 08 April 2015), of 6 trials with a total of 1539 participants. Of four product comparisons, only one contained data from more than one RCT, and the overall quality of evidence was very low.

Simple (non-bordered) Polyurethane dressings were associated with less dislodgement (Risk Ratio [RR] 0·40, 95% CI 0·17–0·92; 2 trials, N=278) than Gauze with Tape, but the effect (3 trials, N=379) on phlebitis (RR 0·89, 95% CI 0·47 to 1·68), and infiltration (RR 0·80, 95% CI 0·48 to 1·33) was unclear. One study (N=703) reported an unclear effect of non-bordered Polyurethane on dislodgement (RR 1·34, 95% CI 0·72 to 2·47) and phlebitis (RR 0·89, 95% CI 0·53 to 1·49), compared to Sticking Plaster.

Individual trials reported Bordered Polyurethane to: (i) reduce dislodgement (RR 0·14, 95% 0·03 to 0·63), but increase phlebitis (RR 8·11, 95% CI 95% CI 1·03 to 64·02), compared to Securement Devices, with unclear effect on infiltration (RR 0·79, 95% CI 0·47 to 1·33) or overall failure (RR 0·86, 95% CI 0·64 to 1·16) (one study; N=302); (ii) and to have unclear effect on PIVC failure (RR 1·84, 95% CI 1·09 to 3·11) and dislodgement (RR 1.46, 95% CI 0·51 to 4·14) compared to Tape (one trial, N=153).

Previous studies did not conclusively identify the optimal PIVC dressing and securement method. Some were limited to particular patient groups, outcome measures were often one type of complication, not overall PIVC failure, and costs were rarely considered. We concluded that a large trial was needed.

Added value of this study

We undertook a large randomised controlled trial in two hospitals. Patients with a PIVC were randomised to i) Tissue Adhesive with Polyurethane, (ii) Securement Device with Polyurethane, (iii) Bordered Polyurethane, or (iv) Polyurethane (controls). There was no significant difference in PIVC failure between groups. Total costs (dressing and securement products, staff time, response to PIVC failure and treatment of infections) were not significantly different between the four approaches; although if treatment cost for infection (uncommon but costly) were removed, Polyurethane was the least costly option. In all groups,

PIVC failure was common, and products had poor durability, often requiring reinforcement. Skin adverse events occurred in 2% of patients.

Implications of all the available evidence

Our trial suggests that choice of PIVC dressing or securement should be mainly based on cost, with no tested alternative clinically superior to low-cost Polyurethane. A previous trial (N=360) found significantly reduced PIVC failure using Tissue Adhesive with Bordered Polyurethane; we did not observe this effect when combining Tissue Adhesive with non-bordered Polyurethane. Our study highlights an unmet need to prevent PIVC failure through dressing and securement innovation.

Word Count: 4558

INTRODUCTION

Peripheral intravenous catheters (PIVCs) are the most common invasive medical device. Around two billion are sold globally each year, with almost all hospital patients requiring intravenous therapy.[1-3] PIVC failure is unacceptably common, with up to 69% removed for dislodgement, phlebitis, occlusion, infiltration or infection.[4-7] Such events cause pain and anxiety, interrupted therapy, infection-related morbidity and mortality, additional procedures for replacement catheters, and substantially increase healthcare costs and workloads.

Effective dressing and securement should prevent many PIVC complications, avoiding gross dislodgement from the vein, but also micro-motion of the device within the vessel that precipitates venous inflammation, occlusion, and entry of skin site bacteria into the PIVC wound.[8, 9] Global clinical practice guidelines require PIVC dressings to be clean, dry and intact, with devices well secured.[10, 11] In contrast, 21%–71% of PIVC dressings are soiled, moist, loose, and/or inadequately secured at any timepoint.[1, 12]

The traditional PIVC dressing is commercially-manufactured, sterile, adhesive, transparent polyurethane film, with sterile gauze alternatively used for ooze/diaphoresis. [10, 13] Non-sterile tape is commonly added to both approaches. There is growing realisation that polyurethane dressings provide inadequate securement.[10] More recently available products may improve securement through an additional reinforced tape/cloth border (Bordered Polyurethane), adhesive Securement Devices (applied in addition to the dressing), and cyanoacrylate adhesive added to the PIVC entry point/hub (under the dressing). These increase purchase cost and complexity but would be desirable if PIVC failure is prevented.

PIVC dressing and securement is a poorly-researched area of patient safety. A 2015 Cochrane review noted current evidence is low quality with no superior method identified.[14] We tested the efficacy, cost, and acceptability to patients and clinicians of traditional low-cost Polyurethane compared to three alternatives – Bordered Polyurethane, Securement Device with Polyurethane, and Tissue Adhesive with Polyurethane. We aimed to assist policy makers with decision making about the best PIVC dressing and securement choice.

METHODS

Study design and participants

We undertook a randomised, controlled, pragmatic trial of parallel, superiority design at two hospitals in Queensland, Australia. Human research ethics committee approval was obtained from the health services (HREC/11/QRCH/152) and Griffith University (NRS/46/11/HREC) and the protocol was published.[15] We recruited adults from medical-surgical departments who had a PIVC of expected use >24 hours. Intensive care units (ICUs) were not included as PIVCs are rarely used in Australian ICUs. Only one PIVC was studied per patient (the first for each patient that met the inclusion criteria). Exclusions were: non-English speaking patients without interpreters; PIVCs inserted through damaged skin; severe diaphoresis; known study product allergies; terminal care; current or high risk of a skin tear (clinician opinion). A small team of Research Nurses (ReNs) screened for and explained the study to eligible patients, and requested written, informed consent from patients/representatives.

Randomisation, allocation concealment and blinding

Randomisation was computer-generated per participant using a centralised, web-based service (https://www151.griffith.edu.au/). We used randomly varied block sizes, stratification by

hospital, and a 1:1:1:1 ratio to: (i) Tissue Adhesive with Polyurethane, (ii) Bordered Polyurethane, (iii) Securement Device with Polyurethane, or (iv) Polyurethane (controls). Allocation was concealed until after patient consent, at which time the ReN contacted the randomisation service, advised the inserter of the allocation and documented this. Due to the nature of the intervention, clinical and research staff were not masked, however infection endpoints were adjudicated by a blinded rater. A Study Manager trained and supervised ReNs, audited data quality and randomisation compliance. Standard operating procedures and study manuals were in place.

Study Products

Study products are shown in Figure 1. The study products were chosen as globally market leading products typical of their category, and available in Australia. Control participants had an unbordered Polyurethane (Tegaderm™ Transparent Film Dressing 1624W/1626W, 3M, St Paul) to affix the PIVC. Product size was chosen by inserters to suit patient size and insertion site (approximately 60% were 6cm x 7cm [1624W] and 40% were 10 x 12 cm [1626W]).

The Tissue Adhesive with Polyurethane group had 1–2 drops of cyanoacrylate (Histoacryl™ Blue, BBraun #1050044, Ann Arbor) applied to the PIVC insertion wound and 1–2 drops under the PIVC hub (and PIVC wings, if present). This dried in approximately 10 seconds while the PIVC was held in position, before the Polyurethane (as before) was applied.

The Bordered Polyurethane group had a Tegaderm™ I.V Advanced Securement dressing 10 x 7cm (Ref # 1683, 3M, St Paul) placed on the PIVC. This had a central polyurethane component, with a reinforced adhesive border on three sides.

The Securement Device with Polyurethane group had a StatLock® IV Select (Ref #IV0525, Bard Access Systems, Utah) (Site 1), or GripLok™ Medium Universal Securement with Wide Silicone Adhesive area (Ref #330MWA) (TIDI, Wisconsin) (Site 2), and Polyurethane (as before) applied to the PIVC. These were selected to suit the winged/non-winged PIVC used routinely at the site. Securement Devices were placed outside of (not under) the Polyurethane.

One strip (approximately 12·5 cm) of non-sterile tape (3M™ Micropore™ 25mm x 9·1m, Ref # 1530–1) was standardly applied on the short extension set in all groups, except Securement Device with Polyurethane participants at Site 2 since this product itself secured the extension set.

Procedures

We chose a pragmatic design, so as to understand how the interventions worked under 'real-world' conditions, this included the intra and inter-hospital heterogeneity typical of PIVC care. PIVCs were inserted by ward nurses and doctors or an experienced nurse inserter; ultrasound was not used. PIVC site, catheter gauge and attachments were chosen by the inserter in consideration of patients' needs. Skin preparation was alcoholic chlorhexidine (CHG) (SoluPrep™ Swab 2% CHG in 70% isopropyl alcohol [IPA], Ref #102.03 [3M, St Paul] at Site 1, and Persist™ Plus 1% CHG in 70% IPA [BD, Utah] at Site 2). PIVCs were Insyte™ Autoguard™ Blood Control (non-winged) (BD) at Site 1, and Introcan Safety®3 (winged) (B Braun) at Site 2. Smart-Site™ Needle-Free Valve (Ref # 2000E, BD) (Site 1) or MaxPlus™ Clear Needle-Free Valve (Ref #MP1000C–0006, BD) (Site 2) were connected to PIVCs directly or via an extension set. Site 1 used 10cm extension sets with bonded 3-way Connecta™ (Ref #394995, BD) and Smart-Site™, or for Securement Device participants, a 15cm luer lock

extension with Smart-Site™ was included. Site 2 used 15 cm extension sets with bonded Smart-Site™ (Ref#10010511).

All post-insertion care was by clinical, not research staff, or IV teams. Bedside nurses decided if replacement/reinforcement of study products was required during PIVC dwell (i.e. when products became loose, moist or soiled). ReNs recorded product replacements or modifications and advised staff about study products prior to study commencement and during the trial. The decision to remove PIVCs was that of the clinical (not research) staff. The Site 1 policy for PIVC removal was initially only for therapy completion or complications; this changed mid-trial to a 72–96 hour removal policy. Site 2 had a routine 72–96 hour removal policy throughout with stricter enforcement. In both sites, dwell time could be extended >96 hours if the PIVC was still needed, had no signs or symptoms of catheter dysfunction or infection, and there was a clinical justification (e.g. patient had poor veins).

ReNs visited participants daily while the PIVC was *in situ*, or until skin adverse events resolved. Baseline patient and PIVC characteristics were recorded. During dwell, data were collected on PIVC therapy, dressing and securement type and condition, and insertion site condition (redness, pain, tenderness, swelling, purulence, palpable cord or vein streak). At PIVC removal, ReNs recorded complications present, dwell time, current clinical variables, and verbal patient (if able) overall satisfaction with the study products (0=completely dissatisfied, 10=completely satisfied). ReNs also asked the nurse who removed the products to verbally rate the difficulty of removal (0=very difficult, 10=very easy). At 48 hours post PIVC removal, ReNs checked the hospital pathology system for blood, PIVC tip or insertion site culture results.

All data were entered into password-protected, portable electronic device with REDCap (Research Electronic Data CAPture, http://project-redcap.org/) database and form-based interface. Clinical staff did not have access to this data and continued routine practices for PIVC monitoring. A Project Manager audited data quality, completeness and protocol adherence with at least monthly site visits for training and monitoring.

As per usual practice, clinical staff ordered blood, PIVC tip or site swab cultures if patients were suspected of PIVC associated infection. These were obtained by bedside nurses, processed in the hospital pathology laboratory by blinded staff, with results accessed by researchers. To further determine infection risk associated with the study products, a sub-study of PIVC tip and insertion site skin cultures was undertaken by the researchers using a blinded microbiologist. [12, 16] For this, convenience sampling was used when ReNs were available at the time of PIVC removal to take specimens, which were then cultured within 24 hours.

Outcomes

The primary outcome was all-cause PIVC failure. This was a composite measure of complications at PIVC removal: dislodgement (Partial dislodgement: PIVC retracted so that tip is no longer in the vein but remains under the skin +/- IV fluids leaking from insertion site. Complete dislodgement: entire PIVC dislodged from patient's body), occlusion (includes infiltration and extravasation), phlebitis (one or more signs/symptoms), or infection (primary bloodstream [BSI], or laboratory confirmed local PIVC infection).[13, 17] All-cause PIVC failure is often used in PIVC trials since the common outcome is a non-functional device. Outcome data were collected by ReNs by patient examination, from hospital and pathology records, or reports from bedside nurses, doctors or competent patients. Infection outcomes were blind-rated by an infectious diseases physician.

Secondary outcomes included sub-types of PIVC failure (as above), PIVC dwell, and study product dwell (durable hours from application). Secondary endpoints from the substudy were PIVC and skin colonisation (>15 colony forming units [CFU]).[16] Patient satisfaction (overall with product) and staff satisfaction (with removal) were verbally ranked on a 11-point ordinal scale.

ReNs assessed daily for adverse events potentially associated with the study products including rash, blister, itchiness, as well as adhesive residue or skin tears on product removal. Serious adverse events (death, admission to intensive care, and/or primary BSIs) were monitored from hospital records and reported to the Human Research Ethics Committee. A Data Safety Monitoring Committee was not formed due to the rapid recruitment.

Total resource use and costs were calculated for each group. This included products applied at PIVC insertion and staff time to apply these, plus products used for replacement or reinforcement, additional PIVC insertions (if the device failed and was replaced), and costs of treating local or primary BSIs (appendix table 1). Purchase costs were 2016 Queensland Health prices (Australian dollars [AU$]). The time taken to apply study products was recorded for 127 insertions selected at random (minimum 26 per group). Nursing and medical staff time was based on published staff salaries, updated to 2016.[18] Costs for treatment of local PIVC infections or primary BSIs used the National Efficient Price Determination (2015–16), and for other complications/adverse events by cost of a replacement PIVC and/or dressing.[5, 19] If a primary BSI infection and a local PIVC infection co-occurred, only the cost of the primary BSI was attributed.

Statistical analysis

The pre-study prevalence of PIVC failure at the study sites using Polyurethane was 40%.[5] We hypothesised that each of the three alternatives would reduce failure by an absolute 10%, i.e. to 30%. This difference was considered clinically important.[20, 21] Sample sizes were calculated for three superiority tests of two proportions with 90% power at p=0·05. Alpha adjustment was not undertaken consistent with our study design of separate hypothesis testing of the effect of multiple alternative treatments (that did not inform a single claim of effectiveness) on one primary endpoint, with a shared control group.[22] This resulted in each group requiring 388 participants, plus 10% for potential attrition (1708 in total).

Data cleaning involved checks of missing, outlier and improbable values with source data verification and corrections for ~10% of patients. Categorical data were summarised as counts and proportions, and continuous/ordinal data as means (standard deviation) or median (interquartile limits), if not normally distributed. Comparability of groups at baseline for risk of device failure was by clinical criteria. Missing data for primary and secondary endpoint variables were not imputed.

In the primary analysis, all randomised patients with the primary endpoint available were analysed by intention to treat (ITT), with the patient as the unit of measurement. Relative incidence rates of PIVC failure per 100 devices and per 100 device days with incident rate ratios and 95% confidence intervals were used to summarise the effectiveness of each intervention, and to test for group differences. Kaplan-Meier survival curves (with log rank Mantel-Cox test) compared failure over time. Multivariate Cox regression was used to calculate hazard ratios for PIVC failure, adjusted for treatment group, for variables associated with PIVC failure at p<0·2 on bivariate regression, and for study site because of significantly different

average PIVC dwell times, i.e. different duration of exposure to risk. Variances in effect sizes between study sites were assessed and although absolute failure incidence differed, this was not different per 100 hours.

Secondary endpoints were compared between groups using parametric or nonparametric techniques as appropriate to level of measurement. A per protocol analysis included patients who had one of the four study treatments for at least 24 hours from PIVC insertion, with censoring if the treatment was modified (i.e. additional products added later). A cost analysis was undertaken from the perspective of public hospitals, as they are the main purchasers of PIVC dressings and securements. Mean costs (including costs of responding to all adverse events) for the three treatment groups were compared with Polyurethane controls using non-parametric bootstrapping. P values <0·05 were considered significant. The trial was registered with the Australian New Zealand Clinical Trials Registry (ACTRN 12611000769987).

RESULTS

Sample

Between March 18, 2013, and September 9, 2014, we screened 2382 patients and randomly allocated 1807 participants to Tissue Adhesive with Polyurethane (446), Bordered Polyurethane (454), Securement Device with Polyurethane (453) or Polyurethane (454) (Figure 2). In total, 98/1807 (5·4%) randomised patients had a failed or cancelled PIVC insertion so the study products were never applied and no data were collected on these patients (Fig 2). No patients withdrew consent. The primary endpoint was unable to be determined in full (with the exception of infection outcomes) for 12 participants (4 each in Tissue Adhesive with Polyurethane and Bordered Polyurethane groups; 2 each in Securement Device with

Polyurethane and Polyurethane groups), thus 1697 of the 1709 (99%) who had a PIVC inserted were included in the ITT analysis. There were 115,408 PIVC hours/4,809 PIVC days studied, with the proportion of PIVCs removed by day of dwell being: Day 1 (16%), 2 (26%), 3 (20%), 4 (16%), 5 (9%), 6 (5%), 7 (3%), 8 (2%), 9 (1%), 10 (1%) or 11–18 (1%). Clinical and demographic characteristics were similar between groups for both patients and PIVCs (table 1).

For the primary outcome of PIVC failure, absolute risk differences between groups were less than the predefined 10% margin, therefore we rejected the superiority hypotheses. PIVC failure was experienced by 38% (Tissue Adhesive with Polyurethane, 13·3/100 days), 40% (Bordered Polyurethane 14·6/100 days), 41% (Securement Device with Polyurethane, 14·2/100 days) and 43% (Polyurethane, 15·1/100 days) of participants (table 2). PIVC failure was not significantly different between any of the three intervention groups and controls for per patient (p=0·21 to 0·74, table 2), per 100 PIVC days (p=0·25 to 0·82, table 2), or survival (p=0·57, figure 3) analyses. Sensitivity analyses of group differences by site did not indicate confounding by use of different PIVC and Securement Device brands at the two study sites (all p>0·05).

Most (1685 of 1709, 98·6%) participants with a PIVC received the allocated intervention (figure 2). Of the remaining 24 participants, 17 received an incorrect study group allocation, and 7 received non-study products. Additional dressings and/or securements were added for 1130 (66%) participants on some/all dwell days (N=585 within 24 hours of PIVC insertion). This involved 71% of Tissue Adhesive with Polyurethane, 61% of Bordered Polyurethane, 56% of Securement Device with Polyurethane, and 77% of Polyurethane participants. In the per protocol analysis (n=1100), 17 patients changed groups and we included 746 participants who received no treatment modification and 354 participants who received at least the initial

24 hours of allocated treatment (with censoring if alterations occurred later). In this analysis, Tissue Adhesive with Polyurethane, but not Bordered Polyurethane or Securement Device with Polyurethane, was associated with significantly less PIVC failure compared to Polyurethane controls (table 2).

Regarding secondary outcomes, occlusion was significantly less frequent for Tissue Adhesive with Polyurethane than Polyurethane controls (5.6 *vs* 7.9 per 100 days, p=0·027, table 2), but did not significantly differ for Bordered Polyurethane or Securement Device with Polyurethane, compared to Polyurethane. Dislodgement and phlebitis incidences were not statistically different between any of the intervention groups, and Polyurethane controls.

Three patients developed a primary BSI, two in the Bordered Polyurethane group (one patient with *Pseudomonas aeruginosa*; one patient with *Enterobacter cloacae* [*E. cloacae*] and *Citrobacter braakii*), and one in the Polyurethane group (*E. cloacae*) (table 2). Of these, one was confirmed as catheter-related (CRBSI) via a matching positive tip culture (Polyurethane group; *E. cloacae*). There was one laboratory confirmed local site infection which occurred in the Polyurethane group (*E. cloacae* – this event was also the CRBSI described above).

The median PIVC dwell time was 54 hours (interquartile range [IQR] 29, 94). This did not differ significantly between any of the three intervention groups and the Polyurethane group (table 2). The average dwell time differed between Site 1 (72·7 hours) and Site 2 (58·2 hours). Although commonly reinforced, the initial study products were rarely replaced, remaining on average for 52 hours (IQR 28, 92; not significantly different between any intervention group and controls).

The microbiological sub study found positive tip cultures in 0–4% per group, which was not significantly different between intervention and control groups (table 2). Skin cultures were positive (any growth) in 10% to 19% per group (not significantly different between intervention and control groups).

The initial mean (95% CI) costs were substantially higher per patient for products and staff time for all three experimental groups compared to the control group (table 3). When the costs of replacement for failed PIVC devices and replacement/reinforcement of study products were added, costs were significantly ($p<0.001$) higher per patient for all three experimental groups compared to the control group (difference in means AU$15.53 [15.27-15.78], AU$3.86 [3.78-3.94], AU $7.51 [7.41-7.61] for Tissue Adhesive with Polyurethane, Bordered Polyurethane, and Securement Device with Polyurethane respectively compared to Polyurethane). However, overall mean costs per patient were not significantly different between any experimental group and the control group, once treatment costs for the three primary BSIs were included.

There were 39 skin injury adverse events associated with study products (14 rash, 12 pruritus, 8 skin tear, 4 blister, and 1 pressure area) in 34 patients, occurring in all groups. Only Tissue Adhesive with Polyurethane was significantly different to controls (4.0% vs 1.7%, p=0·04, table 2). Serious adverse events (death, ICU admission or primary BSI) occurred in 15 (0·9%) patients overall. Deaths and ICU admissions were not related to study participation.

Patients and bedside nurse satisfaction scores were generally satisfied with all products tested (table 2). Tissue Adhesive with Polyurethane received a significantly higher rating from patients, but a significantly lower rating from nurses, compared to Polyurethane, however these differences were <1 point on an 11-point scale.

DISCUSSION

This large pragmatic randomised controlled trial of PIVC dressing and securements found PIVC all-cause failure to be highly prevalent, at 41% overall. We tested three alternatives against a traditional low-cost Polyurethane control dressing, but none significantly reduced PIVC failure. Overall, there was no significant difference in costs between dressing and securement alternatives, although this included infection treatments, which were high cost but uncommon and not different between groups. Excluding infection treatment costs, the total mean costs per patient of Polyurethane were significantly less than those of any of the three alternatives and represented savings of up to AU$15.53 (95%CI 15.27-15.78) per patient. All products tested, including Polyurethane, were commonly associated with PIVC failure, and often needed reinforcement – innovation to achieve effective, durable products is urgently needed.

This study indicates potential substantial savings to the health system if clinicians 'choose wisely' and opt for low cost Polyurethane for PIVCs, in the absence of clinical rationale for use of a more expensive product.[23, 24] A recent cross-sectional study in 51 countries reported 56% of PIVCs as secured with Polyurethane, 22% with Bordered Polyurethane, 5% with Securement Devices, and Tissue Adhesive use unknown but growing.[1, 25] With two billion PIVCs used globally each year, disinvestment of AU$3.86 to AU$15.53 per PIVC so that 100% are secured with Polyurethane could save AU$3.4 to AU$13.7 billion per year in products, staff time and responses to PIVC failure (excluding infections).[3]

Bordered Polyurethane dressings were developed to improve securement over traditional Polyurethane dressings, but we found these to have no less complications and failure,

confirming results of smaller studies.[26, 27] Further, the durability of both Polyurethane and Bordered Polyurethane (one of which was used in all four study groups) was poor, with reinforcement frequently required, commonly due to lost adherence at one or more parts of the dressing. This occurred in over half of our patients, indicating poor performance during typical clinical conditions, even with a short (average 2·4 days) PIVC dwell. Securement Devices with Polyurethane had non-statistically lower PIVC failure compared to Polyurethane dressings in one previous small randomised trial, but no benefit was seen in our study.[26]

Our secondary outcomes included significantly reduced occlusions in the Tissue Adhesive with Polyurethane group, although the 6% absolute reduction was less than the significant 10% reduction in failure observed in a smaller study which followed patients for a shorter, 48 hour maximum PIVC dwell.[25] Tissue Adhesive is applied directly at the PIVC skin entry point and under the PIVC hub (+/- wings), possibly reducing micro-motion and internal vein damage.[26] Our per protocol analysis further suggested Tissue Adhesive's potential benefit, but many patients required additional dressing reinforcement, and its use in combination with Polyurethane alone is unlikely to benefit the hospital population at large. If more durable dressings are identified, Tissue Adhesive may be a useful adjunct in the future. The low BSI incidence precludes definitive conclusions about comparative infection risk between study products, however we noted no infections associated with Tissue Adhesive, which has antimicrobial properties[28], nor in the Securement Device group, a product which may discourage skin microorganism entry into the wound via PIVC micro-motion.

A recent, large, prospective cohort study supports the need for extra securement to reduce high PIVC failure, and the shortcomings of current approaches.[29] Any additional securement (e.g. tape, elasticised tube, additional dressing) added to a Bordered Polyurethane was associated

with significant large reductions (HR 0·3–0·6) in occlusion, phlebitis and dislodgement.[29] These associations suggest multi-product combinations i.e. 'securement bundles' may be more effective for prevention of PIVC failure, than any one product alone, and should be tested in randomised studies.

To our knowledge, no previous study has systematically tracked skin related adverse events associated with PIVCs. We observed one or more such complications in 2% of all patients. Rashes were most commonly, possibly reflecting irritation from the adhesive, or incorrect application of the dressing to skin still moist from pre-insertion antiseptics. Bruising was evident at 4% of PIVCs insertion sites, likely reflecting traumatic insertion, since ultrasound/other vein identification technologies were not used.

Strengths of this study were its rigorous randomisation, daily follow up and prospective data collection processes. Generalisability of results was maximised by the heterogeneous nature of patients and PIVCs studied, with participants commonly at high risk due to age, obesity and multiple comorbidities. We avoided interfering with usual post-insertion care of PIVCs by bedside staff so as to understand real world effectiveness. Although 5% of randomised patients did not go on to receive a PIVC and were therefore excluded, this could not have been impacted upon by the choice of dressing and securement product. For those patients with a PIVC, 99% received the allocated intervention and 99% were included in the primary analysis.

The bottom-up, micro-costing approach including detailed costing for staff time associated with study products is also a strength. Although the protocol specified a cost-effectiveness analysis to estimate incremental cost per PIVC failure avoided[15], we considered this of little value since no group had superior primary outcomes. Instead, our economic analysis is

pragmatic and incorporates costs of the interventions and those of managing complications and adverse events. In keeping with the hospital perspective, post discharge costs were not studied which is a potential limitation. However the complication most plausible to have post discharge costs (primary BSIs) had treatment costs included up until hospital discharge, by which time all six cases had resolved, thus our approach was unlikely to have altered study conclusions.

Study limitations included the majority of PIVC insertions by RN expert inserters which may have reduced the risk of PIVC failure. However the incidence of 41% PIVC failure is consistent with our previous studies using less experienced inserters, thus poor securement may outweigh benefits of optimal insertion.[5, 29] The products used were unable to be blinded, and we did not formally assess inter-rater reliability, but risk of bias was reduced by outcome assessment using a small number of trained observers using clear definitions, blinded infection outcome assessors (100% agreement), all supervised and audited by a study manager. We have previously established 98% agreement (Cohen's kappa 0.33) for phlebitis measures in our group.[8] The study sites used different PIVC and securement devices, but there was no significant confounding in effect sizes by site, suggesting that this did not introduce bias. We tested various product 'categories' (e.g. Bordered Polyurethane), but results may not reflect all product types within these categories, or be generalizable to other patient groups such as paediatrics. Our sample size was adequate to test our *a priori* hypotheses of 10% absolute reduction in the primary endpoint for all three intervention groups, but observed reductions were 2% to 5%. To confirm the largest observed difference in PIVC failure (Tissue Adhesive with Polyurethane 38%; Polyurethane 43%) would require a study of approximately 3000 patients (p=0·05, 80% power). We acknowledge some published views differ, but we did not undertake alpha adjustment as our study design tested separate hypotheses of three alternative

treatments (not varying doses of the same treatment) for one primary endpoint against a shared control group.[22, 30, 31]

Both the Centers for Disease Control Guidelines and the Infusion Therapy Standards of Practice consider optimal PIVC dressing and securement to be unresolved.[10, 13] Both documents reflect the conclusions of a 2015 systematic review and meta-analysis which highlighted the paucity of high quality randomised studies. Regulatory bodies currently do not require evidence of effectiveness for device (e.g. dressing) registration (unlike pharmaceuticals), and manufacturers and independent funders rarely support randomised trials for efficacy or cost-effectiveness. With extensive global use of PIVCs, highly prevalent PIVC failure, and substantial costs to healthcare providers for dressing and securement products, further investment and innovation for effective products are urgently needed.

CONCLUSION

Almost all hospitalised patients worldwide receive one or more PIVCs, of which up to half are removed due to complications, causing substantial waste, discomfort, cost and harm. Better dressing and securement would likely prevent many complications but the optimal method remains elusive. Until a superior method is identified, cost should be the major factor to consider in choice of products.

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AUTHORS CONTRIBUTIONS

Study conception: CMR, NMM, JW, JFF

Protocol design: CMR, NMM, JW, MRM, JAW, HT, DM, EGP

Funding application: CMR, NMM, JW, MRM, JAW, DM, JFF, AM, EGP

Health economic analysis: JAW, EB, HT

Microbiological analysis: MAC, DM

Infection adjudication: NR, EGP

Project Management: NMM, EL

Patient recruitment, data collection and supervision of research nurses: NMM, JW, FF, EL, EGP

Data management and access to all data: CMR, NMM, EL, MRM

Statistical analysis: MRM

First draft and coordinate manuscript preparation: CMR

Critical review of drafts and approval of final manuscript: All authors

Final responsibility for the decision to submit for publication: CMR

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COMPETING INTERESTS STATEMENT (past 36 months)

CMR's employer has received on her behalf from manufacturers of vascular device dressing and securement products: investigator initiated research grants and unrestricted educational grants from 3M, Adhezion, Bard, Baxter, BBraun, BD, Centurion Medical Products, Entrotech, Medtronic; and consultancy payments for educational lectures/expert advice from 3M, Bard; BBraun, BD, ResQDevices.

NMM's employer has received on her behalf from manufacturers of vascular device dressing and securement products: investigator initiated research grants and unrestricted educational grants from 3M, BD, Centurion Medical Products, Entrotech; and consultancy payments for educational lectures from BD.

EL's employer has received on her behalf from manufacturers of vascular device dressing and securement products: consultancy payment for an educational lecture from 3M.

Other authors: no relevant competing interests.

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Figure 1. Dressing and securement products studied

Fig 1a. Tissue Adhesive with Polyurethane

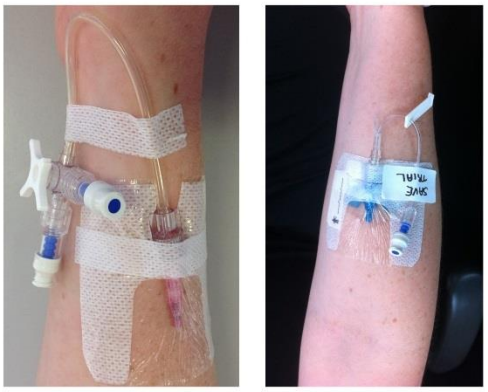


Fig 1b Bordered Polyurethane

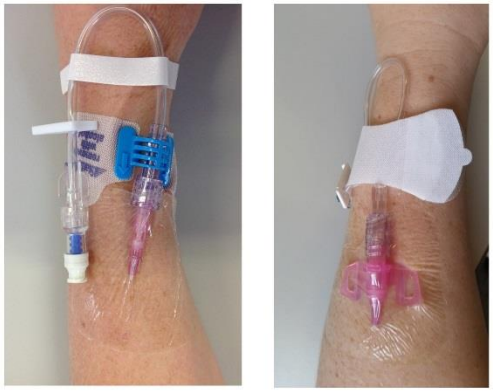


Fig 1c Sutureless Device with Polyurethane

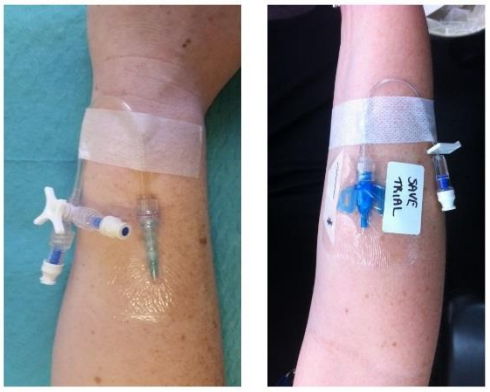
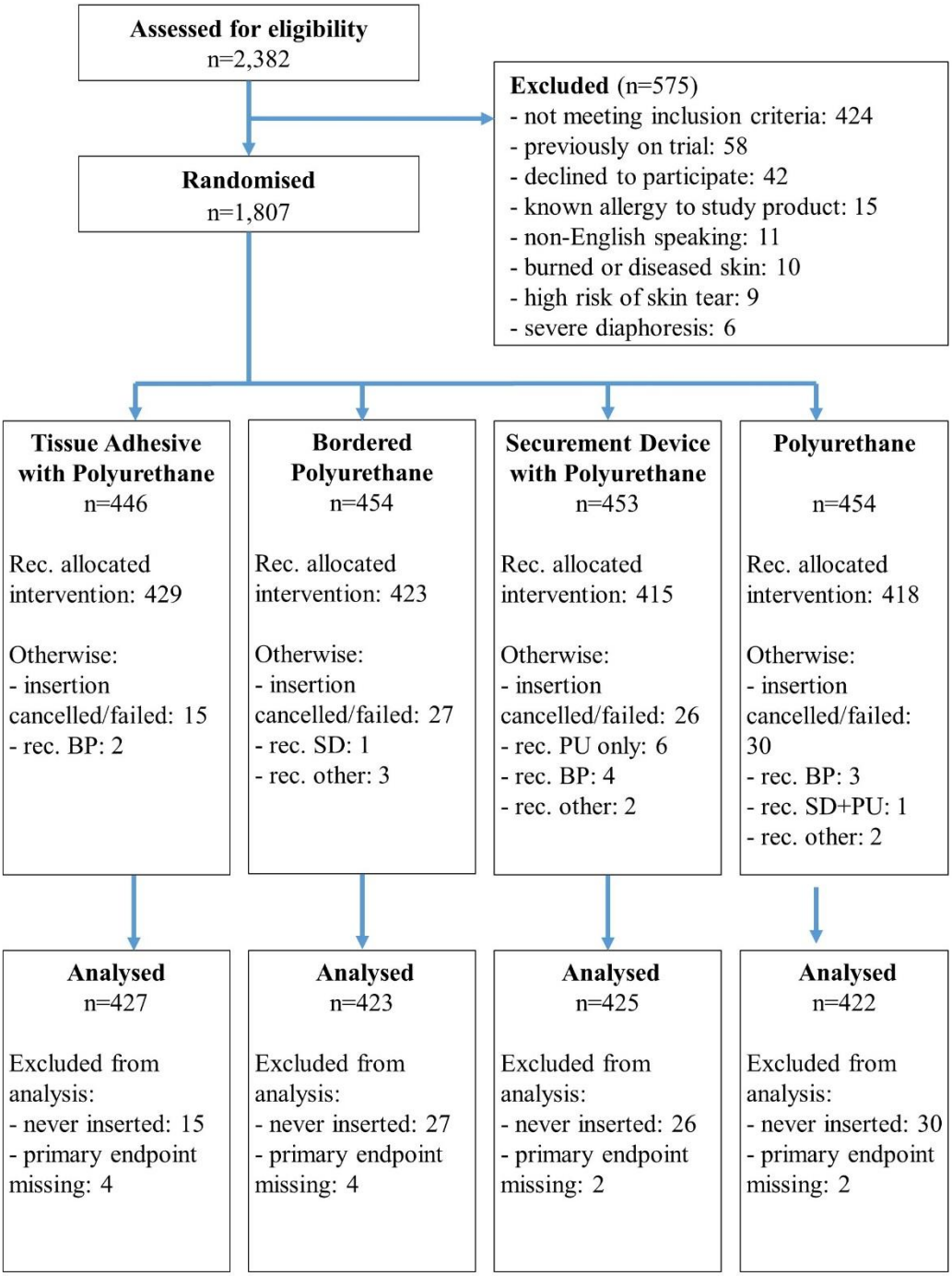


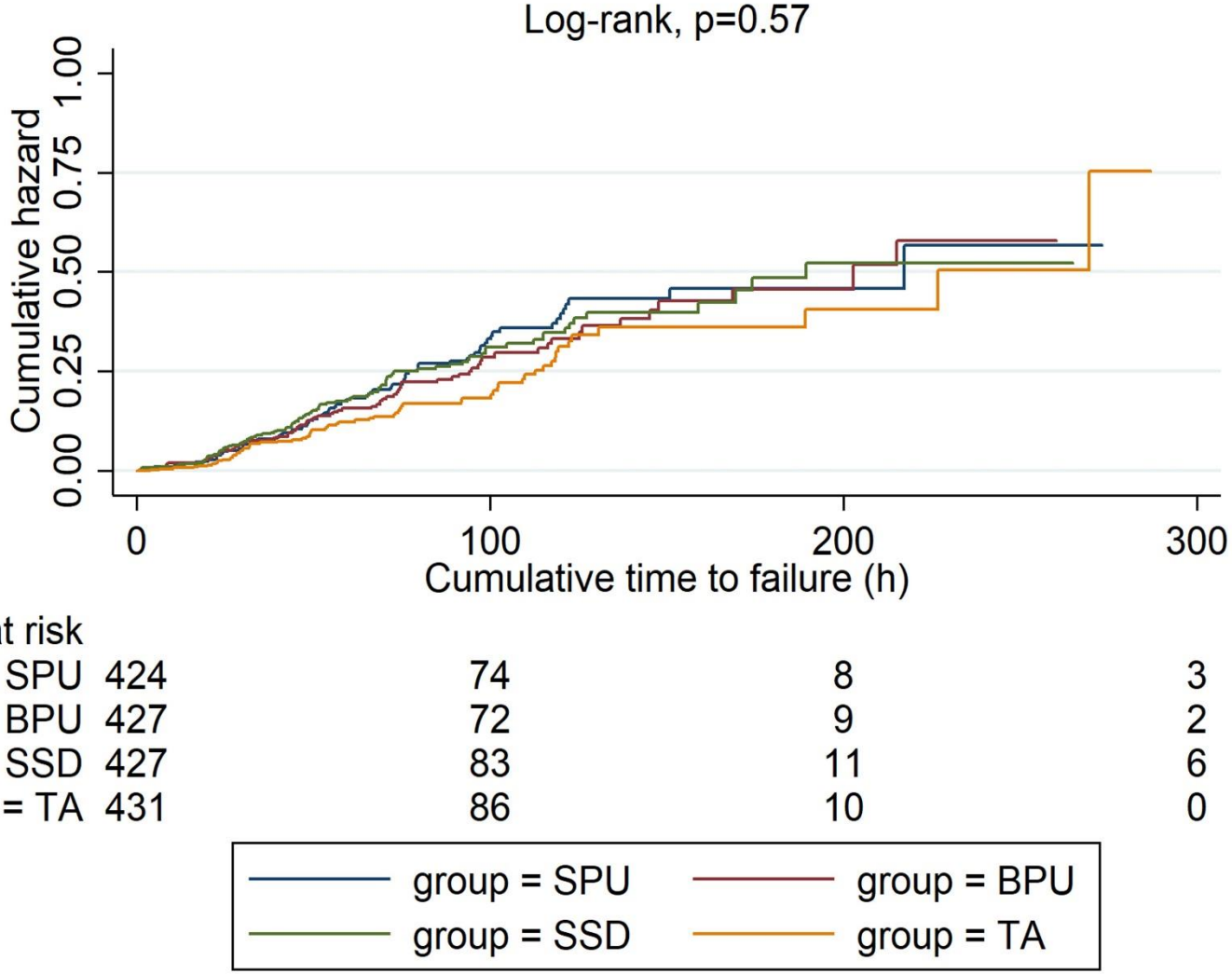
Fig 1d. Polyurethane (controls)

Figure 2. CONSORT Flowchart



BP = Bordered Polyurethane; SD = Securement Device; rec. = received; PU = polyurethane.

Figure 3: Kaplan-Meier analysis of survival from failure



	Tissue adhesive with Polyurethane group (n=431)	**Bordered Polyurethane group (n=427)**	**Securement Device with Polyurethane group (n=427)**	**Polyurethane control group (n=424)**
Days studied (n)	1228	1154	1239	1188
Age (median, IQR)	59 (45, 71)	61 (44, 72)	61 (44, 74)	61 (48, 72)
Male	256 (59%)	241 (56%)	237 (56%)	253 (60%)
Female	175 (41%)	186 (44%)	190 (44%)	171 (40%)
Medical	209 (48%)	217 (51%)	220 (52%)	222 (52%)
Surgical	194 (45%)	187 (44%)	182 (43%)	186 (44%)
Oncology	28 (6%)	23 (5%)	25 (6%)	16 (4%)
Three or more co-morbidities	196 (45%)	195 (46%)	201 (47%)	213 (50%)
Obese	61 (14%)	54 (13%)	60 (14%)	59 (14%)
Overweight	123 (29%)	123 (29%)	121 (29%)	131 (31%)
Healthy weight	192 (45%)	207 (48%)	209 (49%)	180 (43%)
Emaciated	55 (13%)	43 (10%)	34 (8%)	53 (13%)
Leucocytes <1000 / µl abs.	1 (0.2%)	0 (0%)	2 (0.5%)	2 (0.5%)
Any infection at recruitment	77 (18%)	86 (20%)	84 (20%)	85 (20%)

Wound (pre-existing)	183 (42%)	184 (43%)	170 (40%)	176 (42%)
Stoma	23 (5%)	37 (9%)	21 (5%)	23 (5%)
Tracheostomy	7 (2%)	11 (3%)	11 (3%)	10 (2%)
"Good" skin integrity	171 (40%)	180 (42%)	169 (40%)	164 (39%)
Skin type: Fitzpatrick scale				
Pale white	60 (14%)	65 (15%)	70 (17%)	67 (16%)
White	269 (63%)	265 (62%)	263 (62%)	263 (62%)
Light Brown	70 (16%)	74 (17%)	65 (15%)	87 (16%)
Moderate Brown/Dark brown/Deeply pigmented dark	31 (7%)	22 (6%)	26 (7%)	27 (6%)
IV antibiotics during dwell	257 (60%)	249 (58%)	265 (62%)	270 (64%)
Regular flush (documented)	13 (3%)	12 (3%)	14 (3%)	13 (3%)
Dominant side insertion	235 (57%)	214 (53%)	228 (55%)	220 (53%)
IV expert nurse	369 (86%)	373 (87%)	379 (89%)	377 (89%)
Bedside nurse	38 (9%)	31(7%)	27 (6%)	28 (7%)
Medical officer	22 (5%)	22 (5%)	19 (4%)	19 (4%)
Anterior upper forearm	130 (31%)	132 (31%)	106 (25%)	128 (30%)
Posterior lower forearm	123 (29%)	125 (29%)	107 (25%)	107 (25%)
Wrist	52 (12%)	65 (15%)	69 (16%)	67 (16%)

Posterior upper forearm	41 (10%)	25 (6%)	32 (8%)	30 (7%)
Hand	27 (6%)	31 (7%)	32 (7%)	25 (6%)
Cubital fossa	20 (5%)	22 (5%)	27 (6%)	17 (4%)
Anterior lower forearm	17 (4%)	19 (4%)	21 (5%)	21 (5%)
Anterior upper arm	18 (4%)	7 (2%)	26 (6%)	24 (6%)
Posterior upper arm	5 (1%)	1 (0%)	7 (2%)	3 (1%)
Insertion attempts: single	346 (80%)	350 (82%)	337 (79%)	331 (78%)
Bruised insertion site	17 (3·9%)	10 (2·3%)	18 (4·2%)	23 (5·4%)
Skin prep CHG in alcohol*	422 (98%)	421 (99%)	424 (99%)	419 (99%)
22G	303 (71%)	300 (71%)	303 (71%)	311 (73%)
20G	118 (28%)	116 (27%)	117 (28%)	104 (25%)
18G	5 (1%)	5 (1%)	2 (1%)	5 (1%)
10–15cm extension tubing	156 (36%)	149 (35%)	425 (100%)¶	145 (34%)
3 way connector	268 (63%)	274 (64%)	10 (2%)	276 (65%)
Multiple pieces of non-sterile tape on device ≥1 dwell days	107 (25%)	83 (19%)	80 (19%)	123 (29%)
Infusion tubing (if used) is secured on all days§	69 (19%)	80 (25%)	72 (21%)	78 (23%)
Hair unclipped at PIVC site	192 (45%)	184 (43%)	191 (45%)	182 (43%)

Data are median (IQR) or n (%). *Skin prep 70% alcohol swab (N=5), skin prep missing (n=18); ¶Securement Device required an extension tubing to apply; §n=1363 had one or more days with infusion tubing

Table 1: Baseline, demographic and clinical characteristics of 1709 randomised patients who received a PIV

	Tissue adhesive with Polyurethane group (n=427)	Bordered Polyurethane group (n=423)	Securement Device with Polyurethane group (n=425)	Polyurethane control group (n=422)	Overall (n=1697)
Primary Endpoint, ITT					
PIVC failure/patient, p-value˜	163 (38%), p=0·21	169 (40%), p=0·46	176 (41%), p=0·74	180 (43%)	688 (41%)
PIVC failure/100 PIVC days (95% CI)	13·3 (11·2–15·3)	14·6 (12·4–16·8)	14·2 (12·1–16·3)	15·1 (12·9–17·4)	
Relative risk (95% CI), p- value*)	HR 0·96 (0·89–1·03), p=0·25	HR 0·98 (0·79–1·20), p=0·82	HR 0·96 (0·87–1·07), p=0·47	-	
Per protocol					
PIVC failure/patient, failure/100 days	74/281 (26%), 12·7	96/273 (35%), 19·6	100/296 (34%), 15·9	86/250 (34%), 18·3	
Relative risk (95%CI), p-value*)	HR 0·88 (0·79– 0·98), p=0·018	HR 1·10 (0·82–1·48), p=0·52	HR 0·91 (0·79–1·05), p=0·20		
Secondary outcomes					
Occlusion, n/100 days (HR, 95% CI, p-value*)	69 (16%), 5·6 (HR 0·89, 0·80–0·99, p=0·027)	82 (19%), 7·1 (HR 0·91, 0·68–1·22), p=0·54)	98 (23%), 7·9 (HR 1·00, 0·87–1·15), p=0·99	94 (22%), 7·9	343 (20%)

Phlebitis (≥1 sign/symptom), n/100 days (HR, 95% CI, p-value*)	108 (25%), 8·8 (0·98, 0·90–1·07, p=0·66)	94 (22%), 8·2 (0·87, 0·66–1·15, p=0·33)	109 (26%), 8·8 (0·95, 0·83–1·08, p=0·42)	112 (27%), 9·4	423 (25%)
Dislodgement, n/100 days (HR, 95%CI, p value*)	29 (7%), 2·4 (0·86, 0·74–1·01, p=0·07)	40 (9%), 3·5 (0·97, 0·63–1·50, p=0·89)	37 (9%), 3·0 (0·94, 0·75–1·17, p=0·55)	42 (10%), 3·5	148 (9%)
Primary bloodstream infection	0	2 (0·47%)	0	1[#] (0·24%)	3
Local PIVC infection	0	0	0	1[§] (0·24%)	1
PIVC dwell time, median h, (IQR)	56 (29, 95)	50 (28, 92)	55 (28, 94)	55 (30, 92)	54 (29, 94)
1st study product dwell time, median h, (IQR)[¥, Ω]	55 (28,95)	50 (28,91)	52 (26,90)	52 (29,89)	52 (28,92)
Substudy (n=137)					
Tip colonised >15cfu[¥]	2/48 (4%)	1/52 (2%)	0/59 (-)	1/56 (2%)	4/215 (2%)
Skin colonised >0cfu[¥]	9/48 (19%)	10/52 (19%)	6/59 (10%)	7/56 (13%)	32/215 (15%)
Skin adverse events	17 (4·0%)[Ψ]	2 (0·5%)[¥]	8 (1·9%)[¥]	7 (1·7%)	34 (2·0%)
Serious adverse events[¥]	4 (0·9%)	4 (0·9%)	4 (0·9%)	3 (0·7%)	15 (0·9%)

Patient overall satisfaction$^{\phi}$ (0-10 scale) mean, median (IQR), p-value$^{\wedge}$	N=363 8·6, 9 (8,10) p<0·001	N=368 8·3, 9 (8,10) p<0·001	N=360 7·9, 8 (7, 10) p=0·15	N=380 7·7, 8 (7, 10) referent	N=1,471 8·1, 0 (8, 10)
Nurse satisfaction with removal (0-10 scale) mean, median (IQR), p-value$^{\wedge}$	N=324 8·2, 9 (8,10) p<0·001	N=338 8·8, 9 (8,10) p=0·99	N=333 8·2, 9 (7,10) p<0·001	N=343 8·7, 9 (9,10) referent	N=1338 8·5, 9 (8, 10)

Data are n (%). Patients with missing primary endpoint data (n=12) not included in this analysis. HR=Hazard ratio. H=hours. IQR= inter-quartile range (25th and 75th percentiles). $^{\sim}$Fisher exact test of independence (2-sided). *Cox regression. $^{\#}$PIV-related bloodstream infection (matched colonised tip and exudate). §associated with a BSI (matched organism). $^{\Psi}$p=0.04. $^{¥}$p>0·05 for each study group against control; $^{\Omega}$98/1687 had initial products replaced. $^{\phi}$13·5% missing data. $^{\wedge}$Wilcoxon rank-sum test.

Table 2: Study outcomes by treatment group (per patient analysis, MV logistic and Cox regression models, adjusted for study site)

	Mean costs per patient, AU$ (95% CI)				
	Tissue Adhesive with Polyurethane group	**Bordered Polyurethane group**	**Securement Device with Polyurethane group**	**Polyurethane control group**	**Overall**
N	427	423	425	422	1,697
Initial dressing and securement products	$12·85 (12·64–13·05)	$3·31 (3·26–3·36)	$5·39 (5·32–5·46)	$0·48 (0·45–0·51)	$5·53
Staff time costs to apply products	$0.81	$0.72	$1.21	$0.60	$0.84
Costs associated with initial PIVC	**$13·66** (13·45–13·86)	**$4·01** (3·96–4·07)	**$6·62** (6·55–6·70)	**$1·08** (1·05–1·11)	**$6·37**
Replacement PIVC[a], dressing and securement products, and staff time	$4·12 (4·07–4·17)	$2·10 (2·08–2·11)	$3·14 (3·12–3·15)	$1·17 (1·16–1·18)	$2·64
Costs associated with initial and replacement PIVC	**$17·78** (17·52–18·03)	**$6.11** (6.04, 6.18)	**$9·76** (9·67–9·85)	**$2.25** (2.21, 2.29)	**$9.00**
Difference in means compared to polyurethane control	$15.53 (15.27 – 15.78)	$3.86 (3.78 – 3.94)	$7.51 (7.41 – 7.61)	Referent	

p-value [c]	< 0.001	< 0.001	< 0.001		
Treatment of primary bloodstream infections[b]	$0	$29.41	$0	$14.98	$11.06
Total costs	**$17·78** (17·52–18·03)	**$35.52** (-5.57, 76.61)	**$9·76** (9·67–9·85)	**$17·23** (-12·16–46·63)	**$20.06**
Difference in means compared to polyurethane control	$0·55 (-28·92 – 30·01)	$18.29 (-32.63 – 69.20)	-$7·47 (-36·94 – 21·99)	Referent	-
p-value [c]	0.972	0.457	0.620		

Table 3. Costs associated with PIVC dressings by treatment group (ITT analysis)

AU$ = Australian dollars; CI = confidence interval; PIVC = peripheral intravenous catheter. [a] Replacement PIVCs required in 22·7% of Tissue Adhesive with Polyurethane; 27·9% of Bordered Polyurethane; 26·6% of Securement Device with Polyurethane; and 26·1% of Polyurethane control group patients; [b] two primary bloodstream infections in Bordered Polyurethane and one in Polyurethane controls; [c] non-parametric bootstrapping.

	Product	Cost per unit AU$	Assumptions/ percentage of patients
Polyurethane dressing	Tegaderm™ Transparent Film dressing – 1624W (6 cm x 7 cm) (3M)	$0·2437	85% of Site 1 patients 15% of Site 2 patients
	Tegaderm™ Transparent Film dressing – 1626W (10 cm x 12 cm) (3M)	$0·56	15% of Site 1 patients 85% of Site 2 patients
Bordered Polyurethane dressing	Tegaderm™ IV Advanced Securement dressing – 1683 (10 cm x 7 cm) (3M)	$3·264	100% of patients
Securement Device	StatLock® IV Select – IV0525 (Bard)	$5·254	100% of Site 1 patients
	GripLok™ Medium Universal Securement with Wide Silicone Adhesive area – 330MWA (TIDI)	$3·75	100% of Site 2 patients
Tissue Adhesive	Histoacryl™ Blue – 1050044 (Aesculap)	$11·80	100% of patients
	Uni-solve® wipes (Smith & Nephew)	$0·1696	2 per removal
PIVC costs	Insyte™ Autoguard™ Blood Control (non-winged) (BD)	$1·99	100% of Site 1 patients
	Introcan Safety® 3 (winged) (B Braun)	$1·47	100% of Site 2 patients
Additional product costs	Micropore™ non-sterile tape – 1530-1 (25 mm x 9·1 m) (3M)	$0·006	Per 12·5 cm strip
	Sterile gauze	$0·034	Per use
	Tubifast® – medium (Molnlycke)	$0·1238	Per 12·5 cm length; 50%
	Tubifast® – large (Molnlycke)	$0·1365	Per 12·5 cm length; 50%
	Sterile tape	$0·798	Per use
	Local infection (J64B)	$3,739·60	Per patient affected

Infection treatment costs[19]	Primary bloodstream infection (T60C)	$6,351·94	Per patient affected
Staff costs updated to 2016 costs[18]	Registered nurse	$0·6228	Per minute
	Junior medical staff	$0·8692	Per minute
	Senior medical staff	$1·2702	Per minute

Appendix Table 1. Costs associated with each study group: initial, additional and replacement products and staff time, and costs of responding to PIVC failure

AU$ = Australian dollars; PIVC = peripheral intravenous catheter