Development and implementation of blood pressure screening and referral guidelines for German community pharmacists

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Abstract
Involvement of community pharmacists in the detection and control of hypertension improves patient care. However, current European or North-American guidelines do not provide specific guidance how to implement collaboration between pharmacists and physicians, especially when and how to refer patients with undetected or uncontrolled hypertension to a physician. The German Society of Cardiology and the ABDA – Federal Union of German Associations of Pharmacists developed and tested referral recommendations for community pharmacists, embedded in two guideline worksheets. The project included a guideline-directed blood pressure (BP) measurement and recommendations when patients should be referred to their physician. A “red flag” referral within 4 weeks was recommended when SBP was >140 mm Hg or DBP >90 mm Hg (for subjects <80 years), and >160 mm Hg or >90 mm Hg (≥80 years) in undetected individuals, or >130 mm Hg or >80 mm Hg (<65 years) and >140 mm Hg or >80 mm Hg (≥65 years) in treated patients. BP was measured in 187 individuals (86 with known hypertension, mean ± SD age 62 ± 15 years, 64% female, and 101 without known hypertension, 47 ± 16 years, 75% female) from 17 community pharmacies. In patients with hypertension, poorly controlled BP was detected in 55% (n = 47) and were referred. A total of 16/101 subjects without a history of hypertension were referred to their physician because of uncontrolled BP. Structured BP testing in pharmacies identified a significant number of subjects with undetected/undiagnosed hypertension and patients with poorly controlled BP. Community pharmacists could play a significant role in collaboration with physicians to improve the management of hypertension.

[Correction added on 11 November 2020, after first online publication: Projekt DEAL funding statement has been added.]
1 | INTRODUCTION

Arterial hypertension is the most important risk factor for cardiovascular diseases worldwide. In developed countries, prevalence among adults is at least 30%. Prevalence is age-related to about 71% of 65 to 79-year-olds being affected. A high number of hypertensive persons are unaware of their disease. Although hypertension care has improved, the blood pressure (BP) control rates in Germany remain unsatisfactorily low with 30% of patients being not at target. The latest EURO-ASPIRE V study showed that BP remained uncontrolled (<140 mm Hg systolic [SBP] and <90 mm Hg diastolic blood pressure [DBP]) in 42% of patients even after a cardiovascular event.

Community pharmacies are an accessible and frequent point of contact for many people for various health issues. Pharmacies offer BP measurement as health service in several countries. However, current guidelines do not provide guidance on this service in collaboration with physicians. In particular, when pharmacists should refer a patient to a physician for further evaluation has not been defined. This holds true for both undetected/undiagnosed persons and hypertensive patients with poorly controlled BP. In order to enable community pharmacists to provide recommendations based on the measured BP values, and to judge the size of their impact, referral recommendations were developed by the German Cardiac Society (DGK) and the ABDA – Federal Union of German Associations of Pharmacists which were embedded in two guideline worksheets. The purpose of this study was to evaluate the implementation of these guidelines.

2 | METHODS

Two different guideline worksheets were developed (Figure 1) for the target groups "Subjects without known hypertension" (Figures S1 and S2) and "Patients with known hypertension" (Figures S3 and S4). They were based on a previously designed worksheet for community pharmacists with regard to blood glucose measurements. We used the current hypertension guideline of the European Society of Cardiology (ESC) and the European Society of Hypertension (ESH) to specify BP threshold values for the recommended measures and to agree on further content and design.

In short, the current ESC/ESH guideline recommends to base the diagnosis of hypertension on repeated office BP measurements or out-of-office BP measurement with ambulatory BP monitoring (ABPM) and/or home BP monitoring (HBPM). According to guideline recommendations, the BP in the pharmacy should be taken after a 5-minute resting period, with three BP measurements while seated with each measurement at intervals of 1 to 2 minutes. Triple measurement minimizes the impact of interfering factors, such as stress, excitement or pain, and natural BP fluctuations. Pauses of at least one minute between the individual measurement cycles are necessary to normalize blood circulation in the arm.

What is known about this topic?
- There is strong evidence for the efficacy of pharmacist care in hypertension.
- There is a lack of guidance on how to implement this care, especially on how to establish collaboration between pharmacists and physicians.
- A recommendation when and how to refer patients with undetected or uncontrolled hypertension to a physician is absent.

What this study adds?
- We developed and tested recommendations for referral, embedded in two guideline worksheets for community pharmacists in Germany.
- Structured blood pressure testing in community pharmacies identified a significant number of patients with undetected/undiagnosed hypertension and patients with poorly controlled blood pressure.
- Community pharmacists could play a significant role in collaboration with physicians to improve the management of hypertension.

According to the ESC/ESH guideline, the diagnosis of hypertension is based on an office-based BP of >140/90 mm Hg and an 24-hour average of >130/80 mm Hg. During the day, BP should not exceed 135/85 mm Hg, and at night, values should not exceed 120/70 mm Hg. The office BP criteria were the basis for the risk categories of the guideline worksheets. The risk categories enable a recommendation of the appropriate action based on the measured values.

The measured BP values (including pulse rates) and the mean of the last two BP measurements should be recorded on the guideline worksheet (Figure 1). Based on this, the appropriate risk category is selected. The guideline worksheets offer three risk categories following a traffic light scheme for interpretation of the calculated mean values: red, yellow, and green. For classification, both mean SBP and DBP values are considered. Additionally, the categorization is subdivided by patients’ age (<65/≥65 years for patients with hypertension and <80/≥80 years for persons with no known hypertension). If the SBP or DBP mean value results in different measurements in each case, the higher risk category shall be selected. It must be noted that the respective BP values and the recommended measures differ on both guideline worksheets (Figure 1 and Figures S1-S4).

For patients with hypertension, the green category corresponds to a well-controlled BP which should be regularly monitored. Measured values of the yellow category should be submitted to the general practitioner or family physician at the next regular visit. Subjects without hypertension should take their BP measurement at least every 3 years (green category) or annually (yellow category). For
BP values in the red range, all patients should consult their primary care physician for evaluation within the next four weeks (Figure 1). BP values higher than 180/110 mm Hg constitute an emergency situation and require immediate physician follow-up.

As some BP monitoring devices can also detect arrhythmias, documentation was also provided on the guideline worksheets (Figures S1–S4). If there is evidence of previously unknown arrhythmias, this should be promptly evaluated by a physician, irrespective of the measured BP. The same applies to a sustained resting pulse rate of >100 beats per minute.

Finally, known cardiovascular risk factors and in case of patients with hypertension cardiovascular drugs should be documented (Figures S1–S4).

In the development stage, nine community pharmacists from five different Federal States received drafts of the guideline worksheets. A standardized questionnaire was used to assess understandability during a telephone interview. The guideline worksheets were optimized based on the feedback provided.

We intended to test the guideline worksheets in at least 15 different community pharmacies from different regions, and at least 150 patients: 75 patients with known hypertension and 75 individuals without a history of hypertension. Eligible community pharmacies had previous trial experience and were approached for participation personally. Community pharmacists were asked to participate because they were personally known to members of the study team. They were contacted via phone, and in case of consent, they received written material for comprehensive information on the study procedures. To standardize the measuring process, they got the updated standard operating procedure “Blood Pressure Measurement in Community Pharmacies.” For documentation, they received a sufficient number of worksheets and documentation forms to answer questions about each measurement. Copies of the filled-in worksheets and documentation forms were to be send back at the end of the study. No further training was provided.

Participants were asked to measure the BP of five patients with previously known hypertension, and of five persons without diagnosed hypertension, using the provided BP guideline worksheets (Figures S1–S4).

At baseline, we conducted an online survey to assess the current procedure of BP measurement in the participating pharmacies. Thus, we asked for the type (upper arm or wrist) and functions (detection of arrhythmias) of the BP device used in general, the frequency of measurements, the reasons to measure BP, and the procedure

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**FIGURE 1** Traffic light guidelines for referral in community pharmacies. A, Screening for hypertension. B, Patients with hypertension. Abbreviations: DBP, diastolic blood pressure; SBP, systolic blood pressure [Color figure can be viewed at wileyonlinelibrary.com]
According to the standard operating procedure, BP shall be measured in a quiet and separated area in the pharmacy. Before the measurement, the person was instructed to sit calmly for at least five minutes. Upper arm monitors with a suitable cuff size were used. All measured values, known cardiovascular risk factors, and the risk category were recorded on the worksheet (Figures S1-S4). For each measurement, feedback on the procedure and feedback received by the patients were documented so that the acceptance could be assessed.

Additionally, we conducted an online survey at the end of the study to better understand the feasibility of the guideline worksheets. We asked for the general feasibility, for missing information, for future use of the worksheets, and for the possible impact on their future BP measurements. They were also encouraged to give further considerations on the use of the worksheets.

### 2.1 | Statistical analysis

Descriptive statistics were used to report patient characteristics. Means ± standard deviations (SD) for continuous variables, and frequencies and percentages for categorical variables were presented. For non-normal continuous outcomes, medians with interquartile ranges (IQR) were also provided. Microsoft Excel® 2016 was used for these analyses. Mean differences were tested with Mann-Whitney U test. For all nominal values, differences in frequencies between groups were tested with Fisher's exact test. Comparison of risk categories between groups was analyzed by the chi-square test.

### TABLE 1 Results of the survey before study participation (at baseline); N = 17

| Item                                      | Category                        | n (%)       | Free text answers (examples)                                      |
|-------------------------------------------|---------------------------------|-------------|------------------------------------------------------------------|
| Type of generally used BP device          | Upper arm                       | 17 (100)    |                                                                  |
|                                           | Wrist                            | 0 (0)       |                                                                  |
| Device is able to perform triple          | Yes                              | 1 (6)       | Within health assessments provided by the pharmacy; support of bonus programs of health insurers; reference measurements to verify functioning of patients’ BP device |
| measurements                               | No                               | 14 (82)     |                                                                  |
|                                           | Unknown                          | 2 (12)      |                                                                  |
| Device is able to detect arrhythmias      | Yes                              | 14 (82)     |                                                                  |
|                                           | No                               | 3 (18)      |                                                                  |
| Frequency of BP measurements in pharmacy  | Daily                            | 2 (12)      |                                                                  |
|                                           | >2 times/wk                      | 1 (6)       |                                                                  |
|                                           | 1-2 times/wk                     | 8 (47)      |                                                                  |
|                                           | Once per month                   | 6 (35)      |                                                                  |
| Reasons for measuring BP                  | Patient request                  | 16 (94)     |                                                                  |
|                                           | During campaign weeks            | 8 (47)      |                                                                  |
|                                           | Indication identified during consultation | 12 (71) |                                                                  |
|                                           | Other                            | 4 (24)      |                                                                  |
| Duration of resting period [min], median (IQR) | - | 5 (2.5-10) |                                                                  |
| Repetition of measurement after 1-2 min   | Yes                              | 5 (29)      |                                                                  |
|                                           | No                               | 12 (71)     |                                                                  |
| Reasons for repetition                    | Verify first measure to exclude technical errors | 3 (60) |                                                                  |
|                                           | Verify first measure to exclude false measurements | 3 (60) |                                                                  |
|                                           | Repetition to calculate mean of BP values | 2 (40) |                                                                  |
|                                           | Other                            | 1 (20)      | Following general recommendations                                |
| Documentation of results for patient      | Yes                              | 16 (94)     |                                                                  |
|                                           | No                               | 1 (6)       |                                                                  |

Abbreviations: BP, blood pressure; IQR, interquartile range.
Statistical analyses were conducted using IBM SPSS® 22. P-values <.05 were considered statistically significant.

3 | RESULTS

Of 24 community pharmacies approached, 18 agreed to participate. Eventually, 17 pharmacies located in nine different Federal States provided a full data set of BP measurements. The median (IQR) number of filled-in guideline worksheets provided was 10 (9-13), range 4-20.

According to the baseline survey, all participating pharmacies used an upper arm BP monitoring device, and 82% of the devices were able to display signs of arrhythmias. One pharmacy used a device to perform automatic triple measurement. One third took BP measurements at least once a month; half of them, 1-2 times/wk. The remaining pharmacies responded to take BP measurements more frequently (Table 1). One main reason to take the BP measurements was the wish of the patient (94%). Pharmacies offered also BP measurement when detecting signs of elevated BP during counseling (71%) or conducted hypertension awareness weeks (47%).

3.1 | Patient characteristics

Pharmacists recorded measurements from 187 subjects, who were predominantly female (70%), mean (±SD) age of 54 ± 17 years. Of these, 86 (46%) had known hypertension. In 58% of patients with previously known hypertension, the diagnosis had been known for more than five years. A total of 92% of the patients with known hypertension stated to be treated with antihypertensive drugs, including angiotensin-converting enzyme inhibitors (23%), angiotensin-II receptor blockers (51%), beta-blockers (43%), diuretics (17%), or calcium channel blockers (28%). These patients were on average older (62 ± 15 vs 47 ± 16 years, P < .001) and had more comorbidities such as diabetes (P < .001) or coronary artery disease (P = .006) compared with 101 subjects without a previous history of hypertension (Table 2).

3.2 | Blood pressure measurements

Pharmacists took a median of 12 (IQR: 10-15) minutes for collection of cardiovascular risk factors as well as the subsequent triple BP measurement and the assessment of the appropriate action based on the measured values (Figure 1). None of the 187 procedures were interrupted at patient’s request or due to other problems, which indicates that a triple measurement is feasible in pharmacies. The majority of individuals (80%) rated the duration quite acceptable. Underlying cardiovascular risk factors were completed by 89% of the individuals independently, 9% completed this part with the help of pharmacy staff.

3.3 | Final survey

The community pharmacists provided individual feedback at the termination of the study, which are included in the further improvement of the guideline worksheets provided in the Figures S1-S4 as well as online in fillable PDF forms.19 The survey illustrated that the procedure with the aid of the guideline worksheets exceeds the standard offer of a simple BP measurement in a pharmacy. Therefore, some pharmacists concluded that this guideline-directed BP algorithm can realistically only be offered as a service with appropriate remuneration. Nevertheless, the majority (64% of the respondents) wanted to continue using the guideline worksheets (Table 5).

4 | DISCUSSION

Hypertension remains the single most important risk factor for premature morbidity and mortality worldwide. Yet, control of this risk factor has remained elusive.17 In response to this, we developed guideline worksheets for community pharmacists to screen patients with suspected or known hypertension. Our worksheets offer three risk categories showing the recommendation of the appropriate action and urgency based on the measured BP values. We demonstrated that guideline-directed BP measurements, documentation, and application of referral criteria are feasible in German community pharmacies. In addition, implementation of the guideline worksheets uncovered 16% of patients with undetected/undiagnosed hypertension and 55% of hypertensive patients with poorly controlled BP, illustrating the potential public health importance.

Current evidence around the clinical interpretation of community pharmacy BP measurement is mixed. A systematic review and meta-analysis suggested a threshold of 135/85 mm Hg for definition...
of hypertension as reasonable, potentially resulting in a higher sensitivity for detecting patients with truly increased BP in pharmacies. However, the impact of this threshold on increased rate of referrals to primary care physicians should be considered. 

Interestingly, an examination on the "New Medicine Service" in England showed that a structured involvement of pharmacists with the first prescription of an antihypertensive drug did not result in a relevant increase in the workload for the prescribing physicians.

### TABLE 2 Patient characteristics

|                                | Total       | Subjects with no history of HTN | Patients with HTN | P-value |
|                                | Number, n (%) | 187 (100) | 101 (54) | 86 (46) | - |
| Age, mean ± SD (y)             | 54 ± 17 | 47 ± 16 | 62 ± 15 | <.001 *** |
| Female sex, n (%)              | 131 (70) | 76 (75) | 55 (64) | .106 ** |
| Antihypertensive pharmacotherapy*, n (%) | - | - | 20 (23) | - |
| ACE inhibitor                  | - | - | 20 (23) | - |
| Angiotensin receptor blocker   | - | - | 44 (51) | - |
| Beta-blocker                   | - | - | 37 (43) | - |
| Calcium channel blocker        | - | - | 24 (28) | - |
| Diuretic                       | - | - | 15 (17) | - |
| Number of AHT, n (%)           | No AHT | - | - | 8 (9) |
| 1                              | - | - | 25 (29) | - |
| 2                              | - | - | 25 (29) | - |
| 3                              | - | - | 18 (21) | - |
| 4                              | - | - | 3 (3) | - |
| Number of AHT not specified    | - | - | 7 (8) | - |
| Comorbidities*, n (%)          | Diabetes | 21 (11) | 2 (2) | 19 (22) | <.001 ** |
| Coronary artery disease        | 18 (10) | 4 (4) | 14 (16) | .006 ** |
| Myocardial infarction          | 3 (2) | 1 (1) | 2 (2) | .595 ** |
| Heart failure                  | 11 (6) | 0 (0) | 11 (13) | <.001 ** |
| Stroke                         | 6 (3) | 0 (0) | 6 (7) | .009 ** |
| CKD                            | 6 (3) | 2 (2) | 4 (5) | .416 ** |
| Family history for cardiovascular diseases*, n (%) | 104 (56) | 44 (44) | 60 (70) | <.001 ** |
| Smoking*, yes, n (%)           | 33 (18) | 15 (15) | 18 (21) | .337 ** |

Abbreviations: ACE, angiotensin-converting enzyme; AHT, antihypertensive medication; CKD, chronic kidney disease; HTN, hypertension.

*As stated by the patient.

**Mann-Whitney U test.

***Fisher’s exact test.

### TABLE 3 Results of guideline-directed blood pressure measurements in n = 86 patients with diagnosed hypertension

| Blood pressure measurement | SBP [mm Hg], mean ± SD, median (IQR) | DBP [mm Hg], mean ± SD, median (IQR) | Pulse rate [min⁻¹], mean ± SD, median (IQR) |
|----------------------------|-------------------------------------|-------------------------------------|-------------------------------------|
| 1st                        | 141 ± 17 138 (129-151)              | 86 ± 14 84 (76-91)                  | 75 ± 13 76 (67-83)                  |
| 2nd                        | 137 ± 16 137 (127-145)              | 84 ± 10 83 (75-90)                  | 75 ± 13 75 (67-83)                  |
| 3rd                        | 135 ± 17 135 (125-143)              | 83 ± 11 83 (75-87)                  | 74 ± 13 74 (66-81)                  |
| Mean of 2nd and 3rd        | 137 ± 15 136 (128-146)              | 83 ± 10 83 (76-88)                  | 74 ± 12 76 (66-82)                  |

Abbreviations: DBP, diastolic blood pressure; IQR, interquartile range; SBP, systolic blood pressure.
The current guidelines of the ESC/ESH discuss screening programs for detection of hypertension. Depending on BP level, recommendations for the time intervals for repeat examinations were provided. With an optimal BP of \(<120/80\) mm Hg, repeat measurements should be taken every 5 years; with normal BP (120–129/80–84 mm Hg), every 3 years; and with high normal values (130–139/85–89 mm Hg), at least annually. To support this monitoring process and to identify persons with critical BP in community pharmacies, our guideline worksheets were based on the office BP criteria defined by the ESC/ESH. Our worksheets enable a standardized procedure to handle the results of the measurement based on evidence, thus supporting adequate patient care.

At present, hypertension is mainly detected through either opportunistic or routine systematic screening by primary care physicians. However, both methods exclude individuals who do not routinely see a physician, or those in whom routine screening is not practiced by the physician. BP screening in community pharmacies takes advantage of the fact that community pharmacists are the most accessible primary care provider. It has also been shown that 24-hour ABPM is feasible in community pharmacies.

Patients are supportive of screening by their pharmacist, improving awareness on their BP status, and if referred, a median of 44% received a new hypertension diagnosis or antihypertensive medication.

In a commentary to the 2017 American College of Cardiology/American Heart Association hypertension guideline, Dixon et al highlighted the opportunity for community pharmacies to “serve as a central hub in local communities for BP screening and overall cardiovascular health awareness.” We agree that face-to-face consultations with a community pharmacist should replace BP kiosks for screening and monitoring purposes. Some studies show, however, that quality enhancements in community pharmacies need to be implemented. Nevertheless, broad implementation of screening and monitoring protocols at every pharmacy could significantly abate the harm of undiagnosed and uncontrolled hypertension.

Together with the standard operating procedures for BP measurement in community pharmacies, the guideline worksheets presented may help implementing standardized high-quality hypertension screening in community pharmacies to take advantage of this underutilized public health resource.

There are numerous randomized controlled trials of pharmacist-led and interdisciplinary interventions investigating the impact on BP reduction, BP control rates, and reduced cardiovascular

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**TABLE 4** Results of guideline-directed blood pressure measurements in \(n = 101\) subjects with no history of hypertension

| Blood pressure measurement | SBP [mm Hg], mean ± SD, median (IQR) | DBP [mm Hg], mean ± SD, median (IQR) | Pulse rate [min\(^{-1}\)], mean ± SD, median (IQR) |
|-----------------------------|--------------------------------------|--------------------------------------|-----------------------------------------------|
| 1st                         | 129 ± 14 (126 (119-136))             | 80 ± 8 (74-86)                       | 73 ± 11 (73 (66-80))                           |
| 2nd                         | 127 ± 14 (125 (118-134))             | 80 ± 9 (74-86)                       | 72 ± 11 (72 (65-80))                           |
| 3rd                         | 125 ± 14 (123 (116-132))             | 80 ± 10 (75-85)                      | 72 ± 10 (72 (64-80))                           |
| Mean of 2nd and 3rd         | 126 ± 13 (125 (118-131))             | 80 ± 9 (74-84)                       | 73 ± 10 (72 (65-81))                           |

Abbreviations: DBP, diastolic blood pressure; IQR, interquartile range; SBP, systolic blood pressure.
risk as well as several systematic reviews and meta-analyses published. These data indicate that compared with usual BP management, interventions by pharmacists working in community pharmacies were associated with clinically important improvement in BP control, whether or not hypertension was associated with cardiovascular comorbidities. In comparison with patients receiving usual care, both SBP and DBP were more decreased and medication adherence improved as did control of other cardiovascular risk factors. This evidence has led to recommend pharmacy-based management of hypertension by some guidelines and position papers.

In developed countries, nearly 1 in 3 adults have hypertension and another 1 in 5 are undiagnosed. In Germany, approximately 13% of women and 18% of men aged 18 to 79 years have uncontrolled high BP (≥140/90 mm Hg) and, between 2008 and 2011, BP among hypertensive patients was controlled in only 51.2% (women 57.5%, men 45.4%). This translates into approximately 4 million adults with unknown hypertension and nearly 10 million hypertensive patients with uncontrolled BP in Germany. In Europe, more than 20 million and in Germany more than 3 million people visit a pharmacy every day. BP checks delivered in community pharmacies can be more convenient, as patients see their pharmacist more frequently than they see their physician and without the need for appointments. This also allows pharmacists to be proactive in screening and monitoring, as asymptomatic patients often do not seek care or advice. Community pharmacists have the opportunity to collaborate with patients and physicians in the screening and management of hypertension.

### 4.1 Limitations

This study tested the feasibility and implementation of measuring guideline-directed BP in a selected sample of community pharmacies and in a relatively small number of subjects. This sets the stage for a more widespread implementation of the guideline worksheets. Further, it is likely that there was volunteer bias in the pharmacies who participated. Nevertheless, the high number of hypertensive patients with poorly controlled BP suggests a clinically important impact.

Because of the sample size of pharmacies and subjects, we cannot give any recommendations on an adequate reimbursement for the use of the screening process using the worksheets. The study does also not allow interpretations on further interventions regarding BP control, such as adjusting medical regimens, as we did not perform medication reviews or assessments of adherence to find reasons for the poor BP control in 55% of the hypertensive patients. Finally, we did not perform a follow-up to assess whether the identified persons actually went to see a physician.

### 5 Conclusion

The development and implementation of a hypertension screening and referral guideline were both feasible and identified large numbers of patients with suboptimal blood pressure treatment. This provides vast opportunities to improve hypertension management with a likely significant impact on public health. The guideline worksheets...
now need to be implemented on a larger scale to more fully assess their impact. Indeed, a widespread implementation could bring up to 52,000 community pharmacists in Germany alone to help manage this important public health issue.

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CONFLICT OF INTEREST
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AUTHOR CONTRIBUTIONS
Martin Schulz conceived the idea and was involved in the study conception and design, interpretation of the data, and drafting of the manuscript and critical revisions. Nina Griese-Mammen, Pia M. Schumacher, Dorothea Strauch, Leonard Freudewald, and André Said were involved in the study conception and design, data cleaning, analysis and interpretation of the data, and critical revisions. Ross T. Tsuyuki was involved in interpretation of the data, drafting of the manuscript and critical revisions. Ulrich Laufs and Michael Böhm were involved in interpretation of the data and critical revisions of the manuscript. Ulrich Kintscher and Felix Mahfoud were involved in the study conception and design, interpretation of the data, and critical revisions of the manuscript. All authors approved the final manuscript.

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SUPPORTING INFORMATION
Additional supporting information may be found online in the Supporting Information section.

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