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100 years of insulin: Why is insulin so expensive and what can be done to control its cost?

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Abstract

The discovery of insulin 100 years ago and subsequent improvements in insulin formulations and delivery devices have changed the lives of people with diabetes. Unfortunately, the average price of insulin in the United States has nearly tripled over the past decade, and the high cost of insulin has become a barrier to diabetes treatment. On the 100th anniversary of insulin's discovery, this life-saving treatment is financially out of reach for as many as one-third of people with diabetes. The challenge now is to ensure that insulin is available for all people with diabetes who need it. We explore reasons for the high cost of insulin and recommend some clinical and policy interventions to improve insulin access and affordability.

Keywords

Insulin; Cost; Access; Affordability; Biosimilar medications; Value-based pricing

DISCOVERY AND EVOLUTION OF INSULIN THERAPY

One hundred years ago – in August 1921 – Frederick G. Banting and Charles H. Best, working in the laboratory of John J. R. Macleod, prepared an extract from a canine pancreas that effectively reduced blood glucose levels in a pancreatectomized dog. Shortly thereafter, in January 1922, the first clinical use of insulin occurred when Leonard Thompson, a 14-year-old boy with type 1 diabetes, responded spectacularly to injections of the active glucose-lowering component purified from the extract by James B. Collip.[1,2] At that time, Banting stated "Insulin does not belong to me, it belongs to the world." In January 1923, Banting, Best, and Collip were awarded an American patent for insulin and their method of making it, and sold their patent rights to the University of Toronto for $1 each.[3,4] Their goal

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was to keep this life-saving treatment accessible and affordable for everyone with diabetes.[4] By the end of 1923, developments from other laboratories and the pharmaceutical industry allowed for the large-scale commercial production and distribution of insulin.[5]

The last century has seen innovation and evolution in the field of insulin therapy.[5-7] Insulin was isolated, purified, and concentrated from animal pancreatic extracts. Formulations with longer duration of action were introduced in the 1920s-1970s. Advances in genetic engineering technologies allowed human insulin to be brought to the market in the 1980s. Rapid-acting and long-acting insulin analogs were introduced in the 1990s. Inhaled insulin was developed in the 2000s. Ultra-rapid acting and ultra-long acting insulin analogs as well as biosimilar rapid-acting and long-acting insulin analogs were introduced in the 2010s.[5-7] Efforts continue to improve insulin pharmacokinetics, make insulin treatment easier, and reduce undesirable side effects of insulin therapy. They include once-weekly insulins, hepato-preferential insulins, oral insulins, and glucose-responsive “smart” insulins that only act when blood glucose levels are high.[8]

New technologies for insulin delivery and blood glucose monitoring have also improved the effectiveness and safety of insulin therapy – from vials and glass syringes to insulin pens and pumps, and from self-monitoring of blood glucose using lancets and test strips to continuous glucose monitoring (CGM) systems, real-time CGM systems, and flash glucose monitoring systems.[5-7] In September 2016, the United States Food and Drug Administration (FDA) first approved artificial pancreas systems to allow for automated adjustment of basal insulin infusion rates and/or for automated bolus corrections based on CGM readings to better mimic physiological insulin delivery.[5,9]

EXPENDITURES FOR INSULIN BY PEOPLE WITH DIABETES

The global insulin market was valued at approximately $21 billion in 2012.[10] The global insulin market is dominated by three multi-national insulin manufacturers, Eli Lilly, Novo Nordisk and Sanofi, with these companies controlling 99% of the market by value and 96% of the market by volume.[11] The increasing use of more expensive insulin analogs to replace less expensive human and animal insulins has led to an increase in insulin prices and spending and negatively affected the affordability of insulin for health systems and individuals around the world.[11-14] Data from the Addressing the Challenges and Constraints of Insulin Sources and Supply (ACCISS) study involving 26 countries found a wide range of government procurement prices for human insulins with a 10-ml, 100-IU/ml vial of human insulin costing between $1.00 and $18.10 with a median price of $4.30 (in 1996 US dollars).[12,14] The price of a 10-ml, 100-IU/ml vial of human insulin varied across country income groups with the highest median prices in low-income and lower middle-income countries. The range of prices was $2.50-$11.50 (median $6.90) in low-income countries and $1.00-$12.50 (median $4.70) in lower middle-income countries. In contrast, prices were $3.20-$18.10 (median $4.00) in high-income countries and $1.50-$7.10 (median $3.10) in upper middle-income countries.[12,14]

The availability and affordability of insulin are worse in low- and middle-income countries than in high-income countries, but affordability is an issue even in high-income

countries.[11-13,15,16] The Prospective Urban Rural Epidemiology (PURE) study, a prospective cohort study involving 22 countries, provided a global perspective on the availability and affordability of essential medicines for diabetes.[15] The PURE study reported that insulin was available in 48% of pharmacies overall: 94% in high-income countries, 40% in upper middle-income countries, 29% in lower middle-income countries, 10% in low-income countries excluding India, and 76% in India.[15] Due to its high cost, insulin was often unaffordable. Overall, an estimated 37% of households with individuals with diabetes were unable to afford insulin, ranging from 3% in high-income countries, to 47% in upper middle-income countries, to 35% in lower middle-income countries, to 63% in low-income countries excluding India, and 51% in India.[15]

In the United States, expenditures for insulin and non-insulin antihyperglycemic medications among adults with diabetes ≥18 years of age increased from $10 billion to $22 billion between 2002 and 2012. This increase was primarily driven by expenditures for insulin which increased from $2.6 billion in 2002 to $15.4 billion in 2012. The increase in expenditures for insulin was primarily due to the change in prescribing from less expensive animal and human insulins to more expensive insulin analogs and by an increase in the price of all available insulins.[17,18] The increase in the number of people treated with insulin and the increase in per-person insulin doses related to obesity and insulin resistance also contributed, but to a lesser degree.[17] Expenditures for non-insulin antihyperglycemic medications were relatively stable in the United States between 2002 and 2012 at approximately $7 billion per year.[17] Over the same time period, total and per capita expenditures for antihypertensive medications and lipid-lowering medications decreased due to the approval and widespread availability of generic preparations of the most commonly prescribed medications in those classes.[17]

An analysis using data from the Medical Expenditure Panel Survey showed that the mean price of insulin nearly tripled between 2002 and 2013.[19] Another analysis using the Health Care Cost Institute's healthcare claims data found that the mean price of an insulin prescription nearly doubled between 2012 and 2016.[20] The United States has the highest manufacturer prices for insulin among 33 nations with similar high-income economies. In 2018, the United States manufacturer prices for insulin ranged from 3.9 times those in Chile to 27.7 times those in Turkey, with an average of 8.1 times those in all 32 non-United States countries combined.[21] In the United States in 2018, expenditures for prescription drugs were $476.2 billion. The second leading drug by total expenditures was insulin glargine ($9.34 billion), a long-acting insulin analog. Six more medications used to treat diabetes were among the top 15 drugs according to expenditures. These included the short-acting insulin analogs, insulin aspart ($5.94 billion) and insulin Lispro ($5.72 billion).[22] High out-of-pocket costs for insulin are a problem because they are associated with worse adherence to treatment.[18,23,24]

IMPACT OF COST AND COST-SHARING ON INSULIN USE

Affordable prescription medications are critical to the effective treatment of diabetes. Unfortunately, approximately 25-30% of Americans with diabetes report rationing or skipping their insulin due to its high cost.[25-27] Policies intended to contain medication

costs including deductibles, coinsurance, copayments, and formulary restrictions can adversely impact the appropriate use of medications. An analysis of the association between cost-sharing features in prescription drug plans and the use of prescription medications demonstrated that increased cost-sharing is associated with lower rates of drug treatment, worse adherence among current users, and more frequent discontinuation of therapy.[28] For each 10% increase in cost-sharing, prescription drug spending decreases by 2% to 6% depending on the therapeutic class of the drug and the condition being treated. Doubling copayments has been associated with as much as a 25% reduction in overall use of antidiabetic medications.[29] Increased cost-sharing tends to decrease the use of "nonessential" drugs with over-the-counter alternatives (for example, nonsteroidal anti-inflammatory drugs and antihistamines) more than the use of "essential" drugs (for example, antidiabetic and antidepressant medications).[29] At the same time, higher cost-sharing is associated with increased use of medical services for patients with diabetes.[28]

The negative impact of medication cost-sharing is greater among low-income individuals. A recent study compared medication utilization among Medicare Part D beneficiaries who were eligible for the Part D low-income subsidy and those with Medicare Part D whose incomes were just above the eligibility threshold. The latter group faced substantially higher out-of-pocket costs despite having minimally higher incomes. Not receiving prescription drug subsidies was associated with a 16% higher probability of incurring high out-of-pocket costs and 19% fewer prescription drug claims.[30] Other studies among patients with multiple chronic medical conditions have demonstrated that increases in average beneficiary cost-sharing are associated with substantial decreases in drug spending. These decreases in drug spending are offset by increases in medical spending including emergency department visits and hospital stays.[31] Furthermore, increased out-of-pocket costs for medications might lead to adverse health outcomes among fragile Medicare patients with limited financial resources.[31]

MAKING INSULIN MORE AFFORDABLE FOR PEOPLE WITH DIABETES

Introducing generic drugs and biosimilars, addressing the period of market exclusivity for brand-name drugs, and eliminating anticompetitive pay-for-delay arrangements that curtail access to lower-cost alternatives can make medications more affordable for people with diabetes. Additional actions to make mediations more affordable include ensuring greater transparency in drug pricing and providing the federal government additional flexibility to negotiate drug prices especially in the Medicare Part D program.

Generic Medications

Generic medications are created with the same active ingredients as brand-name drugs. They work the same as their branded counterparts but are generally less expensive. The proportion of generic drugs versus brand-name drugs dispensed in the United States has increased dramatically over time. In 2005 ~50% of drugs dispensed were generic drugs and 40% were brand-name drugs.[32] By 2019, over 86% of dispensed prescription drugs were generics whereas 10% were brand-name drugs.[32] Generic drugs provide substantial savings to the United States health system although the direct savings to consumers vary depending on the

payer. Nevertheless, while generic drugs account for ~90% of prescription drugs dispensed, they account for only ~30% of total United States pharmaceutical expenditures.[33]

There are three major insulin manufacturers serving the United States market: Eli Lilly, Novo Nordisk, and Sanofi. MannKind markets an inhaled insulin.[34] Generic competition is critical to increasing access and controlling the cost of prescription drugs. When a single generic competitor is introduced, the average manufacturer price is ~39% lower than the price of the brand-name drug before generic competition. With two competitors, the average price is 54% lower, and with four competitors, generic drugs cost 79% less than the brand-name drug.[35] Ensuring the timely availability of generic drugs is an important means to reduce prices of prescription drugs.[33] Several strategies may also mitigate the risk of drug supply disruptions and shortages and ensure the long-term quality and security of drugs. These include providing economic and policy incentives for the initiation or restitution of drug manufacturing capability and sites located in the United States and overseas, recognizing and rewarding quality manufacturing to achieve greater reliability in drug production, and strengthening the government oversight of drug manufacturers and their overseas facilities.[36,37]

The Patent System and Market Exclusivity

Patents are a form of intellectual property that grant a holder 20 years of protection from the initial patent filing date. Exclusivity is a form of marketing protection granted at the time the FDA approves a drug product which delays the approval of generic or follow-on drug products. While patents and exclusivities serve to promote innovation, they can negatively impact competition. Unfortunately, patents and exclusivities intended to stimulate innovative drug development have been used by manufacturers to extend monopolies and to keep lower-cost generics and biosimilars off the market.

Strategies used by pharmaceutical manufacturers to extend patent protection include applying for multiple patents on a single drug, making slight but not clinically significant modifications to old drugs to obtain new patents, and executing pay-for-delay or reverse patent settlement agreements by which a brand-name manufacturer compensates a generic manufacturer to delay entry into the market after the patent expires.[38] Between 2005 and 2015, 78% of drugs that were issued new patents were already on the market.[39] In addition, more than 70% of the 100 best-selling drugs had their patent protection extended at least once, and 50% had their patent protection extended more than once.[39] Another anticompetitive behavior involves exploiting the 180-day exclusivity period given to the first manufacturer to file a generic drug application. In some instances, first filers do not seek final approval of their generic drugs, thus blocking additional generics from entering the market.[40]

In addition, when only a few manufacturers produce a drug, they may capitalize on their strategic positions to minimize competition and drive up prices. One of these strategies is “shadow pricing” in which the prices of competitor products increase at similar rates around the same time.[41]

Biosimilar Insulins

Like generic medications, biosimilar insulins have been slow to come to market. Biosimilars are developed from biological sources rather than as chemical entities, and as such, are not considered interchangeable. Although biosimilars may have only minor variations in clinically inactive components and no clinically meaningful differences in purity, potency, or safety compared to the reference product, they are not considered generic medications. The Affordable Care Act included provisions to encourage market competition for biosimilars, but awarded biological products 12 years of market exclusivity during which no biosimilars can enter the market. After that time, biosimilar manufacturers can obtain FDA approval to market biosimilars through an abbreviated licensure pathway.

Unfortunately, manufacturers of biological products have exploited the patent system and market exclusivity in the same ways that manufacturers have done for generic drugs to extend the reference biological product's period of protection from competition during which time they can continue to charge a high price. For example, although the primary patent on Lantus (insulin glargine) expired in 2015, more than 70 additional patent applications were filed. If all the applications were granted, the manufacturer of Lantus would have gained 37 years of additional patent protection.[42] In addition, there has been evidence of shadow pricing. Between 2009 and 2015, the prices of the two long-acting insulin analogs, Lantus and Levemir, increased at about the same time on 13 occasions. Similarly, the prices of the fast-acting insulin analogs, Humalog and Novolog, increased in parallel 17 times over 10 years.

Basaglar was the first FDA-approved "follow-on" biosimilar insulin glargine. It was similar to Lantus, but not interchangeable with Lantus.[5,34] Likewise, Admelog was a "follow-on" biosimilar insulin lispro. It was similar to Humalog, but not interchangeable with Humalog.[5,34] On July 28, 2021, the FDA approved the first interchangeable biosimilar insulin product, Semglee (insulin glargine U-100).[43] As an interchangeable biosimilar product, Semglee may be substituted for Lantus at the pharmacy without the need for a different prescription. The wholesaler acquisition cost for a 3-mL U-100 prefilled, disposable pen of Lantus is $85.10 while that for Semglee is $29.60.[44] The approval of Semglee can thus provide patients with a less expensive option for treating diabetes without requiring the prescriber to write a specific alternative to Lantus.

Structural Factors

Structural factors that contribute to higher insulin costs include limited flexibility for the federal government to negotiate drug prices and lack of transparency in negotiations with pharmacy benefit managers.

In 2011, the federal government paid for prescription drugs for 114.4 million beneficiaries through Medicaid, the Department of Defense (DOD), and Medicare Part D. Each program reimbursed retail pharmacies for outpatient prescriptions filled by their beneficiaries. In 2014, the United States Government Accountability Office (GAO) compared prices paid for prescription drugs across these federal programs.[45] The study revealed that post-purchase price adjustments from the drug manufacturers (refunds, rebates, and price concessions after

the drugs were dispensed) resulted in discounts from the gross price that ranged from nearly 53% for Medicaid to 31% for DOD and 15% for Medicare Part D.[45] Overall, Medicaid paid the lowest price for both generic and brand-name drugs. Despite being required to cover essentially all FDA-approved drugs, Medicaid uses a best price requirement to limit its costs.[46] The basic Medicaid rebate is either a standard percentage of the medication's average net price or the average net price minus the "best price" the manufacturer has provided to another payer. If a manufacturer's rebate agreement with a non-Medicaid pharmacy benefit manager or health plan results in a net price lower than the net price that Medicaid would receive using the standard percentage rebate calculation, the manufacturer must use that rebate agreement amount to calculate the medication's rebate for all Medicaid enrollees. In addition, if a medication's average net price has increased by more than the rate of inflation, the manufacturer must pay an additional rebate to Medicaid.[18] Compared to Medicaid, DOD paid 50% more for generic drugs and 34% more for brand-name drugs and Medicare Part D paid 4% more for generic drugs and 69% more for brand-name drugs.[45]

Medicare Part D

To gain legislative approval, the law establishing Medicare Part D explicitly prohibited the federal government from directly negotiating or setting drug prices for Medicare Part D. Instead, Medicare Part D relied on competition among private plans to design formularies and negotiate with manufacturers to enhance drug choice and lower prices.[47]

A study by the GAO in 2019 assessed the role that pharmacy benefit managers played in the cost of drugs to the Medicare Part D program.[48] Medicare Part D plan sponsors used pharmacy benefit managers to provide 74% of drug benefit management services in 2016. Pharmacy benefit managers primarily earned Part D revenue through a volume-based fee paid based on processed claims; a per-member per-month fee; and the rebates they negotiated through manufacturers for Part D drugs. Although rebates may be used to offset drug costs or reduce premiums, it is not transparent how these funds are used. In general, pharmacy benefit managers retained <1% of the rebates, passing the rest on to plan sponsors. Because Medicare Part D beneficiaries pay coinsurance based on the list price of a drug, the financial burden borne by Medicare Part D beneficiaries does not account for rebates or the actual drug cost.

Medicare Part D plans typically have formularies and lists of covered medications. The covered medications are grouped into tiers that have different costs for beneficiaries: 1) medications in the preferred generic tier frequently have low or even no copays; 2) medications in the non-preferred generic tier have slightly higher copays; 3) medications in the preferred brand-name tier have higher copays; and 4) non-preferred brand medications have the highest copays. The high cost of insulin for Medicare Part D beneficiaries is due in part to the fact that as a therapeutic biological product, insulin is a brand-name medication and there are no generic insulins. Beneficiaries who need to take medications classified as non-preferred brand-name drugs often need to pay coinsurance or a percentage of the price of the medication. An issue with coinsurance is that a person's out-of-pocket cost depends on the list price of the drug, not the net price after rebates.

HOW CAN INSULIN ACCESSIBILITY AND AFFORDABILITY BE IMPROVED?

Increased access to insulin for people with diabetes can be facilitated by controlling its cost. This may be achieved by encouraging providers to prescribe lower-cost insulins. It can also be accomplished by facilitating the introduction of biosimilars, addressing the period of market exclusivity for biosimilar drugs, and eliminating anticompetitive pay-for-delay arrangements that curtail access to lower-cost alternatives.[49] Additional actions to improve access to insulin and control costs include providing payers additional flexibility to negotiate prices especially in the Medicare Part D program, ensuring greater transparency in drug pricing, and encouraging value-based pricing.[49]

Encourage/Teach Providers to Consider Using Lower-cost Insulins

Studies have demonstrated widespread adoption of newer insulin analogs by physicians over the past two decades in the United States.[50-52] Providers must, however, weigh the advantages of insulin analogs against their costs and be aware of lower-cost insulins as alternatives. Human NPH and regular insulins are less expensive than long-acting and short-acting insulin analogs (e.g., wholesaler acquisition cost of $137.70 per 10-mL vial of Novolin N and R versus $283.60 per 10-mL vial of Lantus and $289.40 per 10-mL vial of Novolog), and they are available through Walmart pharmacies as ReliOn/Novolin N and R at $24.90 per 10-mL vial.[34] In late June 2021, Walmart also announced that it had partnered with Novo Nordisk to launch the first-ever private brand insulin analog labeled as ReliOn/Novolog insulin (insulin aspart). It could help patients save 58-75% off the cash price of the branded insulin analog product.[53,54] With availability expected in Walmart and Sam's Club pharmacies by mid-July, the ReliOn/Novolog insulin will be available in both vials and pens.[53,54]

In clinical trials of patients with type 2 diabetes, long-acting insulin analogs modestly reduce the risk of nocturnal hypoglycemia compared with human NPH insulin, but have not been shown to reduce the risk of severe hypoglycemia or to improve glycemic control.[34,55] A real-world study using data from Kaiser Permanente of Northern California suggested that the use of long-acting insulin analogs compared with human NPH insulin among patients with type 2 diabetes is not associated with a reduced risk of hypoglycemia-related emergency department visits or hospital admissions or with improved glycemic control.[56] In clinical trials of insulin analogs compared with human insulins in patients with type 1 diabetes, insulin analogs cause less hypoglycemia and weight gain and produce lower A1C levels. Human NPH and regular insulins are thus a reasonable choice for many patients with type 2 diabetes who cannot afford insulin analogs.[57-60] Both prescribing physicians and patients must carefully weigh advantages and costs.

Encourage Competition in the Market Place for Biosimilars

Weak competitive pressure may lead to higher prices. Pay-for-delay arrangements that block access to lower-cost biosimilar drugs should be curtailed to address anticompetitive behaviors and gaming. Similarly, the 180-day exclusivity period given to generic manufacturers to provide an incentive for taking the financial risk associated with being the first-to-file generic manufacturer should be revised to close loopholes that limit competition

beyond 180 days without a reasonable justification for the delay. Laws should be modified to discourage manufacturers from applying for multiple patents on a single drug and from making slight modifications to old drugs to obtain new patents to extend a drug's patent protections. Shadow pricing should be curtailed for drugs with few manufacturers. Consideration should be given to reduce the period of market exclusivity for biological products and remove barriers to biosimilar market entry.

Increase the Flexibility of the Payers to Negotiate Drug Prices

By statute, Medicaid is permitted to negotiate drug prices and by doing so is able to provide beneficiaries with an extensive choice of medications at low out-of-pocket costs. This is in sharp contrast to Medicare Part D which is prohibited from negotiating drug prices. To reduce government spending on prescription drugs, all federal drug benefit programs can be given greater flexibility to negotiate medication prices with manufacturers and pharmacy benefit managers to capitalize on their market shares and volumes. Similar to Medicaid, these programs can then elicit best price requirements and protections against medication net price increases greater than the rate of inflation.

Increase Transparency in the Pharmaceutical Distribution System

For every $100 spent on retail drugs, $41 go to parties in the distribution chain: wholesalers, pharmacies, pharmacy benefit managers, and insurers.[49] The growing difference between the list price and the net price of a drug reflects negotiated rebates and discounts put into place to influence formulary placement among competing brands within a drug class. High list prices disadvantage patients who pay the list price or pay coinsurance based on the list price of the medication and impact both medication adherence and health outcomes. To address these issues, greater transparency and simplicity should be introduced into drug pricing to eliminate distortions that are currently beyond individual payers' ability to address.

Reduce Regulatory Barriers to Value-based Pricing and Expand Promising Value-based Pricing Programs

Value-based pricing has been proposed as an approach to improve access to lifesaving medications and improve clinical outcomes for people with diabetes. Using such an approach, the price paid for a medication is based on the benefits to the patient as indicated by clinical or financial measures. Clinical measures may include laboratory values or patient-reported outcomes. Financial measures may include health care interventions prevented such as hospitalization.[49] Such schemes, termed outcomes-based pricing,[61] are particularly useful for new biopharmaceutical products used to treat common, costly, chronic diseases when there is uncertainty about the medication's real-world efficacy. This would certainly appear to apply to the new ultra-fast-acting insulin analogs.

An alternative and perhaps more feasible approach to value-based pricing is value-based insurance design (V-BID).[62] V-BID aligns patient out-of-pocket costs with the value of a health service regardless of its actual price. The focus is on cost to the patient, not price. V-BID plans encourage patients to use high-value medications such as insulin by lowering its cost to patients, and discourage the use of low-value medications through higher costs to patients. Tools employed by V-BID include covering high-value treatments without applying

their costs to the patient's deductible (predeductible coverage) and covering high-value treatments without any patient coinsurance or copayment.

V-BID principles were incorporated into the Affordable Care Act which requires health plans to include certain preventive services without a copayment for the patient. Guidelines for V-BID implementation were issued by the Secretary of Health and Human Services and have required group health plans and health insurance issuers to cover preventive services rated A or B by the U.S. Preventive Services Task Force at no out-of-pocket cost to patients.[63]

Part D Senior Savings Model

Regulatory barriers currently restrict value-based pricing and value-based insurance design that might better align the price of medications and patient out-of-pocket costs to their benefits. In January 2021, the Centers for Medicare & Medicaid Services Innovation Center launched a promising new model for pharmacy payment called the Part D Senior Savings Model.[64] The model is testing the impact of offering beneficiaries an increased choice of enhanced alternative Part D plan options that offer lower out-of-pocket costs for insulin. The program is available to beneficiaries who receive Part D coverage through stand-alone prescription drug plans and Medicare Advantage Prescription Drug plans. Beneficiaries have broad access to multiple types of insulin at a maximum copay of $35 per insulin per month in the deductible, initial coverage, and coverage gap phases of the Part D benefit. Participating pharmaceutical manufacturers pay the 70% discount in the coverage gap for the Part D insulins they market. Part D sponsors are required to encourage healthy behaviors and medication adherence through Part D rewards and incentive programs.

Given that this program has the potential to provide stable, predictable co-pays for the insulins that beneficiaries with diabetes need throughout the different phases of the Part D benefit, widespread testing, rigorous evaluation, and if effective, broad implementation of the Part D Senior Savings Model can improve access to lifesaving insulins for Medicare beneficiaries with diabetes.

SUMMARY

The discovery of insulin and advances in insulin formulations and delivery devices have changed the lives of people with diabetes. Insulin is lifesaving for people with type 1 diabetes and is needed by many people with type 2 diabetes to improve glycemic control and health outcomes. Insulin is included on the Model Lists of Essential Medicines formulated by the World Health Organization.[65] Unfortunately, on the 100th anniversary of insulin's discovery, one of every two patients with diabetes worldwide who need insulin cannot access it or afford it,[66,67] and as many as 25-30% of people with diabetes in the United States report rationing or skipping their insulin due to cost.[25-27] Globally, 6.5% of patients in high-income countries excluding the United States and 22-68% of patients in low- and middle-income countries report skipping insulin due to access or cost.[25-27] Substantial improvements in availability and affordability of insulin are needed to reduce inequalities in access and to prevent complications. New developments have the potential to further improve the safety and effectiveness of insulin therapy. The challenge now is to ensure

that insulin is available for all people with diabetes who can benefit from it. Government agencies, professional societies, pharmacy benefit managers, and insulin manufacturers must work together to ensure the accessibility and affordability of insulin for all people with diabetes.

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KEY POINTS:

- Insulin therapy was introduced 100 years ago.
- Insulin prices and expenditures have increased dramatically over the past decade in the United States, and high prices and out-of-pocket costs are barriers to insulin treatment for people with diabetes.
- The increased cost of insulin is due to several factors including the shift from less expensive animal and human insulins to more expensive insulin analogs, substantial price increases for all available insulins, clinician prescribing practices, policies limiting payers' abilities to negotiate prices, and lack of transparency throughout the insulin supply chain.
- Clinical and policy strategies can be implemented to improve insulin access and affordability. These include shifting clinician prescribing practices to lower-cost insulins, ensuring timely availability of biosimilar insulins, enforcing more stringent requirements for the extension of patents and market exclusivities, providing greater opportunities for price negotiation by payers, increasing transparency in the drug pricing and distribution system, and implementing value-based pricing for insulin.

CLINICS CARE POINTS:

- Insulin is essential for the survival of people with type 1 diabetes and may be needed for the glycemic management of many people with type 2 diabetes.
- The high cost of insulin has been associated with underuse, which can lead to increased risks of short- and long-term complications and premature death for patients with diabetes.
- Both clinicians and patients must carefully weigh the advantages and costs of insulin therapy.
- Human insulins (NPH and regular) may be appropriate alternatives to more expensive insulin analogs for some people with type 2 diabetes including those with less intensive A1C goals, low rates of hypoglycemia, prominent insulin resistance, and/or cost concerns and for people with type 1 diabetes who cannot afford insulin analogs including biosimilars.
- Professional organizations, government agencies, health plans, insulin manufacturers, pharmacy benefit managers, and pharmacies must work together to ensure the accessibility and affordability of insulin for all people with diabetes.