IN.PACT™ Admiral™ DCB: Safety and Effectiveness in Treating Complex Lesions

Discussing trends demonstrated in existing clinical data and practice for the endovascular treatment of complex femoropopliteal lesions.

BY GARY M. ANSEL, MD, FACC

In relation to femoropopliteal lesions, the term *complex* inspires in each of us our own personal definition, usually comprising morphologic elements of the target lesion such as length, degree of calcium, and presence of an occlusion. Our approach is equally personal, as it is often based on the physician's training, experience, opinion leader presentations, and interpretation of available clinical data. As a result, I am pleased to be accompanied in this supplement by clinicians representing various specialties, each with their own experiences and philosophies, to offer their perspectives on treating complex femoropopliteal lesions.

CURRENT CLINICAL DATA FOR COMPLEX LESIONS

At some point, I expect most physicians will have all seen a graphic similar to Figure 1. I always warn that comparing patency rates across multiple trials is fraught with limitations due to various types of bias as well as variations in populations, lesions, study protocols, definitions, and follow-up, among others. However, Figure 1 does offer us insight into the overall clinical data landscape of core laboratory–adjudicated femoropopliteal studies of FDA class 3 devices and their respective control arms when employed. Since the modest beginning of Figure 1's data points more than 10 years ago, the landscape has certainly evolved, but a few particular trends have become apparent and seem to persist. This article highlights and discusses each of these trends.

DATA EXIST MOSTLY FOR LESIONS ≤ 10 CM

At first glance, we see a majority of data clustered toward shorter lesions. As you might expect, these lesions range from approximately 5 to 12 cm and typically comprise the simple disease process often encountered in investigational device exemption (IDE) studies that device manufacturers are required to perform to gain FDA approval (Figure 1; data points 1-8, 10-16, 23-33, 36-38). However, these lesions are fairly uncommon in many of our own practices, and extrapolating these data sets to longer, more complex lesion types beyond the IDE studies is challenging. Surveying the data for more moderate lesion lengths of approximately 15 to 20 cm, we are limited to five studies consisting of the prespecified in-stent restenosis (ISR) cohort of IN.PACT Global (Figure 1; 17); the randomized ISR cohorts treated with either heparin-bound stent graft or percutaneous transluminal angioplasty (PTA) of the RELINE study (Figure 1; 9, 40); the cohorts of heparin-bound stent graft and nonbound stent graft randomized against their bare-metal stent (BMS) control arms of VIASTAR (Figure 1; 34, 42) and VIBRANT (Figure 1; 35, 41), respectively; and the ZEPHYR single-arm Japan postmarket approval study of a drug-eluting stent (DES) (Figure 1; 39). Beyond 20 cm, the data are similarly sparse, with outcomes reported from four drug-coated balloon (DCB) studies and a single peripheral stent graft study (Figure 1; 18-21, 43). The message here is that although many of us practice in the domain beyond 15 cm, the vast majority of adjudicated outcomes lie below this range.

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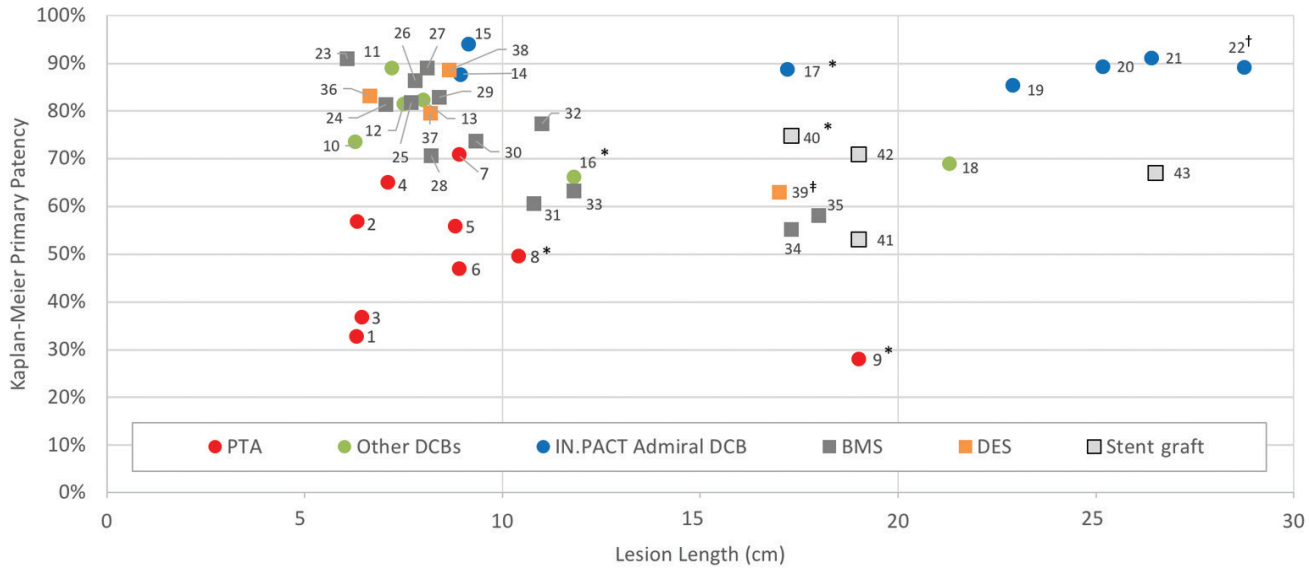
CONVENTIONAL PTA PATENCY CLUSTERS TOWARD LOW END

Once we dig into the landscape, we see the points representing PTA clustering toward the low patency end of the shorter lesions. Although certainly a variation exists within the PTA cohorts, we have to keep in mind that the study protocols, endpoint definitions, and technical practices evolved during the course of these studies. For instance, compare the two control arms of the Zilver PTX and RESILIENT randomized trials, which

FIGURE 1. CORE LAB-ADJUDICATED 12-MONTH PRIMARY PATENCY BY KAPLAN-MEIER ESTIMATE OF FDA-APPROVED CLASS 3 DEVICES AND THEIR CONTROL ARMS.



Qualitative comparison for illustration purposes only. Not meant for head-to-head comparison.

Data point	Cohort	Patency definition
1	Zilver PTX RCT: PTA arm[1]	PSVR < 2.0 or < 50% stenosis
2	LEVANT II RCT: PTA arm[2]	PSVR < 2.5 and freedom from TLR
3	RESILIENT RCT: PTA arm[3]	PSVR < 2.5 and freedom from TLR
4	ILLUMENATE EU RCT: PTA arm[4]	PSVR ≤ 2.5 and freedom from TLR
5	IN.PACT SFA RCT: PTA arm[5]	PSVR ≤ 2.4 and freedom from CD-TLR
6	IN.PACT Japan RCT: PTA arm[6]	PSVR ≤ 2.4 and freedom from CD-TLR
7	ILLUMENATE Pivotal RCT: PTA arm[7]	PSVR ≤ 2.5 and freedom from TLR
8*	SFA ISR IDE RCT: PTA arm[8]	Freedom from restenosis and CD-TLR
9*	RELINE RCT: PTA arm[9]	PSVR < 2.5 and freedom from TLR
10	LEVANT II RCT: Lutonix 035 DCB (BD Interventional) arm[2]	PSVR < 2.5 and freedom from TLR
11	ILLUMENATE EU RCT: Stellarex DCB (Philips) arm[4]	PSVR ≤ 2.5 and freedom from TLR
12	ILLUMENATE Global: Stellarex DCB[10]	PSVR ≤ 2.5 and freedom from TLR
13	ILLUMENATE Pivotal RCT: Stellarex DCB arm[7]	PSVR ≤ 2.5 and freedom from TLR
14	IN.PACT SFA RCT: IN.PACT™ Admiral™ DCB arm[5]	PSVR ≤ 2.4 and freedom from CD-TLR
15	IN.PACT Japan RCT: IN.PACT™ Admiral™ DCB arm[6]	PSVR ≤ 2.4 and freedom from CD-TLR
16*	SFA ISR IDE RCT: Lutonix 035 DCB arm[8]	Freedom from restenosis and CD-TLR
17*	IN.PACT Global - ISR: IN.PACT™ Admiral™ DCB[11]	PSVR ≤ 2.4 and freedom from TLR
18	Lutonix Long Lesion: Lutonix 035 DCB[8]	Freedom from restenosis and CD-TLR
19	IN.PACT Global - CTO: IN.PACT™ Admiral™ DCB[12]	PSVR ≤ 2.4 and freedom from CD-TLR
20	SFA-Long Study: IN.PACT™ Admiral™ DCB[13]	Freedom from > 50% restenosis and CD-TLR
21	IN.PACT Global - Long Lesion: IN.PACT™ Admiral™ DCB[14]	PSVR ≤ 2.4 and freedom from CD-TLR
22†	IN.PACT Global - Complex Lesion post-hoc subset: IN.PACT™ Admiral™ DCB[5]	PSVR ≤ 2.4 and freedom from CD-TLR
23	Complete SE SFA - Complete SE Stent[15]	PSVR < 2.0 and freedom from revascularization
24	RESILIENT RCT: LifeStent stent (BD Interventional) arm[3]	PSVR < 2.5 and freedom from TLR
25	STROLL: SMART stent (Cordis, a Cardinal Health company)[16]	PSVR < 2.5/50% diameter stenosis and freedom from TLR
26	SUPERB: Supera stent (Abbott Vascular)[17]	PSVR ≤ 2.0 and freedom from TLR
27	SIROCCO RCT: SMART stent arm[18]	≤ 50% stenosis by angiography
28	BioFlex 1: Astron and Pulsar stents (Biotronik)[19]	PSVR ≤ 2.4 and freedom from CD-TLR
29	OSPREY: Misago stent (Terumo Europe)[20]	PSVR < 2.5 and freedom from TLR
30	SuperNOVA: Innova stent (Boston Scientific Corporation)[21]	PSVR < 2.4 and freedom from TLR
31	TIGRIS RCT: Tigris stent (Gore & Associates) arm[22]	PSVR ≤ 2.5 and freedom from TLR
32	DURABILITY II: Protégé EverFlex stent (Medtronic)[23]	PSVR < 2.0 and freedom from CD-TLR
33	TIGRIS RCT: LifeStent stent arm[22]	PSVR ≤ 2.5 and freedom from TLR
34	VIASTAR RCT: BMS arm[24]	PSVR ≤ 2.5 or < 50% stenosis
35	VIBRANT RCT: BMS arm[25]	PSVR < 2.5 and freedom from TLR
36	Zilver PTX RCT: Zilver PTX DES (Cook Medical) arm[1]	PSVR < 2.0 or < 50% stenosis
37	IMPERIAL RCT: Zilver PTX DES arm[26]	PSVR ≤ 2.4 and freedom from CD-TLR
38	IMPERIAL RCT: Eluvia DES (Boston Scientific Corporation) arm[26]	PSVR ≤ 2.4 and freedom from CD-TLR
39‡	ZEPHYR: Zilver PTX DES[27]	PSVR ≤ 2.4 or < 50% stenosis
40*	RELINE RCT: Viabahn heparin-bonded stent-graft (Gore & Associates) arm[9]	PSVR < 2.5 and freedom from TLR
41	VIBRANT RCT: Viabahn stent-graft arm[25]	PSVR < 2.5 and freedom from TLR
42	VIASTAR RCT: Viabahn heparin-bonded stent-graft arm[24]	PSVR ≤ 2.5 or < 50% stenosis
43	Viabahn-25cm: Viabahn heparin-bonded stent-graft[28]	PSVR ≤ 2.5 and freedom from TLR

*In-stent restenosis studies.

†Subset analysis of previously reported data. IN.PACT Global Complex Lesion cohort consists of 227 subjects enrolled in the three IN.PACT Global prespecified imaging cohorts (long lesion, CTO, and in-stent restenosis) exhibiting lesion lengths > 18 cm.

‡Report proportion-based patency of the ZEPHYR study.

Abbreviations: BMS, bare-metal stent; CD-TLR, clinically driven target lesion revascularization; CTO, chronic total occlusion; DCB, drug-coated balloon; DES, drug-eluting stent; PTA, percutaneous transluminal angioplasty; PSVR, peak systolic velocity ratio; RCT, randomized controlled trial; SFA, superficial femoral artery.

posted PTA patency rates of 32.8% and 36.7%, respectively (Figure 1; 1, 3), in lesions of approximately 6.5 cm, against a contemporary DCB control arm such as the ILLUMENATE Pivotal trial control patency rate of 70.9% (Figure 1; 7). In doing so, we see how factors such as randomization after successful predilatation and sustained balloon inflation complicate comparisons across studies. Despite this variability, PTA clearly occupies the low end of the patency spectrum.

PRIMARY PATENCY IS INVERSELY PROPORTIONAL TO LESION LENGTH

The next trend we see is the declining patency rate associated with increasing lesion length, underscoring a pitfall of extrapolating data captured in short-lesion studies to our own practices, where much longer lesions are commonplace. Less is known about length-dependent performance of DESs given the lack of available data. The core lab–adjudicated ZEPHYR DES study reports positive 12-month outcomes in a challenging population exhibiting a mean lesion length of 17 cm (Figure 1; 39), which adds to the experience of shorter-lesion DES cohorts studied as part of the Zilver PTX and IMPERIAL trials (Figure 1; 36-38). Diverging from independently adjudicated patency outcomes, both the all-comers Japan Zilver PTX postmarket surveillance study and a single-center retrospective analysis demonstrate patency consistent with outcomes observed in the shorter-lesion randomized controlled trial (RCT) despite reported mean lesion lengths of 14.7 and 24.2 cm, respectively.[29,30] Importantly, further analysis of Phillips et al did discern higher patency in DES-treated lesions ≤ 20 cm compared with those > 20 cm, which also exhibited a higher proportion of occlusions. This once again suggests a length-dependency effect on patency for lesions treated with DESs.[30] However, as stent length increases, the discussion of stent fracture cannot be totally ignored. Consider 12-month outcomes of two cohorts employing the same stent: the RESILIENT study's BMS arm reported a fracture rate of 3.1% for lesions averaging 7.1 cm (Figure 1; 24) compared with a fracture rate of 27.1% for lesions averaging 11.8 cm in the TIGRIS study BMS arm (Figure 1; 33). Despite being a well-known phenomenon,[31] the consequences of lesion length and fracture are not fully understood or consistent between stent designs.

IN.PACT GLOBAL PRESPECIFIED IMAGING COHORTS BUCK THE TREND IN LESION LENGTH

Very few adjudicated data exist for treatment of lesion lengths > 20 cm; the only data available is composed of four DCB cohorts (Figure 1; 18-21) and a single heparin-bound stent graft study (Figure 1; 43). Historically, studies in this range came late in the evolution of these data. Zeller et al reported the outcomes associated with the 25-cm heparin-bound stent graft in lesions averaging 26.5 cm, (Figure 1; 43) with interestingly non–length-dependent patency rates similar to those reported in the RELINE and VIASTAR studies (Figure 1; 40,42). For the DCB cohorts, the Lutonix Long Lesion study reported a mean lesion length of 21.3 cm (Figure 1; 18), the chronic total occlusion and long lesion prespecified imaging cohorts of the IN.PACT Global study posted mean lesion lengths of 22.8 and 26.4 cm, respectively (Figure 1; 19, 20), and the SFA-Long Study performed by Micari et al averaged 25.2-cm lesion lengths (Figure 1; 20). Importantly, when considering the IN.PACT™ Admiral™ DCB (Medtronic) cohorts, the patency definition is identical across the two RCTs and the three prespecified imaging cohorts of IN.PACT Global, therefore facilitating patency comparisons across cohorts and underscoring the consistency in patency beyond 20-cm lesions, despite variation in study populations and lesion morphologies. However, it is also worth highlighting that these long-lesion DCB studies are not without significant stent usage; in three of these four cohorts, provisional stent rates of approximately 40% and higher are reported (Figure 1; 18, 19, 21). The one exception to this trend of provisional stenting is reported by the SFA-Long study that demonstrated similar patency results while only resorting to stenting in 10.5% of their lesions (Figure 1; 20). In this supplement, we have commentary from Prof. Micari on his approach to PTA vessel preparation and minimizing stent use when employing DCB in challenging lesions.

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SUPPORT FOR EXPANDING INDICATION

Finally, to support recent FDA indication expansion of the IN.PACT Admiral DCB to lesion lengths up to 36 cm, a post hoc analysis was performed on all core lab–adjudicated IN.PACT Global subjects exhibiting lesions ≥ 18 cm, including ISR subjects (Figure 1; 22). The outcomes

are consistent with the other IN.PACT Admiral DCB trends as demonstrated in Figure 1, and 96 (42.5%) of 227 patients received provisional stenting of various lengths. This observation indicates that a DCB with optimal use of stents led to patency similar to the simpler lesions treated with DCBs alone.

CONCLUSION

From the simple, single-digit lesion lengths to the truly long lesions, we certainly have more insight today than 10 years ago. Each of us is left with our own interpretation of these data, but a few trends are evident: (1) PTA is at the low end of the performance range; (2) length-dependent patency is a consistent observation for PTA and BMSs; and (3) DCBs and, if needed, provisional stent optimization may yield consistent patency with apparently less lesion length dependence. Of course, the data continue to evolve, and we hope it will not take us another 10 years to identify new trends, possibly aided by the evolution of lesion preparation with new specialty balloon technologies, atherectomy, and yet-to-be-developed devices that may be used prior to DCBs. For now, we will leave Figure 1 behind, and begin our panel discussion to explore individual opinions on complex lesion treatment. ■

1. Dake MD, Ansel GM, Jaff MR, et al. Paclitaxel-eluting stents show superiority to balloon angioplasty and bare metal stents in femoropopliteal disease: twelve-month Zilver PTX randomized study results. Circ Cardiovasc Interv. 2011;4:495-504.
2. Rosenfield K, Jaff MR, White CJ, et al. Trial of a paclitaxel-coated balloon for femoropopliteal artery disease. N Engl J Med. 2015;373:145-153.
3. Laird JR, Katzen BT, Scheinert D, et al. Nitinol stent implantation versus balloon angioplasty for lesions in the superficial femoral artery and proximal popliteal artery: twelve-month results from the RESILIENT randomized trial. Circ Cardiovasc Interv. 2010;3:267-276.
4. Schroeder H, Werner M, Meyer DR, et al. Low-dose paclitaxel-coated versus uncoated percutaneous transluminal balloon angioplasty for femoropopliteal peripheral artery disease: one-year results of the ILLUMENATE European randomized clinical trial (randomized trial of a novel paclitaxel-coated percutaneous angioplasty balloon). Circulation. 2017;135:2227-2236.
5. IN.PACT Admiral DCB [Instructions for Use M052624T001 Rev. 1H]. Minneapolis, MN: Medtronic; 2018.
6. Iida O, Soga Y, Urasawa K, et al. Drug-coated balloon vs standard percutaneous transluminal angioplasty for the treatment of atherosclerotic lesions in the superficial femoral and proximal popliteal arteries: one-year results of the MDT-2113 SFA Japan randomized trial. J Endovasc Ther. 2018;25:109-117.
7. Krishnan P, Faries P, Niazi K, et al. Stellarex drug-coated balloon for treatment of femoropopliteal disease: 12-month outcomes from the randomized ILLUMENATE pivotal and pharmacokinetic studies. Circulation. 2017;136:1102-1113.
8. Lutonix 035 DCB [Instructions for Use BAW1387400r3]. Tempe, AZ: Bard Peripheral Vascular, Inc.; 2016.
9. Bosiers M, Deloose K, Callaert J, et al. Superiority of stent-grafts for in-stent restenosis in the superficial femoral artery: twelve-month results from a multicenter randomized trial. J Endovasc Ther. 2015;22:1-10.
10. Schroë H, Holden AH, Goueffic Y, et al. Stellarex drug-coated balloon for treatment of femoropopliteal arterial disease—the ILLUMENATE Global study: 12-month results from a propspective, multicenter, single-arm study. Catheter Cardiovasc Interv. 2018;91:497-504.
11. Brodmann M, Keirse K, Scheinert D, et al. Drug-coated balloon treatment for femoropopliteal artery disease: the IN.PACT Global study de novo in-stent restenosis imaging cohort. JACC Cardiovasc Interv. 2017;10:2113-2123.
12. Tepe G. IN.PACT Global drug-coated balloon for treatment of chronic total occlusions in the SFA. Paper presented at: the 38th Charing Cross Symposium; April 26-29, 2016; London, UK.
13. Micari A. The drug-eluting balloon superficial femoral artery-long study: the DEB SFA-LONG study. J Am Coll Cardiol: Cardiovasc Interv. 2016;9:950-956.
14. Scheinert D. Drug-coated balloon treatment for patients with intermittent claudication: new insights from the IN.PACT Global study long lesion (≥ 15 cm) imaging cohort. Paper presented at: EuroPCR 2015, the European Association of Percutaneous Cardiovascular Interventions; May 19-22, 2015; Paris, France.
15. Complete SE stent [Instructions for Use M729425B001 Rev. 1B]. Minneapolis, MN: Medtronic; 2018.
16. Gray WA, Feiring A, Cioppi M, et al. S.M.A.R.T. self-expanding nitinol stent for the treatment of atherosclerotic lesions in the superficial femoral artery (STROLL): 1-year outcomes. J Vasc Interv Radiol. 2015;26:21-28.
17. Garcia L, Jaff MR, Metzger C, et al. Wire-interwoven nitinol stent outcome in the superficial femoral and proximal popliteal arteries: twelve-month results of the SUPERB trial. Circ Cardiovasc Interv. 2015;8:e000937.
18. Duda SH, Bosiers M, Lammer J, et al. Drug-eluting and bare nitinol stents for the treatment of atherosclerotic lesions in the superficial femoral artery: long-term results from the SIROCCO trial. J Endovasc Ther. 2006;13:701-710.
19. Astron Pulsar stent [Instructions for Use 364736/C/2016-07]. Lake Oswego, OR: Biotronik; 2016.
20. Ohki T, Angle JF, Yokoi H, et al. One-year outcomes of the U.S. and Japanese regulatory trial of the Misago stent for treatment of superficial femoral artery disease (OSPREY study). J Vasc Surg. 2016;63:370-376.
21. Innova stent [Instructions for Use 90958202-01B]. Natick, MA: Boston Scientific Corporation; 2015.
22. Laird JR, Zeller T, Loewe C, et al. Novel nitinol stent for lesions up to 24 cm in the superficial femoral and proximal popliteal arteries: 24-month results from the TIGRIS randomized trial. J Endovasc Ther. 2018;25:68-78.
23. Matsumura JS, Yamanouchi D, Goldstein JA, et al. The United States study for evaluating endovascular treatments of lesions in the superficial femoral artery and proximal popliteal by using the Protégé Everflex nitinol stent system (DURABILITY II). J Vasc Surg. 2013;58:73-83.
24. Lammer J, Zeller T, Hausegger KA, et al. Heparin-bonded covered stents versus bare-metal stents for complex femoropopliteal artery leisons: the randomized VIASTAR trial (Viabahn endoprosthesis with PROPATEN bioactive surface [VIA] versus bare nitinol stent in the treatment of long lesions in superficial femoral artery occlusive disease). J Am Coll Cardiol. 2013;62:1320-1327.
25. Ansel G. 1-year results of the VIBRANT trial. Presented at Vascular InterVentional Advances (VIVA); October 19–23, 2009; Las Vegas, Nevada.
26. Gray W. Twelve-month results of the imperial randomized trial comparing the Eluvia and Zilver PTX stents for treatment of femoropopliteal arteries. Presented at Transcatheter Cardiovascular Therapeutics (TCT); September 21–25, 2018; San Diego, California.
27. Iida O, Takahara M, Soga Y, et al. 1-year results of the ZEPHYR registry (Zilver PTX for the femoral artery proximal popliteal artery). JACC Cardiovasc Interv. 2015;8:1105-1112.
28. Zeller T, Peeters P, Bosiers M, et al. Heparin-bonded stent-graft for the treatment of TASC II C and D femoropopliteal lesions: the Viabahn-25 cm trial. J Endovasc Ther. 2014;21:765-774.
29. Yokoi H, Ohki T, Kichikawa K, et al. Zilver PTX post-market surveillance study of paclitaxel-eluting stents for treating femoropopliteal artery disease in Japan: 12-month results. JACC Cardiovasc Interv. 2016;9:271-277.
30. Phillips JA, Falls A, Kolluri R, et al. Full drug-eluting stent jacket: two-year results of a single-center experience with Zilver PTX stenting for long lesions in the femoropopliteal arteries. 2018;25:295-301.
31. Scheinert D, Scheinert S, Sax J, et al. Prevalence and clinical impact of stent fractures after femoropopliteal stenting. J Am Coll Cardiol. 2005;4:312-315.

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