Cancer and Venous Access (CAVA): a randomised controlled trial of central venous access devices for the delivery of systemic anti-cancer therapy

Authors

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SUMMARY

Background: Hickman-type tunnelled catheters (Hickman), peripherally inserted central catheters (PICCs), and totally implanted ports (PORTs) are used to deliver systemic anti-cancer treatment (SACT) via a central vein. We aimed to compare complication rates and costs.

Methods: An open multicentre randomised trial of three comparisons: (i) PICCs versus Hickman (non-inferiority); (ii) PORTs versus Hickman (superiority); and (iii) PORTs versus PICCs (superiority). Adults (aged ≥18 years) receiving SACT (≥12 weeks) for solid or haematological malignancy from 18 UK oncology units. The primary outcome was complication rate (composite of infection, venous thrombosis, pulmonary embolus, inability to aspirate blood, mechanical failure, other) assessed until device removal, withdrawal from study or one year follow. Four randomisation options were available: Hickman-PICCs-PORTs, PICCs-Hickman, PORTs-Hickman, and PORTs-PICCs. Randomisation was performed using a minimisation algorithm stratifying by centre, body mass index, oncology disease, device history and treatment mode.

Findings: Between November 2013 and February 2018, 1061 patients were randomised. PICCs (n=212) and Hickman (n=212) had similar complication rates; 52% and 49%. Although the observed difference was less than 10%, non-inferiority of PICC was not confirmed (OR 1.15, 95% CI; 0.78-1.71) potentially due to a lack of power. PORTs (n=253) were found superior to Hickman (n=303); complication rate 29% versus 43%, (OR 0.55, 95% CI; 0.38-0.79). PORTs (n=147) were found superior to PICCs; (n=199) complication rate 32% versus 47% (OR 0.52, 95% CI; 0.33-0.83). PICCs had lower costs than Hickman (-£1553, 95% CI; -£2639, -£468). Total costs of PORTs were comparable with Hickman (-£45, 95% CI; -£744, £655), but higher than PICCs (£1665, 95% CI; £766, £2,564). When catheter dwell time was calculated, costs of PORTs were lower than PICCs, whilst the other comparisons remain comparable.

Interpretation: PORTs are more effective and safer than both Hickman and PICCs. A PORT first strategy for SACT should be considered a new standard of care.

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Registration number ISRCTN44504648.

Introduction

Cancer requiring systemic anti-cancer therapy (SACT) is common. Between March 2017 and February 2018, the SACT dataset for Public Health England recorded 175,520 patients aged ≥25 years receiving it.[1] Intravenous SACT administration can be given through a peripheral cannula, a short catheter (midline) into an upper arm vein, or a central venous access device (CVAD). The latter are indicated when the duration of SACT is several months and/or there is a lack of adequate peripheral veins.[2] Furthermore, CVADs can be used to withdraw blood and administer other agents such as radiographic contrast media, both very common in these patients.[3] CVADs include Hickman-type tunnelled catheters (Hickman), peripherally inserted central catheters (PICCs), and totally implanted ports (PORTs), which deliver drugs and fluids into a large central vein (typically the superior vena cava). This avoids local vein damage from the irritant nature of SACT, which can rapidly occlude peripheral arm veins and cause tissue necrosis with extravasation.

Decision-making processes behind the choice of device are poorly understood in the UK. PICC usage has increased over the last decade and is now the dominant strategy in many centres. This may be due to ease of insertion and removal by nurse-led teams, technical issues such the avoidance of the vital structures in the neck including the risk of pneumothorax and perceived lower up-front costs. PORTs, in contrast, are the most expensive and least frequently used of the three devices.

A systematic review[4] and pilot randomised controlled trial (RCT)[12] comparing PORTs with Hickman have suggested PORTs may be superior and possibly more cost-effective. A further systematic review evaluated the complications and costs of PICCs compared with PORTs.[5] Based on 15 cohort studies, PICCs were associated with an increased risk of complications including thrombosis, occlusion, infection, malposition and accidental removal compared with PORTs. Two further RCTs compared PICCs with PORTs and both indicated a higher adverse event rate with PICCs.[6, 7] The existing evidence is however heterogeneous with regards study population, design and overall quality; there is also a paucity of data on quality of life (QoL) and cost-effectiveness. Currently, there is no direct comparison of the three devices. Consequently, neither the European Society of Medical Oncology nor the American Society of Clinical Oncology makes specific recommendations regarding type of device.[2, 8] In 2011, the UK National Institute for Health Research Health Technology Assessment (NIHR HTA) Programme commissioned the CAVA trial with associated qualitative research, to evaluate the clinical effectiveness, cost-effectiveness, and acceptability of all three devices.

Methods

Study design

CAVA was a pragmatic open-label, multicentre, mixed methods RCT of three routinely used CVADs: Hickman, PICCs and PORTs. Ethics approval was received from West of Scotland Research Ethics Service (REC 1), (reference 13/WS/0056). The trial protocol has been published prospectively.[9]

Participants

Patients were recruited from 18 UK oncology units. Patients ≥18 years expected to receive SACT for ≥12 weeks to treat solid or haematological malignancy, and in whom CVAD insertion was possible via a suitable upper body vein, but for whom there was clinical uncertainty about the best device, were screened by their consulting clinician or nursing team during routine appointments, before being randomised. Patients were excluded if treatment or life-expectancy were <3 months, they had previously been randomised to CAVA, had CVADs removed within 2 weeks prior to randomisation, active infection, need for high-flow volume CVADs, or need for CVADs to be placed in a lower body vein. All patients provided written informed consent.

Randomisation and masking

Eligible patients were randomised through one of four randomisation options: (i) Hickman versus PICCs versus PORTs (2:2:1 to over-recruit to the non-inferiority comparison); (ii) PICCs versus Hickman (1:1); (iii) PORTs versus Hickman (1:1); and (iv) PORTs versus PICCs (1:1). Clinicians could choose from these options depending on patient needs and local practice. Treatment allocations were obtained from the Cancer Research UK Glasgow Clinical Trials Unit.

Randomisations were performed using minimisation algorithms incorporating random components. The stratification factors were: centre, body mass index (BMI; <20, 20-<30, 30-<40, ≥40 kg/m^2), CVADs history (no prior devices fitted, ≥1 device fitted ≤3 months prior to study, ≥1 device fitted >3 months prior to study), type of disease (haematological malignancies, solid tumours), and planned treatment mode (inpatient, outpatient). The study was necessarily open-label with all parties aware of treatment allocation.

Procedures

Hickman are “tunnelled” under the skin before exiting and have a Dacron cuff, which allows tissue ingrowth, to improve catheter anchorage and reduce infection risk. These are inserted via the jugular or subclavian vein. Removal requires minor surgical dissection to free the Dacron cuff. PICCs are placed using an upper arm vein. Removal simply involves withdrawing the device usually at the bedside . Maintenance for both typically involves regular dressing change and weekly line flushing.

PORTs are completely implanted (usually on chest wall) with nothing exiting the skin; there is no long-term dressing and flushing is typically only required monthly. The catheter is placed via the jugular or subclavian vein. The PORT has to be accessed through the skin with a non-coring needle each time it is used. PORTs are the most complicated to insert and remove, requiring minor surgical procedures.

Ultrasound is used to target access veins for all three devices, which are inserted by a variety of specialists (nurse practitioners, interventional radiologists, anaesthetists and surgeons). Currently UK nursing experience in Hickman and particularly PORT placement is very limited. The pragmatic nature of the study meant that insertion-related procedures, aftercare, management of complications and removal were not controlled and followed usual practices at each centre. The comparisons were of three different types of CVAD and their overall package of care.

Outcomes

The primary outcome was complication rate, a composite of infection (suspected or confirmed) and/or mechanical failure. This comprised the following individual components: inability to aspirate blood, infection associated with the device (suspected, confirmed or exit site), (definitions in Supplementary Appendix 2), upper extremity venous thrombosis related to device (confirmed with imaging), pulmonary embolus related to the device, mechanical failure (line fracture, line separation from chest wall port, exposure of line cuff, exposure of chest wall port or breakdown of wound, chest wall port dislodgement, line fallen out or line migration requiring intervention), and other.

The secondary outcomes were:

- Incidence of individual complications: inability to aspirate blood from device, venous thrombosis related to device, pulmonary embolus related to device, laboratory-confirmed blood stream infection, suspected catheter-related blood stream infection, exit site infection, mechanical failure and other.

- Complications per catheter week: the number of complications divided by number of weeks device was in place.
- Time to first complication from randomisation. Patients without complications were censored at device removal or last available date on-study (last chemotherapy date, last status assessment date, or date of death) if the device was still in place at the end of the study.
- Duration of chemotherapy treatment interruptions: overall and by complication.
- Health-related QoL: measured by the EuroQol-5 Dimensions (EQ-5D) 3-level version including the visual analogue score for general health.[10]
- Cancer QoL: measured by the EORTC QLQ-C30: comprising 5 functional scales, 9 symptom scales and a global health status score.[11]
- Venous access device-specific QoL: questionnaire comprising 16 questions (Supplementary Appendix 3).[12]
- Costs: comprising device cost, device insertion cost, and unplanned follow-up costs (hospital admissions and outpatient visits).

Data were collected monthly until device removal for a maximum of 12 months.

Statistical Analysis

The sample size was based on three hypotheses:
(i) PICCs are non-inferior to Hickman: assuming that the Hickman complication rate is 55%, PICCs would be considered non-inferior if their complication rate is no more than 10% higher, 65%. This 10% non-inferiority margin corresponds to an odds ratio (PICCs/Hickman) limit of 1.519. To rule out this difference with 80% power, 1-sided, significance level 2.5% required 778 patients (1:1 ratio; 389/arm). (ii) PORTs are superior to Hickman: assuming that the Hickman complication rate is 55%, we aimed to detect a 15% reduction with PORTs, based on the 40% complication rate for PORTs reported in the pilot study[12]. To detect this with 95% power, 2-sided, significance level 5% required 550 patients (1:1 ratio; 275/arm). (iii) PORTs are superior to PICCs: assuming that the PICCs complication rate is 55%, we aimed to detect a 15% reduction with PORTs, based on the 40% complication rate for PORTs reported in the pilot study[12]. To detect this with 80% power, 2-sided, significance level 5% required 341 patients (1:1 ratio; 171/arm).

The statistical analyses were performed separately for the three pairwise comparisons and were based on the intention-to-treat (ITT) populations, defined as all randomised patients; study arms were based on the device patients were assigned at randomisation as opposed to the device fitted

where these differed. Per-protocol (PP) sensitivity analyses were undertaken for the primary analysis of each comparison excluding patients not fitted with the device assigned at randomisation.

The primary endpoint was complication rate, analysed using logistic regression including study arm, randomisation stratification factors and whether the data came from the relevant 2-way or 3-way randomisation (Figure 1). The incidence of venous thrombosis was compared using the same approach. The total duration of treatment interruption was compared using Mann-Whitney U-tests overall and for each complication. The binary stratification factors of treatment mode and type of disease were excluded due to small numbers of patients in one category (inpatient and haematological cancers) across all comparisons (≤13% and ≤10% respectively). BMI, device history and centre were re-parameterised for the same reason. BMI was dichotomised into <30 and ≥30 kg/m^2, previous device history was categorised as yes or no, and centre retained the six sites with the highest recruitment (Beatson West of Scotland Cancer Centre (BWoSCC) , Freeman Hospital, Newcastle upon Tyne Hospitals, St James's University Hospital, Leeds, The Christie NHS Foundation Trust and Charing Cross Hospital, Imperial College Healthcare) while the remaining were combined as "other" centre.

Network meta-analysis (NMA) of the four randomisation options was also carried out (Supplementary Table 6).[13] Relative effects of all devices compared with every other were estimated using direct and indirect evidence, therefore generating a more precise estimate of relative treatment effects. Direct evidence is based on the head-to-head randomisation options, while indirect evidence is based on the estimates of the direct estimates from the other two comparisons.

Multiple imputations were applied to missing EQ-5D data[14] prior to estimating the area under the curve (AUC)[15] for each patient, which was standardised by the period on study and adjusted for the baseline value (value reported prior to the device being fitted). These scores were compared across arms using Mann-Whitney U-tests. The same approach was taken for the EQ-5D visual analogue scale for health. The p-values for the index values and health state scores were adjusted for multiple comparisons using the false-discovery rate approach (calculated using the p.adjust function (fdr option) of the stats library in R (http://www.r-project.org).[16] EORTC QLQ-C30 data were imputed and analysed as the EQ-5D data. P-values were obtained for the differences between arms for the five functional scales (physical, role, emotional, cognitive, social), nine symptom scales (fatigue, nausea and vomiting, pain, dyspnoea, insomnia, appetite loss, constipation, diarrhoea, financial difficulties) and the global health status score, and these were also adjusted for multiple

comparisons. The worst responses for each question from the venous access device questionnaire were summarised and compared across arms via Mann-Whitney U-tests, and the p-values for the individual questions were adjusted for multiple comparisons.

Mean total costs were estimated by fitting a generalised linear model with gamma distribution and log link, adjusting for age, sex, BMI, device history, and study arm. Based on the estimation of the final statistical model, the predicted mean total cost associated with each device was estimated. Cost per catheter week was calculated by dividing time on device (catheter weeks) per patient by total cost per patient. The same regression approach used for total costs was used to estimate cost per catheter week. Non-parametric bootstrapping (1000 iterations) was used to estimate 95% confidence intervals for the total mean cost and total mean cost per catheter week.

Analyses were conducted in a range of packages: SAS 9.3/9.4 (SAS Institute, Cary NC), SAS Enterprise Guide 5.0/7.1, IBM SPSS Statistics for Windows Version 23.0/25.0 (IBM Corp., Armonk, N.Y., USA), R Core Team (2018) and Stata 14 (StataCorp).

Role of the funding source

The study funder had no role in study design, data collection, analysis or interpretation, or writing of the report. The corresponding author had full access to all study data and had final responsibility for the decision to submit for publication. Several PORTs manufacturers provided free PORTs to centres where local NHS funding barriers prevented purchase.

Results

Recruitment commenced on 8th November 2013 and was completed on 28th February 2018.

Procedural details associated with device insertion including operator specialism, setting, type of anaesthesia and antibiotic usage are shown in Table 1. Hickman were most commonly placed by radiologists (46-48%) followed by nurses (23-35%) and anaesthetists (13-20%). PICCs were most commonly placed by nurses (67-73%). PORTs were most commonly placed by radiologists, followed by nurses (2-24%) and anaesthetists (10-11%). With the exception of five PORT patients who received a general anaesthetic, all devices were inserted under local anaesthetic. The use of prophylactic antibiotics was uncommon, and non-antimicrobial dressing was most commonly applied across all three devices. Manufacturer details, catheter diameter and material, presence of a Groshong valve and CT pump compatibility in Supplementary Table 1.

PICC versus Hickman

424 patients (212 in each group) were included in this comparison (Figure 2). The 2-way and the 3-way randomisation options contributed equal numbers of patients to each group. All patients were included in the ITT analysis. Device insertion was attempted in 202 (95%) and 205 (97%) of patients randomised to PICCs and Hickman, respectively. Of these patients, 20 (10%) PICCs and 11 (5%) Hickman patients received a different device from that assigned. The per-protocol population only consisted of patients who received the device they were randomised (182 PICCs and 194 Hickman; 86% and 92% respectively).

Patient characteristics were generally similar at baseline (Table 2). The majority (87%) were metastatic solid tumour patients. 61% of the solid tumour patients had colorectal primary tumours; a greater proportion in the Hickman arm (65% versus 56%). The proportion of patients with pancreatic cancer was greater in the PICCs arm (15% versus 8%). There were no differences between the arms in any baseline QoL measure.

Peri-procedural complications were rare in both groups, 2 (1%) in Hickman and 4 (2%) in PICCs. There were no pneumothoraces, arterial punctures, mediastinal damage, haemorrhage or cardiac arrythmias. The tip of the catheter lay in the superior vena cava (SVC) or right atrium (RA) in 87% of patients in both groups.

Overall complication rates were similar (52% with PICCs and 49% with Hickman, Table 3). However, it could not be concluded that PICCs were significantly non-inferior (10% margin) to Hickman in terms of complication rate via the primary analysis (OR 1.15, 95%CI; 0.78-1.71) or the NMA (OR 1.10; 95%CI; 0.78-1.55). The PP analysis drew the same conclusion. PICCs were in situ for a shorter duration than Hickman (difference in median of 25 days). PICCs were associated with a higher complication per catheter week (0.12±0.02) compared with Hickman (0.07±0.01). Device removal as a result of complications was common in both arms (42% PICCs and 32% Hickman). PICCs were associated with higher rates of inability to aspirate blood (21% PICCs versus 16% Hickman) and mechanical failure (15% PICCs versus 8% Hickman). In contrast, Hickman were associated with higher rates of all types of infections than PICCs (11% PICCs versus 30% Hickman). Similar rates of venous thrombosis, pulmonary embolism and other complications were reported; the analysis of venous thrombosis data was not statistically significant (p=0.359). There were no statistically significant differences in QoL as measured by the EQ-5D or the EORTC QLQ-C30 (Supplementary

Tables 2 and 3). The device-specific QoL instrument showed a significant benefit in favour of Hickman for 2 of the 16 questions (hygiene and hobbies), but this significance was lost when adjusted for multiple testing (Supplementary Table 4). Compliance with QoL questionnaires reduced with time so that by 1 year only 28.6% (PICC) and 13.3% (Hickman) returned data for any of the 3 questionnaires (Supplementary Table 5). The use of PICCs compared with Hickman was associated with a substantially lower total cost (difference in costs -£1554; 95%CI -2639, -468)). However, when catheter dwell times were taken into account, the difference in cost per catheter week was substantially reduced (-£126; 95%CI -279, 28). A detailed breakdown of total costs are provided in Supplementary Table 7.

PORT versus Hickman

556 patients were included in the PORT (n=253) versus Hickman (n=303) comparison (Figure 2). The 2-way randomisation contributed 71% of the patients. All patients were included in the ITT analysis. Device insertion was attempted in 245 (97%) and 283 (93%) of patients randomised to PORT and Hickman, respectively. Of these patients, 5 (2%) PORT and 6 (2%) Hickman patients received a different device from that assigned. The per-protocol population only consisted of patients who received the device they were randomised (239 PORT and 277 Hickman; 94% and 91% respectively).

Patient characteristics were similar at baseline (Table 2). The majority (93%) were metastatic solid tumour patients. 59% of the solid tumour patients had colorectal primary tumours. There were no differences between the arms in any baseline QoL measure.

Peri-procedural complications were rare in both groups, 4 (1%) in Hickman and 3 (1%) in PORTs. There were 2 arterial punctures in the Hickman group. There were no pneumothoraces, mediastinal damage, haemorrhage or cardiac arrythmias. The tip of the catheter lay in the SVC or RA in 89% (Hickman) and 86% (PORTs).

PORTs were found to be statistically significantly superior to Hickman in terms of complication rate via the primary analysis (OR 0.54, 95%CI; 0.37-0.77). The NMA and PP analysis drew the same conclusion. PORTs were in situ for a substantially longer period than Hickman (difference in median of 202 days; Table 3). PORTs were associated with 0.02±0.00 complication per catheter week compared with 0.06±0.01 in the Hickman arm. Device removal as a result of complications was far less frequent in the PORTs arm (14%) compared with the Hickman arm (32%). PORTs were associated with substantially lower rates of laboratory-confirmed blood stream infection (6% PORT

versus 16% Hickman) and exit site infection (4% PORT and 9% Hickman); however, suspected catheter-related blood stream infection was slightly higher in the PORT arm (8%) compared with Hickman (5%). Venous thrombosis was rare; (1% of the PORT and 2% Hickman) and not statistically significantly different between arms (p=0.557). Other complications rates were similar in both groups. There were no statistically significant differences in QoL as measured by the EQ-5D or the EORTC QLQ-C30 (Supplementary Tables 2 and 3). In contrast, the device-specific QoL instrument did show a significant benefit in favour of PORTs for 11 of the 16 questions (Supplementary Table 4). Compliance with QoL questionnaires reduced with time so that by 1 year 49.1% (PORT) and 36.7% (Hickman) returned data for any of the 3 questionnaires (Supplementary Table 5). PORTs compared with Hickman was associated with a lower total cost (difference in costs -£45; 95%CI -744, 655) and lower cost per catheter week (-£47; 95%CI -166, 73). The difference was not statistically significant.

PORT versus PICCs

346 patients were included in the PORT (n=147) versus PICC (n=199) comparison (Figure 2). The 2-way randomisation contributed 54% of the participants. All participants were included in the ITT analysis. Device insertion was attempted with 143 (97%) and 187 (94%) of patients randomised to PORT and PICC, respectively. Of these patients, 12 (8%) PORT and 28 (15%) PICC patients received a different device from that assigned. The per-protocol population only consisted of participants who received the device they were randomised (131 PORT and 159 PICC; 89% and 80% respectively).

Patient characteristics were similar at baseline (Table 2). The majority (93%) were metastatic solid tumour patients. 46% of the solid tumour patients had colorectal primary tumours (46%). There were no differences between the arms in any baseline QoL measure.

Peri-procedural complications were rare in PICCs 6 (4%). There were no pneumothoraces, arterial punctures, mediastinal damage, haemorrhage or cardiac arrythmias. There were no recorded complications in PORTs. The catheter tip lay in the SVC or RA in 89% (PICC) and 90% (PORTs).

PORTs were found to be associated with statistically significantly lower complication rate than PICCs via the primary analysis (OR 0.52, 95% CI; 0.33-0.83). The NMA and PP analysis drew the same conclusion. PORTs were in situ for a substantially longer period than PICCs (difference in median of 274 days; Table 3). PORTs were found to be associated with 0.05±0.02 complications per catheter week compared with 0.13±0.02 in the PICCs arm. Device removal as a result of complications was less frequent in the PORT arm (24%) compared with the PICC arm (38%). Mechanical failure was

reported in 3% of PORTs compared with 11% of the PICCs. Venous thrombosis was reported in 2% of PORTs but 11% of PICCs (p=0.002). Although infections rates (any type) were reported in a greater proportion of PORTs than PICCs (12% PORT versus 8% PICC), the mean number of infections per catheter week was similar (0.02 in both arms; data not shown). We found no significant difference in the QoL as measured by the EQ-5D or the EORTC QLQ-C30 (Supplementary Tables 2 and 3). In contrast, the device-specific QoL instrument showed a significant benefit in favour of PORTs for 8 of the 16 questions (Supplementary Table 4). Compliance with QoL questionnaires reduced with time so that by 1 year only 38.8% (PORT) and 31.6% (PICC) returned data for any of the 3 questionnaires (Supplementary Table 5). PORTs compared with PICCs were associated with a substantially higher cost (£1665; 95% CI £766, £2564). However, when catheter dwell time was taken into account, the reverse was observed (difference in and cost per catheter week -£41; 95% CIs -227, 147).

Discussion

CAVA recruited 1061 participants and is to date the largest trial conducted comparing Hickman, PORT and PICC for SACT administration. It is also the only mixed methods study, incorporating extensive qualitative research, as well as a health economic evaluation from the UK NHS perspective. The qualitative results have been published separately[17, 18] and the full health economic evaluation will shortly be available in the NIHR/HTA report (in press).

The comparison between PORTs and Hickman showed a significant reduction in the overall complication rate of around 50% with PORTs. This was mainly driven by the difference in infections (Hickman 25% and PORTs 14%). Slightly more than double the number of Hickman were removed due to a complication compared with PORTs. Venous thrombosis was uncommon but twice as frequent with Hickman. Hickman were associated with higher total costs than PORTs (difference in cost £45) and when adjusted for the longer dwell time of PORTs (£47 per catheter week), although these differences were not statistically significant. There seems little justification for placing a Hickman provided a PORT is deemed clinically appropriate.

The comparison between PORTs and PICCs showed a significant reduction in the overall complication rate of around 50% with PORTs. This difference was largely explained by a reduction in both mechanical and thrombotic complications with PORTs. The risk of a patient suffering a venous thrombosis was around five times higher with a PICC (2% vs 11%). This has been reported by several other groups[6, 7, 19] and may be related to the presence of the PICC in a much smaller calibre arm vein

over a longer length than a centrally placed PORT. Pulmonary embolus was rare but more common in the PICC group. Interestingly, we found infection rate to be a little higher with PORTs (12% vs 8%). This was unexpected but has been reported by others.[6] This may be due to the skin being breached by the access needle every time a PORT is used and skin bacteria introduced via the needle.[20] Another possibility is a learning curve phenomenon in the aftercare of PORTs in centres where PORTs were recently introduced. Further, skin inflammation around the PORT from drug extravasation due to a misplaced needle could be confused with infection. PORTs were more than twice the cost of PICCs (£2706 vs £1041). However, when dwell time was taken into consideration, PORTs were slightly cheaper (£263 versus £304 per catheter week). These data suggest, that in patients with metastatic solid cancers receiving palliative chemotherapy where the expected duration of SACT is expected to exceed 3 months, or where patients are likely to receive multiple lines of SACT over a prolonged period, PORTs offer a distinct advantage to PICCs, with lower complication rates at similar costs.

The comparison between Hickman and PICC showed no difference in complication rates but was underpowered to conclude on non-inferiority. This was partly due to a marked reduction in the use of Hickman during the course of the trial, coupled with a large expansion of nurse-led PICC services across UK oncology sites. Approximately half of the patients in both groups reported at least one complication however we found a higher complication rate per catheter week associated with PICC. Interestingly, the dominant complication for Hickman was infection, while for PICCs, it was mechanical failure. The presence of a cuff and subcutaneous tunnel with a Hickman is thought to reduce the risk of both mechanical problems and infections; although we found a much lower risk of mechanical complications with Hickman, the risk of infection was nearly three times that of PICCs. Venous thrombosis was similar between the two devices (Hickman 5%, PICC 6%), as were most of the other complications. PICCs were associated with substantially lower total cost (difference in costs £1,554). Allowing for the longer dwell time of Hickman still made them more costly at an extra £126 per catheter week. We think there is little justification for placing a Hickman except in special circumstances for example in haematology patients where a large catheter diameter is needed for blood products or very protracted treatment regimens where the anchor cuff may confer an advantage.

There were no significant differences in QoL based on the EQ-5D and the EORTC QLQ-30 in any comparison. It appears these instruments are not sensitive to the device but more influenced by the underlying disease state and treatment. In contrast the device-specific questionnaire showed many

aspects of QoL to be significantly better with a PORT than a Hickman, and particularly a PICC. This was further reinforced by the findings of our qualitative study, which sought to explore the acceptability of the three devices among patients and staff.[18] In particular, although all three devices were found to be well accepted by patients and preferable to peripheral cannulation, PORTs were perceived to offer unique psychological benefits, including a greater sense of freedom and less intrusion in the context of personal relationships.[17] The practical benefits associated with their lack of external lines (i.e. less visible, easier maintenance) meant that PORTs were less psychologically burdensome, with participants with PORTs repeatedly stressing that it was easy for them to 'forget' about their device. Interestingly, despite considering them more challenging from a clinical and management perspective, staff also favoured them because they were seen as better for patients. Indeed, staff were very well-attuned to patient experiences and cited the same practical conveniences of PORTs, as well as the emotional and psychological benefits of a less conspicuous or obtrusive device that patients themselves raised. [17, 18]

The median dwell time of PORT (over 350 days) was much greater than Hickman (around 160 days) and PICC (around 120 days). This difference can be partly explained by the lower incidence of device removal as a result of a complication than the other two devices. PORTs are the most complex to place and remove; PICCs being the easiest with Hickman in-between. Therefore, it is highly likely the threshold for removal due to complication was lowest with a PICC and highest with a PORT. Another factor likely to influence device removal and hence dwell time would be a treatment break; PICCs and Hickman are more likely to be removed whereas PORTs would be left in-situ in these circumstances. Extended periods of PORT placement are likely to represent a period of "rest" for the PORT and the patient, with only periodic flushes, absence of SACD, and overall lower risks of introducing infection.

Peri-procedural or immediate technical complications were rare across all devices. In particular there were no instances of pneumothorax or mediastinal damage. We believe concerns regarding complications of a "neck puncture" are exaggerated and largely historical. Provided there is adequate training and the use of ultrasound guidance, neck puncture (Hickman and PORT) should be no more risky than cannulating an arm vein for a PICC.

Strengths and Limitations

CAVA's strengths lie in its size, the inclusion of all three CVADs, QoL assessment and full economic evaluation. The inclusion of all cancer types also makes the findings more generalisable. In contrast

a recent RCT[7] for example only included patients with breast cancer. CAVA also, unlike most other similar trials, included haematological cancer patients; although the numbers were very small, 89 patients (8%). A very high infection rate with PORTs was observed in this group which warrants further research. Due to small numbers of haematological malignancies in CAVA we cannot make any suggestions as to the preferred device in this patient group.

A further strength is that our primary endpoint consisted of an exhaustive list of complications including some that other studies had excluded such as suspected infection and inability to aspirate blood, all of which impact directly on clinical care. We also included "Other" complications to ensure that no relevant data were missed. This clarification of the primary endpoint included in the published protocol as "a composite of infection (suspected or confirmed) and/or mechanical failure" resulted from the initial discussions surrounding data capture for the study and ensured that all individual component complications were recorded for all patients from the first randomisation. A limitation of the study is that this clarification was not specifically noted in the protocol, however it was supported by the CAVA Independent Data Monitoring Committee who reviewed the emerging study data annually.

Limitations of the trial included a reduction in power of two of the comparisons after 18 months. All comparisons were initially designed with 90% power, however a protocol mandated review of recruitment at this time allowed adjustments to be made on the basis of actual recruitment to each comparison and the results of the pilot study. As a result, the power for both Hickman versus PICC and PICC versus PORT were reduced to 80%. In contrast though, the power for Hickman versus PORT was increased to 95%. Unfortunately, recruitment to the PICC versus Hickman comparison was not completed, and the final analysis was underpowered. This was due to a change in landscape with regards to clinical practice over the duration of CAVA. PICCs were becoming the preferred option to Hickman as PICC nurse-led teams expanded. However, the clear superiority of PORTs over both the other two devices makes the PICC versus Hickman comparison less relevant in clinical practice.

A further weakness was that we did not capture any further device insertion data following removal of the index device. Had we done so it is likely the cost of both Hickman and PICCs would be higher given the potential need for more re-insertions.

Although the majority of our patients had either colorectal or breast cancer we feel the results are generalisable to the cancer cohort requiring a CVAD. It is likely (although untested) that the results of CAVA may be generalisable to other patients needing these devices for example parenteral nutrition and antibiotics.

Finally, we had a mix of different staff groups placing the devices, and in general PICCs were placed by nurses and the other two by medical staff (Interventional radiologists or anaesthetists). However, there were some centres where nurse-led teams placed all three and this could be a model for the future to bring down costs and providing a more responsive service. It is possible that larger numbers of PORT procedures could further reduce complication rates as experience grew and different designs of PORTs could increase the ease of insertions and removals, for instance by not requiring use of full theatre or imaging suite capabilities, further increasing the cost-effectiveness of PORTs over the other CVADs.

CAVA has expanded the knowledge base on these CVADs and the case for a PORT-dominant strategy has been strengthened. These findings should prove useful for updating national and international guidelines to recommend the adoption of PORT delivered services for relevant patient groups.

Data sharing statement

The CAVA investigators are committed to furthering cancer research by sharing de-identified individual-patient data (IPD) from CAVA with others in the field, who wish to use the data for high quality service. We are happy to consider proposals from researchers and will share IPD to the maximum extent, subject to individual study constraints relating to:

- Ethical approval and informed consent
- Contractual and legal obligations, including a data sharing agreement
- Publication timelines (data will not normally be shared prior to the publication of the primary results)

All proposals will be reviewed for their scientific merit by the Trial Management Group. Only data relevant to the objectives of a particular proposal will be provided.

If you wish to have an initial discussion about accessing data from CTU studies please contact:
Jonathan G. Moss (Chief Investigator) – jonathan.moss@glasgow.ac.uk

Contributors

JM, OW, EMcC led the conception, design and management of the study. AB, RA, TM, BJ, SH contributed to the conception, design and management of the study. EMcC designed and performed the statistical analyses. EG was responsible for the qualitative components of the study. OW designed and RH performed the health economic evaluation. JD-H and ES managed the trial. SD was responsible for data collection. All authors read and approved or commented on the final publication.

Declaration of interests

JM is paid a personal fee to run PORT training courses for Smith Medical and received PORTS free of charge from four manufacturers.

OW is Deputy Chair of NIHR HTA General Funding Board (2020 onwards) and was a committee member of NIHR HTA General Funding Board 2016-2019.

BJ receives payment for lectures from MSD and Pfizer, attendance at advisory board for Menarini, owns shares in Novartis and Gilead Sciences, and is a member of the Scottish Medicines Consortium.

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Table 1 **Procedure Details for All Comparisons**

	PICC vs Hickman				PORT vs Hickman				PORT vs PICC			
	PICC		Hickman		PORT		Hickman		PORT		PICC	
	n	%	n	%	n	%	n	%	n	%	n	%
Primary operator												
Nurse	128	67.4	47	22.7	59	24.3	97	34.6	3	2.2	125	73.1
Radiographer	10	5.3	15	7.2	5	2.1	10	3.6	3	2.2	7	4.1
Anaesthesiologist	7	3.7	42	20.3	27	11.1	36	12.9	14	10.2	5	2.9
Radiologist	24	12.6	96	46.4	144	59.3	133	47.5	107	78.1	18	10.5
Doctor	1	0.5	4	1.9	7	2.9	4	1.4	5	3.6	1	0.6
Surgeon	3	1.6	1	0.5	0	0	0	0	5	3.6	0	0
Other	16	8.4	1	0.5	0	0	0	0	0	0	13	7.6
Missing	1	0.5	1	0.5	1	0.4	0	0	0	0	2	1.2
Setting												
Theatre	11	5.8	61	29.5	57	23.5	50	17.9	28	20.4	5	2.9
Procedure/treatment room	103	54.2	39	18.8	9	3.7	86	30.7	1	0.7	61	35.7
Radiology department	50	26.3	103	49.8	171	70.4	140	50	106	77.4	42	24.6
Bedside	12	6.3	0	0	0	0	0	0	0	0	44	25.7
Missing	0	0	0	0	5	2.1	4	1.4	2	1.5	17	9.9
Other	14	7.4	4	1.9	1	0.4	0	0	0	0	2	1.2
Type of anaesthesia												
Local only	188	98.9	180	87	216	88.9	268	95.7	115	83.9	168	98.2
Local and conscious sedation	1	0.5	26	12.6	27	11.1	12	4.3	17	12.4	1	0.6
General anaesthesia	0	0	0	0	0	0	0	0	5	3.6	0	0
Missing	1	0.5	1	0.5	0	0	0	0	0	0	2	1.2
Prophylactic antibiotics given												
Yes	3	1.6	4	1.9	34	14	2	0.7	24	17.5	3	1.8
No	179	94.2	199	96.1	200	82.3	272	97.1	109	79.6	160	93.6
Missing	8	4.2	4	1.9	9	3.7	6	2.1	4	2.9	8	4.7
Type of dressing applied												
Non-antimicrobial	159	83.7	144	69.9	226	93	221	78.9	121	88.3	140	81.9
Antimicrobial	29	15.3	60	29	10	4.1	58	20.7	12	8.8	25	14.6
Missing	2	1.1	3	1.4	7	2.9	1	0.4	4	2.9	6	3.5

Table 2 Baseline Characteristics for All Comparisons

	PICC vs Hickman				PORT vs Hickman				PORT vs PICC			
	PICC		Hickman		PORT		Hickman		PORT		PICC	
	n	%	n	%	n	%	n	%	n	%	n	%
Mean age in years (SD [range])	62 (11 [19-85])		61 (12 [20-87])		59 (13 [19-86])		60 (13 [20-87])		61 (12 [28-86])		61 (13 [19-84])	
Gender												
Female	102	48.1	96	45.3	112	44.3	151	49.8	81	55.1	107	53.8
Male	110	51.9	116	54.7	141	55.7	152	50.2	66	44.9	92	46.2
BMI (mg/kg^2)*												
<20	10	4.7	12	5.7	13	5.1	16	5.3	9	6.1	8	4.0
20-<30	145	68.4	145	68.4	171	67.6	209	69.0	98	66.7	139	69.8
30-<40	51	24.1	49	23.1	61	24.1	70	23.1	36	24.5	47	23.6
≥40	6	2.8	6	2.8	8	3.2	8	2.6	4	2.7	5	2.5
Ethnic origin												
White	204	96.2	210	99.1	246	97.2	293	96.7	137	93.2	182	91.5
Asian	3	1.4	1	0.5	4	1.6	1	0.3	3	2.0	5	2.5
South East Asian	0	0.0	0	0.0	1	0.4	0	0.0	3	2.0	0	0.0
Afro/Caribbean	1	0.5	1	0.5	2	0.8	3	1.0	3	2.0	6	3.0
Other	0	0.0	0	0.0	0	0.0	1	0.3	1	0.7	4	2.0
Missing	4	1.9	0	0.0	0	0.0	5	1.7	0	0.0	2	1.0
Type of disease*												
Solid tumour	185	87.3	184	86.8	235	92.9	280	92.4	142	96.6	190	95.5
Colorectal	104	56.2	120	65.2	138	58.7	168	60.0	65	45.8	89	46.8
Breast	21	11.4	21	11.4	27	11.5	42	15.0	22	15.5	27	14.2
Pancreas	27	14.6	15	8.2	16	6.8	18	6.4	12	8.5	25	13.2
Other (missing)	31 (2)	16.8	28	15.2	54	23.0	48 (4)	17.1	43	30.3	48 (1)	25.3
Haematological malignancy	27	12.7	28	13.2	18	7.1	23	7.6	5	3.4	9	4.5
Acute myeloid leukaemia	7	25.9	11	39.3	5	27.8	13	56.5	2	40.0	1	11.1
High grade non-Hodgkin's lymphoma	5	18.5	8	28.6	4	22.2	3	13.0	0	0.0	4	44.4
Hodgkin's disease	4	14.8	3	10.7	4	22.2	3	13.0	0	0.0	1	11.1
Other (missing)	10 (1)	37.0	6	21.4	5	27.8	3 (1)	13.0	3	60.0	2 (1)	22.2
Metastatic disease (solid tumour patients only)												
Yes	114	61.6	108	58.7	156	66.4	191	68.2	93	65.5	123	64.7
No	68	36.8	76	41.3	79	33.6	85	30.4	48	33.8	65	34.2
Missing	3	1.6	0	0.0	0	0.0	4	1.4	1	0.7	2	1.1
Patients being administered 5 fluorouracil	137	64.6	143	67.5	179	70.8	198	65.3	91	61.9	122	61.3

* stratification factor

Table 2 Baseline Characteristics for All Comparisons (Continued)

	PICC vs Hickman				PORT vs Hickman				PORT vs PICC			
	PICC		Hickman		PORT		Hickman		PORT		PICC	
	n	%	n	%	n	%	n	%	n	%	n	%
Planned treatment mode*												
Inpatient	17	8.0	19	9.0	25	9.9	26	8.6	5	3.4	6	3.0
Outpatient	195	92.0	193	91.0	228	90.1	277	91.4	142	96.6	193	97.0
Device history*												
No prior device	181	85.4	180	84.9	198	78.3	239	78.9	123	83.7	168	84.4
≥1 prior device inserted >3 months before study entry	26	12.3	26	12.3	46	18.2	53	17.5	21	14.3	27	13.6
≥1 prior device inserted <3 months before study entry	5	2.4	6	2.8	9	3.6	11	3.6	3	2.0	4	2.0
Baseline quality of life scores												
Mean EQ5D index value (SD) [range]	0.7 (0.3) [-0.3-1.0]		0.8 (0.2) [-0.2-1.0]		0.7 (0.3) [-0.1-1.0]		0.7 (0.3) [-0.3-1.0]		0.8 (0.2) [0.0-1.0]		0.8 (0.2) [0.0-1.0]	
Mean EQ5D health state score (SD) [range]	70.6 (20.7) [10.0-100.0]		70.3 (18.6) [10.0-100.0]		71.0 (21.0) [0.0-100.0]		69.4 (19.8) [0.0-100.0]		74.3 (17.5) [30.0-100.0]		73.6 (19.6) [20.0-100.0]	
Mean QLQ-C30 global health status (SD) [range]	65.3 (22.6) [0.0-100.0]		68.0 (21.1) [0.0-100.0]		66.0 (21.9) [0.0-100.0]		64.2 (221.) [0.0-100.0]		67.8 (19.9) [0.0-100.0]		69.8 (20.6) [0.0-100.0]	

* stratification factor

Table 3 Outcomes for All Comparisons

	PICC vs Hickman		PORT vs Hickman		PORT vs PICC	
	PICC	**Hickman**	**PORT**	**Hickman**	**PORT**	**PICC**
Number of Complications (patients (%))						
0 complications	102 (48.1%)	109 (51.4%)	180 (71.1%)	172 (56.8%)	100 (68.0%)	106 (53.3%)
1 or more complications	110 (51.9%)	103 (48.6%)	73 (28.9%)	131 (43.2%)	47 (32.0%)	93 (46.7%)
Total number of patients	212	212	253	303	147	199
Complication type						
Inability to aspirate blood						
Patients (%)	45 (21.2%)	33 (15.6%)	38 (15.0%)	42 (13.9%)	23 (15.6%)	37 (18.6%)
Complications (%)	66 (38.2%)	43 (25.3%)	63 (47.7%)	60 (30.0%)	33 (38.8%)	55 (39.6%)
Venous thrombosis						
Patients (%)	13 (6.1%)	10 (4.7%)	3 (1.2%)	7 (2.3%)	3 (2.0%)	22 (11.1%)
Complications (%)	14 (8.1%)	10 (5.9%)	3 (2.3%)	7 (3.5%)	3 (3.5%)	24 (17.3%)
Pulmonary embolism						
Patients (%)	6 (2.8%)	4 (1.9%)	3 (1.2%)	4 (1.3%)	3 (2.0%)	1 (0.5%)
Complications (%)	6 (3.5%)	4 (2.4%)	3 (2.3%)	4 (2.0%)	3 (3.5%)	1 (0.7%)
Any Infection						
Patients (%)	23 (10.8%)	63 (29.7%)	36 (14.2%)	77 (25.4%)	18 (12.2%)	16 (8.0%)
Complications (%)	27 (15.6%)	78 (45.9%)	47 (35.6%)	102 (51.0%)	24 (28.2%)	16 (11.5%)
Laboratory confirmed blood stream infection						
Patients (%)	10 (4.7%)	41 (19.3%)	14 (5.5%)	49 (16.2%)	8 (5.4%)	7 (3.5%)
Complications (%)	11 (6.4%)	43 (25.3%)	16 (12.1%)	54 (27.0%)	9 (10.6%)	7 (5.0%)
Suspected catheter-related blood stream infection						
Patients (%)	10 (4.7%)	18 (8.5%)	19 (7.5%)	15 (5.0%)	8 (5.4%)	5 (2.5%)
Complications (%)	12 (6.9%)	23 (13.5%)	21 (15.9%)	16 (8.0%)	11 (12.9%)	5 (3.6%)
Exit site infection						
Patients (%)	4 (1.9%)	19 (9.0%)	10 (4.0%)	26 (8.6%)	4 (2.7%)	4 (2.0%)
Complications (%)	4 (2.3%)	22 (12.9%)	10 (7.6%)	32 (16.0%)	4 (4.7%)	4 (2.9%)
Mechanical failure						
Patients (%)	31 (14.6%)	7 (3.3%)	2 (0.8%)	9 (3.0%)	4 (2.7%)	21 (10.6%)
Complications (%)	31 (17.9%)	7 (4.1%)	2 (1.5%)	9 (4.5%)	4 (4.7%)	21 (15.1%)
Other						
Patients (%)	23 (10.8%)	16 (7.5%)	14 (5.5%)	17 (5.6%)	16 (10.9%)	19 (9.5%)
Complications (%)	29 (16.8%)	18 (10.6%)	14 (10.6%)	18 (9.0%)	18 (21.2%)	22 (15.8)

Table 3 Outcomes for All Comparisons (Continued)

	PICC vs Hickman		PORT vs Hickman		PORT vs PICC	
	PICC	**Hickman**	**PORT**	**Hickman**	**PORT**	**PICC**
Total number of complications	173	170	132	200	85	139
1 or more severe SIR complications* (% patients with complications)	28 (25%)	52 (50%)	33 (45%)	62 (47%)	16 (34%)	24 (26%)
Median device dwell time (days; 95% CI)	133 (106, 123)	158 (140, 175)	367 (324, 393)	165 (149, 177)	393 (324, 393)	119 (109, 130)
Mean complications per catheter week (SE)	0.12±0.02	0.07±0.01	0.02±0.00	0.06±0.01	0.05±0.02	0.13±0.02
Mean infective complications per catheter week (SE)	0.02±0.01	0.04±0.01	0.01±0.00	0.03±0.01	0.02±0.01	0.02±0.01
Mean non-infective complications per catheter week (SE)	0.10±0.02	0.04±0.01	0.01±0.00	0.03±0.01	0.04±0.02	0.10±0.02
Planned removal/end of treatment	91 (49.5%)	99 (52.7%)	80 (56.3%)	131 (52.2%)	44 (58.7%)	85 (51.5%)
Removal due to complications	78 (42.4%)	61 (32.4%)	20 (14.1%)	80 (31.9%)	18 (24.0%)	63 (38.2%)
Removal due to other reasons	15 (8.2%)	28 (14.9%)	42 (29.6%)	40 (15.9%)	13 (17.3%)	17 (10.3%)
Total devices removed (% device insertions attempted)	184 (91.1%)	188 (91.7%)	142 (58.0%)	251 (88.7%)	75 (52.4%)	165 (88.2%)
Total cost (£, mean and 95% CI)	1,708 (1,153, 2,262)	3,262 (2,227, 4,296)	2,436 (1,927, 2,946)	2,481 (2,007, 2,954)	2,706 (1,899, 3,513)	1,041 (764, 1,316)
Cost per catheter week (£, mean and 95% CI)	248 (161, 336)	374 (244, 505)	210 (120, 300)	257 (161, 353)	263 (133, 394)	304 (153, 455)

* classed as SIR classification C or above (see Supplementary Appendix 4