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ORIGINAL RESEARCH ARTICLE

10 Years of AMNOG: What is the Willingness-to-Pay for Pharmaceuticals in Germany?

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Abstract

Objectives The German Pharmaceutical Market Restructuring Act (AMNOG, 2011) is a two-stage process to regulate the price of new pharmaceuticals in which price negotiations are conducted based on evidence-based medical benefit assessments using data from prior clinical trials. Although the act does not explicitly set a willingness-to-pay (WTP) threshold, the process itself implicitly establishes a WTP for health improvement. We evaluated the implicit WTP for prescription pharmaceuticals post-AMNOG in the German healthcare system from the decision-maker/payer perspective.

Methods We extracted data on patient-group-specific annual treatment costs and endpoints from 2011 to 2021 from the dossiers assessed by the German Federal Joint Committee (FJC; Gemeinsamer Bundesausschuss). Using incremental cost-effectiveness ratios (ICERs), we calculated a WTP for the indications (I) diabetes, (II) cardiovascular disease, and (III) psoriasis weighted according to patient group size, first from the perspective of the decision-maker (approach A), and second from the perspective of the industry (approach B). To put clinical outcome measures into relation to one another, minimum clinically important differences (MCIDs) were derived from the literature and compared.

Results The annual treatment costs of newly authorized drugs were substantially higher (both pre- and post-negotiation) than that of their comparators (e.g., psoriasis, pre-negotiation: €20,601.59, post-negotiation: €16,763.57; comparators: €5178.00). However, although newly launched drugs were more expensive than their comparators, they brought greater medical benefits and were more aligned with value ($r = 0.59$, $P < 0.001$) than older drugs. We estimated WTP to vary widely by indication group [€33,814.08 per 1 percentage point hemoglobin A1c (HbA1c) reduction for diabetes, €10,970.83 per life year gained for cardiovascular disease, and €663.46 per 1% PASI decrease for psoriasis; approach A]. WTP was converted to MCID thresholds: diabetes: €16,907.04; cardiovascular drugs: no MCID existent to convert; and psoriasis: €33,173.00. WTP remained constant over time for diabetes and cardiovascular drugs but increased for psoriasis drugs.

Conclusion This paper is one of the first to estimate the implicit WTP for prescription pharmaceuticals post-AMNOG and suggests that the WTP may vary between different therapeutic areas. Additionally, making different assumptions (approach A versus approach B) with regard to the assumed effectiveness in indication areas that had been declared as having no additional benefit by the FJC may explain the different perspectives of decision-makers and of the pharmaceutical industry on the value of a pharmaceutical.

1 Introduction

Over the past three decades, pharmaceutical spending has increased dramatically in most high-income countries, reaching €190 billion (bn) in Europe in 2018 [1]. In response, European countries began implementing health technology assessments (HTAs) in the 1990s. In Germany, one of the most important reforms in this regard was the Pharmaceutical Market Restructuring Act [Arzneimittelmarktneuordnungsgesetz (AMNOG)], which came into effect in large part in 2011 [2]. The act introduced a mechanism for regulating the price of new pharmaceuticals that involves a two-stage process in which price negotiations are conducted

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Key Points for Decision-Makers

Implicit WTPs for prescription pharmaceuticals post-AMNOG vary substantially between different therapeutic areas.

WTP values vary between €33,814.08 per 1 percentage point HbA1c reduction for diabetes, €10,970.83 per life year gained for cardiovascular disease, and €663.46 per 1% PASI decrease for psoriasis.

The different perspectives between the decision-maker (approach A) versus the industry (approach B) may explain their different views on the value of a pharmaceutical and how it should be priced.

based on evidence-based medical benefit assessments carried out using data from prior clinical trials [3]. To do this, the Institute for Quality and Efficiency in Healthcare (Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen) performs an initial advisory assessment, followed by a final evaluation of the Federal Joint Committee (FJC; Gemeinsamer Bundesausschuss). The FJC operates in this context as a regulator and decision-maker, and the decisions it reaches by means of the AMNOG process are binding for statutory health insurers, which, as the main payers in the German healthcare system, provide health insurance coverage to almost 90% of the population in Germany [4]. Although the act does not explicitly set a willingness-to-pay (WTP) threshold, the process itself implicitly establishes a WTP for health improvement. This is because the medical benefit assessments and price negotiations that take place as part of the AMNOG process involve comparisons to the current standard therapy. These comparisons can be seen as implicit cost-effectiveness analyses, resulting in an implicit WTP that has rarely been analyzed to date.

Several studies have examined the willingness of patients and payers in other countries to pay for a few specific pharmaceuticals, prophylactic vaccines [for example, the coronavirus disease 2019 (COVID-19) vaccine] or other healthcare products [5–14]. For instance, one study found that patients' WTP for healthcare was significantly influenced by age, education, income, household size, perception, the quality of healthcare services, living in a rural versus an urban area, and ability to pay [14]. Another study found that a sample of healthcare payers in the USA showed a strong preference for genetic tests that improved quality of life, increased life expectancy, and were accompanied by high expert agreement on a change in a patient's medical treatment [10]. Additionally, there is a large body of research on cost-effectiveness thresholds, especially in oncology and cardiology (e.g., Ratushnyak et al.; van Baal et al.; Perry-Duxbury et al.; Brouwer et al.) [15–18].

Only a few studies have investigated WTP in the German healthcare system, probably because WTP is not used in an explicit manner. For example, one study found that, from the point of view of a patient with low-risk melanoma, the WTP for a hypothetical cure involving a one-time payment was €10,000, but this sum was far higher if the (hypothetical) patient being asked was a physician (i.e., €100,000) [19]. Another study looked at the WTP among a representative sample of the German population for a quality-adjusted life year (QALY), which was estimated to range from €9902 to €19,754 and was, as the authors of that study report, no higher than that seen among other European populations [20]. Furthermore, for prescription pharmaceuticals, prior research suggests that the implementation of the price-regulating mechanism of AMNOG was associated with drug prices being more closely aligned with clinical benefit, e.g., association between life-months gained and treatment costs after price negotiation in the use of anticancer drugs in Germany ($+0.030$, $p<0.001$) [21]. All of these studies, however, represent attempts to measure the alignment of costs and effectiveness in Germany, but not the implicit WTP of the German health decision-maker within the AMNOG process.

In summary, little is known about payers' WTP for prescription pharmaceuticals in Germany, especially in terms of different indications and different patient groups. Thus, there is no official threshold that can be cited. Additionally, there has not been any research on factors that might influence payers' WTP for pharmaceuticals in Germany. This represents a considerable research gap given that the German system allows price decisions but does not itself address the topic of WTP. We therefore use results from past AMNOG decisions to estimate the implicit WTP for pharmaceuticals from the perspective of the German healthcare decision-maker/payer. To do so, we evaluated the WTP for pharmaceuticals used to treat three different diseases in Germany after the introduction of the AMNOG process in 2011: diabetes, cardiovascular disease, and psoriasis.

2 Methods

We focused on the benefit and price decisions of the FJC with regard to newly authorized pharmaceuticals first approved for use by the European Medicines Agency (EMA) in one of the three following therapeutic areas: diabetes, cardiovascular disease, and psoriasis. We defined a subgroup as a patient group listed in the official FJC dossiers (= specific patient populations in a clinical study). We excluded products with a lack of pricing data ($n=1$). We also excluded the drug selexipag ($n=1$) as an outlier, as its annual treatment

costs were more than 50 times larger than the average. Our final sample consisted of 33 substances. A full list of study sample drugs can be found in Appendix A. Because the decisions of the FJC are binding for the statutory health insurers in Germany, we henceforth refer to the analytical perspective taken in this paper as that of the payer.

2.1 Data Sources

We extracted the annual treatment costs of newly authorized drugs and their comparators, as well as data on indication-specific outcomes, patient group size, and added benefit, from FJC dossiers (https://www.g-ba.de/bewertungsverfahren/nutzenbewertung/) published between 2011 and 2021 [22]. We focused on the markets for drugs used to treat diabetes, cardiovascular disease, or psoriasis because endpoints within each indication were comparable and data on patient subgroups publicly available. As we only looked at the assessment following the first approved indication by EMA, this also ensures—at least for these three therapeutic areas—that we only looked at one indication per pharmaceutical. We used the German pharmaceutical pricing register to extract the pharmacy retail price of the new drug after price negotiations [23].

2.2 WTP Model

We looked at the following outcomes at baseline and follow-up for each new drug and its comparator: hemoglobin A1c (HbA1c) for diabetes drugs, life years gained for cardiovascular drugs, and the Psoriasis Area and Severity Index (PASI) score for psoriasis drugs. All three outcomes are commonly used as primary endpoints to measure incremental health benefits and conduct comparative effectiveness analyses in the three indication areas [22]. Related research has also used such primary endpoints for this kind of analysis (e.g., "progression-free survival" or "overall survival" for oncology drugs) [21, 24–26].

For cardiovascular drugs, we converted mortality reduction into life years gained by multiplying the mortality reduction by the difference between life expectancy and the average age of the study population. Life years gained is a common measure for studies of this nature on cardiovascular disease, making our results more comparable to those obtained in other countries [27–29].

Our calculations of WTP were based on the incremental cost-effectiveness ratio (ICER) after negotiations and comprised the difference in cost between two pharmaceuticals ($C_1 - C_0$) divided by the difference in their effectiveness ($E_1 - E_0$). The ICER represents the average incremental cost associated with one additional unit of outcome gained [27].

$$\text{ICER} = \frac{C_1 - C_0}{E_1 - E_0} = \frac{\Delta C}{\Delta E} = \text{WTP}. \tag{1}$$

We operationalized the implicit WTP for each new drug after negotiations in two ways to mirror the different points of view of payer versus industry. First, we calculated it as (A) a patient-group-size-weighted ICER following the decision rules of the FJC (that is, to assume that $\Delta E_i = 0$ if the FJC decided that a patient subgroup i had no added benefit; approach A). Second, we took the approach that would be preferred by the industry—i.e., in the case of missing data for a patient subgroup for it to automatically transfer from other subgroups. Thus we calculated the WTP (B) as a patient-group-size-weighted ICER, either taking ΔE_i from the dossier or automatically transferring ΔE_i from those patient subgroups for which it was reported (as a weighted average of ΔE when reported for multiple patient subgroups; approach B).

In the case of multiple patient subgroups, we calculated the WTP as the weighted average of the difference in cost between two pharmaceuticals after negotiations divided by the weighted average of the difference in their effectiveness. For weighting, we used the size of the patient population p_i for each patient subgroup i from the FJC dossiers.

$$= \frac{\left(\left(p_1 * C_{1_{p1}} - p_1 * C_{0_{p1}}\right) + \cdots + \left(p_N * C_{1_{pN}} - p_N * C_{0_{pN}}\right)\right) / \sum_{i=1}^{i=N} p_i}{\left(\left(p_1 * E_{1_{p1}} - p_1 * E_{0_{p1}}\right) + \cdots + \left(p_N * E_{1_{pN}} - p_N * E_{0_{pN}}\right)\right) / \sum_{i=1}^{i=N} p_i} \tag{2}$$

ICER = incremental cost-effectiveness ratio, C_1 = cost of the new pharmaceutical, C_0 = cost of the comparator, E_1 = effect of the new pharmaceutical, E_0 = effect of the comparator, p_i = specific subgroup (with $i = 1$ *to* $i = N$).

To put clinical outcome measures into relation to one another, minimum clinically important differences (MCIDs) were derived from the literature and compared. The MCID constitutes the smallest improvement deemed valuable by patients, a panel of experts or both [30].

2.3 Regression Model

Previous research has examined whether price premiums reflect (1) the FJC's assessments of pharmaceuticals' added benefit and (2) the criteria outlined in the framework agreements between pharmaceutical companies and statutory health insurers [31], such as the size of the patient population [32], but no one has analyzed WTP as a dependent variable. To assess how WTP for pharmaceuticals in Germany has changed over the past 10 years of the AMNOG process, we used a linear regression model to calculate the relationship between WTP at the substance level (dependent variable) and time (as independent variable) in a linear regression model. We performed all analyses using Stata SE 16.

3 Results

3.1 Sample Descriptives

Our sample for the patient group analysis comprised 33 drugs launched in Germany between 2011 and 2021. Of these, 22 were authorized for the treatment of diabetes, 4 for cardiovascular disease, and 7 for psoriasis. Altogether we investigated 95 patient subgroups for diabetes, 11 for cardiovascular disease, and 14 for psoriasis. The average annual treatment costs at launch differed widely depending on the indication (diabetes: €1136.11; cardiovascular disease: €1210.13; psoriasis: €20,601.59).

For diabetes drugs, the average HbA1c reduction from baseline to the end of follow-up (on average 6 months) was 0.09 percentage points, with a range from 0.00 to −0.90 percentage points when we assumed ΔE to be 0 if the new drug had been judged by the FJC as having no additional benefit (approach A). When we calculated ΔE a patient-group-size-weighted ICER, either taking ΔE_i from the dossier or automatically transferring ΔE_i from those patient subgroups for which it was reported, the average HbA1c reduction was 0.29 percentage points, with a range from +0.32 (i.e., an increase) to −0.90 percentage points (approach B).

For cardiovascular drugs, mortality at 12 months decreased on average by 0.75 percentage points, with a range from 0.00 to −4.14 percentage points when we assumed ΔE to be 0 if the new drug had been judged by the FJC to have no added benefit (approach A). When we calculated ΔE as a patient-group-size-weighted ICER, either taking ΔE_i from the dossier or automatically transferring ΔE_i from those patient subgroups for which it was reported, the average mortality at 12 months decreased by 1.26 percentage points, with a range from +0.19 (i.e., an increase) to −4.14 percentage points. The average number of life years gained per patient was 0.224 years, with a minimum of 0 and a maximum of +0.873 (approach A), or 0.267 years, with a minimum of −0.056 (i.e., a loss) and a maximum of +0.873 (approach B).

For psoriasis drugs, the PASI score decreased (i.e., improved) from baseline to follow-up (on average 24 weeks) by an average of 20.93%, with a range from 0.00 to −69.40% when we assumed ΔE to be 0 if the drug had not been judged by the FJC as having an additional benefit (approach A). When we calculated ΔE as a patient-group-size-weighted ICER, either taking ΔE_i from the dossier or automatically transfer ΔE_i from those patient subgroups for which it was reported, the PASI score decreased by an average of 28.92%, with a range from +2.80% (i.e., an increase) to −69.40% (approach B).

Our descriptive results suggest that, in most cases, the annual treatment costs of newly authorized drugs are on average substantially higher, both pre- and post-negotiation, than those of their comparators across all three indications (i.e., for diabetes, pre-negotiation: €1136.11, post-negotiation: €579.39 versus comparator: €300.33; for cardiovascular disease, pre-negotiation: €1210.13, post-negotiation: €794.07 versus comparator: €65.79; for psoriasis, pre-negotiation: €20,601.59, post-negotiation: €16,763.57 versus comparators: €5178.00). For more details see the circular nets in Appendix B.

3.2 Δcosts and Δeffectiveness at the Level of Patient Subgroups

Although newly launched drugs were more expensive than their comparators, they usually offered greater medical benefit. Because ΔE and ΔC were correlated ($r = 0.59$, $P < 0.000$), we can also see that greater medical benefit corresponds to higher costs. The graphs in Fig. 1 show the indication-specific Δcosts and Δeffectiveness at the level of patient subgroups for the newly authorized drugs and their respective comparators for approach A (left) versus approach B (right). These suggest that, as the difference in the effectiveness between a new and comparator drug (= ΔE) increases, so too does the difference between their costs (= ΔC)—in other words: the higher the ΔE, the higher the ΔC.

3.3 Willingness-to-pay and Regression Results

For approach A, we found that the WTP at the substance level was an average of €33,814.08 (median: €7212.29) for a 1 percentage point HbA1c reduction for diabetes, €10,970.83 (median: €8466.15) for one life year gained for cardiovascular disease, and €663.46 (median: €417.27) for a 1% PASI decrease for psoriasis. For approach B, we found WTPs of €4596.26 (median: €1601.44) for a 1 percentage point HbA1c reduction for diabetes, €7753.18 (median: €4881.25) for one life year gained for cardiovascular disease, and €325.64 (median: €325.16) for a 1% PASI decrease for psoriasis.

Our regression results indicate that the implicit WTP was constant over time for diabetes and cardiovascular drugs, but significantly increased over time for psoriasis drugs ($c = 284.95$, $P = 0.004$; Table 1; for an additional figure, see Appendix C).

4 Discussion

In this study of pharmaceutical pricing in Germany, we analyzed the implicit willingness-to-pay (WTP) for newly authorized drugs in three indications—diabetes, cardiovascular disease, and psoriasis—from the perspective of the

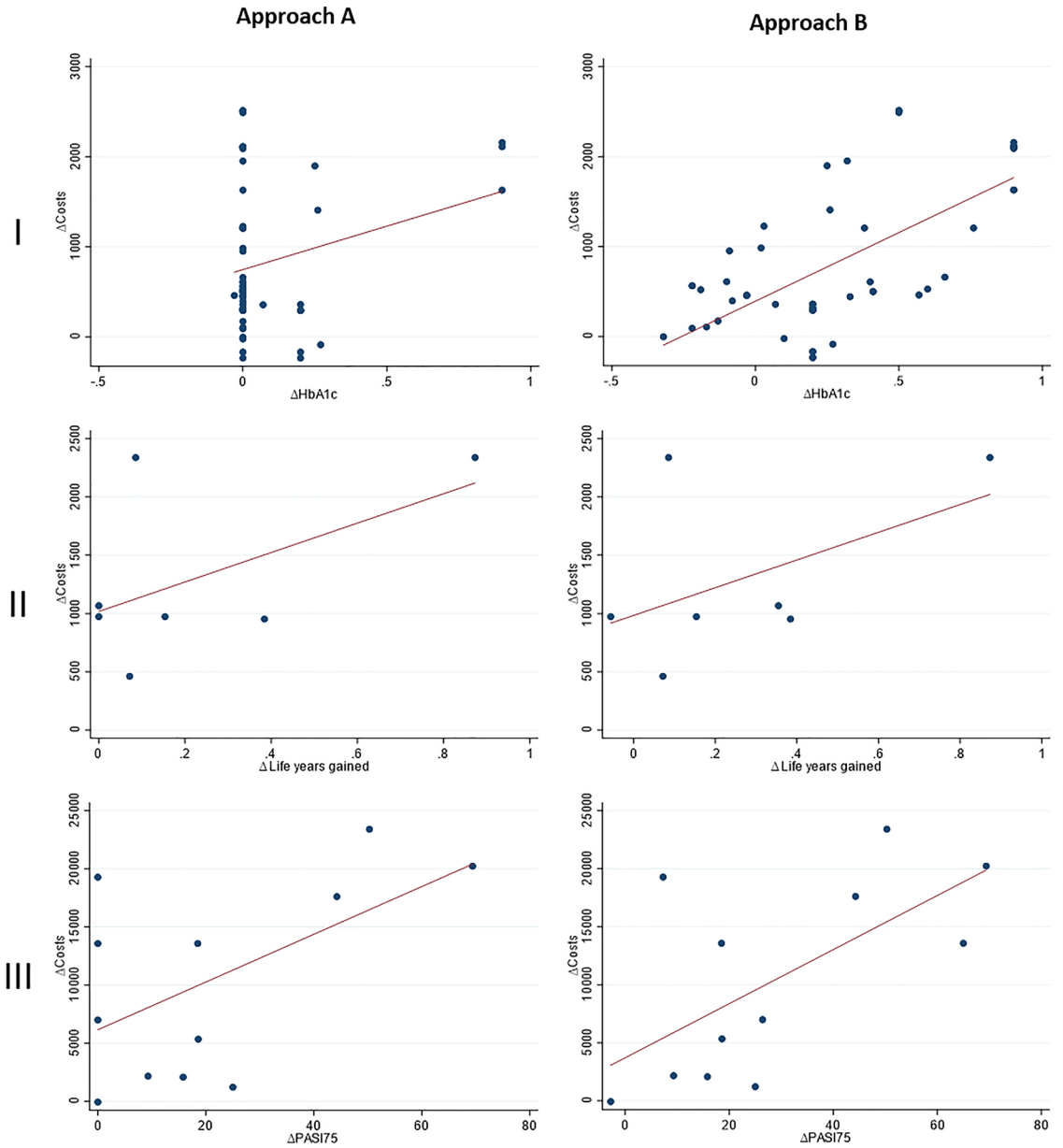

Figure 1 Correlation between Δcosts after negotiation and Δeffectiveness for (I) diabetes, (II) cardiovascular disease, and (III) psoriasis at the level of patient subgroups according to approach A (left column) versus approach B (right column). The red line indicates the linear fitted values, which we calculated based on the Δcosts and Δeffectiveness

German decision-maker/payer. We found that the WTP was €33,814.08 per 1 percentage point HbA1c reduction for new diabetes drugs, €10,970.83 per life year gained for new drugs to treat cardiovascular disease, and €663.46 per 1% PASI decrease for new drugs to treat psoriasis. Making different assumptions (approach A versus approach B) for subgroups for which the FJC declared that there was no added benefit does matter when calculating WTP and may explain the different perspectives decision-makers and the pharmaceutical industry have with respect to the value of a pharmaceutical. We also found that WTP remained constant over time for diabetes and cardiovascular drugs, but increased over time for psoriasis drugs.

Table 1 Willingness-to-pay regression results for (I) diabetes, (II) cardiovascular disease, and (III) psoriasis (approach A)

	Approach (A)		
	Coefficient	SE	*P*-value
(I) Diabetes			
_cons	6,752,942.00	9,227,686.00	0.467
Time	−3335.61	4580.95	0.470
(II) Cardiovascular			
_cons	478,923.60	1,844,092.00	0.802
Time	−232.44	915.99	0.806
(III) Psoriasis			
_cons	−574,090.80	146,654.70	0.004***
Time	284.95	72.70	0.004***

SE standard error

*$P<0.1$, **$P<0.05$, ***$P<0.01$

When comparing the WTP for new drugs to treat each of the three indications, it should be noted that there are different perceptions of what an important change might be for each outcome. For example, a change in HbA1c is considered to be clinically important if it has a value greater than 0.5% or 5 mmol/mol [33, 34]. For diabetes, this would mean that our WTP of €33,814.08 for a 1 percentage point HbA1c reduction would translate to a WTP of €16,907.04 for a clinically important change (i.e., 0.5% point reduction in HbA1c). For psoriasis, a reduction in the PASI score of 50% would be considered clinically important [35, 36]. Thus, our calculated WTP for psoriasis of €663.46 for a 1% decrease in the PASI translates to a WTP of €33,173.00 for a clinically important change. For life years gained, no thresholds for clinical importance exist, because an increase of any magnitude is already relevant to the patient. Looking at WTP in this manner, it is noticeable that the WTP for new pharmaceuticals to treat psoriasis is far higher than it is for diabetes. There are three potential explanations, none of which are mutually exclusive: (1) Health gains in psoriasis might be considered more important than those in diabetes in Germany; (2) the differences in WTP reflect that the reward for the degree of innovation per patient has to be higher in psoriasis than in diabetes because of the lower number of patients who have the former; or (3) most of the newer psoriasis drugs are monoclonal antibodies, which are more expensive to produce and require more difficult manufacturing processes than, for example, chemically synthesized substances [37].

For cardiovascular drugs we found a WTP of €10,970.83 per life year gained. Previous research found costs of US$24,219 per additional life year gained for anti-cancer drugs in Germany [21]. In England and Wales, the National Institute for Health and Care Excellence (NICE) considers one year of quality life gained to be worth between £20,000 and £30,000 (i.e., between €23,068.84 and €34,602.00 at the current exchange rate) [38], whereas before the Affordable Care Act in the US was signed into law in 2010, a hypothetical WTP for one quality-adjusted life year of US$50,000 had been under discussion for a number of years (= €49,729.25 at current exchange rate) [39]. Both are much higher than our (most likely underestimated) WTP of €10,970.83 per life year gained for cardiovascular drugs.

Previous research suggests that the different methods used by different countries to elicit information on WTP and the value of a quality-adjusted or statistical life year [40] have resulted in a wide range of estimates, also depending on the stakeholder [41]. For example, from a patient's point of view, WTP for diabetes drugs was found to be as low as €36.72 for a 1 percentage point reduction in HbA1c [42], compared with our finding of a payer's WTP of €33,814.08 for a 1 percentage point reduction. However, it is common that payers' WTP is generally much higher than that of patients [19].

Our WTP estimates are based on the results of price negotiations from the AMNOG process, which follows a value-based approach, meaning that greater benefits usually lead to higher price premiums on existing treatments [32]. It is important to bear in mind, however, that value-based pricing is not automatically associated with a decrease in pharmaceutical spending and, indeed, can even lead to higher prices for some products, resulting in a reallocation of revenue [43]. Additionally, patient-group-specific pricing (or, as others call it, indication-based pricing), which is currently under intense discussion in the USA [44], has already been implemented in Germany through the AMNOG process, whether intentionally or by chance, with manufacturers being granted a volume-weighted average price per pharmaceutical.

4.1 Limitations

Our analyses are subject to several important limitations. First, we investigated only three indications: diabetes, cardiovascular disease, and psoriasis. Investigating most other indications using our approach would be challenging because they do not involve the same clinical endpoints, making comparisons difficult. Future researchers might seek to investigate more indication areas if comparable endpoints are available.

Second, we did not adjust our analyses of average costs per clinical endpoint for changes in any other outcome, and thus our results reveal only a part of ΔE, also limiting comparisons of WTP across different areas of disease. Nevertheless, our findings, together with those of Lauenroth et al. [21], can serve as a starting point to understand implicit WTP in AMNOG negotiations and pave the way

to establishing a more explicit (i.e., transparent) threshold as happened previously in England and Wales with NICE.

Third, our quantification of German payers' spending on newly authorized drugs is based on aggregate average values. A more detailed approach would be challenging because AMNOG price negotiations are strictly confidential, and analyses can be based only on the published results. For example, we weighted patient subgroups using data published from the dossiers and could not control for compromises that were made on patient subgroup sizes in real-life price negotiations.

Fourth, although FJC methodology has not substantially changed over time, there might be changes in the perception of measurements of endpoints and indications. Also, it should also be taken into account that requirements reaching benefit levels differ by endpoint category, thus adding another dimension influencing the price. To add to that, the missing of other endpoints is a strong limitation.

Fifth, due the low number of observations, we refrained from including additional variables into our regression models. Thus, our models are underspecified, and results only provide evidence of correlation between WTP and time.

Sixth, our one indication area "cardiovascular diseases" is a very broad therapeutic area comprising various different indications (e.g., hypertension, stroke prophylaxis, etc.) Thus, results should be interpreted with caution. Further, our analysis does not consider potential cost offsets (e.g., from reduced hospitalization) that could potentially contribute to the willingness to pay.

Lastly, it is likely that our measure underestimates the true WTP because our results stem from negotiations in which payers probably accepted some bids that were below their actual WTP.

5 Conclusion

We found that the decision-maker's/payer's willingness-to-pay (WTP) for new pharmaceuticals in Germany after the price negotiating mechanism of the German Pharmaceutical Restructuring Act (AMNOG) came into effect over a decade ago varies widely by indication group, averaging €33,814.08 for 1 percentage point reduction in HbA1c for diabetes, €10,970.83 for one life year gained for cardiovascular disease, and €663.46 for a 1% decrease in PASI score for psoriasis (WTP converted to MCID thresholds: diabetes: €16,907.04; cardiovascular drugs: no MCID existent to convert; psoriasis: €33,173.00). Furthermore, we found that WTP remained constant over time for diabetes and cardiovascular drugs, but significantly increased over time for psoriasis drugs. Making different assumptions with regard to the assumed effectiveness of indication areas that had been declared to have no additional benefit by the FJC does matter and may explain the different perspectives of decision-makers and pharmaceutical industry on the value of a pharmaceutical.

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Declarations

Conflict of Interest None.

Ethics Approval Not applicable.

Consent to Participate Not applicable.

Consent for Publication (From Patients/Participants) Not applicable.

Data Availability The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Code Availability The codes generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Author Contributions MB and TS developed the research question and the study design. MB did the literature review, data preparation, statistical analysis, and drafting of the manuscript. MB and TS did the interpretation of results and a critical revision of the manuscript.

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