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Determining the Price for Pharmaceuticals in Germany

Comparing a Shortcut for IQWiG's Efficiency Frontier Method with the Price Set by the Manufacturer for Ticagrelor

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Determining the Price for Pharmaceuticals in Germany: Comparing a shortcut for IQWiG's efficiency frontier method with the price set by the manufacturer for ticagrelor

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Conflict of interest declaration

There are no potential conflicts of interest.

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Abstract

Under the recently enacted pharmaceutical price and reimbursement regulation in Germany, new products are subject to a rapid assessment to determine whether there is sufficient evidence of added clinical benefits compared to existing standard treatment. If such added benefits are confirmed, manufacturers and representatives of the statutory health insurance (SHI) are expected to negotiate an appropriate reimbursement price. If parties fail to reach an agreement, a final decision on the reimbursement price will be made by an arbitration body. If one of the parties involved wishes so, a formal evaluation of costs and benefits of the product in question can be initiated, which will be conducted by the Institute for Quality and Efficiency in Health Care (IQWiG). IQWiG makes recommendations for a reimbursement price based on the "efficiency frontier" in a therapeutic area. The analysis requires, when applicable, to calculate savings in other areas of the health care system (cost offsets) and health care costs during the years of life gained (i.e., downstream costs). A recent paper described the conditions under which calculation of downstream costs is not required when one clinical outcome is used as a measure of effectiveness or several outcomes are used and affected to the same degree. This reduction in the data required helps to avoid complex modeling and reduces the burden and time of producing evaluations. The purpose of this paper is to use ticagrelor as an example to demonstrate this "shortcut" for the efficiency frontier method. Ticagrelor was the first pharmaceutical product undergoing the new pricing process. Specifically, ticagrelor is compared to clopidogrel in patients with non-ST-segment elevation myocardial infarction from the perspective of the SHI. The analysis shows that the

price of ticagrelor as originally set by the manufacturer is at least twice the reimbursement price that would result from an application of IQWiG's methodology.

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Introduction

In Germany, new legislation regulating the reimbursement of drugs within the statutory health care system (Arzneimittelmarktneuordnungsgesetz [AMNOG]) was introduced January 1, 2011. According to this law, new products are subject to a rapid assessment to determine whether there is sufficient evidence of added clinical benefits compared to the existing standard of treatment. If such added benefits are confirmed, manufacturers and representatives of the statutory health insurance (SHI) are expected to agree on an appropriate reimbursement price within six months, starting from the completion of the benefit assessment by the German Federal Joint Committee. The first price negotiation between drug makers and health insurers took place for the drug ticagrelor, an antiplatelet agent, which had been found to reduce the incidence of re-infarction and cardiovascular mortality in patients with non-ST-segment elevation myocardial infarction (NSTEMI) compared to clopidogrel (Wallentin et al., 2009; IQWiG, 2011). In this negotiation process the parties involved relied on international reference pricing. This caused an intense debate, particularly about the selection of countries to be considered for reference pricing (and, notably, the inclusion of Portugal and Greece). The price negotiation was completed in June 2012.

If drug makers and health insurers cannot agree on the price, a final decision on the reimbursement price will be made by an arbitration body. If one of the parties involved wishes so, the Institute for Quality and Efficiency in Health Care (Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen, IQWiG) will be commissioned with a formal evaluation of costs and

benefits of the product in question. IQWiG will make a recommendation for a reimbursement price based on the "efficiency frontier" in a therapeutic area (IQWiG, 2009a). The methodology of IQWiG, which is briefly summarized below, aims at proposing a price that is "cost-effective" as defined by IQWiG; however, the final decision is made by the relevant committees and not by IQWiG (IQWiG, 2009a, p. 2).

To determine reimbursement prices, IQWiG suggests the following criterion (called proportional rule[1] (Gandjour, 2011 and 2012)): the ratio between the difference in costs and effectiveness of a new drug compared with the next effective intervention (for the same indication) (CER) should not be higher than that of the difference in the costs and effectiveness of the next effective intervention compared to its next effective intervention (IQWiG, 2009a, p.viii). Comparators do not need to be drugs, but can be any health intervention for the same indication. According to IQWiG the various alternatives are placed on a "cost-benefit plane" (Figure 1), an "efficiency frontier" is drawn along non-dominated alternatives (A and B in the figure), and the reimbursement price C'' is determined by an extension of the last segment of the "efficiency frontier" (from A to B). Stricter variations of this rule, leading to lower reimbursement prices, exist. They determine reimbursement prices either based on i) the CER of the currently most effective intervention compared to no intervention (IQWiG, 2009a, p. ix), thus yielding C', or ii) the average CER of all non-dominated alternatives (IQWiG, 2009a, p. ix).

[1] The term 'rule' is used in its usual sense, ie, it does not preclude that other criteria may lead to a change in recommendation.

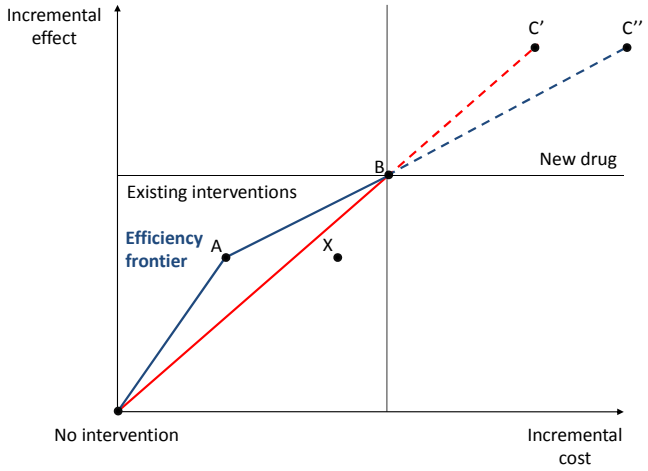

***Figure 1**: Decision rules for setting reimbursement prices by the Institute for Quality and Efficiency in Health Care (IQWiG). A, B, and X are pairs of incremental costs and effects of existing interventions and C' and C'' are cost and effect pairs of the new drug. The reference point is 'no intervention'.*

IQWiG's efficiency frontier method requires, when applicable, to calculate savings in other areas of the health care system (cost offsets) and health care costs during the years of life gained (i.e., downstream costs) (see appendix for further details of IQWiG's methodology). A recent paper by Gandjour and Gafni (2011) described the conditions under which calculation of downstream costs is not required when one clinical outcome is used as a measure of effectiveness or several outcomes are used and affected to the same degree. The purpose of this paper is to use ticagrelor as an example to demonstrate this shortcut for the efficiency frontier method. The analysis is based on the current price of clopidogrel and the health benefit of ticagrelor + aspirin compared to clopidogrel + aspirin. While other comparators for

ticagrelor such as prasugrel exist, the German Federal Joint Committee determined clopidogrel to be the appropriate comparator for the treatment of NSTEMI. Given that the negotiation process on the reimbursement price of ticagrelor relied on international reference pricing, decision rules and ethical values from other European countries may have been imported to Germany (Gandjour, 2013). This paper thus allows for a more transparent and clearer determination of the price of ticagrelor under IQWiG's approach, and enables a comparison of the so calculated price with that originally set by the manufacturer for ticagrelor and that obtained through the price negotiation.

Methods

Based on IQWiG's methodology, we determined a comparator for clopidogrel (+ aspirin). We used aspirin (+ placebo) based on a previous effectiveness evaluation by IQWiG (2009b). Therefore, the evaluation had three comparators: 1) ticagrelor + apirin, 2) clopidogrel + aspirin, and 3) placebo + aspirin. The annual price of ticagrelor as originally set by the manufacturer was €1074.46 including a discount for the social health insurance (IQWiG, 2011). After negotiation with SHI representatives the annual price was set at €730 in June 2012.

As a basis for determining the reimbursement price we used two randomized controlled trials (RCTs), both of which were conducted in patients with acute coronary syndromes without ST-segment elevation who were hospitalized within 24 hours after the onset of symptoms: the Study of Platelet Inhibition and Patient Outcomes (PLATO) comparing ticagrelor + aspirin with

clopidogrel + aspirin (Wallentin et al., 2009) and the Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) trial comparing clopidogrel + aspirin with placebo + aspirin (Yusuf et al., 2001). These were the only two RCTs considered valid by IQWiG based on a systematic search and appraisal of the literature (IQWiG, 2009b; IQWiG, 2011).

***Table 1**: Characteristics of PLATO and CURE trials.*

Study	**N**	**Age (years)**	**Gender f/m (%)**	**Caucasians/others (%)**
PLATO				
Ticagrelor	4725	64	32 / 68	93 / 7
Clopidogrel	4751	64	32 / 68	93 / 7
CURE				
Clopidogrel	6259	64	39 / 61	82 / 18
Aspirin	6303	64	38 / 62	

In PLATO patients received ticagrelor (180 mg immediately, followed by 90 mg twice daily) or clopidogrel (300 mg immediately, followed by 75 mg once daily) in addition to aspirin (75 to 100 mg daily) for 6 to 12 months. In the CURE trial patients received clopidogrel (300 mg immediately, followed by 75 mg once daily) or placebo in addition to aspirin (75 to 325 mg daily) for 3 to 12 months. While PLATO patients

were enrolled eight years after the CURE trial, all-cause mortality in the clopidogrel + aspirin arm was comparable (5.9% vs. 5.7%) (Serebruany, 2011). Tab. 1 provides further characteristics of the two trials and Tab. 2 shows trial results.

Based on the two trials we assumed a treatment duration and effectiveness over one year. Therefore, we did conduct a base-case analysis, which refers to the RCT period, but not a secondary analysis, which extrapolates costs and effects beyond an RCT. The perspective of the analysis was that of the SHI, in line with the treatment cost analysis by IQWiG (2011). Given the average age of patients in both trials (64 years), the impact of productivity gains from treatment on revenues of the SHI was considered to be negligible. Given the time horizon of one year, costs and health benefits were not discounted.

Shortcut evaluation

In a recent paper Gandjour and Gafni (2011) described the conditions under which calculation of downstream costs for the comparators is redundant when one clinical outcome is used as a measure of effectiveness or several outcomes are used and affected to the same degree. Under the assumptions of constant returns to scale and perfect divisibility of programs downstream costs have a proportional linear relationship with the number of clinical events prevented. That is, doubling the number of clinical events prevented leads to doubling of downstream costs. Hence, the ratio of downstream costs to clinical events prevented stays the same across comparators and thus cancels out. This reduction in the data required helps to avoid complex modeling and reduces the burden and time of producing evaluations. Furthermore, it helps to reduce uncertainty in the determination of reimbursement prices according to IQWiG's

approach stemming from two sources: (i) unit prices and quantities of resources consumed associated with downstream costs and (ii) extrapolation of the magnitude of clinical events into the future.

To further discuss applicability of the shortcut method to our case study, consider that in the case of several outcomes one approach recommended by IQWiG is to determine the relationship between costs and effectiveness for each outcome separately. However, CVS mortality was only affected by ticagrelor and IQWiG does not provide a specific rule regarding what to do when a drug affects more outcomes than its comparator. Therefore, we used an alternative approach and first applied the shortcut to the outcome affected by both interventions (MI) and then conducted a nested evaluation, which incorporated the outcome only affected by ticagrelor (CVS mortality). Thus, the pricing exercise considered all relevant outcomes, ie, MIs and CVS mortality. Bleeding was not considered as there was no significant difference between ticagrelor and clopidogrel (ie, there was no justifiable deviation from the price of clopidogrel on this ground).

To determine the incremental price of ticagrelor by first considering MI as the only outcome, we used the following equation (Gandjour and Gafni, 2011):

$$\frac{\Delta C_{\text{T vs C}}}{\Delta MI_{\text{T vs C}}} - \frac{\Delta MI_{\text{T vs C}} \times (1-\alpha) \times C_{\text{MI}}}{\Delta MI_{\text{T vs C}}} + \frac{\Delta MI_{\text{T vs C}} \times \alpha \times C_{\text{MI}}}{\Delta MI_{\text{T vs C}}} = \frac{\Delta C_{\text{C vs A}}}{\Delta MI_{\text{C vs A}}} - \frac{\Delta MI_{\text{C vs A}} \times (1-\alpha) \times C_{\text{MI}}}{\Delta MI_{\text{C vs A}}} + \frac{\Delta MI_{\text{C vs A}} \times \alpha \times C_{\text{MI}}}{\Delta MI_{\text{C vs A}}} \quad (1)$$

where C is costs, ΔC is the difference in drug-related costs (including costs of treating SEs and drug-related services such as counseling, monitoring, and testing) between one drug and its comparator, C_{MI} is the unit cost of a myocardial infarction (MI), ΔMI is the number of MIs prevented, and α is the proportion of MIs that is fatal.

As the second and third term on each side of the equation cancel out (Gandjour and Gafni, 2011), we obtain:

$$\frac{\Delta C_{\mathrm{T\,vs\,C}}}{\Delta MI_{\mathrm{T\,vs\,C}}} = \frac{\Delta C_{\mathrm{C\,vs\,A}}}{\Delta MI_{\mathrm{C\,vs\,A}}} \qquad (2)$$

Adding the benefit of reducing CVS mortality to the denominator yields:

$$\frac{\Delta C_{\mathrm{T\,vs\,C}}}{\Delta MI_{\mathrm{T\,vs\,C}} \times (1-\alpha) \times w_1 + \Delta\alpha_{\mathrm{T\,vs\,C}} \times w_2} = \frac{\Delta C_{\mathrm{C\,vs\,A}}}{\Delta MI_{\mathrm{C\,vs\,A}} \times ((1-\alpha) \times w_1 + \alpha \times w_2)} \qquad (3)$$

where w is a severity weight defined over the interval [0,1]. Note that the weighted-average severity of MI is calculated considering the indirect impact of MI on mortality. This is necessary because otherwise the severity weight for MI would be inappropriately applied to MIs that are fatal.

We did not consider life extension costs due to CVD mortality reduction by ticagrelor as this would result in an unwarranted "punishment" for the manufacturer of ticagrelor. The reason is that according to the shortcut by Gandjour and Gafni (2011) life extension costs would cancel out from the analysis even if there was an infinitesimally small CVD mortality reduction under

clopidogrel. In other words, the only reason for including life extension costs is the absence of a mortality reduction by clopidogrel. Again note that IQWiG does not yet provide guidance regarding what to do when a drug affects more outcomes than its comparator.

Rearranging equation (3) yields:

$$\Delta C_{\mathrm{T\,vs\,C}} = \frac{\left(\Delta MI_{\mathrm{T\,vs\,C}} \times (1-\alpha) \times w_1 + \Delta\alpha_{\mathrm{T\,vs\,C}} \times w_2\right) \times \Delta C_{\mathrm{C\,vs\,A}}}{\Delta MI_{\mathrm{C\,vs\,A}} \times \left((1-\alpha) \times w_1 + \alpha \times w_2\right)} \quad (4)$$

As $\Delta C_{\mathrm{T\,vs\,C}}$ represents the incremental price of ticagrelor compared to clopidogrel, the price of ticagrelor is calculated as follows:

$$C_{\mathrm{T}} = \Delta C_{\mathrm{T\,vs\,C}} + C_{\mathrm{C}} \quad (5)$$

Data

Data used for the analysis are shown in Tab. 2 and 3. The annual cost of clopidogrel considers a rebate from the social health insurance (IQWiG, 2011). Costs of aspirin were not included in the analysis as they cancel out (they are the same for all comparators) (IQWiG, 2011).

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***Table 2**: Hazard ratios, relative risks, and absolute risk reductions (95%-confidence intervals) of ticagrelor + apirin vs. clopidogrel + aspirin vs. placebo + aspirin in patients with non-ST-segment elevation myocardial infarction (IQWiG, 2011). Values used in the evaluation are highlighted. Ninety-five percent confidence intervals of ARRs were only calculated when required for pricing.*

	Ticagrelor + apirin vs. clopidogrel + aspirin	Clopidogrel + aspirin vs. placebo + aspirin
Total mortality	HR 0.73 (0.60 - 0.89) ARR 1.5%	No significant difference
Cardiovascular mortality	HR 0.70 (0.56 - 0.87) **ARR 1.5% (0.7 - 2.3)**	No significant difference
Myocardial infarction (fatal and non-fatal)	**HR 0.85 (0.72 - 1.00)** **ARR 1.1% (0.1 - 2.1)**	**RR 0.77 (0.67 - 0.89)** ARR 1.4%
Stroke	No significant difference	No significant difference
Bleeding	No significant difference	RR 1.69 (1.48 – 1.94) ARI 3.5%

HR = hazard ratio
RR = relative risk
ARR = absolute risk reduction
ARI = absolute risk increase

***Table 3**: Additional data used for pricing of ticagrelor.*

Variable	Base case	Range tested	Reference(s)
Annual treatment cost of clopidogrel	€131.11	-	IQWiG, 2011
Health reduction by MI	0.12	0.07 - 0.16	Tsevat et al., 1993
Health reduction through death	1	1	Gold et al., 1996
1-year mortality after MI	30%	26% - 33%	Günther, 2010

MI = myocardial infarction

To determine the weight of health decrease by MI the analysis considered that some MIs are fatal. Fatal MI per definition receives the weight of death, ie, the maximum weight, which is one. To attribute a weight to the health decline by non-fatal MI, we searched the Cost-Effectiveness Analysis (CEA) Registry at the Institute for Clinical Research and Health Policy Studies at Tufts Medical Center (www.cearegistry.org) on January 20, 2012. The most commonly used preference weight (0.88) was elicited by the time trade-off questionnaire in a survey of 67 U.S. survivors of a recent MI (Tsevat et al., 1993; see also the discussion). The MI fatality rate (30%) was calculated based on

an analysis of 701 German patients with acute MI in 2005 (Günther, 2010). The weight of health decrease by MI was therefore 0.38 (= 0.12 x 0.7 + 1.0 x 0.3).

Sensitivity Analysis

To address uncertainty around the annual price of ticagrelor, we conducted univariate sensitivity analyses of effectiveness parameters and severity weights. We ran the analyses using the upper and lower bound of the 95 percent confidence interval (CI) of the mean (see Tab. 2 and 3 for uncertainty ranges).

To assess how a simultaneous change of several variables affects the annual price of ticagrelor, we performed a Monte Carlo simulation, a type of multivariate sensitivity analysis. A Monte Carlo simulation runs a large number of simulations (here: 1000) by repeatedly drawing samples from probability distributions of input variables. Thus, it provides a probability distribution for the output variable, that is, annual costs.

Probabilities and the preference weight of MI were assumed to follow a beta distribution because they are restricted to take on values between 0 and 1. Relative risk of clopidogrel for MI was assumed to follow a lognormal distribution.

Results

The shortcut evaluation considering a reduction both in MIs and CVS mortality yields an annual reimbursement price of ticagrelor of €530. As the price of clopidogrel considers a rebate from the SHI, the price of ticagrelor also includes these rebates

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***Table 4**: Univariate sensitivity analyses: effects of varying base-case estimates on the annual price of ticagrelor.*

	Annual price of ticagrelor (€)
Base case	530
Health reduction by MI	
Lower bound (0.07)	559
Higher bound (0.16)	509
1-year mortality after MI	
Lower bound (26%)	565
Higher bound (33%)	499
ARR of ticagrelor for cardiovascular mortality	
Higher bound (2.3%)	730
Lower bound (0.7%)	329
ARR of ticagrelor for MI (fatal and non-fatal)	
Higher bound (2.1%)	551
Lower bound (0.1%)	509
RR of clopidogrel for MI (fatal and non-fatal)	
Lower bound (0.67)	1094
Higher bound (0.89)	373

MI = myocardial infarction
HR = hazard ratio
RR = relative risk

(i.e., the price of ticagrelor without rebates would be higher). Considering costs of a test for kidney function (€4 per year; IQWiG, 2011) slightly lowers the annual price of ticagrelor to €526. The sensitivity analysis (Tab. 4) shows that the effectiveness of clopidogrel has the largest impact on the price of ticagrelor. In fact, assuming low effectiveness of clopidogrel yields approximately the price as originally set by the manufacturer of ticagrelor.

The Monte Carlo simulation shows the overall uncertainty around the annual reimbursement price of ticagrelor: the simulated 95% confidence interval is between €368 and €1088 (mean: €573). The probability of obtaining a price below the negotiated price (€730) is 86%.

Discussion

Based on IQWiG's methodology, the shortcut evaluation yields an annual reimbursement price (€530), which is approximately half the annual price of ticagrelor before negotiation (€1074) and three fourths of the price after negotiation (€730). As revealed by the sensitivity analysis, according to IQWiG's methodology, the price as originally set by the manufacturer is only justifiable under the assumption of low effectiveness of clopidogrel.

While the shortcut evaluation did consider the health benefit from reducing CVS mortality, it did not consider the costs of life extension from reducing CVS mortality. The exclusion was necessary because clopidogrel does not reduce CVS mortality and therefore influences fewer outcomes than ticagrelor. A

similar adjustment would be necessary when a new drug would affect fewer outcomes than its comparator.

It should be noted further that the evaluation took the price of clopidogrel as given assuming that clopidogrel as currently priced is not dominated by any other treatment. If a prior evaluation had determined the price of clopidogrel based on the price of aspirin, the cost-effective price of ticagrelor most likely would have been lower than estimated in this paper.

As illustrated in this paper, an important advantage of the shortcut evaluation is that it requires less data and fewer assumptions. Still, the shortcut evaluation is not without assumptions. As further discussed in the appendix, using clinical outcomes as a measure of effectiveness presupposes that they have cardinal properties. Also, the calculation of savings from avoiding nonfatal clinical events assumes constant returns to scale and perfect divisibility of programs, as in the case of traditional cost-effectiveness analysis (Birch and Gafni, 1992; Birch and Gafni, 1993; Weinstein and Zeckhauser, 1973). Moreover, the shortcut assumes that end-of-life costs are the same in both arms and thus cancel out. Again, this assumption is common to traditional cost-effectiveness analysis.

Other limitations relate to the sources used in our model. First, the source of the weight for the health decline by non-fatal MI (U.S. patients around the year 1990) may be disputed. Yet, our sensitivity analysis showed little change in the price of ticagrelor when varying this weight. Noteworthy, assuming a larger health decline does not increase the price of ticagrelor but decrease it as the relative importance of avoiding death diminishes. Also note that QALYs are not explicitly excluded by IQWiG's methodology (IQWiG, 2009a, p.4). Furthermore, there may be differences in study populations and co-treatments

in the underlying RCTs (CURE and PLATO trials), which limit inclusion of both trials in one model. Consideration of results from CURE, however, is supported by comparable mortality rates in the clopidogrel + aspirin arm (Serebruany, 2011). Moreover, we incorporated results from the CURE trial based on a relative risk measure, thus improving applicability.

Additional limitations that relate to the comprehensiveness of our analysis but not the shortcut as such are as follows. First, pricing according to IQWiG also depends on the results of the secondary analysis, which extrapolates costs and effects beyond the end of the RCT. Second, IQWiG's reimbursement price is also influenced by its alternative decision rules. As stated in the introduction, a reimbursement price is also determined based on the CER of the currently most effective intervention compared to no intervention. Third, pricing according to IQWiG may also depend on the projected total budget impact of ticagrelor. And forth, the German Federal Joint Committee also found a "non-quantifiable" benefit of ticagrelor compared to prasugrel in patients with ST-segment elevation MI (STEMI) receiving a percutaneous coronary intervention. Again, this clinical benefit will influence pricing. Note that while addressing the first limitation has an ambiguous effect on the price of ticagrelor, addressing the second, third, and forth limitation may reduce the price of ticagrelor even further. With regard to the forth limitation this would occur when the benefit in STEMI patients were smaller than in NSTEMI patients.

In conclusion, the shortcut evaluation approach yields a considerably lower price for ticagrelor than originally set by the manufacturer. The calculated price is also lower than the one obtained through the price negotiation. While this may not hold for all evaluations of this type, in the case of ticagrelor, our short-cut evaluation indicates that applying the IQWiG

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approach would result in substantial savings for the SHI and, correspondingly, reduced returns on investment for the manufacturer of ticagrelor. As suggested in the previous paragraph savings may even be underestimated when considering additional factors. Therefore, both payers and manufacturers may use the shortcut method to conduct a rapid assessment of the appropriateness of drug prices and define their reservation price during price negotiations.

Finally, we note that each of the approaches to set "fair reimbursement prices" is associated with its own set of normative and methodological issues (cf. Schlander et al., 2012, 2013). Hence, the present analysis should neither be interpreted as an endorsement nor as a rejection of IQWiG's efficiency frontier approach, as it is beyond the scope of the present paper to address the normative underpinnings of pharmaceutical price regulation.

References

1. Birch S, Gafni A. Cost effectiveness/utility analyses. Do current decision rules lead us to where we want to be? *J. Health Econ.* 1992;11 (3): 279-296.
2. Birch S, Gafni A. Changing the problem to fit the solution: Johannesson and Weinstein's (mis) application of economics to real world problems. *J. Health Econ*. 1993;12 (4): 469-476.
3. Gandjour A, Gafni A. The German method for setting ceiling prices for drugs: in some cases less data are required. *Expert Rev. Pharmacoecon. Outcomes Res.* 2011;11 (4): 403-409.

4. Gandjour A. Germany's decision rule for cost-effectiveness analysis on drugs: a comparative analysis with other decision rules. *Appl. Health Econ. Health Policy.* 2011; 9 (2): 65-71.
5. Gandjour A. Presenting Germany's drug pricing rule as a cost-per-QALY rule. *Health Care Manag. Sci.* 2012; 15 (2): 103-107.
6. Gandjour A. Reference pricing and price negotiations for innovative new drugs: viable policies in the long term? *Pharmacoeconomics.* 2013; 31 (1): 11-14.
7. Gold MR, Siegel JE, Russell LB, Weinstein MC (eds.). *Cost-effectiveness in health and medicine.* New York: Oxford University Press, 1996.
8. Günther K. Identifikation von Risikogruppen für myokardinfarktbedingte Letalität und nicht-leitlinien-gerechte Versorgung unter Patienten mit Nicht-ST-Strecken-hebungs-Myokardinfarkt (NSTEMI) oder ST-Strecken-hebungs-Myokardinfarkt (STEMI) in Bremen. *PhD Dissertation.* University of Bremen; 2010.
9. Institute for Quality and Efficiency in Health Care. *General methods for the assessment of the relation of benefits to costs* - version 1.0 (in German). October 12, 2009a.
10. Institute for Quality and Efficiency in Health Care. *Clopidogrel plus acetylsalicylic acid in acute coronary syndrome* (in German). January 28, 2009b.
11. Institute for Quality and Efficiency in Health Care. *Ticagrelor – benefit assessment according to § 35a Social Code Book V* (in German). September 29, 2011.
12. Schlander M, Jaecker A, Voelkl M. Arzneimittelpreise: Preisbildung in einem besonderen Markt. *Dtsch. Ärztebl.* 2012; 109 (11): A524-A528.

13. Schlander M, Jaecker A, Voelkl M. Arzneimittelpreis-regulierung nach den Prinzipien der Sozialen Markt-wirtschaft. *Pharm. Ind.* 2013; 75 (3): 384-389 (Part 1) and *Pharm. Ind.* 2013; 74 (4): 589-594 (Part 2).
14. Serebruany VL. V iewpoint: paradoxical excess mortality in the PLATO trial should be independently verified. *Thromb. Haemost.* 2011; 105 (5): 752-759.
15. Tsevat J, Goldman L, Soukup JR, Lamas GA, Connors KF, Chapin CC, et al. Stability of time-tradeoff utilities in survivors of myocardial infarction. *Med. Decis. Making.* 1993; 13 (2): 161–165.
16. Wallentin L, Becker RC, Budaj A, Cannon CP, Emanuelsson H, Held C, Horrow J, Husted S, James S, Katus H, Mahaffey KW, Scirica BM, Skene A, Steg PG, Storey RF, Harrington RA; PLATO Investigators, Freij A, Thorsén M. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. *N. Engl. J. Med.* 2009; 361 (11): 1045-1057.
17. Weinstein MC, Zeckhauser R. Critical ratios and efficient allocation. *J. Public Econ.* 1973; 2: 147-157.
18. Yusuf S, Zhao F, Mehta SR, Chrolavicius S, Tognoni G, Fox KK; Clopidogrel in Unstable Angina to Prevent Recurrent Events Trial Investigators. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. *N. Engl. J. Med.* 2001; 345 (7): 494-502.

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Appendix - further details on IQWiG's methodology

Each therapeutic area is assessed separately; this means that no direct comparisons between therapeutic areas are performed. While measures of effectiveness may differ between therapeutic areas and within a therapeutic area for different indications, they need to be the same for the interventions compared in order to determine the reimbursement price. As potential measures of effectiveness, IQWiG allows the use of either health consequences (i.e., clinical outcomes such as mortality, morbidity (e.g., disease complications), health-related quality of life, and validated surrogates (IQWiG, 2009a, p.18)); or a preference-based measure of health outcome (IQWiG, 2009a, p.17). While effectiveness should be (ideally) measured on a cardinal scale, IQWiG also allows the use of clinical outcomes as a measure of effectiveness based on the assumption that they can be seen as having cardinal properties (IQWiG, 2009a, p.17/18). Hence, there is no requirement to formally transform health consequences and clinical outcomes into a cardinal scale.

When several relevant clinical outcomes exist, including side effects (SEs) from drug treatment, IQWiG allows for an aggregation; still, as IQWiG considers existing methods of aggregation (such as quality-adjusted life years (QALYs)) to be controversial, IQWiG currently investigates the role of analytic hierarchy process and conjoint analysis as alternative options (IQWiG, 2009a, p.20). As an alternative to aggregation, IQWiG recommends determining the relationship between costs and effectiveness for each outcome separately (IQWiG, 2009a, p. x,2,&18). "A price can be appropriate if it does not lead to a deterioration in efficiency in at least one non-marginally weighted aspect of benefit" (IQWiG, 2009a, p. xiii).

In terms of costs, IQWiG considers i) drug-related costs which includes costs of the drug and treatment of SEs, ii) savings from avoided clinical outcomes or events (CEs), and iii) change in future healthcare costs due to life prolongation stemming from the reduction in CEs. Unrelated healthcare costs during extended lifetime are not considered in the base case, but are included in a sensitivity analysis (IQWiG, 2009a, p.23). In a primary or base-case analysis IQWiG requires to take into account only costs and effects that occurred during the time period documented by randomized controlled trials (RCTs) (IQWiG, 2009a, p.51). An extrapolation of costs and effects beyond the end of the RCT is considered in a secondary analysis (IQWiG, 2009a, p.35&51) when it is relevant for decision-making.

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