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Economics of drug-coated balloons for arteriovenous fistula stenosis in Japan and Korea based on the IN.PACT AV access trial

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Abstract

Aim: The recent IN.PACT AV Access study found drug-coated balloon therapy to be associated with reduced reinterventions compared to percutaneous transluminal angioplasty using standard balloons in the management of arteriovenous fistula stenosis. The economic implications of drug-coated balloon use in Asia, including Japan and Korea, remain unknown.

Methods: A decision-analytic model was developed to calculate strategy-specific costs for Korea and Japan through 5-year follow-up. The analysis assumed maintained therapy benefit beyond current trial follow-up of 1 year in the base case, with several alternative scenarios explored in sensitivity analysis. Costs were derived from claims and reimbursement data, and projections were evaluated at 3 and 5 years post-index procedure.

Results: Model-projected access circuit reintervention events for drug-coated versus standard balloons were 1.70 versus 2.76 (−1.06) and 2.53 versus 4.10 (−1.57) at 3 and 5 years in the base case. Corresponding 3- and 5-year costs were ₩6 211 103 versus ₩7 605 553 (−₩1 394 451) and ₩7 766 051 versus ₩10 124 954 (−₩2 358 904) in Korea, and ¥1 469 824 versus ¥1 504 161 (−¥34 337) and ¥1 956 931 versus ¥2 106 632 (−¥149 701) in Japan. In scenario analyses, drug-coated balloons remained cost saving at 3- and 5-year follow-up in Korea, but required up to 5 years to reach cost-savings in Japan. Drug-coated balloon use in reinterventions increased projected savings, as did younger treatment age.

Conclusion: Treatment of arteriovenous fistulas with the IN.PACT AV drug-coated balloon, based on preliminary data, may lead to meaningful reductions in reintervention costs that would render it cost-saving at timeframes of around 1 year in Korea and between 3 and 5 years in Japan.

KEYWORDS
arteriovenous fistula/graft, clinical trials, economic evaluation, Haemodialysis, vascular access

Summary at a Glance

This study investigated the health-economic value proposition of the IN.PACT AV drug-coated balloon compared to standard balloon treatment of arteriovenous fistula stenosis in the Japanese and Korean healthcare systems. It found drug-coated balloon treatment to be associated with meaningful reductions in reinterventions that can be expected to lead to overall cost savings in both countries.

1 | INTRODUCTION

End-stage renal disease (ESRD) and its associated treatment continues to present a major clinical and economic challenge for healthcare systems worldwide, including in Asian countries.[1,2] Due to the aging population and the concomitant rise of diabetes and dyslipidaemia, the prevalence of ESRD in Japan and South Korea (for the remainder of this manuscript, referred to as 'Korea') has steadily risen over the past decade, with 339 841 and 103 984 patients reported on dialysis in 2018, respectively—corresponding to the third and sixth highest per-capita prevalence of ESRD globally.[2-6] Haemodialysis (HD) or haemodiafiltration (HDF) remain the predominant treatment for ESRD in both countries, with 96.6% and 74.6% of Japanese and Korean dialysis patients treated with either modality.[1,7] For these patients, arteriovenous (AV) fistulas remain the primary mode of vascular access, present in 89% and 77% of HD patients in Japan and Korea respectively, resulting in more than 290 000 Japanese and close to 60 000 Korean patients with AV fistulas.[1,7] In both countries, the costs of maintaining vascular access with percutaneous transluminal angioplasty (PTA) has been identified as a significant and growing contributor to the overall costs of HD,[8,9] with a substantial share of these costs related to reintervention procedures required to maintain access circuit patency.

Drug-coated balloons (DCB) have emerged as a novel alternative to PTA using a standard balloon in the management of stenotic AV fistulas for HD patients, with the expectation that the lower reintervention burden associated with DCB use might not only benefit patients, but importantly also reduce clinical resource utilization and treatment expenses. The IN.PACT AV Access Study recently reported an improved target lesion primary patency for DCBs versus PTA at 12 months (63.8% [90 of 141] versus 43.6% [61 of 140], with an absolute difference in risk of 20.3%, 95% confidence interval [CI], 8.8–31.7%; $p < .001$), and access circuit reintervention events that were 38% lower in the DCB cohort (0.65 versus 1.05, $p < .001$).[10]

With recent regulatory approvals in Japan and Korea of the Medtronic DCBs for AV treatments (*IN.PACT AV DCB*, Japan; *IN.PACT Admiral DCB*, South Korea), our objective was to study how the clinical benefits of DCB might affect long-term per-patient AV access costs in each of the two healthcare systems, and thereby lead to potential cost savings with DCB therapy.

2 | METHODS

A decision-analytic model was constructed to project access circuit reintervention events and total treatment cost for index and applicable reinterventions over a horizon of up to 5 years—a time frame previously used to assess the cost-effectiveness of AV fistulas in patients undergoing haemodialysis[11,12] and a clinically appropriate timeframe as patency has previously been reported to remain constant beyond 5 years, indicating no additional benefit with a longer time horizon.[13] Although the primary endpoint of the study was target lesion primary patency, access circuit primary patency provided a more complete representation of reintervention costs and target lesion reintervention might impact the entire access circuit. Clinical event projections relied on a constant hazard assumption in the base case, with other scenarios explored in sensitivity analyses. As reinterventions in future real-world practice might involve DCB use not only for index treatment, but also subsequent reinterventions, country-specific scenarios were developed for the base case and the effect of variation in these assumptions was explored in sensitivity analyses.

2.1 | Study data

Cohort characteristics and 6- and 12-month access circuit reintervention rates for PTA and DCB were obtained from the IN.PACT AV Access study.[10,14] This study was a prospective, single-blinded, multicentre randomized clinical trial that compared the IN.PACT™ AV paclitaxel-coated balloon (Medtronic Inc., Santa Rosa, USA) with PTA in 330 participants with a new or restenotic lesion in native upper-extremity AV fistulas ($n = 170$ and $n = 160$ in the DCB and PTA groups, respectively). Of these, 112 participants (34% of total) were treated in Japan. The primary effectiveness endpoint of the trial was target lesion primary patency, defined as freedom from clinically-driven target lesion revascularization (CD-TLR) or access circuit thrombosis measured through 6 months after the index procedure, whilst the primary safety endpoint was the serious adverse event rate involving the AV access circuit (SAE-AC) within 30 days. Additional study details have been previously published.[14]

For the current analysis, access circuit reintervention events were utilized as the primary clinical outcome measure, as this metric is most reflective of resource utilization.[15] Further, the number of DCB

TABLE 1 Analysis inputs

Variable	Japanese analysis	Korean analysis	Source
Clinical parameters			
Age (years)	65.6 ± 13.3		From full clinical cohort of 330 participants; Lookstein et al. 2020[14]
Gender (% male)	64.5%		
Mortality HR of ESRD population on haemodialysis, relative to general population mortality	10.50	11.20	Calibrated based on pooled mortality estimates at 12 months as reported in Holden et al, 2022[10,23,24]
Effectiveness: access circuit re-intervention events			
PTA, at 6 months	0.65 ± 0.8		From full clinical cohort of 330 participants; Lookstein et al. 2020[10,14]
DCB, at 6 months	0.32 ± 0.7		
Difference in access circuit re-intervention events at 6 months	−0.33 ($p < .001$)		
PTA, at 12 months	1.05 ± 1.18		From full clinical cohort of 330 participants; Holden et al, 2022[10] and study data
DCB, at 12 months	0.65 ± 1.05		
Difference in access circuit re-intervention events at 12 months	−0.40 ($p < .001$)		
Utilization of devices, per respective re-intervention procedure			
DCB	1.23		Utilization in IN.PACT AV Access trial, post-hoc analysis of study data
Cost parameters			
PTA procedure cost	¥220 016	₩1 915 201	Japanese costs based on current procedure costs and 4th NDB Open Data values[18] assuming a weighted-average site-of-service mix of 10.9% DPC hospital, 23.7% non-DPC hospital and 65.4% outpatients as per reported volumes, and Korean costs based on NHIS claims data[21] assuming 100% outpatient procedures. Breakdown of costs detailed in Supplementary Material S.2
DCB procedure cost	¥432 806	₩2 710 593	
Stent procedure cost	–	₩3 071 278	Korean costs based on NHIS claims data[21] assuming 100% outpatient procedures. Breakdown of costs detailed in Supplementary Material S.2
Re-intervention cost	¥220 016	₩2 211 623	Japanese costs based on current procedure costs and 4th NDB Open Data values[18] assuming a weighted-average site-of-service mix of 10.9% DPC hospital, 23.7% non-DPC hospital and 65.4% outpatients as per reported volumes, assuming 100% plain balloon treatment, and Korean costs based on NHIS claims data[21] assuming 65% PTA, 30% DCB and 5% stent treatment
Discounting			
Discount rate on costs, p.a.	2.0%	4.5%	Based on Chuikyo (Japan) and HIRA (Korea) pharmacoeconomic guidelines[29,30]

Abbreviations: AVF, arteriovenous fistula; DCB, drug-coated balloon angioplasty; DPC, diagnosis procedure combination; ESRD, end-stage renal disease; HIRA, Health Insurance and Review Assessment; HR, hazard ratio; NDB, national database; p.a., annually; PTA percutaneous transluminal angioplasty.

devices used during index treatment, the proportion of required surgical interventions, and the utilization of duplex ultrasound was captured from study data.

Cost data were country- and setting-of-care specific and were derived from national claims and reimbursement data. For Korea, outpatient treatment was considered as the most appropriate setting-of-care assumption as it resembles predominant clinical practice.[16,17] For Japan, a blend of hospital and outpatient clinic treatment was assumed based on reported treatment volumes available at time of model development. Specifically, hospital care could take place in hospitals participating in Japan's Diagnosis Procedure Combination (DPC) reimbursement system (so-called 'DPC hospitals', in which AV fistula balloon procedure cases would commonly involve same-day discharge) or those not participating in this system ('Non-DPC hospitals', in which AV fistula balloon procedures typically involve an overnight stay). The remaining cases would be treated in outpatient clinics. A

weighted average treatment cost was calculated for index cost and applicable reinterventions based on government-published data for 2017.[18,19] For the Korean analysis, procedure costs were obtained from Korean National Health Insurance Service (NHIS) data.[20] As the Korean healthcare system reimburses for duplex ultrasound imaging in outpatient settings, the Korean model also accounted for this expense. Conversely, the Japanese analysis accounted for the possibility of an additional surgical AVF creation procedure in inpatient settings if the current AVF had to be abandoned.

The cost of DCB procedures—per reimbursement rules in each country—was calculated as the PTA procedure cost plus the country-specific per-device DCB reimbursement of ¥173 000 for Japan and ₩646 660 for Korea.[21,22] Re-intervention options consisted of DCB, plain balloon and stenting in the Korean context, with a case-mix of 65% plain balloon, 30% DCB and 5% stent in the base case, informed by available data and estimated use patterns in Korea.[20] For Japan, 0% DCB use was assumed for reinterventions in the base case, as no data currently exist to inform real-world practice patterns. For both countries, scenario analyses explored variations of these device use assumptions, including 0%, 25%, and 50% DCB use in reinterventions. Further, all reinterventions in the Japanese analysis were assumed to be balloon treatments, as—to-date—stents have not been approved for this indication in Japan. Where required, costs were inflated to 2021 based on country-specific consumer price indices. See Table 1 for full model inputs, and Supplementary Materials S.1 for additional detail.

2.2 | Model projections and scenarios

The decision-analytic model tracked a cohort of participants after treatment for a stenotic lesion and was constructed with three states—'before re-intervention', 'after re-intervention' and 'death', with reintervention events included as nested substates. A decision tree is shown in Supplementary Materials S.1. Participants in the

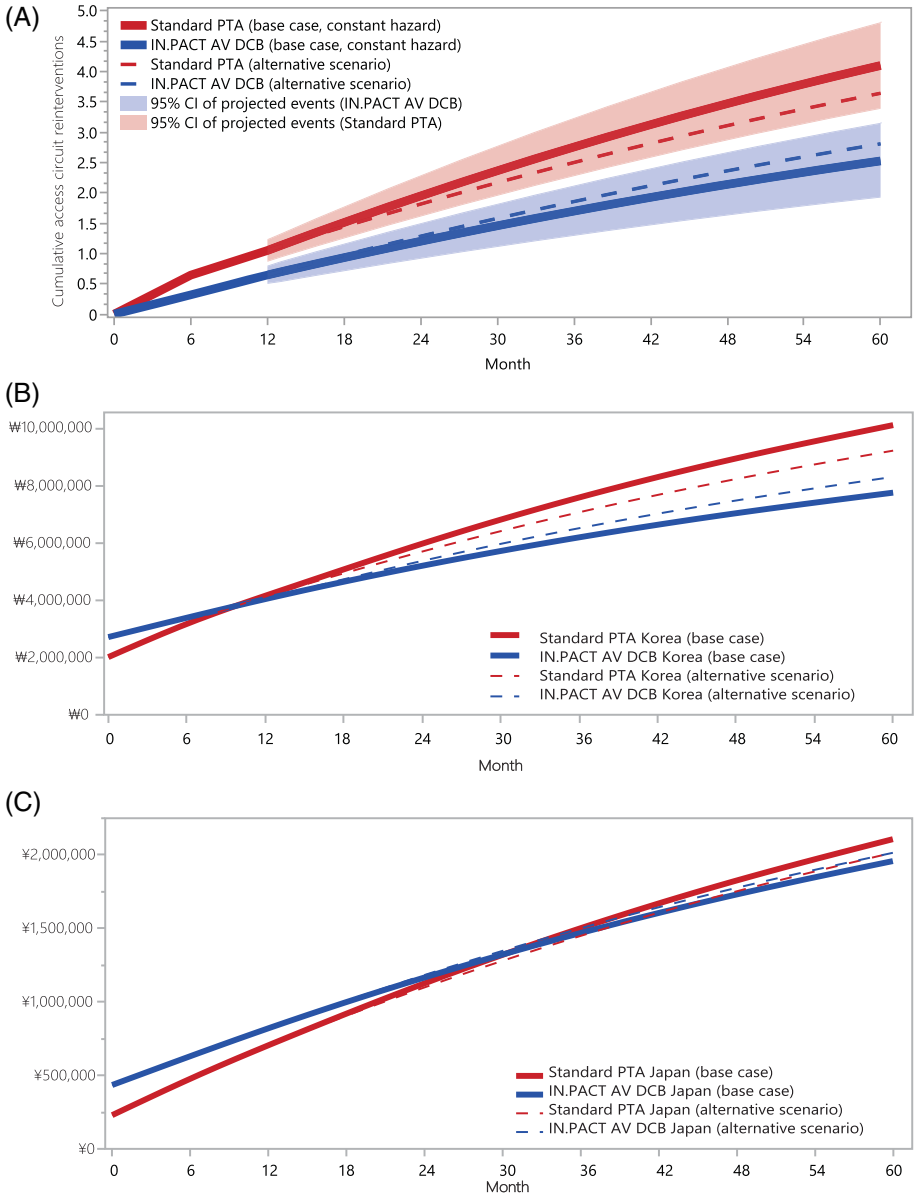

FIGURE 1 Access circuit reintervention events over 5 years (A), Cumulative costs by strategy, Korean analysis (B), and Japan analysis (C). DCB, drug-coated balloon angioplasty; PTA, percutaneous transluminal angioplasty

model progressed through these states based on therapy-specific event rates for re-intervention and death. The cycle length of the model was 1 month. Through 1 year, reintervention data were based on trial data reported at 6 and 12 months, with events assumed equally distributed across the months for each half-year period. For the following model cycles up to the maximum analysis horizon of 60 months, the base case analysis assumed a reintervention burden similar to the first year applied to all surviving participants. An alternative scenario was explored that assumed a reduction in PTA events (15% fewer reinterventions than in the first year) with a concurrent increase in DCB events (15% more reinterventions than in the first year), resulting in a reintervention benefit for years two and following that was around 60% lower than in the base case.

As no statistically significant mortality differences were reported at 12 months in the clinical study, no survival difference was assumed between therapies. Country-specific survival for the modelled cohort

TABLE 2 Projected cost difference for DCB versus PTA treatment at 1, 3 and 5-years for different effectiveness and retreatment assumptions in Korea and Japan

KOREA

Cost difference DCB vs. PTA, assuming constant hazard for reinterventions in DCB and PTA in yrs. 2 and beyond	1 year	3 years	5 years
0% DCB re-intervention	₩ 34,734	-₩ 1,160,137	-₩ 2,021,401
25% DCB re-intervention	-₩ 41,227	-₩ 1,355,399	-₩ 2,302,653
50% DCB re-intervention	-₩ 117,189	-₩ 1,550,660	-₩ 2,583,906
75% DCB re-intervention	-₩ 193,151	-₩ 1,745,921	-₩ 2,865,158
100% DCB re-intervention	-₩ 247,031	-₩ 1,884,421	-₩ 3,064,652

Cost difference DCB vs. PTA, Scenario (15% fewer reinterventions in PTA strategy in yrs. 2 and beyond and 15% more reinterventions in DCB strategy)	1 year	3 years	5 years
0% DCB re-intervention	-₩ 34,734	-₩ 412,324	-₩ 734,564
25% DCB re-intervention	-₩ 41,227	-₩ 532,218	-₩ 886,124
50% DCB re-intervention	-₩ 117,189	-₩ 652,112	-₩ 1,037,684
75% DCB re-intervention	-₩ 193,151	-₩ 772,005	-₩ 1,189,243
100% DCB re-intervention	-₩ 247,031	-₩ 857,046	-₩ 1,296,746

JAPAN

Cost difference DCB vs. PTA, assuming constant hazard for reinterventions in DCB and PTA in yrs. 2 and beyond	1 year	3 years	5 years
0% DCB re-intervention	¥ 119,038	-¥ 34,337	-¥ 149,701
25% DCB re-intervention	¥ 92,976	-¥ 93,886	-¥ 234,441
50% DCB re-intervention	¥ 66,913	-¥ 153,436	-¥ 319,180
75% DCB re-intervention	¥ 40,850	-¥ 212,986	-¥ 403,920
100% DCB re-intervention	¥ 14,787	-¥ 272,536	-¥ 488,660

Cost difference DCB vs. PTA, Scenario (15% fewer reinterventions in PTA strategy in yrs. 2 and beyond and 15% more reinterventions in DCB strategy)	1 year	3 years	5 years
0% DCB re-intervention	¥ 119,038	¥ 50,063	-¥ 1,813
25% DCB re-intervention	¥ 92,976	¥ 11,669	-¥ 49,483
50% DCB re-intervention	¥ 66,913	-¥ 26,726	-¥ 97,154
75% DCB re-intervention	¥ 40,850	-¥ 65,120	-¥ 144,824
100% DCB re-intervention	¥ 14,787	-¥ 103,514	-¥ 192,495

Note: Results presented as a 'heat map', with red colour indicating cost increase with DCB and green documenting cost savings with DCB. More pronounced colouring shows extent of cost difference. The Japanese analysis assumes 0% stent use and the Korean analysis 5% stent use (except for the 100% DCB scenario).

Abbreviations: DCB, drug-coated balloon angioplasty; PTA, percutaneous transluminal angioplasty.

was based on official Japanese and Korean lifetables,[23,24] adjusted to match IN.PACT AV Access trial-observed mortality at 12 months.[14]

The primary model outcomes were the strategy-specific treatment cost and corresponding cost difference between the DCB and PTA, evaluated at 3 and 5 years. An additional analysis for a one-year horizon was included to facilitate perspective on short-term cost difference at current trial follow-up. In addition to base case and alternative reintervention scenario, several other sensitivity analyses were performed to assess the effect of treatment age, higher or lower ESRD cohort survival, and different therapy benefit assumptions including no DCB benefit beyond the first year.

Cost data for each year between 1 and 5 years were calculated to facilitate threshold analyses documenting when cost savings would be reached in each of the scenarios. To complement per-patient cost findings, numbers needed to treat (NNT) to avoid one reintervention were also calculated, and the potential budget impact of a hypothetical 50% adoption of DCB was quantified for both countries based on the prevalence of AV fistulas in haemodialysis identified in the Introduction section, and assuming an average 1.05 events per year based on the PTA arm of the IN.PACT AV Access study (refer to Supplementary Material S.3 for additional detail). The DCB price required to achieve cost neutrality was calculated for both the Japanese and Korean base cases at the 5-year horizon. All analyses were performed with TreeAge Pro (TreeAge LLC, Williamstown, MA), JMP 15 (SAS Institute, Carey, NC), and Stata MP15 (Stata Corp, College Station, TX).

3 | RESULTS

The mean number of model-projected access circuit reintervention events for DCB versus PTA were 1.70 versus 2.76 (−1.06) at 3 years and 2.53 versus 4.10 (−1.57) at 5 years for the base case. In the studied alternative scenario, where PTA events were 15% lower and DCB events 15% higher than in year one, 3- and 5-year events were 1.86 versus 2.50 (−0.64) and 2.81 versus 3.64 (−0.83) (Figure 1A).

Corresponding 3- and 5-year costs for DCB and PTA in the Korean analysis were ₩6 211 103 versus ₩7 605 553 (−₩1 394 451) and ₩7 766 051 (95% CI ₩6 581 754 to ₩8 995 321) versus ₩10 124 954 (95% CI ₩8 727 021 to ₩11 522 888) (−₩2 358 904, 95% CI ₩2 145 267 to ₩2 527 567), and for the Japan analysis ¥1 469 824 versus ¥1 504 161 (−¥34 337)

TABLE 3 Cost difference over time for explored scenarios in Korean analysis

Scenario	1-yr. cost diff.	2-yr. cost diff.	3-yr. cost diff.	4-yr. cost diff.	5-yr. cost diff.
Base Case	-₩ 56,420	-₩ 776,990	-₩ 1,394,450	-₩ 1,918,509	-₩ 2,358,903
Sensitivity Analysis					
Mortality HR 8.0 (3-yr. survival 79.8%)	-₩ 65,465	-₩ 819,073	-₩ 1,485,907	-₩ 2,071,708	-₩ 2,582,433
Mortality HR 15.0 (3-yr. survival 65%)	-₩ 45,679	-₩ 728,072	-₩ 1,290,671	-₩ 1,749,069	-₩ 2,118,152
Age 53 (1 standard deviation below the mean)	-₩ 75,473	-₩ 867,012	-₩ 1,593,584	-₩ 2,258,590	-₩ 2,865,197
Age 79 (1 standard deviation above the mean)	₩ 73,800	-₩ 246,830	-₩ 395,597	-₩ 461,572	-₩ 489,252
100% male	-₩ 46,936	-₩ 732,757	-₩ 1,298,137	-₩ 1,757,009	-₩ 2,123,170
100% female	-₩ 73,651	-₩ 857,358	-₩ 1,569,444	-₩ 2,211,938	-₩ 2,787,208
Cost undiscounted	-₩ 70,838	-₩ 841,643	-₩ 1,531,850	-₩ 2,143,988	-₩ 2,681,531
Cost discounted at 7.5% p.a.	-₩ 47,325	-₩ 737,396	-₩ 1,312,230	-₩ 1,786,506	-₩ 2,173,953
53-year old males	-₩ 289,799	-₩ 1,270,568	-₩ 2,159,133	-₩ 2,960,584	-₩ 3,679,760
53-year old females	-₩ 305,169	-₩ 1,334,554	-₩ 2,300,716	-₩ 3,206,489	-₩ 4,054,328
79-year old males	-₩ 16,528	-₩ 309,610	-₩ 399,612	-₩ 419,779	-₩ 422,528
79-year old females	-₩ 160,266	-₩ 766,559	-₩ 1,131,417	-₩ 1,329,100	-₩ 1,422,421
Scenario Analysis					
IN.PACT AV Japanese Subgroup	-₩ 266,192	-₩ 1,174,737	-₩ 1,953,274	-₩ 2,614,042	-₩ 3,169,322
No incremental benefit for DCB beyond year 2	-₩ 56,420	-₩ 776,990	-₩ 782,140	-₩ 786,510	-₩ 790,183
No incremental benefit for DCB beyond year 1	-₩ 56,420	-₩ 62,429	-₩ 67,578	-₩ 71,949	-₩ 75,621
PTA events year 2 and 3 10% lower than first year, DCB events 10% higher than first year	-₩ 56,420	-₩ 476,040	-₩ 835,615	-₩ 1,140,797	-₩ 1,397,258
PTA events year 2 and beyond 15% lower than first year, DCB events 15% higher than first year	-₩ 56,420	-₩ 325,565	-₩ 556,197	-₩ 751,941	-₩ 916,436
PTA events year 2 and beyond 20% lower than first year, DCB events 20% higher than first year	-₩ 56,420	-₩ 175,090	-₩ 276,779	-₩ 363,085	-₩ 435,613
Additional incremental benefit for DCB in years 2 and beyond (0.50 annual events instead of 0.65)	-₩ 56,420	-₩ 1,037,779	-₩ 1,878,711	-₩ 2,592,436	-₩ 3,192,218
Revascularization events in years 2 and beyond at 80% of their respective first-year values	-₩ 56,420	-₩ 634,078	-₩ 1,129,076	-₩ 1,549,197	-₩ 1,902,247
Revascularization events in years 2 and beyond at 80% and 60% of their first year values, respectively	-₩ 56,420	-₩ 634,078	-₩ 1,006,614	-₩ 1,322,797	-₩ 1,588,503
Revascularization events in years 2 and beyond at 120% of their respective first-year values	-₩ 56,420	-₩ 919,903	-₩ 1,659,825	-₩ 2,287,821	-₩ 2,815,560
Use of 2 DCB devices per procedure	₩ 384,445	-₩ 384,389	-₩ 1,043,207	-₩ 1,602,366	-₩ 2,072,258
Reintervention modality - DCB 20% / PTA 75% / Stent 5%	-₩ 26,035	-₩ 720,907	-₩ 1,316,346	-₩ 1,821,714	-₩ 2,246,403
Reintervention modality - DCB 40% / PTA 55% / Stent 5%	-₩ 86,804	-₩ 833,074	-₩ 1,472,555	-₩ 2,015,303	-₩ 2,471,405
Reintervention modality - DCB 60% / PTA 35% / Stent 5%	-₩ 147,574	-₩ 945,240	-₩ 1,628,764	-₩ 2,208,893	-₩ 2,696,407
Reintervention modality - DCB 0% / PTA 90% / Stent 10%	₩ 12,653	-₩ 649,498	-₩ 1,216,898	-₩ 1,698,469	-₩ 2,103,159
Reintervention modality - DCB 0% / PTA 100%	₩ 56,816	-₩ 567,983	-₩ 1,103,376	-₩ 1,557,781	-₩ 1,939,642

Note: Results presented as a 'heat map', with red colour indicating cost increase with DCB and green documenting cost savings with DCB. More pronounced colouring shows extent of cost difference.

Abbreviations: DCB, drug-coated balloon angioplasty; HR, hazard ratio; PTA, percutaneous transluminal angioplasty.

and ¥1 956 931 (95% CI ¥1 836 957 to ¥2 081 462) versus ¥2 106 632 (95% CI ¥1 965 016 to ¥2 248 249) (−¥149 701, 95% CI ¥128 059 to ¥166 787). Under the studied alternative effectiveness scenario, DCB remained cost saving at both the 3- and 5-year horizon in the Korean analysis (−₩556 197 and −₩916 436, respectively), while DCB had higher cost than PTA at the 3-year horizon (+¥50 063), but remained cost saving at 5 years (−¥1813) in Japan. At the one-year horizon, which relied on the trial-observed 1.05 and 0.65 reinterventions for PTA and DCB without need for event projection, DCB was found to be cost-saving in the Korean analysis (−₩56 420), but associated with higher costs in the Japanese analysis (+¥119 038) (Figures 1B and C).

Higher utilization of DCB in reintervention events reduced costs of the DCB strategy in both country settings (Table 2). Under a theoretical assumption of 50% DCB use, the time-to-cost savings for DCB in the Japanese analysis would shift markedly toward a shorter time horizon (Table 2).

Additional sensitivity and scenario analysis results are detailed in Tables 3 and 4 for Korea and Japan, respectively. In the Korean analysis, all scenarios in the outpatient setting resulted in cost savings at

TABLE 4 Cost difference over time for explored scenarios in Japanese analysis

Scenario	1-yr. cost diff.	2-yr. cost diff.	3-yr. cost diff.	4-yr. cost diff.	5-yr. cost diff.
Base case	¥ 119,038	¥ 37,351	-¥ 34,337	-¥ 96,554	-¥ 149,701
Sensitivity Analysis					
Mortality HR 13.0 (3-yr. survival 67%)	¥ 119,975	¥ 41,410	-¥ 25,680	-¥ 82,082	-¥ 128,296
Mortality HR 9.0 (3-yr. survival 79%)	¥ 118,476	¥ 34,884	-¥ 39,675	-¥ 105,597	-¥ 163,223
Age 53 (1 standard deviation below the mean)	¥ 116,426	¥ 25,686	-¥ 60,080	-¥ 140,939	-¥ 217,037
Age 79 (1 standard deviation above the mean)	¥ 130,702	¥ 83,887	¥ 56,569	¥ 43,648	¥ 44,076
100% male	¥ 120,079	¥ 41,967	-¥ 24,225	-¥ 79,243	-¥ 123,596
100% female	¥ 117,149	¥ 28,964	-¥ 52,708	-¥ 128,006	-¥ 197,132
Cost undiscounted	¥ 118,242	¥ 33,993	-¥ 41,420	-¥ 108,178	-¥ 166,345
Cost discounted at 4% p.a.	¥ 119,810	¥ 40,556	-¥ 27,659	-¥ 85,725	-¥ 134,373
53-year old males	¥ 116,682	¥ 26,867	-¥ 57,360	-¥ 136,065	-¥ 209,412
53-year old females	¥ 115,961	¥ 23,540	-¥ 65,022	-¥ 149,796	-¥ 230,892
79-year old males	¥ 134,253	¥ 97,090	¥ 80,214	¥ 76,870	¥ 85,979
79-year old females	¥ 124,249	¥ 59,898	¥ 13,610	-¥ 16,712	-¥ 32,058
Scenario Analysis					
IN.PACT AV Japanese Subgroup	¥ 96,286	-¥ 4,117	-¥ 92,234	-¥ 168,710	-¥ 234,035
No incremental benefit for DCB beyond year 2	¥ 119,038	¥ 37,351	¥ 28,114	¥ 20,103	¥ 13,246
No incremental benefit for DCB beyond year 1	¥ 119,038	¥ 108,496	¥ 99,259	¥ 91,248	¥ 84,391
PTA events year 2 and beyond 10% lower than first year, DCB events 10% higher than first year	¥ 119,038	¥ 67,315	¥ 21,930	-¥ 17,458	-¥ 51,109
PTA events year 2 and beyond 15% lower than first year, DCB events 15% higher than first year	¥ 119,038	¥ 82,297	¥ 50,063	¥ 22,091	-¥ 1,813
PTA events year 2 and beyond 20% lower than first year, DCB events 20% higher than first year	¥ 119,038	¥ 97,279	¥ 78,196	¥ 61,639	¥ 47,483
Additional incremental benefit for DCB in years 2+ (0.50 annual events instead of 0.65)	¥ 119,038	¥ 11,386	-¥ 83,095	-¥ 165,095	-¥ 235,136
Revascularization events in years 2+ at 80% of their respective first-year values	¥ 119,038	¥ 51,580	-¥ 7,618	-¥ 58,993	-¥ 102,883
Revascularization events in years 2 at 80% and in yr. 3+ at 60% of their first year values, respectively	¥ 119,038	¥ 51,580	¥ 4,873	-¥ 35,662	-¥ 70,293
Revascularization events in years 2 and 3+ at 120% of their respective first-year values	¥ 119,038	¥ 23,122	-¥ 61,056	-¥ 134,114	-¥ 196,519
Setting of care for balloon procedures 100% DPC Hospital	¥ 137,548	¥ 71,956	¥ 14,396	-¥ 35,558	-¥ 78,234
Setting of care for balloon procedures 100% Non-DPC Hospital	¥ 67,744	-¥ 58,544	-¥ 169,383	-¥ 265,581	-¥ 347,748
Setting of care for balloon procedures 100% Clinic (outpatient)	¥ 134,541	¥ 66,334	¥ 6,479	-¥ 45,468	-¥ 89,844
Use of DCB device in 50% of PTA retreatments and 50% of DCB retreatments (for DCB index strategy only considered if DCB reintervention after at least 3 months post index)	¥ 66,913	-¥ 50,441	-¥ 153,436	-¥ 242,827	-¥ 319,180
Use of DCB device in 25% of PTA retreatments and 25% of DCB retreatments (for DCB index strategy only considered if DCB reintervention after at least 3 months post index)	¥ 92,976	-¥ 6,545	-¥ 93,886	-¥ 169,690	-¥ 234,441
No separate consideration of surgical intervention	¥ 130,968	¥ 59,823	-¥ 2,628	-¥ 56,834	-¥ 103,124

Note: Results presented as a 'heat map', with red colour indicating cost increase with DCB and green documenting cost savings with DCB. More pronounced colouring shows extent of cost difference.

Abbreviations: DCB, drug-coated balloon angioplasty; HR, hazard ratio; PTA, percutaneous transluminal angioplasty.

the 3- and 5-year horizon. The scenario of no incremental benefit of DCB beyond the first year had the highest effect on projected cost savings, followed by the other scenarios exploring lower treatment effect of DCB over time. Older treatment age led to lower cost savings. Conversely, younger treatment age and assumptions about potential added benefit of DCB in years two and beyond increased cost savings with the DCB strategy. In the Japanese analysis, the relative ranking of scenario effect on DCB cost savings was directionally comparable to the findings for Korea. Notably, cost savings were projected at 5 years (but not 3 years) in the case that plain balloons had 10% and 15% lower re-intervention rates and DCBs had 10% and 15% higher re-intervention rates in years 2 and 3. Based on reimbursement structure, projected cost savings were highest for the non-DPC and lowest for the DPC hospital setting—although this separation by setting-of-care is merely a theoretical consideration.

The NNT to avoid one re-intervention over 5 years was 0.88 in the base case (constant event rates over time), and 1.20 in the alternative scenario. Assuming 50% of the annual access circuit PTA cases are performed with DCB instead of a plain balloon, ¥21.9B of savings might be accomplished in Japan and ₩70.4B in Korea over a 5-year follow-up horizon. The DCB cost required for cost neutrality was ¥294 708 for the Japanese context (1.70× Japanese device price) and ₩2 296 062 for the Korean context (3.55× Korean device price) at the 5-year time horizon.

4 | DISCUSSION

This study explored the potential economic implications of DCB use in the treatment of AV fistula stenoses based on recent clinical data from the IN.PACT AV Access study. By projecting strategy-specific reintervention events and resulting cost implications, insight could be gained about the expected value proposition of DCB in Japan and Korea, two healthcare systems with a large burden of AV access maintenance in ESRD patients. The findings indicate that the higher index treatment costs of the DCB may be amortized within timeframes as short as 1 year in Korea and around 3 years in Japan, with potential for meaningful overall cost savings to payers in both geographies.

The extensive sensitivity analyses performed beyond the base case provided perspective on the effect of variation in long-term clinical performance of DCB versus PTA. While the base case assumed a constant benefit of DCB and showed a highly attractive savings potential, time-to-cost savings was longer and absolute savings amounts lower in the alternative scenario that assumed a DCB reintervention benefit that was around 60% lower in years two and following than the base case. In the absence of multi-year follow-up from the IN.PACT AV Access study, both of these scenarios seem to have merit. The first assumption seems valid in light of evidence from a retrospective single-centre study of AV fistula patients ($n = 720$) that found clinical effectiveness of repeated percutaneous interventions diminished with each successive procedure, suggesting an increasing reintervention burden over time.[25] This would support the base case assumption even if DCB effectiveness would slightly decrease over time. At the same time, evidence from the participants in the PTA group of the recent Lutonix AV Randomized Trial ($n = 144$) suggest somewhat lower number of reinterventions needed to maintain target lesion primary patency in the second compared to the first year.[26] These data directionally support the calculated alternative scenario.

From the current analysis, it is evident that time-to-cost-savings with the DCB strategy can be expected to be shorter in the Korean as opposed to the Japanese context. The primary reason for this difference is the higher relative cost increase associated with DCB versus PTA index treatment. In the Korean analysis, DCB index treatment is approximately 40% more costly than PTA index treatment, while it is almost twice the cost of PTA index treatment in Japan. These factors are largely driven by country-specific reimbursement and are the main reason why the Korean analysis suggests DCB can be cost saving in periods as short as the current IN.PACT AV Access study follow-up of 1 year. In Japan, conversely, continued benefit of DCB versus PTA is required beyond 1 year in order to achieve cost savings in the studied periods of 3–5 years.

For both countries, it should be noted that DCB may be cost-effective and therefore 'of value' to healthcare payers at periods shorter than those found for cost-savings. The rationale is that added costs of the DCB strategy might well be justified as long as there are adequate concurrent gains in quality-adjusted life years (QALYs). Such incremental QALY gains can be expected based on differences in patient quality of life, specifically surrounding necessary reintervention events, as has been documented in prior cost-effectiveness studies, including in the treatment of AV fistulas.[27,28] Future analyses might encompass this additional perspective in a formal cost-utility study.

An interesting finding in both studied geographies was that higher proportions of DCB use in applicable reinterventions procedures improved overall cost savings of the DCB strategy in almost all of the explored scenarios. This makes sense intuitively, as a more costly reintervention that is avoided contributes to larger cost savings. At the same time, such increased use of DCB also in reinterventions increases the budget need for healthcare payers in the short term, even if increasing their cost savings potential in the long-run.

Among the strengths of the current analysis is its reliance on evidence from a large contemporary randomized-controlled trial that collected detailed device utilization and core lab-adjudicated re-intervention data. Further, the extensive scenario analyses conducted provide insight into the effect of different clinical efficacy, cohort characteristics, and settings of care. In addition, the side-by-side comparison of results in two Asian healthcare systems provides insight into the effect of country-specific cost structures – a factor that needs to be considered when considering application of the study findings to other countries in the Asia-Pacific region and beyond.

The current analysis, at the same time, is subject to several limitations. First, underlying clinical evidence was limited to currently available 12-month data. A projection of clinical effectiveness to timeframes of 3- or even 5-years is therefore subject to inherent uncertainty. The study addressed this concern by exploring a range of potential effectiveness scenarios. Second, the Korean analysis was limited to the outpatient setting-of-care as the predominant setting of care. The Japanese analysis, at the same time, considered a weighted average across three settings-of-care. A shift in the proportion of

patients treated in each setting might therefore lead to some variation in analysis results. The setting-of-care-specific scenario analyses provide insight into the effect of such potential shifts. Finally, our findings are based on clinical data from the IN.PACT AV Access study and may therefore not apply to other DCB devices.

In summary, treatment of arteriovenous fistulas with the IN.PACT drug-coated balloon can be expected to lead to meaningful reductions in necessary reintervention costs that may amortize the higher upfront cost of drug-coated balloon treatment in timeframes of around 1 year in Korea and between 3 and 5 years in Japan. This exploratory analysis should be updated and further refined as additional clinical data become available.

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CONFLICTS OF INTEREST

Ho Jong Chun, MD, Ph.D. has no potential conflicts of interest to declare. Khoa N. Cao, MBBS, MS, is an employee of Wing Tech, Inch, which received consulting fees from Medtronic, Inc. to conduct the health economic analyses underlying this study. Hiroaki Haruguchi, MD, is the IN.PACT AV Access Study Principal Investigator in Japan and is a consultant for Medtronic. Hyunsook Choi, MPH, is a full-time employee of Medtronic. Mayuko Yoshikawa, MS, is a full-time employee of Medtronic. Andrew Holden, MBChB, FRANZCR, is a Medical Advisory Board Member at Medtronic, Gore, Boston Scientific, and a Clinical Investigator for Bard-BD, Boston Scientific, Cagent Medical, Cook Medical, Endologix, Endospan, Gore Medical, Intact Vascular, Medtronic, Philips, Reflow Medical, Shockwave Medical, and TriReme Medical. Jan B. Pietzsch, Ph.D. is president, CEO, and shareholder of Wing Tech Inc. which received consulting fees from Medtronic, Inc. to conduct the health-economic analyses underlying this study.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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